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Influence of age, physical activity, and motor cortical excitability on neuromuscular control of the wrist in humans

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INFLUENCE OF AGE, PHYSICAL ACTIVITY, AND MOTOR CORTICAL EXCITABILITY ON NEUROMUSCULAR CONTROL OF THE WRIST IN HUMANS

by

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CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

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ABSTRACT

Injury occurs when people are exposed to an unexpected event. There is a knowledge gap regarding whether people can learn to respond to unexpected events and whether this learning is moderated by age, physical activity level, cognitive function, and motor cortical excitability. The purpose of this research was to examine the influence of: 1) age, 2) physical activity, 3) cognitive function, and 4) motor cortical excitability on motor performance and learning during a novel visual motor task of the wrist.

The major outcomes of this research revealed that the ability to respond to unexpected events is reduced with age; however, with practice, older people retain the capacity to learn to respond to unexpected events. This work also demonstrates that elderly people use both feed-forward and feedback strategies to improve their response to unexpected events. Conversely, young people predominantly use a feed-forward strategy to improve their ability to respond to an unexpected event. Importantly, active older people show greater capacity to respond to unexpected events and to learn to improve responses than less active older people. Older people with higher cognitive function demonstrate a greater capacity to respond to unexpected events than those with lower cognitive function. Furthermore, merely increasing motor cortex excitability does not translate into improved performance after young people have learned a motor task. Taken together, age, physical activity, and cognitive function impact human performance and the capacity to learn to respond to unexpected events. These findings have important implications as to how to rehabilitate and/or prevent injury to unexpected events in older people.

PUBLIC ABSTRACT

Injury occurs when people are exposed to an unexpected event. There is a knowledge gap regarding whether people can learn to respond to unexpected events and whether this learning is moderated by age, physical activity level, cognitive function, and motor cortical excitability. The purpose of this research was to examine the influence of: 1) age, 2) physical activity, 3) cognitive function, and 4) motor cortical excitability on motor performance and learning during a novel visual motor task of the wrist. The major outcomes of this research revealed that the ability to respond to unexpected events is reduced with age; however, with practice, older people retain the capacity to learn to respond to unexpected events. This work also demonstrates that elderly people use both feed-forward and feedback strategies to improve their response to unexpected events. Conversely, young people predominantly use a feed-forward strategy to improve their ability to respond to an unexpected event. Importantly, active older people show greater capacity to respond to unexpected events and to learn to improve responses than less active older people. Older people with higher cognitive function demonstrate a greater capacity to respond to unexpected events than those with lower cognitive function. Furthermore, merely increasing motor cortex excitability does not translate into improved performance after young people have learned a motor task. Taken together, age, physical activity, and cognitive function impact human performance and the capacity to learn to respond to unexpected events. These findings have important implications as to how to rehabilitate and/or prevent injury to unexpected events in older people.

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CHAPTER 1 INTRODUCTION AND SIGNIFICANCE

Neuromuscular control of the wrist is essential to functional use of the hand and fingers for gripping, grasping, and manipulation tasks (Hazelton et al., 1975; Li, 2002; O'Driscoll et al., 1992). The extensor carpi radialis (ECR) is a key muscle that controls the hand by extending the wrist; whereas the flexor carpi radialis (FCR) is a key muscle that controls the hand by flexing the wrist. Together, the flexors and extensors of the wrist work synergistically to provide stability to the hand in order to perform sophisticated movements of the fingers. Neuromuscular control of the wrist is crucial to gaining functional control of the hand and serves as a major challenge to people with neurological injury and disease.

The contralateral primary motor cortex (M1) plays a central role in movement execution and improvement in skilled movement (Lotze et al., 2003; Muellbacher et al., 2001; Muellbacher et al., 2002) . The contribution of M1 to motor function is via the corticospinal tract. After depolarization, pyramidal neurons of the M1 transmit the impulse along their axons, travel through the medulla, and synapse with alpha motor neurons within the grey matter of the spinal cord. The alpha motor neuron innervates the individual muscle fibers and activates the muscle fibers to induce voluntary movement.

Voluntary wrist motor function is influenced by the integrity of the corticospinal tract (Cohen-Adad et al., 2011; Freund et al., 2012). Any injury that causes an interruption of the corticospinal pathway results in functional limitations. For example, following a

stroke, the motor pathways from the motor cortex are damaged causing limited movement of the wrist and hand. Indeed, it is common to observe the wrist in a flexed position from a “flexion synergy” with the inability to extend the wrist and open the hand. Similarly, following spinal cord injury (SCI), the corticospinal pathways from the motor cortex to the motor neurons are disrupted (Alexeeva et al., 1998), resulting in motor deficits below the level of the spinal lesion. Individuals with C6 quadriplegia can grasp objects by developing a tenodesis grip, whereby active extension of the wrist induces a passive force on the long finger flexors so that the fingers are pulled down to form a grip (Mateo et al., 2013).

We present these two clinical examples of people with neurological injury (stroke and SCI) to illustrate the need to understand how people with more subtle central nervous system (CNS) adaptations learn to move the wrist. To this point, in chapters 2, 3, and 4 we intend to examine three natural processes that are known to influence CNS adaptations: age, activity level, and motor cortical excitability. In chapter 4 we intend to manipulate the CNS by changing motor cortical excitability and examining if we can enhance the neuromuscular control of the wrist. An important underlying theme throughout the thesis is that we already know that motor cortical excitability plays a role in motor skill acquisition and learning of new tasks.

Several previous research studies in our laboratory support the conditions that we choose for this upper extremity task (Ballantyne and Shields, 2010; Madhavan and Shields, 2007; Madhavan et al., 2009; Madhavan and Shields, 2009; Madhavan and Shields, 2011; Shields et al., 2005). We manipulate the resistance and speed of wrist movement during a visual motor task. We introduce unexpected “events” in order to

examine the novel question; can people “learn” to respond to unexpected events before volitional reaction time? We propose to use a cohort of young and older people in these studies to provide a rich data set to understand what is possible with natural conditions that manipulate the excitability of the motor cortex (age and activity level) with the intention to next examine people with specific neurological compromise (Parkinson’s Disease, Myotonic Dystrophy, Stroke, Multiple Sclerosis). If our general hypothesis is supported, namely that motor skill is improved during a time before volitional reaction time then it supports that teaching movement control in rehabilitation may be instrumental in preventing injury when the CNS has been fooled.

In the following pages, we offer a review of the key literature that is relevant to this project. Throughout the review, when appropriate, we highlight the relevance of the literature to the studies that are proposed in chapters 2, 3, and 4.

Movement Control Principles: A Review

Reestablishing neuronal connections leads to improved movement control in people with CNS injury. Improved neuronal communication for movement control is often associated with enhanced excitability to the corticospinal tracts (Castel-Lacanal et al., 2007; Castel-Lacanal et al., 2009; Motamed Vaziri et al., 2014) and excitability to the spinal circuitry (Bunday and Perez, 2012). Motor practice of a task is one strategy used to acquire new motor skills, with the ultimate goal to retain the acquired movement. In all three studies proposed for this dissertation, we study a paradigm that enables us to evaluate motor skill acquisition (short- term learning) but also motor skill retention (long-term learning).

Motor learning is a term that has been defined as “a set of processes associated with practice or experience leading to a relatively permanent change in the capability for producing skilled action ” (Shumway-Cook and Woollacott, 2012). The process of motor learning involves fast learning, slow learning, and retention (Dayan and Cohen, 2011; Doyon and Benali, 2005). Initially, in the fast learning stage, motor performance is improved relatively fast; whereas further gains in learning become less and are relatively slow. Motor learning occurs “online” during motor practice, but motor learning is also learned “offline” between practice periods. During online learning, errors are decreased and individuals show proficiency in a new motor skill. During offline learning, a more stable motor skill or “memory trace” emerges that is known as motor consolidation (Doyon and Benali, 2005). After consolidation occurs, the movement skill is retained, more resistant to interference, and may be more adaptable to unexpected events or perturbations. These last points have not been fully demonstrated and represent an important component of the experiments proposed in this project.

The M1 is often the primary focus of studies involved with fast learning, slow learning, and retention stages of learning (Dayan and Cohen, 2011). However, motor practice and learning involve complex neuronal networks involving the cerebellum, striatum, prefrontal cortex, and medial temporal cortex. For example, fMRI studies support that during the fast learning stage, there are high levels of activity in the prefrontal, sensorimotor, hippocampus, and subcortical areas (Doyon and Benali, 2005; Platz et al., 2012). The cortico-cortical and cortico-cerebellar circuits are also believed to be involved in this stage (Dayan and Cohen, 2011; Doyon and Benali, 2005). During slow learning the motor improvement is associated with an increased activation in the

sensorimotor cortex and striatum but a decrease in activity of the cerebellum (Dayan and Cohen, 2011). Interestingly, the number of synapses per neuron increases within layer V of the motor cortex area with motor skill consolidation (Kleim et al., 2002; Kleim et al., 2004). The studies in this dissertation are grounded by the underlying science that supports that age and activity level modulates the excitability of the motor cortex (Bashir et al., 2014; Cirillo et al., 2009; Cueva et al., 2016; Oliviero et al., 2006; Rosenkranz et al., 2007b), which in turn may influence both feedforward and feedback sensory motor learning.

Feedback Control during Human Movement

The CNS must incorporate both feed-forward and feedback strategies during motor skill acquisition, consolidation, and retention (Schmidt and Lee, 2005). This is the basis for the term “sensory-motor” learning as most movements rely on some form of sensory information. At early stages of motor learning, motor performance is cognitively demanding and relies on performance feedback, which is mainly from sensory feedback control. Visual and proprioceptive sensory information is used at the executive level to “tune” the motor commands for an impending movement (Schmidt and Lee, 2005). Hence early motor skill practice is often slow because processing sensory information requires greater time. Importantly, sensory information is used to determine a limb’s initial location and assists in the development of a feed-forward plan. As the motor skill is learned, less feedback is required and the feed-forward contribution is gradually increased. Feed-forward control involves motor plans, often called programs, that are stored in memory and triggered to execute a movement (Schmidt and Lee, 2005). These plans contain information about how a movement is executed in a specific

environment (Schmidt and Lee, 2005). The execution of motor programs is theoretically less reliant on sensory feedback, which allows the plan to be executed more quickly, as the online incoming information is a less stringent requirement to carry out the movement plan.

Our preference with the term “sensory-motor” learning and control emanates from the notion that functional movement relies on a partnership between feed-forward and feedback movement strategies. Because the CNS uses a “predictive” mode to foster efficient and highly skilled movements, there are risks that occur when the feed-forward plan confronts a condition that was “not expected”. A movement plan that is interrupted by an event that was not anticipated must be re-purposed to best accommodate the change and successfully complete the task. We know very little about the extent to which we can learn to accommodate to unexpected events. While still theoretical, our lab has speculated that during high performance tasks the unexpected event may be so severe, that the triggered response designed to “protect” the limb may actually contribute to damage corresponding tissues (bone fractures, tendon avulsions, and muscle tears). If a perturbation is predictable, there is a reduced need for the rapid feedback control strategy. Conversely, if a perturbation is unpredictable, the feedback model may need to be maximally evoked to address the severity of the mismatch between the intended movement plan and the actual strategy needed to accurately perform the task.

Skeletal muscle electrical activity (EMG) can be utilized to estimate the extent of the neural drive to the muscles during both feed-forward as well as feedback control strategies. For this reason, we intend to record EMG in our studies. We know from the

literature and from pilot data that the most rapid EMG latency is associated with the monosynaptic stretch reflex of wrist muscles. These early responses usually occur between 25-45 ms after an induced stretch of the skeletal muscle (Goodin and Aminoff, 1992; Lee and Tatton, 1982) and are associated with the monosynaptic input of Ia primary afferents converging onto the homonymous skeletal muscle. Following the monosynaptic reflex is the long-latency response (LLR), which occurs approximately 50-100 ms following an induced stretch of the skeletal muscle (Goodin and Aminoff, 1992; Lee and Tatton, 1982). The LLR is also mediated by group Ia afferents initially (Schuurmans et al., 2009), and is tuned by a trans-cortical neural pathway (Goodin et al., 1990; Krutky et al., 2004). Areas of the CNS that have been implicated as part of this pathway include the M1, sub-cortical areas, and the cerebellum (Kimura et al., 2006; Kurtzer et al., 2013; Lewis et al., 2004; Shemmell et al., 2009). For the upper extremity, which is the focus of this dissertation, the final response is the volitional reaction time with a latency that is typically beyond 100 ms following an unexpected event (Lee and Tatton, 1982). The volitional muscle response after a perturbation is typically the largest of the responses after an induced stretch.

The studies as proposed in this dissertation, carefully introduce unexpected events, so that we are able to assess the extent to which learning occurs within the feed-forward versus feedback conditions. To reiterate, a central theme in this dissertation, and a primary question that we seek to answer, is whether people can learn to reduce error when exposed to an unexpected event. Many rehabilitation interventions purport to enhance an individual's capacity to respond to an unexpected event and thereby potentially avoid injury (or incur injury with high performance) or reduce error. The

notion that we can learn to respond to unexpected events using a feedback strategy is void of any strong scientific evidence. If rehabilitation interventions regulate feedback control mechanisms, then future research must delineate the best strategy to teach this capability. Because we are in the formative stages of understanding if people can learn to respond to unexpected events, we sought to use naturally occurring events such as age and physical activity level; both conditions known to influence the CNS, in particular, motor cortical excitability (Bashir et al., 2014; Cirillo et al., 2009; Cirillo et al., 2011).

The Long Latency Trans-cortical Reflex

The context of a movement task will influence how we respond to an unexpected event. A recorded EMG analysis supports that a LLR exists and that it plays a role in bringing a "perturbed" limb under control. During certain tasks, the amplitude of the LLR may be increased with stretch amplitude and stretch duration, but inversely related to stretch velocity (Schuurmans et al., 2009). In addition, the LLR is dependent on the central set as supported by a reduced amplitude when the perturbation is expected (Goodin et al., 1990). Furthermore, the LLR is greater when individuals experience perturbations in less stable environments (Doemges and Rack, 1992; Shemmell et al., 2009) supporting that the response is context dependent. In this proposal, we manipulate the resistance and speed components of a visual motor task of the wrist. Indeed, the speed and resistance components of a task may differentially modulate a triggered LLR. For this reason we use three resistance levels and three speed levels based on previous experimentation from our laboratory.

Work from our lab and others support that the LLR may adapt as a result of injury (Dietz et al., 1994; Madhavan and Shields, 2011; Naumann and Reiners, 1997; Shenoy et al., 2013), activity level (Cirillo et al., 2009), and age (Klass et al., 2011; Lin and Sabbahi, 1998; Madhavan et al., 2009). For example, LLRs are increased in individuals with dystonia (Naumann and Reiners, 1997) and in individuals with reconstructive surgery from anterior cruciate ligament injury (Madhavan and Shields, 2011), but decreased in individuals with stroke (Dietz et al., 1994) and low back pain (Shenoy et al., 2013). Our laboratory previously reported that age increases the reliance on the LLR amplitude in lower extremity muscles (Madhavan et al., 2009). We located only one study that supported that the LLR is increased with age of older people in the upper extremity (Lin and Sabbahi, 1998); however, there was no examination of motor skill learning, and there was no clear goal to "normalize" the central set through feedback of task performance.

We know from healthy adult studies that the LLR is modulated during certain types of motor training (Cluff and Scott, 2013; Pruszynski et al., 2008; Wang et al., 2001). Some have suggested that training enhances the LLR amplitude in response to a perturbation and the increased LLR is directly associated with less error during a visual motor tracking task (Cluff and Scott, 2013). However, the LLR of the agonist muscle decreased if a perturbation pushed the hand toward the target, but increased if the perturbation pushed the hand away from the target (Pruszynski et al., 2008). Because the LLR is mediated through a trans-cortical neural pathway (Goodin et al., 1990; Krutky et al., 2004), involving the M1, sub-cortical area, and cerebellum (Kimura et al., 2006; Kurtzer et al., 2013; Lewis et al., 2004; Shemmell et al., 2009), it is reasonable that

changes in central set and task context may have had a significant influence on the response. We believe that our experimental design improves upon these studies in that we use a visual motor task that "incentivizes" people to perform as they focus on achieving the best score after each trial. Preliminary data from our lab supports that people may have a "more common" central set as they focus on a high performance. In addition, the performance declines if a participant chooses to use a central strategy that focuses only on preventing an unexpected event. Indeed, the error induced by the perturbation is highly reproducible even after people have experienced the unexpected condition previously (Madhavan and Shields, 2007; Madhavan and Shields, 2009).

Most studies of motor learning do not include unexpected events, which is the primary focus of these studies. Previous studies have examined ballistic training (Cirillo et al., 2010; Rogasch et al., 2009), finger sequence training (Brown et al., 2009; Daselaar et al., 2003; Ehsani et al., 2015; Zimerman et al., 2013), and visual motor tracking tasks with limited training (Berghuis et al., 2015; Cirillo et al., 2011). Studies have clearly supported that repetitive practice leads to sensory motor performance improvement during these expected tasks.

The Underlying Basis (Neuroplasticity) for Motor Learning

Synaptic connections associated with the corticospinal tract are highly plastic and responsive to repetitive input. Synaptic plasticity can be modified in a bidirectional manner: long-term depression (LTD) and long-term potentiation (LTP). While LTD produces a long-lasting decreased excitability of one synapse, LTP produces a long-lasting increased excitability of one synapse, leading to enhanced neural transmission

between two neurons. Brain stimulators, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), provide opportunities to induce LTD-like or LTP-like plasticity. In addition, immobilization induces LTD-like plasticity (Ngomo et al., 2012), whereas the underlying mechanism for motor learning is an induced LTP-like plasticity.

Synaptic plasticity along the corticospinal tract, quantified as neural excitability, can be assessed by TMS. First introduced in 1985 (Barker et al., 1985), TMS involves inducing a brief magnetic field through a coil (Rossi et al., 2009). The magnetic field penetrates the skull to reach neurons and induces an electrical current to depolarize these neurons which causes a muscle evoked potential (MEP).

The amplitude of MEP from TMS induced stimulation is measured via electromyography (EMG). When the coil is placed over the M1, MEP amplitudes are thought to reflect the excitability along the whole corticospinal tract. Changes in motor cortical excitability are markers for neuroplasticity. The largest MEPs are produced when the coil is held at an angle perpendicular to the central sulcus and the current is induced in the posterior-anterior direction (Hallett, 2007). As related to this study, the cortical excitability is reduced in the non-dominant hemisphere of older people and in people who are less active (Bashir et al., 2014; Cirillo et al., 2009; Cueva et al., 2016; Rosenkranz et al., 2007b).

Long Term Potentiation (LTP) is considered one of the key mechanisms underlying motor learning. LTP, which represents an increased excitability of one synapse, leads to enhanced neural transmission between two neurons. N-methyl-D-aspartate receptors

(NMDARs), one type of glutamate receptor, play an important role in LTP. NMDAR channels are permeable to calcium ions; however, at the resting membrane potential, NMDAR channels are blocked by magnesium ions. Once NMDARs are activated, the magnesium ions are removed from the channels, leading to the high inflow of calcium ions through the NMDAR channels. A rise in the concentration of calcium ions in the postsynaptic neuron serves as a second messenger signal that activates calcium/calmodulin-dependent protein kinase II (CaMKII) (Lisman et al., 2012). CaMKII then translocates to the postsynaptic density, where it phosphorylates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and Stargazin (Lisman et al., 2012). The phosphorylation of Stargazin leads to the insertion of additional AMPA receptors. The increased density of AMPA receptors enhances the response of postsynaptic cells to glutamate, which strengthens the synaptic transmission. The late phase of LTP requires the activation of cAMP-dependent protein kinase (PKA) and the transcription factor cAMP response element-binding protein (CREB), and also involves the synthesis of new mRNA and protein, which consolidates changes in synaptic efficacy.

The corticospinal tract has a key role in producing the LTP-like plasticity following motor learning. Motor training of the fingers leads to the strongest effect on MEP amplitude of the fingers, whereas that of more proximal muscles leads to the least effect of MEP amplitude of these muscles (Krutky and Perreault, 2007). Ballistic behavioral training enhances cortical motor excitability (Muellbacher et al., 2001; Muellbacher et al., 2002; Nuzzo et al., 2015; Rosenkranz and Rothwell, 2006). Similar results have been shown following the visual motor tracking training. For example, an electroencephalogram

(EEG) study shows an increase of corticospinal drive to spinal motoneurons after learning an ankle visual motor task (Perez et al., 2006). Also, four sessions of visual motor tracking task with the dominant arm leads to an increase of MEP amplitudes (Leung et al., 2015). Furthermore, twelve sessions of visual motor skill training induces an increase of cortical motor excitability assessed by maximal MEPs (Jensen et al., 2005). A significant correlation between the change of motor performance after the visual motor training and maximal MEP is also supported (Jensen et al., 2005). Confirmation that the cervicomedullary MEP is unchanged following a visual motor task supports that the plasticity involves the motor cortex (Giesebrecht et al., 2012).

TMS-induced Synaptic Plasticity

While delivering a repetitive TMS pulse, known as rTMS, we can temporarily alter cortical motor excitability of stimulated M1, leading to LTP-like or LTD-like plasticity. The rTMS protocols which increase cortical motor excitability induce a prolonged depolarization, which expels magnesium ions from the NMDAR channel pore and allows calcium ions to enter the postsynaptic neuron. The increased concentration of calcium ions within the dendritic spines of the postsynaptic cell then triggers LTP-like plasticity. To the contrary, in rTMS protocols which decrease motor cortical excitability, the pore of the NMDAR channel is blocked by magnesium ions and no calcium current flows, leading to a decrease of synaptic strength.

In rTMS, two major strategies can be used to change excitability: up-regulation with high-frequency rTMS (HF rTMS) and down-regulation with low-frequency rTMS (LF rTMS) (Chen et al., 1997; Gangitano et al., 2002; Maeda et al., 2000; Pascual-Leone et al., 1994). A frequency of higher than 3-20 Hz is usually used for HF rTMS (Gangitano

et al., 2002; Maeda et al., 2000; Pascual-Leone et al., 1994) and this application of high-frequency rTMS is able to increase motor cortical excitability. On the other hand, LF rTMS, in which pulses are usually delivered at approximately 1 Hz, is known to decrease cortical excitability (Chen et al., 1997; Pascual-Leone et al., 1994). This method is routinely utilized in the research lab to investigate the effects of M1 inhibition on activity in cortico-cortical or corticospinal pathways or on motor performance of the contralateral or ipsilateral limb (Dafotakis et al., 2008; Fierro et al., 2001; Kobayashi et al., 2004; Kobayashi et al., 2009; Kobayashi, 2010; Romero et al., 2002). In addition, theta burst stimulation (TBS) is another rTMS protocol which is shown to increase or decrease cortical motor excitability. While intermittent TBS produces a prolonged LTP-like plasticity, continuous TBS produces a LTD-like plasticity (Huang et al., 2005). We did not use the rTMS approach described above in our study. Instead, we have elected to use a different form of rTMS that is referred to as “paired associated stimulation” (PAS) and will be described in the subsequent paragraph.

Paired with a peripheral electric stimulation PAS provides another opportunity to induce spike-timing dependent plasticity (STDP) by conjoining the firing of two neurons (Stefan et al., 2000; Stefan et al., 2002; Wolters et al., 2003). PAS is developed based on the Hebbian theory. The Hebbian theory indicates that the strength of a synapse between pre-synaptic and post-synaptic neurons will increase; leading to LTP-like plasticity, if both pre-synaptic and post-synaptic neurons are activated in near-synchronicity and the pre-synaptic neuron persistently takes part in the firing of the post-synaptic neuron (Classen et al., 2004). Conversely, the strength of a synapse will decrease, leading to LTD-like plasticity, if post-synaptic neurons are firing before pre-synaptic neurons.

STDP has been applied over M1 or spinal cord to investigate LTP-like or LTD-like plasticity effects on cortical motor excitability (Bunday and Perez, 2012; Castel-Lacanal et al., 2007; Castel-Lacanal et al., 2009; Cirillo et al., 2009; De Beaumont et al., 2012; Fathi et al., 2010; Frantseva et al., 2008; Ilic et al., 2011; Jayaram and Stinear, 2008; Jung and Ziemann, 2009; McKay et al., 2002; Meunier et al., 2012; Missitzi et al., 2011; Müller-Dahlhaus et al., 2008; Rajji et al., 2011; Ridding and Flavel, 2006; Rogers et al., 2011; Rosenkranz and Rothwell, 2006; Rosenkranz et al., 2007a; Rosenkranz et al., 2007b; Russmann et al., 2009; Sale et al., 2007; Shin and Sohn, 2011; Stefan et al., 2000; Stefan et al., 2002; Tecchio et al., 2008; Uy et al., 2003; Ziemann et al., 2004), motor function (Bunday and Perez, 2012; Castel-Lacanal et al., 2007), and motor learning (Hamada et al., 2014; Jung and Ziemann, 2009; Player et al., 2012; Rajji et al., 2011). For example, in the PAS protocol targeting the M1 neurons of hand muscles, a peripheral pulse delivered 20-25 ms before a TMS pulse induces LTP-like plasticity (Stefan et al., 2000; Stefan et al., 2002; Wolters et al., 2003), whereas a peripheral pulse delivered 10 ms before a TMS pulse induces LTD-like plasticity (Stefan et al., 2006; Wolters et al., 2003). The LTP-like plasticity is shown as the increase of the cortical motor excitability without the change of F wave (Stefan et al., 2000; Wolters et al., 2003). We use PAS in an effort to enhance cortical motor excitability for participants who already have retained a new movement skill in order to examine if we can enhance learning (Chapter 4).

Despite significant inter-individual variability in the response to TMS protocols (López-Alonso et al., 2014), PAS seems to show the highest correlations as compared to other facilitatory TMS protocols inducing LTP-like plasticity. PAS and intermittent TBS showed

a significant increase of cortical motor excitability (45 - 56%), whereas HF rTMS (5 Hz rTMS) does not change the cortical motor excitability (Di Lazzaro et al., 2011). PAS increases cortical motor excitability more effectively than intermittent TBS (Player et al., 2012).

Enhanced cortical motor excitability using PAS has been shown to improve motor performance in functional tasks. For example, after PAS, individuals with stroke demonstrate improved Fugl-Meyer motor scale scores (Castel-Lacanal et al., 2007). However, it remains unclear whether the increased cortical motor excitability by PAS influences motor skill retention and the ability for a person to respond to an unexpected event. In other words, does increasing cortical motor excitability assist in "tuning" a long latency response? As most PAS studies target hand muscles, only two studies (Castel-Lacanal et al., 2007; Castel-Lacanal et al., 2009) have investigated the PAS-induced effect on wrist muscles in general, with no studies examining the effect on perturbations.

Age, Physical Activity, and Neuroplasticity

During normal aging, the overall brain undergoes a mass reduction in size, ventricle expansion, and a loss of myelination (Peters, 2002; Scahill et al., 2003). Aging specifically affects the basal ganglia (Bastin et al., 2010; Nusbaum et al., 2001), cerebellum (Andersen et al., 2003) and hippocampus structures (Golomb et al., 1993) as well as extensive neurotransmitter reorganization projecting to these brain regions. Older adults have lower glutamate concentration in the motor cortex (Kaiser et al., 2005) and decreased NMDAR density in the cortical areas and the hippocampus (Muller et al., 1994). Age-related deterioration of the vestibular, somatosensory, and visual

systems is well documented (Wright et al., 2011). The well-documented changes in the CNS as a result of age underscore the need to understand how these natural changes impact the ability to learn and retain novel movement tasks; an important element of rehabilitation for our baby boomer population.

Older adults appear to retain the capacity to reorganize the M1 area as a result of motor training. Old and young groups demonstrated an increase in MEP amplitude after learning a novel visual motor task (Cirillo et al., 2011). However, older people showed a decline in training-dependent plasticity in response to ballistic training of the thumb (Sawaki et al., 2003) and show a reduction in the M1 excitability of non-dominant hemisphere with age (Bashir et al., 2014; Cueva et al., 2016; Oliviero et al., 2006). Currently, there are mixed assertions about whether older people experience a reduced capacity to respond to a motor learning training paradigm (Cirillo et al., 2010; Rogasch et al., 2009). A complicating factor, that has not been controlled, is the wide range of activity levels of older adults. Physically active people demonstrate greater motor cortex plasticity induced by a TMS protocol as compared to those with lower physical activity levels (Cirillo et al., 2009). The confounding factor of activity level creates confusion as we attempt to interpret studies supporting that TMS-induced LTD-like plasticity is decreased in the elderly with continuous TBS (Freitas et al., 2011) or LTP-like plasticity by PAS is progressively decreased with advancing age (Fathi et al., 2010; Müller-Dahlhaus et al., 2008; Tecchio et al., 2008).

Research does support that normal aging seems to impair motor skill consolidation to a greater extent than motor skill acquisition. Old adults demonstrate improved motor performance immediately after ballistic training (Cirillo et al., 2010; Rogasch et al.,

2009), finger sequence training (Brown et al., 2009; Daselaar et al., 2003; Ehsani et al., 2015; Zimerman et al., 2013), and visual motor tracking training (Berghuis et al., 2015; Cirillo et al., 2011). However, age appears to deteriorate the motor consolidation and offline motor learning. With mixed results as to learning at 12 hours following motor sequence training (Brown et al., 2009; Nemeth et al., 2010; Nemeth and Janacsek, 2011), age-related decline in motor memory consolidation is shown at 24-hours post, and 1 week post (Nemeth and Janacsek, 2011) learning a novel skill. Moreover, older adults are able to retain the skill at 24-hours, but do not show offline gain following the visual motor training (Berghuis et al., 2015) or the ballistic task training (Roig et al., 2014). These studies show poor motor retention and offline learning in expected events (visual motor training, ballistic task training). To our knowledge, there have been no studies investigating whether old adults show greater motor skill retention and offline learning as associated with unexpected events. We propose to address this question in Aim 1 (Chapter 2).

Associated with aging is a reduction in physical activity level. Physical activity is defined as “any bodily movement produced by skeletal muscles that result in energy expenditure” (Caspersen et al., 1985). As exercise is defined as “planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (Caspersen et al., 1985), exercise is a specific form of physical activity. Physical activity has the potential to decrease the age-associated deterioration in memory and learning and improves motor skill learning as it induces changes at both the molecular and system level of the brain (Voss et al., 2013); which is related to motor learning and LTP. At the systems level, for example, 1-year aerobic exercise offsets the

age-related decline in hippocampus volume and improves memory (Erickson et al., 2011). Also, both endurance sport and martial art athletes show higher gray matter volumes in the premotor cortex and supplementary motor cortex compared to non-exercise group. In addition, endurance sport athletes show higher volume in the hippocampus area (Schlaffke et al., 2014). These areas are keys to motor learning (Doyon and Benali, 2005).

At the molecular level, exercise regulates AMPA-type receptor subunits GluR1 and GluR2 in the M1, cerebellum, and striatum (Real et al., 2010). Acute exercise increases brain derived neurotrophic factor (BDNF), catecholamines, and lactate (Mang et al., 2014; Skriver et al., 2014; Winter et al., 2007), which have shown to correlate to motor acquisition and/or retention (Skriver et al., 2014). BDNF is essential in the LTP process (Bekinschtein et al., 2008), which is believed one mechanism contributing to motor learning. Dopaminergic modulation is also believed to play an important role in synaptic plasticity in the prefrontal cortex and hippocampus (Jay, 2003). On the other hand, dopamine and norepinephrine antagonists significantly depress LTP-like plasticity (Korchounov and Ziemann, 2011). Bioenergetics of the brain supports that astrocytes and neuronal lactate transporters modulate long-term memory formation (Suzuki et al., 2011). Lactate stimulates plasticity-related gene expression by modulating NMDAR activity (Yang et al., 2014). Taken together, it is clear that exercise-induced changes are related to synaptic plasticity and motor skill learning.

Lifelong physical activity is shown to decrease age-related decline in skeletal muscle structure and function (Zampieri et al., 2015). Regular physical activity reduces the age-related decline in proprioception (Ribeiro and Oliveira, 2007; Wright et al., 2011) and

postural instability when experiencing sensory disturbance (Lamoth and van Heuvelen, 2012; Maitre et al., 2013; Maitre et al., 2015), which suggests physically active elderly people have a better ability to use sensory information to maintain postural stability (Lamoth and van Heuvelen, 2012; Maitre et al., 2013; Maitre et al., 2015). Normal aging impairs the predictive motor control because of cerebellar neuron death and increases reliance on feedback control (Boisgontier, 2015). The better utilization of sensory information in physically active elderly people may demonstrate better compensatory strategies when experiencing unexpected perturbations, a key focus of this study.

While some studies have examined the effects of exercise on motor learning in healthy young adults, less is known about its effects in older adults. In young adults, a session of moderate intensity aerobic exercise is beneficial to movement accuracy in the sequential visual isometric pinch task (Statton et al., 2015). Also, a single bout of high-intensity cardiovascular exercise improves motor retention in a wrist visual motor tracking task at day 1 (Skriver et al., 2014) and 1 week post (Roig et al., 2012; Skriver et al., 2014), but has no influence on motor skill acquisition. High intensity aerobic exercise promotes implicit motor acquisition and retention, shown as better temporal precision in a tracking task (Mang et al., 2014). Most of these previous studies assessing the effects of physical activity/exercise have focused on one single bout of aerobic exercise. Less attention has been placed on the effects of regular physical activity on motor skill acquisition and retention. One focus of this study was be to determine if motor skill acquisition and retention in young and old groups would vary with different regular physical activity levels (Chapter 3, Aim 2).

Whether various durations or intensities of physical activity/exercise lead to similar effects on motor learning is still unclear, although previous studies have shown that long-term physical activity/exercise results in greater positive effects on task preparation and executive control than short-term physical activity/exercise (Colcombe and Kramer, 2003; Stroth et al., 2009). In addition, six-min high impact running induces a greater increase in learning speed and better retention in a complex vocabulary learning task compared to 40-min of low impact running or rest (Winter et al., 2007). In motor learning, while a single bout of moderate but not high intensity aerobic exercise improves motor acquisition, a single bout of high but not moderate aerobic exercise improves motor retention (Roig et al., 2012; Skriver et al., 2014). These studies indicate that the effect that physical activity on motor learning may be duration- and intensity-dependent. In the proposed studies, we intended to capture the activity level of the participants for 5-7 days using an ankle activity monitoring system.

TMS-induced Synaptic Plasticity

It may be that subjects who are physically active are more responsive to TMS-induced synaptic plasticity. A bout of exercise is purported to enhance the effectiveness of continuous TBS (McDonnell et al., 2013) or PAS (Mang et al., 2014; Singh et al., 2014) for finger muscles. Although a number of studies have examined the link between exercise and neural plasticity, little is known about the effect of physical activity on TMS-induced plasticity. For example, cortical PAS induces a greater increase in MEP amplitudes of the abductor pollicis brevis in physically active individuals as compared to sedentary individuals (Cirillo et al., 2009). Moreover, effects of PAS on cortical motor excitability in the abductor pollicis brevis muscle are larger in professional musicians

compared to non-musicians (Rosenkranz et al., 2007b). Accordingly, we will explore the relationship between physical activity level and motor cortical excitability as a secondary aim in chapter 4.

Physical activity in both the upper and lower limbs have been shown to modulate TMS-induced neuroplasticity in hand muscles (Cirillo et al., 2009; Mang et al., 2014; McDonnell et al., 2013; Rosenkranz et al., 2007b; Singh et al., 2014). However, these studies often relied on self-reported measures of physical activity rather than quantitative measures. This implies that physical activity measures are being influenced by self-report bias. Another limitation of the self-report is a lack of information about the limb that is involved with the physical activity. Although both upper and lower extremity-driven exercise modulates neuroplasticity, it is unclear whether physical activity of the upper extremities would induce a stronger effect on the upper extremity muscles as compared to the lower extremity muscles.

Overall Goals for each Chapter

Natural conditions that are known to alter the excitability of the motor cortex, such as age and activity level, may influence the extent to which people can learn to respond to a novel task including learning to respond to an unexpected event. In Chapter 2 we focus on the impact of age on motor learning. In Chapter 3 we focus on the impact of activity level on motor learning. In Chapter 4 we strive to manipulate the excitability of the motor cortex in young adults to determine if we can enhance the capacity to learn a novel task. In Chapter 5 we summarize our findings, accept or reject the associated hypotheses, explore future studies, and clarify conclusions and clinical implications.

Chapter 2

Primary Aim 1a

To determine the effect of age on motor skill acquisition (Day1) and retention (Day3; Day7) during both expected and unexpected conditions while performing a visual motor task of the wrist (3 speeds; 3 levels of resistance).

Hypothesis 1a

We expect that the young group will show less error and will demonstrate a greater capacity to acquire (Day1) and retain skill (Day3; Day7) as compared to the older group. We also expect that elderly will have a decreased ability to learn to respond to unexpected events in a timeframe prior to volitional reaction time as compared to a younger cohort. Finally, we expect that the attenuated ability to learn to respond to unexpected events with age will be the greatest in faster movements as compared to slower movements; and greatest in high resistance as compared to low resistance.

Secondary Aim 1b

To explore the strategy used by the young and the old to respond to unexpected events using the extensor carpi radialis (ECR) and flexor carpi radialis (FCR) EMG, triggered at 50-100 ms, following an unexpected perturbation during a visual motor task of the wrist.

Hypothesis 1b

We expect that the older group will use both feed-forward and feedback strategies whereas the young group will use the feed-forward strategy during learning the visual motor task at the wrist.

Chapter 3

Primary Aim 2a

To determine the effect of physical activity on motor skill acquisition (Day1) and retention (Day3; Day7) during both expected and unexpected conditions while performing a visual motor task of the wrist (3 speeds; 3 levels of resistance) in older and younger adults.

Hypothesis 2a

We expect that the young and old adults will show less error and will demonstrate a greater capacity to acquire (Day1) and retain skill (Day3;Day7) if they have a higher overall physical activity level (10-20K steps/day vs 5-9.999K steps/day). We expect that activity level will improve the overall capacity for people, young or old, to learn to respond to unexpected events in the trans-cortical timeframe.

Secondary Aim 2b

To determine the effect of cognitive function on motor skill acquisition (Day1) and retention (Day3; Day7) during both expected and unexpected conditions while performing a visual motor task of the wrist in older adults.

Hypothesis 2b

We expect that the old adults with higher cognitive function will show less error and will demonstrate a greater capacity to acquire (Day1) and retain skill (Day3 and Day7) than those with lower cognitive function. We expect that old adults with higher cognitive function will demonstrate a greater capacity to learn to respond to unexpected events in the trans-cortical timeframe than those with lower cognitive function.

Chapter 4

Primary Aim 3a

To determine the effect of increased cortical motor excitability using paired associated stimulation (PAS) on motor skill performance (Day7) during both expected and unexpected conditions while performing a visual motor task of the wrist (3 speeds; 3 levels of resistance).

Hypothesis 3a

We expect that people who show that PAS increases cortical excitability will demonstrate improved motor performance during both expected and unexpected conditions during the visual motor task of the wrist.

Secondary Aim 3b

To determine the association between increased motor cortical excitability using PAS on the extensor carpi radialis (ECR) and the flexor carpi radialis (FCR) EMG, triggered at 50-100 ms following an unexpected perturbation.

Hypothesis 3b

We expect to see a positive relationship between the ECR LLR and initial M1 evoked potentials induced by the PAS protocol. There will be no correlation between FCR LLR and motor evoked potentials induced by the PAS protocol.

Secondary Aim 3c

To determine the relationship between increased cortical motor excitability using PAS and physical activity level.

Hypothesis 3c

We expect that physical activity level will be associated with the level of motor cortical excitability induced.

CHAPTER 2 AGE IMPACTS FEED-FORWARD AND FEEDBACK CONTROL DURING A NOVEL VISUAL MOTOR TASK IN HUMANS

INTRODUCTION

Physical rehabilitation programs strive to improve motor performance in predicted and stereotypical functional tasks, such as walking (Brach et al., 2015; Song and Kim, 2015). However, because our central nervous system (CNS) must make predictions through motor planning; occasionally, events occur that are not expected, and the CNS is "fooled" leading to injury, imprecise movements, and altered functional performance. The goal of this study is to examine if age modulates the ability to respond to expected and unexpected events during motor skill acquisition and retention during an upper extremity visual motor task.

Age is an important moderating factor that influences the ability to learn through motor practice. Aging affects the basal ganglia (Bastin et al., 2010; Nusbaum et al., 2001), the cerebellum (Andersen et al., 2003) and the hippocampus (Golomb et al., 1993); all structures associated with motor skill acquisition and retention (Dayan and Cohen, 2011; Doyon and Benali, 2005; Platz et al., 2012). Glutamate concentration (Kaiser et al., 2005) and the NMDA receptor density (Muller et al., 1994) are diminished in the motor cortex and hippocampus, respectively, in older people. These CNS transmitters/receptors are associated with the capacity to retain motor skills through long term potentiation (LTP).

Normal aging may impair motor skill consolidation greater than motor skill acquisition, but the findings remain inconsistent (Brown et al., 2009; Nemeth et al., 2010; Nemeth and Janacsek, 2011). Older adults do not appear to show offline learning after a single visual motor training session (Berghuis et al., 2015) or after a novel ballistic movement training session (Roig et al., 2014). Although older people appear to have a reduced rate of motor skill learning (Daselaar et al., 2003), they have demonstrated the ability to learn after ballistic movement training (Cirillo et al., 2010; Rogasch et al., 2009), finger sequence training (Brown et al., 2009; Daselaar et al., 2003; Ehsani et al., 2015; Zimerman et al., 2013), and various visual motor tasks (Berghuis et al., 2015; Cirillo et al., 2011). However, none of these previous studies examined if older people learned to respond to "unexpected events" at a latency related to the long latency reflex (LLR).

The LLR offers a unique strategy to potentially attenuate limb displacement following an unexpected stretch of a muscle (Cluff and Scott, 2013; Pruszynski et al., 2008). The LLR is often mediated by group Ia afferents initially (Schuurmans et al., 2009), is tuned by a trans-cortical neural pathway (Goodin et al., 1990; Krutky et al., 2004), and occurs approximately 50-100 ms following an unexpected event (Goodin and Aminoff, 1992; Lee and Tatton, 1982). Recordings from motor cortical cells support that the frequency of firing modulates the response to a velocity dependent change in skeletal muscle length (Bawa et al., 1979; Cheney and Fetz, 1984), at a latency associated with the LLR. Later studies, in humans, support that the motor cortex excitability contributes to the amplitude of the LLR, lending support to the notion that the motor cortex tunes the LLR (Lewis et al., 2004; Stuart and Taylor, 2006). Importantly, the non-dominant primary motor cortex (M1) of older people shows reduced motor cortical excitability

(Bashir et al., 2014; Cueva et al., 2016; Oliviero et al., 2006), suggesting that the capacity to modulate a LLR during learning is altered. Accordingly, we expect that this altered capacity will impact the LLR, and the associated error as compared to younger adults.

The primary aim of this study was to determine if age impacts motor skill acquisition and retention during both expected and unexpected conditions. We hypothesized that the young group would demonstrate a greater capacity to acquire (Day1) and retain skill (Day3; Day7), especially in response to unexpected events (50-100 ms) as compared to the older group. Our secondary aim was to evaluate the EMG to ascertain the strategy used by the CNS to respond to an unexpected event that occurs before volitional reaction time.

METHODS

Subjects

Thirty-eight young (between 20 and 40 years of age) and 30 old healthy (between 60 and 80 years of age) right-handed individuals participated in this study. The exclusion criteria were that they had no history of current orthopedic or neuromuscular dysfunction, and no consumption of any substances containing alcohol or caffeine for 24 hours. Handedness were verified using the Edinburgh handedness inventory (Oldfield, 1971). Old adults were required to pass the Mini Mental Status Exam (MMSE) (Folstein et al., 1975) with scores greater than 26. This study was approved by the Institutional Review Board of the University of Iowa and all subjects had to provide their written informed consent before participating.

Paradigm

Figure 2.1A shows the schematic overview of the experimental design. Testing procedure consisted of a pre-, post-, and retention tests. Pre- and post-tests performed on Day1 (Day1pre, Day1post), and the retention test for motor consolidation performed 48 hours later on Day3 (Day3) and 1 week later on Day7 (Day7). Each day we recorded three maximal voluntary isometric contractions (MVIC) of the left wrist extensors and flexors followed by the assessment of the visual motor skill. After the pre-test, subjects received a training session comprised of 5 blocks of 3 trials each with 1-minute rest in between. On Day3 and Day7, the same measurements as the pre-test were repeated to quantify the retention of motor skill.

Behavioral Testing and Motor Training

During all testing sessions, subjects sat in a comfortable chair in front of a computer controlled LCD panel. The right forearm was relaxed on a pillow on the lap and the left forearm was supported on a movable table of a custom-built device, allowing movements of wrist flexion and extension only (Shields RK. Patent US 7,011,605 B2). This custom-built device consisted of a force transducer, a braking system, and a potentiometer which were connected together and aligned with the same axis of rotation of the wrist (Figure 2.1B). The styloid process of the ulnar bone was aligned to the axis of rotation of the device. The resting position of the left arm was in 80 degrees of shoulder abduction, 60 degrees of shoulder flexion, 60 degrees of elbow flexion, with the forearm and wrist in a neutral position. Forearm support straps and blocks restricted unwanted movements (i.e. forearm supination/pronation). We tested the left hand because motor training results in more improvement in the non-dominant hand (Ridding

and Flavel, 2006) and elderly people show greater loss in cortical excitability for the non-dominant hemisphere (Bashir et al., 2014; Oliviero et al., 2006).

Data Collection

We developed a task in which subjects were instructed to follow a moving target on a screen using wrist position. Labview (National Instruments Corp., Austin, TX, USA) was used to display the moving sinusoidal target, depicted by a white line on the screen. Subjects were instructed to track the sinusoidal wave by controlling a red line as precisely as possible with their wrist position, moving from wrist extension, to wrist flexion and back to wrist extension to complete one cycle. The lowest trough of the target represented wrist flexion of 37.25 degrees and the highest crest represented wrist extension of 37.25 degrees. The position of the wrist was signaled by a potentiometer. The position was sampled at 4000 Hz and stored for off-line analysis using MATLAB software.

Nine trials (3 velocities x 3 resistance levels) were used in this wrist visual motor manual task (Figure 2.1C). The velocity was set at 30 (Slow speed), 52.25 (Medium speed), and 74.5 (Fast speed) degrees/second; while the resistance was set at 10 (Low resistance), 17.5 (Medium resistance), and 25 (High resistance) % of MVIC of the left wrist extensor muscles. Each trial contained 5 cycles. Unexpected stretches were imposed to the wrist extensor muscles by releasing the resistance of the device when the participant completed the first one third of the flexion phase as determined by the initial starting location, in the 2^{nd}, 3^{rd}, 4^{th}, or 5^{th} cycle in the wrist flexion phase in each trial (stretching the wrist extensors). The cycle for the perturbation was determined randomly.

A training session consisted of 5 blocks of 3 trials (Figure 2.1D). Between training blocks, subjects rested for 1 min. Within the 3 trials, the resistance was set at 17.5% of MVIC of the left wrist extensor muscles and the velocity was set at 30, 52.25, 74.5 degrees/second. The order of the 3 trials was randomized but was the same for each subject at the three tests. Each trial contained one unexpected stretch delivered randomly.

On the first day (Day1pre), subjects completed 9 trials to establish their movement control baseline. Then subjects completed 5 blocks of 3, a total of 9 trials, as training sessions. After the intervention, subjects repeated the same 9 trials used in the pretest to assess the motor acquisition error (Day1post). On Day3 and Day7, subjects repeated the same 9 trials again to assess the motor skill retention.

EMG Recording

Two bipolar electromyographic (EMG) electrodes (Therapeutics Unlimited, Iowa City, IA), each with an inter-electrode distance of 2 cm, were placed over the muscle bellies of the left extensor carpi radialis (ECR) and flexor carpi radialis (FCR) muscles after prepping the skin with light abrasion and an alcohol swab. The electrode for ECR was placed over one third of the distance from the lateral epicondyle of the humerus on a line connecting the lateral epicondyle of the humerus and the styloid process of the radius, whereas the electrode for FCR was placed over one third of the distance from the medial epicondyle of the humerus on a line connecting the medial epicondyle of the humerus and the styloid process of the radius (Chow et al., 1999). The reference electrode was placed over the left lateral epicondyle of the humerus. EMG signals were pre-amplified with a gain of 35 and further amplified by a GCS 67 differential amplifier

(Therapeutics Unlimited, Iowa City, IA) with a gain of 1000-5000. The differential amplifier had an input impedance of 15 MΩ at 100 Hz, a frequency response of 15–1000 Hz, a common mode rejection ratio of 87 dB at 60 Hz, and a bandwidth of 20–400 Hz. EMG was sampled at 4000 Hz and stored for off-line analyses using MATLAB software (The MathWorks, Natick, MA).

Data Analysis

The motor performance data on the visual motor task were analyzed using MATLAB software. Motor learning, as measured as absolute error, was determined by calculating the absolute difference between the target and wrist displacements at each time point. For perturbed cycles, absolute errors at 50-100 ms after the perturbation were calculated. In addition, we calculated the "user rate", defined as the slope of the best-fit straight line through wrist displacements during 100 ms starting from the beginning of the perturbation to 100 ms after the perturbation by using a least squares regression. For unperturbed cycles, absolute errors and user rate over the same period of time in each cycle were calculated, where "time-zero" was defined as the time at which wrist was at the first one third of the flexion phase.

For both errors and user rate, the first cycle of each trial was discarded because it represented purely reaction time data. Absolute errors/user rate in perturbed cycles were defined as absolute errors/user rate in perturbed cycles, whereas absolute errors/user rate in unperturbed events were defined as the average of absolute errors/user rate in the 3rd to 5th unperturbed cycles. Our preliminary studies indicated that for unperturbed cycles, the errors were significantly larger in the 2nd cycle compared

to the 3rd, 4th or 5th cycles (Post-hoc, all P< 0.039). Therefore, we used the 3rd, 4th and 5th cycles to estimate the error during the unperturbed events.

For each subject, the absolute error and user rate from 9 conditions (3 speeds and 3 resistance levels) were averaged as the overall error/user rate. Furthermore, the absolute errors from conditions with the same speed (Slow, Medium, and Fast speed) or resistance (Low, Medium, and High resistance levels) were averaged separately.

The RMS EMG response for the ECR and FCR at 50-100 ms after the perturbation was calculated. The long-latency muscle response in each cycle depends on the pre-perturbation EMG activity. Thus, for each perturbed cycles, we calculated the pre-perturbation RMS EMG background during the 50 ms preceding the perturbation. The EMG response at 50-100 ms would be further normalized to the pre-perturbation EMG.

Statistical Analysis

SAS 9.3 (SAS, Cary, NC) software was used for all statistical analyses. Independent t tests were used to test for differences in continuous variables (age, height, weight, body fat, handedness, and step count) between groups. T-test corrected values were used when equal variances were not assumed. A chi-square test was used to test the sex differences between groups.

Two-way repeated measures mixed model ANOVAs (the between-group factor “AGE” had levels young and old, and the within-group factor “TIME” had levels Day1pre, Day1post, Day3, and Day7) were used to determine the difference in error and user rate between young and old groups. Three-way repeated measures mixed model ANOVAs (the between-group factor “AGE” had levels young and old, the within-group factor

"TIME" had levels Day1pre, Day1post, Day3, and Day7, and the within-group factor "CONDITION (SPEED or RESISTANCE)" had levels Fast, Medium, and Slow speed or Low, Medium, and High resistance levels) were employed for analysis of the effect of task Speed and Resistance level. In addition, in order to investigate mechanisms underlying motor learning in each young and old group, two-way repeated measures mixed model ANOVAs (the within-group factor "TIME" had levels Day1pre, Day1post, Day3, and Day7; the within-group factor "PERTURBATION" had levels expected and unexpected events) were used to determine the difference in user rate and normalized EMG (ECR, FCR) at 50-100 ms between expected and unexpected events across times in each group. If there was any normalized EMG changed from one time point to the next, two-way repeated measures mixed model ANOVAs (the within-group factor "TIME" had levels Day1pre and Day1post; the within-group factor "PERTURBATION" had levels expected and unexpected) were used to determine the difference in EMG at 50-0 ms before the perturbation between these two time points.

If any of the ANOVAs revealed a significant effect, Tukey's HSD test was used for post-hoc comparisons. The significance level was set at $p<0.05$.

RESULTS

There were no differences in sex, handedness, and physical activity level between groups. However, the young group was leaner and taller than the old group. Demographic details for young and old groups are presented in Table 2.1.

Expected Events (Unperturbed) Error Analysis

The mean absolute errors at 50-100 ms on Day1pre were 9.46 and 14.22 degrees for the young and old groups, respectively; while the user rates at the 0-100 ms time for the young and old groups were -90.98 and -112.09 degrees/second, respectively. The percent changes in error from Day1pre to Day1post, Day3, and Day7 were -21.36, -24.29, and -28.41 percent, respectively, for the young group; and -7.87, -12.59, and -14.03 percent for the older group. The percent changes in user rate from Day1pre to Day1post, Day3, and Day7 were -15.54, -14.19, and -19.64 percent, respectively, for the young group; and -16.85, -9.72, and -13.7 percent for the older group. (Figure 2.2A).

For both absolute error at 50-100 ms and user rate, there was a significant main effect for TIME ($P<0.0001$) and AGE ($P<0.0001$), but there were no TIME x AGE interaction ($P>0.176$). Post-hoc testing for TIME revealed that error and user rate were significantly decreased at all times following the Day1pre condition for both young and old groups ($P<0.0001$); however, user rate was worse from Day1post to Day3 ($P=0.012$) but improved from Day3 to Day7 ($P=0.01$).

Unexpected Events (Perturbed Conditions) Analysis

The mean absolute errors at 50-100 ms on Day1pre were 9.75 and 14.09 degrees for the young and old groups, respectively; while the user rates at the 0-100 ms time were -103.7 and -114.03 degrees/second for the young and old groups, respectively. The percent changes for error from Day1pre to Day1post, Day3, and Day7 were -17.83, -23.76, and -29.56, respectively, for the young group; and 0.42, -7.63, and -10.36, for the older group. The percent changes for error from Day1pre to Day1post, Day3, and Day7

were -18.34, -19.46, and -18.47 percent, respectively, for the young group; and -17.51, -15.56, and -17.22 percent for the older group (Figure 2.2B).

For both absolute error at 50-100 ms and user rate there was a main effect for TIME ($P<0.0001$) and AGE (Both: $P<0.007$), but not a TIME x AGE interaction ($P>0.168$). Post-hoc testing for TIME revealed that error and user rate were significantly decreased at all times following the Day1pre condition for both young and old groups ($P<0.048$). While the user rate was similar between Day1post to Day3, and from Day3 to Day7 ($P>0.805$), absolute errors were decreased from Day1post to Day3 ($P=0.044$) but remained similar from Day3 to Day7 ($P=0.262$).

Influence of Movement Speed on Expected and Unexpected Events

Expected Events

The percent changes in user rate for the younger group from Day1pre to Day1post, Day3, and Day7 were -16.74, -11.53, and -19.9 percent, respectively, for the Slow speed; -22.61, -21.25, and -25.83 for the Medium speed; and -10.41, -10.30, and -15.24 for the Fast speed. The percent changes in user rate for the older group from Day1pre to Day1post, Day3, and Day7 were -21.67, -14.07, and -23.75 percent, respectively, for the Slow speed; -22.35, -14.59, and -18.48 for the Medium speed; and -10.44, -4.08, and -5.36 for the Fast speed. The average user rates are shown for all speed levels in Figure 2.3A(1).

There was a significant main effect for TIME ($P<0.0001$), AGE ($P<0.0001$), and SPEED ($P<0.0001$) supporting that the user rate improved with training, but, was different between the young and the old depending on the speed of the task. There was a TIME

x SPEED (P=0.03) and AGE x SPEED interaction (P=0.005). Post hoc analysis showed the greatest user rate in the Fast condition (P<0.0001) and the smallest in the Slow condition (P<0.0001) for both old and young groups (Figure 2.3A(1)). The user rate was greater in the older group for all 3 speeds (P<0.0001).

Unexpected Events

The percent changes in user rate for the younger group from Day1pre to Day1post, Day3, and Day7 were -13.98, -19.23, and -14.19 percent, respectively, for the Slow speed; -29.7, -29.77, and -29.57 for the Medium speed; and -10.83, -11.01, and -11.02 for the Fast speed. The percent changes in user rate for the older group from Day1pre to Day1post, Day3, and Day7 were -10.86, -7.88, and -12.53, respectively, for the Slow speed; -30.88, -27.66, and -26.03 for the Medium speed; and -9.69, -9.27, and -11.86 for the Fast speed. The average user rates for the Slow, Medium, and Fast speeds for the young and old groups across days are presented in Figure 2.3A(2).

There were significant main effects for TIME (P<0.0001), AGE (P<0.006), and SPEED (P<0.0001) and significant TIME x SPEED (P<0.0001) and AGE x SPEED (P=0.046) interactions. The post-hoc testing showed the highest user rate in the Fast condition (P<0.0001) and the smallest user rate in the Slow condition (P<0.0001) for both old and young groups. The user rate was higher in the old group for Medium and Fast speeds (P<0.007).

Influence of Movement Resistance on Expected and Unexpected Events

Expected Events

The percent changes in user rate for the younger group from Day1pre to Day1post, Day3, and Day7 were -14.66, -13.97, and -20.59 percent, respectively, for the Low resistance; -19.93, -17.38, and -22.51 for the Medium resistance; and -11.08, -10.56, and -15.17 for the High resistance conditions. The percent changes in user rate for the older group from Day1pre to Day1post, Day3, and Day7 were -20.99, -14.46, and -15.95, respectively, for the Low resistance; -13.37, -4.02, and -10.05 for the Medium resistance; and -14.53, -8.97, and -13.80 for the High resistance. The average user rates are shown for all resistance levels in Figure 2.3B(1)).

There were main effects for TIME ($P<0.0001$), AGE ($P<0.0001$), and RESISTANCE ($P<0.0001$) supporting that the user rate improved with training, was different between the young and the old, and depended on the resistance of the task. There were higher user rates in the old group for all 3 resistance levels ($P<0.0001$).

Unexpected Events

The percent changes in user rate for the younger group from Day1pre to Day1post, Day3, and Day7 were -18.64, -15.8, and -18.91 percent, respectively, for the Low resistance; -22.19, -22.94, and -20.96 for the Medium resistance; and -14.19, -18.49, and -15.33 for the High resistance. The percent changes in user rate for the older group from Day1pre to Day1post, Day3, and Day7 were -25.97, -21.53, and -20.73, respectively, for the Low resistance; -16.20, -7.52, and -12.62 for the Medium resistance; and -9.4, -16.11, and -17.22 for the High resistance. The average user rates for the Low,

Medium, and High resistances for the young and old groups across days are presented in Figure 2.3B(2).

There were main effects for TIME (P<0.0001), AGE (P=0.007), and RESISTANCE (P<0.0001). There was an AGE x RESISTANCE interaction (P=0.0002). The post-hoc testing indicated that the user rate was the highest in the High resistance conditions and the smallest in the Low resistance condition for both young and older groups (P<0.006).

Feedback Control Analysis (LLR-50-100 ms)

The Medium speed condition caused a high user rate change in response to a perturbation (Figure 2.3; Figure 2.4 (representative analysis). The Medium speed condition also supported that both young and older people learned to respond to an unexpected perturbation within the first day following a brief training protocol. For these reasons, we analyzed the EMG at latencies that reflect a long latency response (50-100 ms) and the anticipatory feed-forward control (50-0 ms before the perturbation), at the Medium speed condition, in an effort to understand the strategy used by both groups to reduce error to the unexpected event.

The percent change in user rate for the younger and older groups from Day1pre to Day1post was -22.61 and -22.35 for the Medium speed unperturbed conditions, respectively; and -29.7 and -30.88 for the perturbed conditions. (Figure 2.5A) The corresponding percent change in the normalized ECR LLR for the younger and older groups from Day1pre to Day1post was 1.09 and 0 for the unperturbed conditions, respectively; and 6.73 and 4.9 for the perturbed conditions. The percent change in the normalized FCR LLR for the younger and older groups from Day1pre to Day1post was

5.26 and 6.74 for the unperturbed conditions, respectively; and 0.97 and -15.52 for the perturbed conditions. The average ECR and FCR LLR for the young and old groups across days are presented in Figure 2.5BC.

There was a significant TIME x PERTURBATION interaction (P=0.023) for the young group supporting that the user rate improved more in the perturbed condition as compared to the unperturbed condition; and a significant TIME main effect (P<0.0001). Conversely, there was no significant TIME x PERTURBATION interaction (P=0.747) for the old group; but a significant main effect for TIME (P<0.0001) supporting that similar learning occurred in both the perturbed and unperturbed events.

There was no significant TIME x PERTURBATION interaction for the young and older groups (P=0.768 and 0.946, respectively) for the ECR long latency reflex. There was a significant PERTURBATION main effect for both young and old (Both: P<0.007) indicating that the perturbation increased EMG of the ECR at a time latency consistent with a long latency reflex. However, there was no TIME effect for either group (P=0.532; P=0.738) indicating that the LLR did not explain the improvement in user rate with learning.

For FCR, there was no significant TIME x PERTURBATION interaction in the young group (P=0.563) and no significant main effects for TIME (P=0.676) or PERTURBATION (P=0.339). However, there was a significant TIME x PERTURBATION interaction for the older group (P=0.047) and a significant PERTURBATION main effect (P=0.0004), but there was no TIME effect (P=0.57),

indicating that they learned to decrease the EMG of the FCR at a time latency consistent with a long latency reflex.

Feed-Forward Control Analysis (50-0 ms before perturbations)

The ECR EMG was ~26% and 29% of MVC for the young and old groups, respectively for the Day1pre condition. However, the ECR EMG was ~23% and 31% of MVC for the young and old groups, respectively, for the Day1post condition. (Figure 2.6A). In the old group, from Day1pre to Day1post there was no TIME x PERTURBATION interaction (P=0.535) and no TIME main effect (P=0.322). The lack of a change in ECR EMG between Day1pre and Day1post indicates that feed-forward control did not contribute to the learned ability to respond to the unexpected event in the old group. However, in the young group, there was no TIME x PERTURBATION interaction (P=0.8) but a TIME main effect (P=0.026). These findings indicate that the young people could use a feed-forward strategy by decreasing ECR activation during both events.

The FCR EMG was ~25% and 27% of MVC for the young and old groups, respectively for the Day1pre condition. However, the FCR EMG was ~19% and 23% of MVC for the young and old groups, respectively, for the Day1post condition. (Figure 2.6B). There was no TIME x PERTURBATION interaction (P=0.727; P=0.408), but there was a significant TIME main effect (P< 0.0001; P=0.0004). These findings indicate that a universal “default” strategy to reduce the FCR occurred for both the perturbed and unperturbed conditions and, therefore, may have contributed to the ability to better respond when an unexpected event occurred.

DISCUSSION

The purpose of this study was to investigate whether age impacts wrist motor learning in both expected and unexpected events and whether task speed and resistance levels impact motor learning. There were several important findings from this study.

First, the novel upper extremity visual motor task was sensitive to the expected loss of human performance as a result of age. That is, the elderly group showed a poorer performance in both expected and unexpected events during this 9-condition, novel upper extremity visual motor task. This decline occurred in expected events with all 3 speeds and all 3 resistance levels. However, the decline occurred in unexpected events primarily with the two faster speeds as well as at the Low resistance level.

Second, motor learning occurred over expected and unexpected events in both young and old adults, with the greatest amount of learning occurring from Day1pre to Day1post at the medium speed. The old and young groups demonstrated a similar amount of improvement in conditions with all 3 speeds and 3 resistance levels over expected and unexpected events.

Third, the older people demonstrated similar ECR but higher FCR activation in the LLR timeframe following perturbations as compared to the young group. There was a trend for a decrease in the FCR activation triggered during the perturbation in the older group, which may explain, in part, a strategy that they learned to better respond to the unexpected event.

Fourth, when looking closely at the changes in EMG prior to the unexpected event, we discovered that the older group and younger group reduced their EMG in the FCR. This

strategy occurred universally during both the perturbed and unperturbed trials suggesting a “default” strategy was developed to allow both groups to better respond during both expected and unexpected conditions.

Taken together, this study presents, for the first time, empirical data regarding the strategy that people use to respond to an event that occurs prior to volitional reaction time. Based on this experiment, we conclude that adaptations that assist in responding to unexpected conditions are likely using a feed-forward mode, which will then influence the feedback capabilities. We cannot support that feedback control mechanisms operated exclusively to modulate the improved ability to perform to unexpected events in either group.

Motor Performance during Expected and Unexpected Events

It is not surprising that our findings showed poorer motor performance in old adults, consistent with previous studies (Leversen et al., 2012). The motor deterioration was seen in expected events with conditions with all speeds and resistance levels. The decline in motor performance in old age has been shown to be related to widespread degeneration in the central and peripheral neuromuscular system (Seidler et al., 2010). Interestingly, while the increased task speed negatively influences motor performance in both groups, the increase in resistance levels is not necessary to increase the user rate in either old or young groups. Unexpectedly, our results showed better performance in the High resistance condition in both groups. We speculate that the higher resistance level might create a higher stiffness condition, which might decrease the capacity to adjust the movement characteristics and/or decrease the movement variability, and further help the performance during the dynamic tracking task.

In unexpected events, both overall error in the trans-cortical timeframe and user rate following perturbations were larger than expected events (Figure 2.2), suggesting that this novel, custom-built device, is able to truly cause greater errors to unexpected conditions. To the best of our knowledge, this is the first study to investigate the motor practice between old and young groups in tasks with various speeds and resistance levels. Our results indicate that old adults do not lose the capacity to learn to respond to unexpected events, particularly when the perturbation is slow (Figure 2.3A(2)). Age, however, deteriorates the motor performance during with faster speed or low resistance level (Figure 2.3). Age-related decrements in the fast task have been well documented in previous studies (Seidler et al., 2010). During this tracking task, subjects must continue to adjust their movement based on feedback from the visual system. Thus, as reaction time increases with age, it may be more difficult for old adults to react to the instantaneous feedback, especially when the task is fast. Age-related decrements in the fast tasks may be due to the slowing of the nervous system processing, deficiencies in inhibition, or decreased conduction velocities. White matter degeneration and myelin breakdown may contribute to the age-related declines in speed during motor performance (Bartzokis et al., 2010; Rabbitt et al., 2007). Moreover, old adults have decreased inhibition (Coppi et al., 2014; Cueva et al., 2016; Marneweck et al., 2011; Sale and Semmler, 2005), which compromises hand motor performance (Coppi et al., 2014). Furthermore, the age-related difference in user rate was shown in the Low, but not Medium or High resistance level conditions. It is possible that the lowest resistance level of 10% MVIC was not strong enough to induce a perturbation. Thus, the results

from the unexpected events with Low resistance level showed similar trends as the expected events.

Motor Learning during Expected and Unexpected Events

Our results were inconsistent with our hypothesis that young group would demonstrate a greater capacity to acquire and retain a new motor skill in both expected and unexpected events. Although older adults demonstrated higher errors at the start, both young and old adults reduced their user rate by ~ 20 degrees/second from Day1pre to Day7 (Figure 2.2), indicating older adults retained the ability to acquire the new skill in both expected and unexpected conditions, consistent with previous studies evaluating only the expected events (Berghuis et al., 2015; Brown et al., 2009; Cirillo et al., 2010; Cirillo et al., 2011; Daselaar et al., 2003; Ehsani et al., 2015; Rogasch et al., 2009; Zimerman et al., 2013). This study showed a similar retention on Day3 and Day7 between groups in both expected and unexpected events across all speeds and resistance levels.

Aging is known to affect brain structures (Andersen et al., 2003; Bastin et al., 2010; Golomb et al., 1993; Nusbaum et al., 2001); decreases motor cortical excitability in the non-dominant hemisphere (Bashir et al., 2014; Cueva et al., 2016; Oliviero et al., 2006) causing decreased human performance and motor skill learning. However, the brain is highly plastic and may adapt to better enable people to offset some of the age-related declines in motor learning. For example, enhanced learning is associated with higher dorsal lateral prefrontal cortex and premotor cortex networks in old adults following motor skill acquisition (Lin et al., 2012b). Old adults appear to be capable of recruiting

more brain activity including M1 and supplemental motor areas to enhance learning (Lin et al., 2012a).

Previous training studies argue smaller improvements in older groups (Rogasch et al., 2009; Zimerman et al., 2013), while other studies demonstrate similar between groups or even better improvement in older groups (Brown et al., 2009; Cirillo et al., 2010; Cirillo et al., 2011; Ehsani et al., 2015). These conflicting results may be due to the speed, resistance, and testing apparatus used to perform the study as task complexity enhances the difference in motor learning between old and young adults (Smith et al., 1999a). We are confident that our novel 9-condition task, mixing a variety of speeds and resistances, offered a battery of test conditions that enabled us to detect sensori-motor performance between groups. To our knowledge, this study represents one of the most comprehensive study evaluation with various level of complexities including the delivery of expected and unexpected events.

Mechanisms Underlying Motor Practice in Old and Young Groups

Our results showed that there were larger LLRs in the elderly, but not to the same extent as previous work in our lab when studying the lower extremity (Madhavan et al., 2009). In our lab's previous work, subjects tracked a target in a closed-kinetic-chain weight-bearing position whereas this task involved an open-chain anti-gravity task. This anti-gravity task was relatively easier with more stability, during which subjects could use a co-contraction strategy to avoid unexpected movements or could rely more on feed-forward control instead of using a LLR feedback strategy. Importantly, the LLR is greater when individuals experience perturbations in less stable environments (Doemges and Rack, 1992; Shemmell et al., 2009)(i.e. the lower extremity task);

involving multiple sources to tune the LLR; most notably, vestibular, visual, and somato-sensory input. Indeed, the LLR induced in this study was smaller than that from our lab's previous studies (Madhavan et al., 2009). Finally, the increase in LLR in the elderly has been attributed to stretch velocity, when the speed is higher than 200 degrees/second (Lin and Sabbahi, 1998). Our fastest speed was 74.5 degrees/second, but, as a result of the perturbation, we triggered speeds close to 150 degrees/second. Thus, we believe we had ample velocity to induce a difference between the young and the old.

Both old and young groups demonstrated similar improvement as a result of motor practice. Our data suggests that learning occurred in both groups and that a feed-forward strategy was used to modulate the LLR and improve the ability to respond to an unexpected event. This is supported by previous studies with postural control (Kanekar and Aruin, 2014a; Kanekar and Aruin, 2014b) demonstrating that old adults adopt a feed-forward control strategy following a single session of training (Aruin et al., 2015). When we analyzed the muscle activation in each condition our results suggested that old people may use a feed-forward strategy to better modulate the feedback strategy. For example, in the condition with Medium speed there was extensive learning from Day1pre to Day1post. When the ECR LLR was normalized to the anticipatory EMG, there was no significant change in the LLR (Figure 2.5B(2)). However, the FCR showed a significant reduction in EMG activity 50 ms before the unexpected event (Figure 2.5C(2)). As a result, the FCR LLR was significantly reduced in the older group. This strategy likely contributed to the overall decline in error during the perturbations in the elderly. Indeed, our results support that motor skill acquisition modulates muscle

activations in the trans-cortical LLR pathways (Cluff and Scott, 2013; Pruszynski et al., 2008; Wang et al., 2001), but not independently from the feed-forward control system. Taken together, we believe that elderly modulated both the feed-forward and feedback control systems, while the young only needed to modulate the feed-forward system. The need for both systems to be modulated was likely influenced by the greater error that elderly people have as compared to the younger group. These findings support, however, that the elderly group may gain extensively from a single visual motor training session.

The link between tracking task error and LLRs have been demonstrated previously (Cluff and Scott, 2013). While our results did not show any strong relationships between changes in ECR/FCR activation and user rate there were important trends identified. The decreased FCR activation from Day1pre to Day1post demonstrated a better improvement without the changes in ECR activation, suggesting that following motor practice, instead of using the cocontraction strategy, old adults are able to use reciprocal activation of muscles that young adults use during compensatory adjustments (Lee et al., 2015).

As with all research, there were several limitations that must be considered when interpreting the findings of this study. First, the sample selectivity may be a factor because we believe that individuals with higher motor function are more likely to participate in a study like this as compared to those with poor motor function. Importantly, our participants were more physically active than typical older adults supported by the average of about 10K steps taken per day. As physical activity level has been shown to be a factor which influences motor learning (Cirillo et al., 2009), the

learning capacity in our old group may be overestimated. Furthermore, we believe that this visual motor task relies on working memory and executive function, all of which was likely higher in this sample than may be typical. It is possible that old adults with cognitive deficits might show less learning and incapable of adapting as well as the subjects in this study. Further studies are underway in our lab to determine the effect of physical activity and cognitive function on motor learning in old adults (Chapter 3 of this dissertation).

SUMMARY AND CONCLUSIONS

We confirmed that motor performance is greatly affected by age as measured using a novel battery of 9 conditions using a custom designed visual motor task. We also confirmed that both young and old may acquire a new motor skill in both expected and unexpected events, and that the strategies involve modulating feed-forward control mechanisms. These findings have important clinical implications. These results lay the foundation for someday being able to assess the impact that our rehabilitation interventions have on feed-forward and feedback control mechanisms. Indeed, developing novel interventions to selectively impact various control centers may be important to establishing dose dependent rehabilitation programs for people with visual motor learning impairments.

TABLES

Table 2.1 Demographic Data of Participants in the Young and Old Groups

	Young (n=38)	**Old** (n=30)	**P Value**
Age	25.26 ± 3.29	65.2 ± 4.74	<0.001*
Sex	23 M, 15 F	13 M, 17 F	0.158
Height (cm)	176.76± 11.45	170.18± 10.9	0.02*
Weight (kg)	75.9 ± 14.43	79.4 ± 16.14	0.348
Body Fat (%)	20.51 ± 7.66	31.79 ± 10.32	<0.001*
Handedness	97.11 ± 6.87	99.33 ± 3.65	0.11
Step per day	10314.6 ± 2615.8	10132.9 ± 4421.9	0.84

M: Male, F: Female , Value = mean ± standard deviation, *: significant

FIGURES

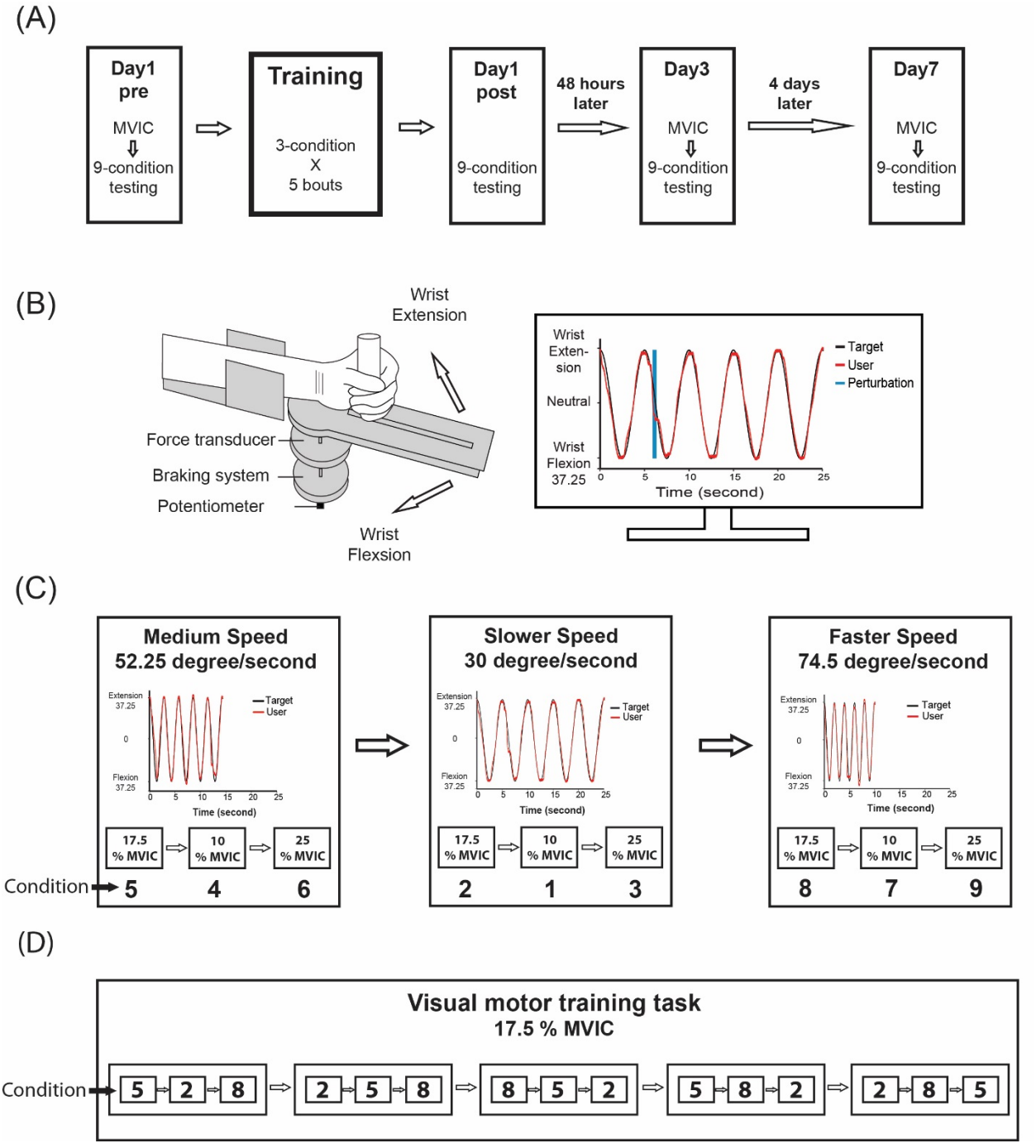

Figure 2.1 Study Paradigm

(A) Schematic overview of the experimental design. (B) Schematic diagram of the device used in the wrist visual motor manual tracking task. (C) Testing paradigm. (D) Training paradigm.

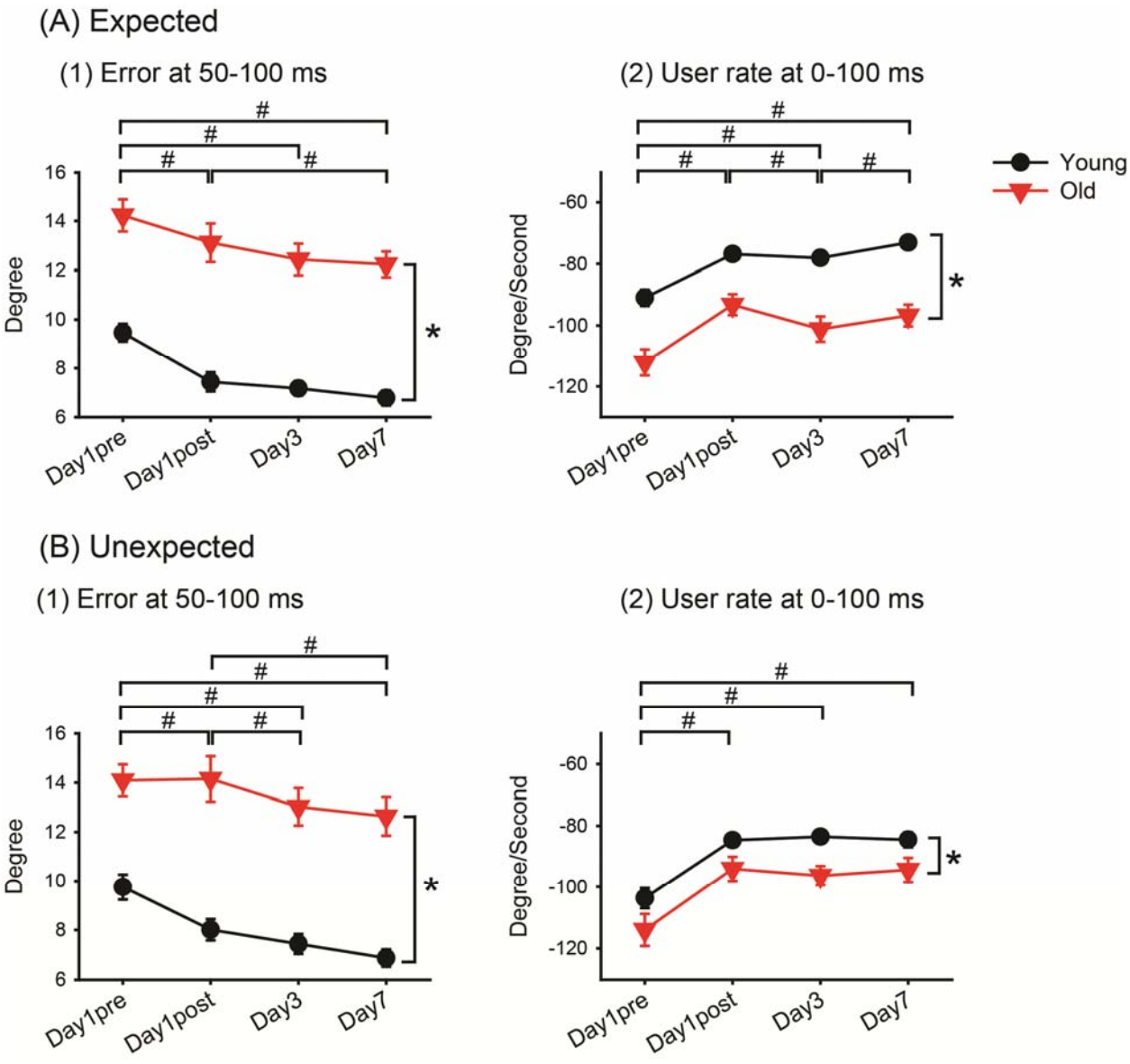

Figure 2.2 Effect of Age on Absolute Error and User Rate

(1) Error at 50-100 ms and (2) User rate at 0-100 ms in (A) expected and (B) unexpected events. Value = mean ± standard error. #: P<0.05 in the post-hoc testing for TIME. *: P<0.05 in the post-hoc testing for AGE.

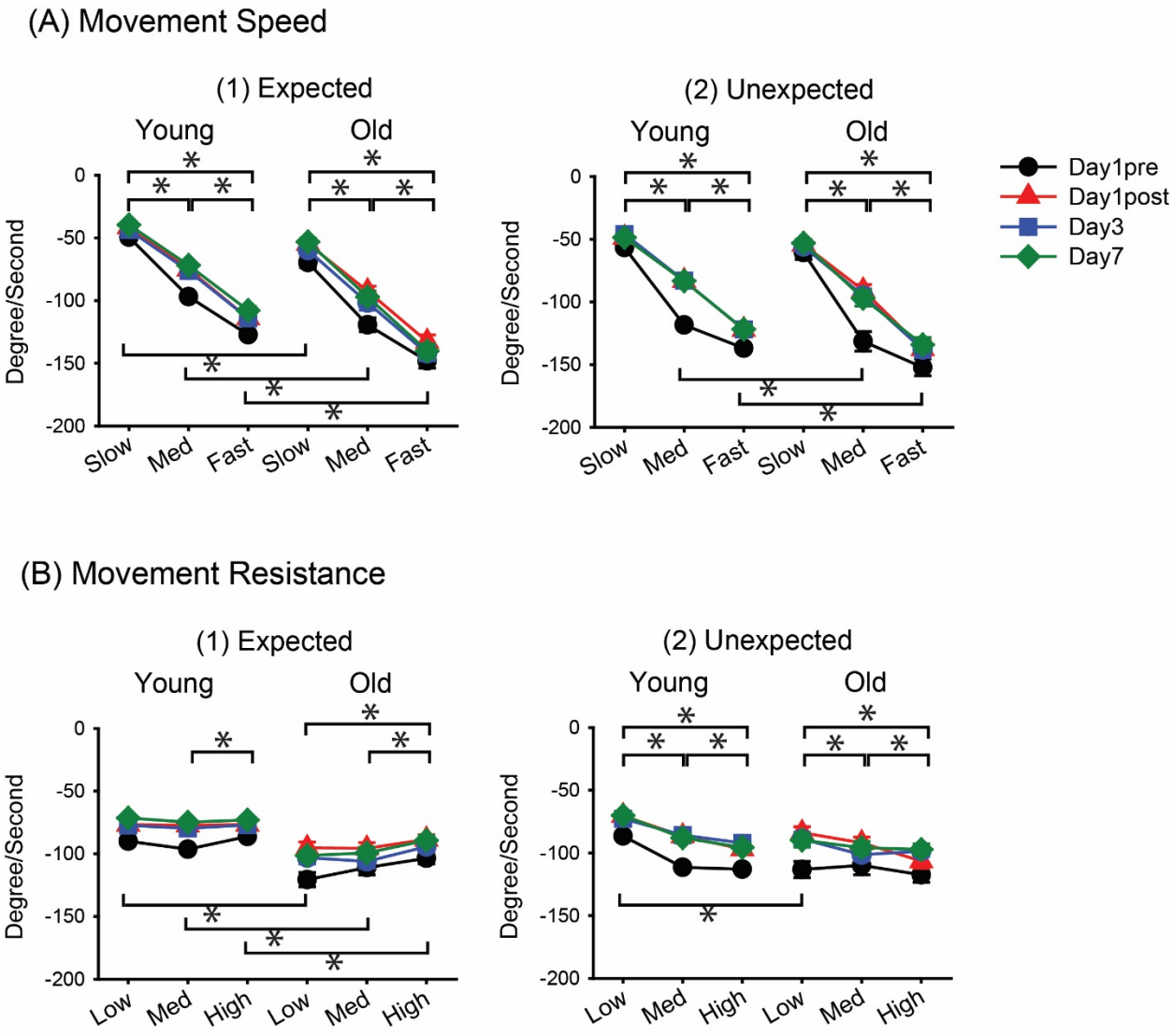

Figure 2.3 Effect of Speed and Resistance Levels

User rate at 0-100 ms during both (1) expected and (2) unexpected events with (A) 3 movement speeds and (B) 3 movement resistance levels. Value = mean ± standard error. *: P<0.05 in the post-hoc testing for AGE x SPEED or AGE x RESISTANCE interaction.

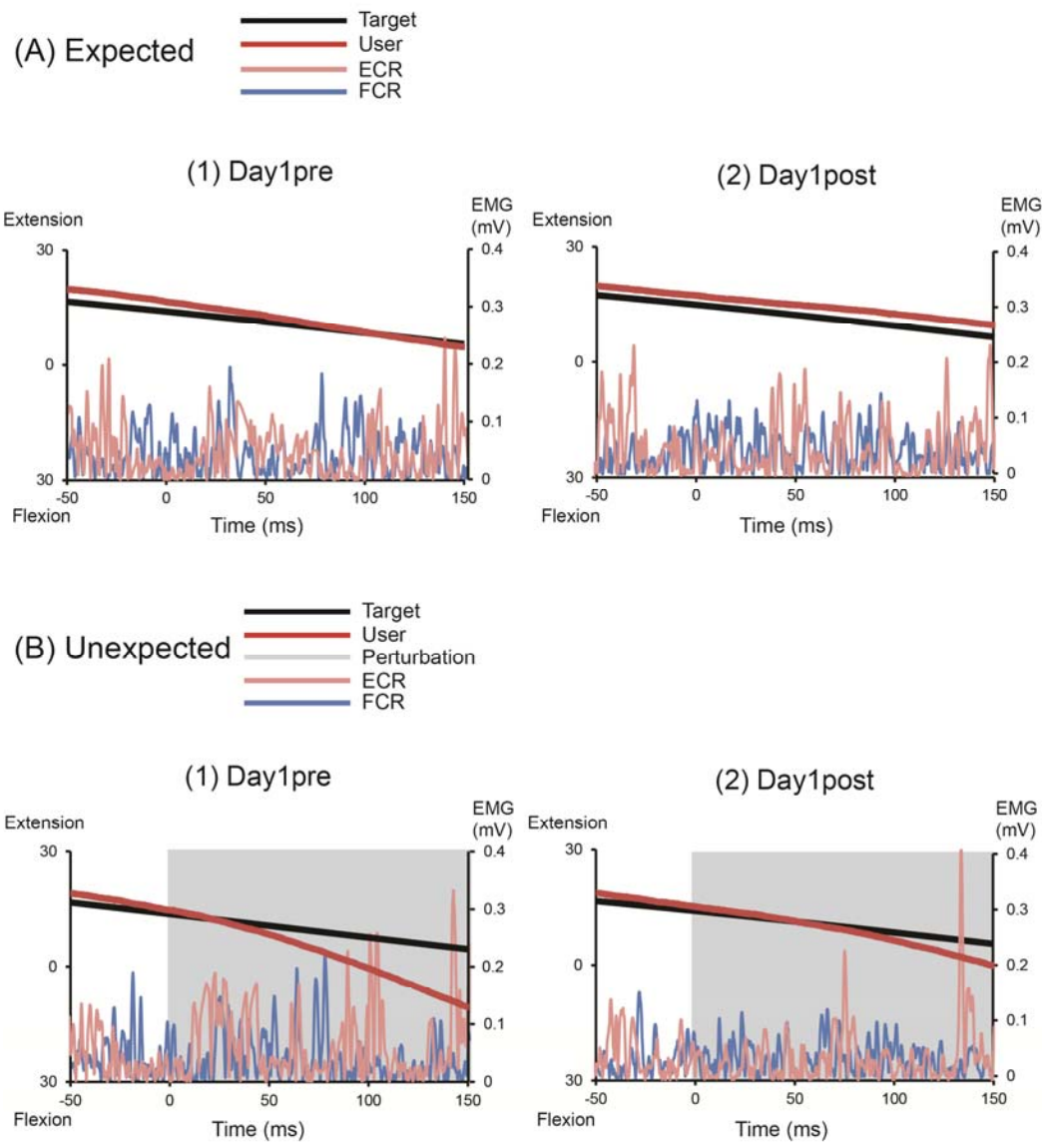

Figure 2.4 An Example from the Young Group

A representative example from the young group in (A) expected and (B) unexpected events (Condition with Medium speed) on Day1pre and Day1post.

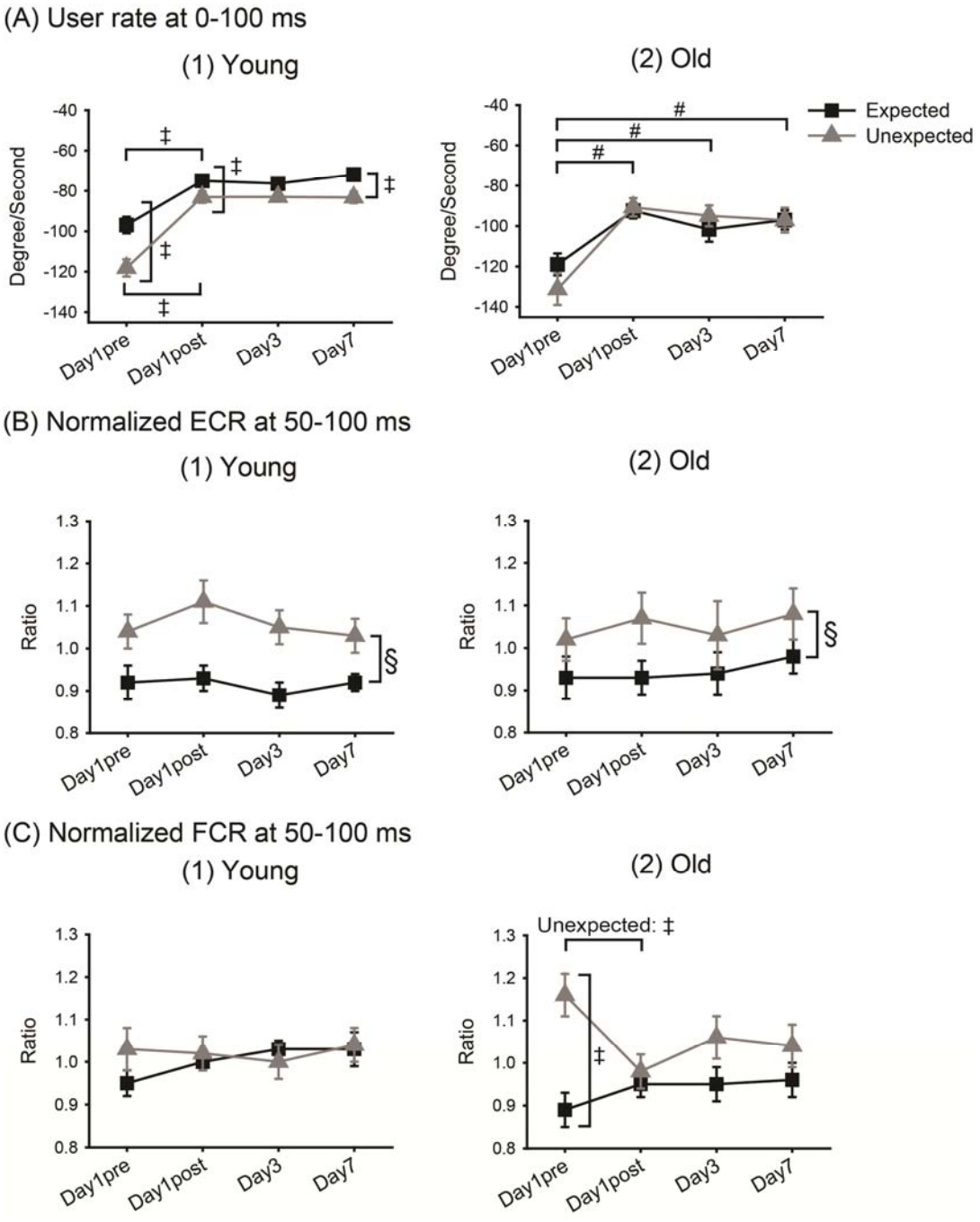

Figure 2.5 Effect of Perturbations on User Rate and EMG

User rate and normalized ECR and FCR at 50-100 ms in the condition with Medium speed. #: P<0.05 in the post-hoc testing for TIME. §: P<0.05 in the post-hoc testing for PERTURBATION. ‡: P<0.05 in the post-hoc testing for TIME x PERTURBATION interaction.

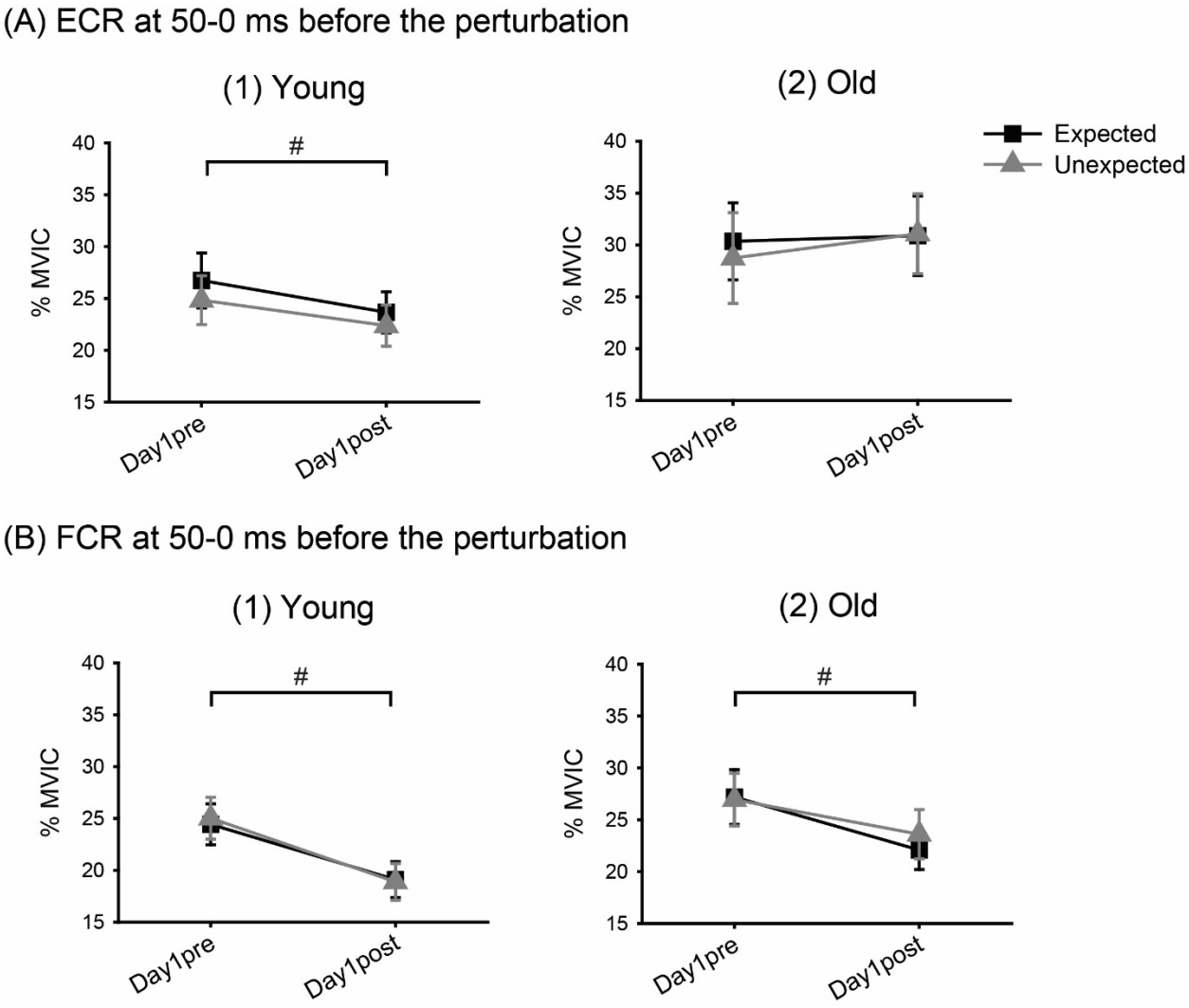

Figure 2.6 Impact of Perturbation on EMG before the Perturbation

Normalized ECR and FCR at 50-0 ms before the perturbation (% MVIC) in the condition with Medium speed. #: P<0.05 in the post-hoc testing for TIME.

CHAPTER 3 THE IMPACT OF PHYSICAL ACTIVITY ON MOTOR SKILL LEARNING DURING BOTH EXPECTED AND UNEXPECTED EVENTS IN HEALTHY YOUNG AND OLD ADULTS

INTRODUCTION

Physical activity level has recently emerged as a powerful factor influencing motor skill acquisition and retention; including the underlying mechanisms related to long-term potentiation (LTP)-like plasticity. The aging process is associated with a reduced capacity to learn new motor skills. Regular physical activity level may attenuate the processes contributing to less learning with age. The goal of this study is to examine if activity level modulates the ability to respond to expected and unexpected conditions during motor skill acquisition and retention during an upper extremity visual motor task in young and old adults.

Acute exercise increases brain derived neurotrophic factor (BDNF), catecholamines, and lactate (Mang et al., 2014; Skriver et al., 2014; Winter et al., 2007), all biomarkers that are correlated to motor skill acquisition and/or retention (Skriver et al., 2014). A single session of moderate and high intensity aerobic exercise improves movement accuracy during visual motor tasks (Mang et al., 2014; Roig et al., 2012; Skriver et al., 2014; Statton et al., 2015). Importantly, acute systemic exercise (Muellbacher et al., 2001; Muellbacher et al., 2002; Nuzzo et al., 2015; Rosenkranz and Rothwell, 2006), acute systemic heat stress (Littmann and Shields, 2016), and acute visual motor

learning increase motor cortical excitability (Jensen et al., 2005; Leung et al., 2015; Perez et al., 2006). Several of the effects of exercise may also be attributed to changes in cognitive function including working memory and executive function (Colcombe and Kramer, 2003; Frederiksen et al., 2015; Stroth et al., 2009).

Regular physical activity has the potential to decrease the age-associated deterioration in learning and cognitive function (Voss et al., 2013). Physical activity is thought to offset the age-related decline in brain volume/area of the hippocampus, the premotor cortex, and the supplementary motor cortex (Schlaffke et al., 2014), all critical brain structures involved with learning new motor skills (Doyon and Benali, 2005). Physical activity level is also associated with improved age-related proprioception (Ribeiro and Oliveira, 2007; Wright et al., 2011), improved postural stability (Lamoth and van Heuvelen, 2012; Maitre et al., 2013; Maitre et al., 2015), and improved use of sensory information (Lamoth and van Heuvelen, 2012; Maitre et al., 2013; Maitre et al., 2015).

In Chapter 2, we demonstrated that age attenuates the ability of older people to respond to unexpected events, at a time prior to volitional reaction time. The long latency reflex (LLR) offers a unique strategy to attenuate limb displacement following an unexpected stretch of a muscle (Cluff and Scott, 2013). The LLR is mediated by group Ia afferents initially (Schuurmans et al., 2009), is tuned by a trans-cortical neural pathway (Goodin et al., 1990; Krutky et al., 2004), and occurs approximately 50-100 ms following an unexpected event (Goodin and Aminoff, 1992; Lee and Tatton, 1982). Physical activity is purported to increase motor cortical excitability (Cirillo et al., 2009; Pearce et al., 2000; Rosenkranz et al., 2007b) and may promote the capacity to optimally “tune” the LLR to minimize error. The impact of physical activity in older people may be even more

profound than in a younger person because they show reduced motor cortical excitability within their non-dominant hemispheres. Accordingly, we expect that this altered capacity may be attenuated in those who are physically active; suggesting an improved capacity to learn to respond to unexpected events.

The primary aim of this study was to determine if activity level would impact motor skill acquisition and retention during both expected and unexpected conditions. We hypothesized that the more active subgroups in each young and old group would demonstrate a greater capacity to acquire (Day1) and retain skilled movement (Day3; Day7), in response to unexpected events (50-100 ms). The secondary aim was to determine if cognitive function would influence motor skill acquisition and retention during both expected and unexpected conditions in the old group. We hypothesized that the groups with higher cognitive function would demonstrate greater motor skill learning and that there would be an association between cognitive function and accelerometer-measured daily physical activity. We explored these effects across time and across various task parameters (speed and resistance) in order to enhance our understanding of task dependency.

METHODS

Subjects

Thirty-seven young (between 20 and 40 years of age) and 30 old healthy (between 60 and 80 years of age) right-handed individuals participated in this study. The exclusion criteria were that they had no history of current orthopedic or neuromuscular dysfunction, and no consumption of any substances containing alcohol or caffeine for 24 hours.

Handedness were verified using the Edinburgh handedness inventory (Oldfield, 1971). Old adults were required to pass the Mini Mental Status Exam (MMSE) (Folstein et al., 1975) with scores greater than 26. Data from 1 older adult was excluded from analysis because of a statistical outlier in terms of physical fitness levels. This study was approved by the Institutional Review Board of the University of Iowa and all subjects had to provide their written informed consent before participating.

Paradigm

Figure 2.1A shows the schematic overview of the experimental design. Testing procedure consisted of a pre-, post-, and retention tests. Pre- and post-tests performed on Day1 (Day1pre, Day1post), and the retention test for motor consolidation performed 48 hours later on Day3 (Day3) and 1 week later on Day7 (Day7). Each day we recorded three maximal voluntary isometric contractions (MVIC) of the left wrist extensors and flexors followed by the assessment of the visual motor skill. After the pre-test, subjects received a training session comprised of 5 blocks of 3 trials each with 1-minute rest in between. On Day3 and Day7, the same measurements as the pre-test were repeated to quantify the retention of motor skill.

Behavioral Testing and Motor Training

During all testing sessions, subjects sat in a comfortable chair in front of a computer controlled LCD panel. The right forearm was relaxed on a pillow on the lap and the left forearm was supported on a movable table of a custom-built device, allowing movements of wrist flexion and extension only (Shields RK. Patent US 7,011,605 B2). This custom-built device consisted of a force transducer, a braking system, and a potentiometer which were connected together and aligned with the same axis of rotation

of the wrist (Figure 2.1B). The styloid process of the ulnar bone was aligned to the axis of rotation of the device. The resting position of the left arm was in 80 degrees of shoulder abduction, 60 degrees of shoulder flexion, 60 degrees of elbow flexion, with the forearm and wrist in a neutral position. Forearm support straps and blocks restricted unwanted movements (i.e. forearm supination/pronation). We tested the left hand because motor training results in more improvement in the non-dominant hand (Ridding and Flavel, 2006) and elderly people show greater loss in cortical excitability for the non-dominant hemisphere (Bashir et al., 2014; Oliviero et al., 2006).

Data Collection

We developed a task in which subjects were instructed to follow a moving target on a screen using wrist position. Labview (National Instruments Corp., Austin, TX, USA) was used to display the moving sinusoidal target, depicted by a white line on the screen. Subjects were instructed to track the sinusoidal wave by controlling a red line as precisely as possible with their wrist position, moving from wrist extension, to wrist flexion and back to wrist extension to complete one cycle. The lowest trough of the target represented wrist flexion of 37.25 degrees and the highest crest represented wrist extension of 37.25 degrees. The position of the wrist was signaled by a potentiometer. The position was sampled at 4000 Hz and stored for off-line analysis using MATLAB software.

Nine trials (3 velocities x 3 resistance levels) were used in this wrist visual motor manual task (Figure 2.1C). The velocity was set at 30 (Slow speed), 52.25 (Medium speed), and 74.5 (Fast speed) degrees/second; while the resistance was set at 10 (Low resistance), 17.5 (Medium resistance), and 25 (High resistance) % of MVIC of the left wrist extensor

muscles. Each trial contained 5 cycles. Unexpected stretches were imposed to the wrist extensor muscles by releasing the resistance of the device when the participant completed the first one third of the flexion phase as determined by the initial starting location, in the 2nd, 3rd, 4th, or 5th cycle in the wrist flexion phase in each trial (stretching the wrist extensors). The cycle for the perturbation was determined randomly.

A training session consisted of 5 blocks of 3 trials (Figure 2.1D). Between training blocks, subjects rested for 1 min. Within the 3 trials, the resistance was set at 17.5% of MVIC of the left wrist extensor muscles and the velocity was set at 30, 52.25, 74.5 degrees/second. The order of the 3 trials was randomized but was the same for each subject at the three tests. Each trial contained one unexpected stretch delivered randomly.

On the first day (Day1pre), subjects completed 9 trials to establish their movement control baseline. Then subjects completed 5 blocks of 3, a total of 9 trials, as training sessions. After the intervention, subjects repeated the same 9 trials used in the pretest to assess the motor acquisition error (Day1post). On Day3 and Day7, subjects repeated the same 9 trials again to assess the motor skill retention.

Physical Activity Measure

Participants wore the physical activity monitor (Actigraph wGT3X-BT, Pensacola, FL, USA) at the left ankle on two Velcro bands at all times during the 5-7 days period, excluding times when the monitor would come into contact with water (e.g. showering, swimming). The monitor was positioned above medial and lateral malleolus. The WGT3X-BT is portable light weight accelerometer and record acceleration ranging from - 8 to 8 g. The data was collected at a sample rate of 30 Hz, stored on the flash memory,

and then downloaded to a computer for processing in the ActiLife software (Actigraph, Pensacola, FL, USA).

Cognitive Function

In older adults, cognitive function was evaluated by using computerized testing of executive function in NIH Toolbox Cognitive Health Battery (Mungas et al., 2014). Cognitive flexibility within executive function was evaluated through Dimensional Change Card Sort Test (DCCS). Inhibitory control within executive function was evaluated through Eriksen Flanker Inhibitory Control Test (Flanker) (Zelazo et al., 2014). In addition, working memory was evaluated through the List Sorting Working Memory Test (LSWM) (Tulsky et al., 2014).

In DCCS, two target pictures with different colors (yellow and blue) and shapes (ball and truck) were presented to participants. This test required participants to match test pictures (yellow balls and blue trucks) to the given target pictures, according to the instruction, “Color” or “Shape”. The instruction was “Shape” in 23 of 30 trials (dominant dimension) and “Color” in the rest of the trials (non-dominant dimension).

The Flanker test required participants to respond to the direction of a target arrow while inhibiting attention to two arrows on each side (flankers) as quickly and accurately as possible. Twenty trials were conducted. In 12 of 20 trials, the target arrow pointed in the same direction as flankers (congruent), whereas in 8 of 20 trials, the target arrow pointed in the different direction as flankers (incongruent).

The List Sorting Working Memory Test (LSWM) required participants to recall and sequence the pictures of different foods and animals in size order from the smallest to

largest. The first session involved one dimension (1-list), foods or animals, and the second session involved two dimensions (2-list), foods before animals.

Data Analysis

The motor performance data on the visual motor task were analyzed using MATLAB software. Motor learning, as measured as absolute error, was determined by calculating the absolute difference between the target and wrist displacements at each time point. For perturbed cycles, absolute errors at 50-100 ms after the perturbation were calculated. In addition, we calculated the "user rate", defined as the slope of the best-fit straight line through wrist displacements during 100 ms starting from the beginning of the perturbation to 100 ms after the perturbation by using a least squares regression. For unperturbed cycles, absolute errors and user rate over the same period of time in each cycle were calculated, where "time-zero" was defined as the time at which wrist was at the first one third of the flexion phase.

For both errors and user rate, the first cycle of each trial was discarded because it represented purely reaction time data. Absolute errors/user rate in perturbed cycles were defined as absolute errors/user rate in perturbed cycles, whereas absolute errors/user rate in unperturbed events were defined as the average of absolute errors/user rate in the 3rd to 5th unperturbed cycles. Our preliminary studies indicated that for unperturbed cycles, the errors were significantly larger in the 2nd cycle compared to the 3rd, 4th or 5th cycles (Post-hoc, all $P < 0.039$). Therefore, we used the 3rd, 4th and 5th cycles to estimate the error during the unperturbed events.

For each subject, the absolute error and user rate from 9 conditions (3 speeds and 3 resistance levels) were averaged as the overall error/user rate. Furthermore, the absolute errors from conditions with the same speed (slow, medium, and fast speed) or resistance (low, medium, and high resistance levels) were averaged separately.

The physical activity data was analyzed by using ActiLife 6.11.5 software (Actigraph, Pensacola, FL, USA). We used step count per day as the primary independent variable, given that it represents a global objective indicator of physical activity. We also used variables which represent how much time in each intensity of physical activity: Light, moderate, vigorous, and very vigorous. The cut-points were 2690-6166 counts min^{-1} for the intensity of Moderate (MET: 3-5.99), 6167-9642 counts min^{-1} for that of Vigorous (MET: 6-8.99), and >9642 counts min^{-1} for that of Very Vigorous (MET: >8.99) (Sasaki et al., 2011). In addition, we defined "less active" people who took the average of 5-9.999K steps/day, "active" people who took the average of more than 10K steps/day (Tudor-Locke and Bassett, 2004).

The DCCS computed score was based on a combination of accuracy and reaction time (RT). Each of accuracy and RT scores varied from 0 to 5 points, which made the total score from 0 to 10. A participant received a value of 0.125 for every correct answer (Zelazo et al., 2014). The RT score was calculated by using participants' raw, non-dominant dimension (Color) median reaction time (Zelazo et al., 2014). The calculation of accuracy and RT scores was generated by using the following equations:

$$\textbf{DCCS Accuracy Score} = \mathbf{0.125} * (\textbf{Number of Correct Responses} + \mathbf{10})$$

$$\textbf{Reaction Time Score} = \mathbf{5} - \left(\mathbf{5} * \left[\frac{\log \mathbf{RT} - \log(\mathbf{500})}{\log(\mathbf{3000}) - \log(\mathbf{500})}\right]\right)$$

In addition, because 17 out of 29 participants were above the 75th percentile (Slotkin et al., 2012), we divided participants into two subgroups, 25th - 74th and ≥ 75th percentile. For participants in 60-69 years old, the cut-points for female were 8.21 and the cut-points for males were 8.06 (Slotkin et al., 2012). For participants in 70-85 years old, the cut-points for female were 7.51 and the cut-points for males were 7.7 (Slotkin et al., 2012).

The Flanker computed score was based on a combination of accuracy and RT. Each of accuracy and RT scores varied from 0 to 5 points, which made the total score from 0 to 10. A participant received a value of 0.125 for every correct answer (Zelazo et al., 2014). The RT score was calculated by using participants' raw, incongruent median reaction time (Zelazo et al., 2014). The calculation of accuracy and RT scores was generated by using the following equations:

$$\textbf{Flanker Accuracy Score} = \mathbf{0.125} * (\textbf{Number of Correct Responses} + \mathbf{20})$$

$$\textbf{Reaction Time Score} = \mathbf{5} - \left(\mathbf{5} * \left[\frac{\log \mathbf{RT} - \log(\mathbf{500})}{\log(\mathbf{3000}) - \log(\mathbf{500})}\right]\right)$$

The LSWM was scored by summing the totally number of items correct on the 1- and 2-list version of the task (Tulsky et al., 2014). This score ranged from 0 to 26.

Statistical Analysis

SAS 9.3 (SAS, Cary, NC) software was used for all statistical analyses. Independent t test was used to test for differences in continuous variables (age, height, weight, body fat, handedness, step count, MMSE, DCCS, Flanker, and LSWM) between active and

less active groups, and between the 25th-74th and ≥75th DCCS groups. T-test corrected values were used when equal variances were not assumed. A chi-square test was used to test the sex differences between groups.

Three-way repeated measures mixed model ANOVAs (the between-group factor "group" had levels less active and active, the within-group factor "TIME" had levels Day1pre, Day1post, Day3, and Day7, and the within-group factor "CONDITION (SPEED or RESISTANCE)" had levels Fast, Medium, and Slow speed or Low, Medium, and High resistance levels) were employed for analysis of the effect of task Speed and Resistance level on user rates between less active and active groups.

In addition, three-way repeated measures mixed model ANOVAs (the between-group factor "GROUP" had levels less active and active or 25th-74th and ≥75th, the within-group factor "TIME" had levels Day1pre, Day1post, Day3, and Day7, and the within-group factor "PERTURBATION" had levels expected, and unexpected events) were used to determine the difference in error and user rate between groups with different activity levels or different cognitive function within the same age group across times.

If any of the ANOVAs revealed a significant effect, Tukey's HSD test was used for post-hoc comparisons. The significance level was set at $p<0.05$. In addition, because the purpose of this study was to understand the impact of physical activity and executive function on motor learning, only those interactions specifically related to GROUP and/or TIME would be addressed in the following sessions.

Furthermore, Pearson's correlations were used to explore associations between physical activity and cognitive function (DCCS, Flanker, and LSWM). The significance level was set at $p<0.05$.

RESULTS

When we collapsed the young and old data, there were no differences in descriptive statistics between less active and active groups. When separately analyzing the data in each age group, less active and active subgroups did not differ with respect to descriptive characteristics. The group with greater (≥75th percentile) executive function was younger, had a higher weight, and higher DCCS and Flanker score (All: P's<0.048). There was a trend supporting that the group with ≥75th percentile in executive function was also a more active group (took more steps; P=0.06). Demographic details are presented in Table 3.1.

Influence of Movement Speed between Less Active and Active Groups during Unexpected Events

Expected Events (Unperturbed Conditions) Analysis

The percent changes in user rate for the less active group from Day1pre to Day1post, Day3, and Day7 were -19.4, -14.63, and -23.26 percent, respectively, for the Slow speed; -18.41, -11.51, and -16.84 for the Medium speed; and -5.9, -4.61, and -6.54 for the Fast speed. The percent changes in user rate for the active group from Day1pre to Day1post, Day3, and Day7 were -18.56, -13.14, and -22.01, respectively, for the Slow speed; -27.68, -24.52, and -28.02 for the Medium speed; and -15.31, -10.75, and -14.99

for the Fast speed. The average user rates for the Slow, Medium, and Fast speeds for the less active and active groups across days are presented in Figure 3.1A(1).

There was a significant main effect for TIME (P<0.0001) and SPEED (P<0.0001), and TIME x SPEED interaction (P=0.029), supporting that the user rate improved with training and the improvement was dependent on the speed of the task. However, there was no main effect for GROUP or any significant interactions related to GROUP (P>0.066), suggesting that both groups were similar in each condition across 4 time points. Post hoc analysis showed that the user rate was decreased at all times following Day1pre in each speed condition (P<0.0003) and the user rate was similar on Day1post, Day3, and Day7 (P>0.069).

Unexpected Events (Perturbed Conditions) Analysis

The percent changes in user rate for the less active group from Day1pre to Day1post, Day3, and Day7 were -14.03, -12.89, and -15.65 percent, respectively, for the Slow speed; -31.83, -32.41, and -27.01 for the Medium speed; and -6.9, -6.51, and -9.25 for the Fast speed. The percent changes in user rate for the active group from Day1pre to Day1post, Day3, and Day7 were -13.24, -15.81, and -13.17, respectively, for the Slow speed; -28.94, -25.62, and -28.87 for the Medium speed; and -14.69, -14.3, and -14.48 for the Fast speed. The average user rates for the Slow, Medium, and Fast speeds for the less active and active groups across days are presented in Figure 3.1A(2).

There was a significant main effect for TIME (P<0.0001) and SPEED (P<0.0001), and TIME x SPEED interaction (P<0.0001), suggesting that the user rate improved with training and the improvement was dependent on the speed of the task. However, there

was no main effect for GROUP or any significant interactions related to GROUP (P>0.327), suggesting that both groups were similar in each condition across 4 time points. Post hoc analysis showed that the user rate was decreased at all times following Day1pre in each speed condition (P<0.025) and the user rate was similar on Day1post, Day3, and Day7 (P>0.378).

Influence of Movement Resistance between Less Active and Active Groups during Unexpected Events

Expected Events (Unperturbed Conditions) Analysis

The percent changes in user rate for the less active group from Day1pre to Day1post, Day3, and Day7 were -15.17, -10.96, and -15.3 percent, respectively, for the Low resistance; -13.33, -6.36, and -11.65 for the Medium resistance; and -8.61, -8.73, and -12.3 for the High resistance. The percent changes in user rate for the active group from Day1pre to Day1post, Day3, and Day7 were -21.39, -17.79, and -22.26, respectively, for the Low resistance; -21.01, -17.75, and -22.4 for the Medium resistance; and -16.78, -10.76, and -16.21 for the High resistance. The average user rates for the Low, Medium, and High resistances for the less active and active groups across days are presented in Figure 3.1B(1).

There was a significant main effect for RESISTANCE (P<0.0001) and TIME (P<0.0001), but there were no significant interactions related to TIME (P>0.052), supporting that the error improved with training, but the improvement was not dependent on the resistance of the task or the activity level. Post hoc analysis showed that the user rate was decreased at all times following Day1pre in each speed condition (P<0.0001).

Unexpected Events (Perturbed Conditions) Analysis

The percent changes in user rate for the less active group from Day1pre to Day1post, Day3, and Day7 were -21.18, -15.71, and -22.21 percent, respectively, for the Low resistance; -18.19, -16.83, and -13.7 for the Medium resistance; and -12.17, -17.92, and -14.39 for the High resistance. The percent changes in user rate for the active group from Day1pre to Day1post, Day3, and Day7 were -25.62, -23.59, and -19.35, respectively, for the Low resistance; -20.82, -15.34, and -20.32 for the Medium resistance; and -13.15, -17.38, and -18.39 for the High resistance. The average user rates for the Low, Medium, and High resistances for the less active and active groups across days are presented in Figure 3.1B(2).

There was a significant main effect for RESISTANCE ($P<0.0001$) and TIME ($P<0.0001$), but there were no significant interactions related to TIME ($P=0.465$), supporting that the error improved with training, but the improvement was not dependent on the resistance of the task or the activity level. Post hoc analysis showed that the user rate was decreased at all times following Day1pre in each speed condition ($P<0.0001$).

In summary, during expected and unexpected events, both less active and more active groups demonstrated similar learning albeit most learning taking place between Day1pre and Day1post. Motor skill practice revealed that from Day1pre to Day1post the greatest improvement occurred in the Medium speed condition (expected events: ~22% decrease; unexpected events: ~30% decrease), compared to Slow (expected events: ~19% decrease; unexpected events: ~13.5% decrease) or Fast speed (expected events: ~10% decrease; unexpected events: ~11% decrease) conditions. Because of these findings, we focused all subsequent analysis on the Medium speed condition to

ascertain if physical activity and cognitive function influenced motor skill acquisition and learning in young and older people.

Physical Activity and Motor Skill Acquisition/Learning (Young Group)

Absolute Errors at 50-100 ms

The mean absolute errors in the expected events on Day1pre were 9.9 and 8.05 degrees, for the less active and active groups, respectively; while the mean absolute errors in the unexpected events for the less active and active groups were 9.18 and 7.45 degrees, respectively. In the expected events, the percent changes in errors from Day1pre to Day1post, Day3, and Day7 were -28.69, -25.05, and -27.17, respectively, for the less active group; and -19, -18.88, and -17.76, respectively, for the active group. In the unexpected events, the percent changes in errors from Day1pre to Day1post, Day3, and Day7 were -11.55, -16.12, and -41.94, respectively, for the less active group; and 0.4, -17.72, and -15.84, respectively, for the active group. (Figure 3.2A).

There was significant main effects for TIME ($P=0.0128$) and GROUP ($P=0.047$), but there was no main effect for PERTURBATION or any interactions ($P>0.056$), supporting that the error improved with training and the less active group had greater errors. Post hoc analysis showed that the error was decreased at all times following Day1pre ($P<0.004$). Errors did not change from Day1post to Day3 and from Day3 to Day7 ($P>0.198$).

User Rates at 0-100 ms

The mean user rates in the expected events on Day1pre were -96.51 and -98.83 degrees/second, for the less active and active groups, respectively; while the mean user

rates in the unexpected events for the less active and active groups were -116.9 and -120.27 degrees/second, respectively. In the expected events, the percent changes in user rates from Day1pre to Day1post, Day3, and Day7 were -22.48, -21.37, and -24.43, respectively, for the less active group ; and -24.13, -22.39, and -28.72, respectively, for the active group. In the unexpected events, the percent changes in user rates from Day1pre to Day1post, Day3, and Day7 were -29.56, -32.41, and -31.81, respectively, for the less active group; and -31.8, -27.32, and -27.14, respectively, for the active group. (Figure 3.2B).

There were significant main effects for TIME (P<0.0001) and PERTURBATION (P<0.0001), as well as TIME x PERTURBATION interaction (P=0.03), supporting that the user rates improved with training and the user rate changes across time differed between expected and unexpected conditions. There was no main effect for GROUP and no interactions related to GROUP (P>0.218), supporting that the improvement was similar between groups. Post hoc analysis for the interaction showed that the user rates were decreased at all times following Day1pre in both expected and unexpected events (P<0.0001) and user rates did not differ following Day1pre (P>0.216). On Day1pre (P<0.0001) and Day7 (P=0.0016), perturbations triggered a significantly greater response.

Physical Activity and Motor Skill Acquisition/Learning (Old Group)

Absolute Errors at 50-100 ms

The mean absolute errors in the expected events on Day1pre were 13.76 and 9.25 degrees, for the less active and active groups, respectively; while the mean absolute errors in the unexpected events for the less active and active groups were 11.22 and

10.12 degrees, respectively. In the expected events, the percent changes in errors from Day1pre to Day1post, Day3, and Day7 were -13.81, -25.51, and -24.42, respectively, for the less active group ; and -16.43, -1.41, and -12, respectively, for the active group. In the unexpected events, the percent changes in errors from Day1pre to Day1post, Day3, and Day7 were 17.91, 2.41, and -4.37, respectively, for the less active group; and -15.42, -17.59, and -12.94, respectively, for the active group. (Figure 3.3A).

There was a significant main effect for GROUP (P=0.007), supporting that greater error occurred in less active elderly people. There were no main effects for TIME and PERTURBATION or any interactions (P>0.163), supporting that the absolute error did not change as a result of motor training and the absolute error did not differ between expected and unexpected events.

User Rates at 0-100 ms

The mean user rates in the expected events on Day1pre were -114.92 and -120.38 degrees/second, for the less active and active groups, respectively; while the mean user rates in the unexpected events for the less active and active groups were -142.39 and -117.63 degrees/second, respectively. In the expected events, the percent changes in user rates from Day1pre to Day1post, Day3, and Day7 were -14.13, -1.17, and -8.88, respectively, for the less active group ; and -31.48, -26.79, and -27.27, respectively, for the active group. In the unexpected events, the percent changes in user rates from Day1pre to Day1post, Day3, and Day7 were -34.17, -32.4, and -22.07, respectively, for the less active group; and -25.13, -23.34, and -31.17, respectively, for the active group. (Figure 3.3B).

There were significant main effects for TIME (P<0.0001) and the TIME x GROUP x PERTURBATION interaction (P=0.023), but there were no main effects for PERTURBATION and GROUP, and no other interactions (P>0.058), supporting that the influence of PERTURBATION differed between groups across the 4 time points. Post hoc analysis showed that on Day1pre, perturbations triggered a greater user rate in the less active (P=0.001), but not in the active group (P=0.765). On Day1post and Day7, both groups demonstrated similar user rates between the expected and unexpected conditions (P>0.451). In the expected events, the user rates were significantly decreased at all times following Day1pre for the active group (P<0.001), whereas the user rates were not changed for the less active group (P>0.052), suggesting greater motor skill learning in the active group. In the unexpected events, although both groups decreased their user rates (improved accuracy) at all times following Day1pre (P<0.004), the user rate was larger in the less active group on Day1pre (P=0.029). However, the less active group was no different than the more active group after the motor skill practice (P>0.586). In summary, the less active elderly group showed poorer performance when exposed to an unexpected event on Day1pre but that same group had the capacity to improve their performance to a level similar to the more active older group until Day7 at which time the skill was not retained. (Figure 3.3B).

Cognitive Function and Motor Skill Acquisition (Old Group)

Absolute Errors at 50-100 ms

The mean absolute errors in the expected events on Day1pre were 14.03 and 10.12 degrees, for the groups with lower and higher cognitive function, respectively; while the mean absolute errors in the unexpected events for the groups with lower and higher

cognitive function were 13.36 and 8.86 degrees, respectively. In the expected events, the percent changes in errors from Day1pre to Day1post, Day3, and Day7 were -13.26, -21.53, and -28.72, respectively, for the group with lower cognitive function; and -16.21, -12.55, and -11.46, respectively, for the group with higher cognitive function. In unexpected events, the percent changes in errors from Day1pre to Day1post, Day3, and Day7 were 3.07, -11.45, and 2.17, respectively, for the group with lower cognitive function; and 4.74, -0.11, and -18.74, respectively, for the group with higher cognitive function. (Figure 3.4A).

There was only a significant main effect for GROUP (P=0.0003), supporting that greater error emerged in the group with lower cognitive function. There were no main effects for TIME and PERTURBATION or any interactions (P>0.081), supporting that the absolute error did not change as a result of motor training and the absolute error did not differ between expected and unexpected events.

User Rates at 0-100 ms

The mean user rates in the expected events on Day1pre were -115.02 and -119.02 degrees/second, for the groups with lower and higher cognitive function, respectively; while the mean user rates in the unexpected events for the groups with lower and higher cognitive function were -143.84 and -122.43 degrees/second, respectively. In the expected events, the percent changes in user rates from Day1pre to Day1post, Day3, and Day7 were -21.32, -13.55, and -15.11, respectively, for the group with lower cognitive function; and -22.65, -12.54, and -18.85, respectively, for the group with higher cognitive function. In the unexpected events, the percent changes in user rates from Day1pre to Day1post, Day3, and Day7 were -42.77, -31.66, and -33.59, respectively, for

the group with lower cognitive function; and -20.39, -26.36, and -19.2, respectively, for the group with higher cognitive function. (Figure 3.4B).

There was a significant main effect for TIME ($P<0.001$), but there were no main effects for GROUP and PERTURBATION or any interactions ($P>0.058$), supporting that user rates were decreased following motor training and the improvement was similar between expected and unexpected events, and between groups. Post hoc analysis showed that the user rates were decreased at all times following Day1pre ($P<0.0001$). User rates did not change from Day1post to Day3 and from Day3 to Day7 ($P>0.098$).

Physical Activity and Cognitive Function

Physical activity was not correlated to either Flanker or LSWM ($P>0.149$). However, there was a trend that physical activity was related to the DCCS score (Table 3.2). Here, a trend was shown between the average step count and DCCS ($R=0.35$, $P=0.06$), between the duration in Light activity and DCCS ($R= -0.37$, $P=0.05$), and between the duration in Very Vigorous activity and DCCS ($R=0.41$, $P=0.03$).

DISCUSSION

The novelty of this study is that we investigated the impact of physical activity and cognitive function on motor performance and learning during expected and unexpected events in young and old populations. The major findings from this study are that: 1) older, less active people show a reduced capacity to respond to both expected and unexpected events; 2) older, less active people have the capacity to learn to respond to both expected and unexpected events with practice; 3) improved executive function is associated with people who are more active; and 4) both activity level and executive

function appear to foster improved movement control of a novel wrist movement task. Taken together, these findings suggest that regular physical activity may “protect” against unexpected event. Moreover, people with reduced activity levels retain the capacity to learn to respond to both expected and unexpected events with practice.

Regular Physical Activity, Performance, and Learning

To the best of our knowledge, this is the first study to investigate the impact of regular physical activity on motor skill learning during both expected and unexpected events. Most previous studies primarily focused on the immediate effects of a single bout of systemic aerobic exercise on motor learning (Mang et al., 2014; Roig et al., 2012; Skriver et al., 2014; Statton et al., 2015). In our study, despite a between-group difference in errors across times (P=0.047), both groups demonstrated similar errors on Day1pre (independent T test, Expected: P>0.134; Unexpected: P>0.167), a time that was not influenced by motor practice. Importantly, the active young group demonstrated similar user rates at most times during both unperturbed and perturbed events compared to the less active young group. Our findings suggest that the regular physical activity levels assessed within the young group did not improve human motor performance.

Previous studies on retention are not directly comparable to this study because others have primarily assessed the impact of aerobic exercise on long term retention of a motor task (Roig et al., 2012; Skriver et al., 2014). Other studies are mixed as some support that physical activity level improves motor skill acquisition in young people (Mang et al., 2014; Statton et al., 2015) while others show a contrary outcome (Roig et al., 2012; Skriver et al., 2014). Two studies did support that long-term physical

activity/exercise results in improved performance on cognitive tests (Colcombe and Kramer, 2003; Winter et al., 2007), a finding that we discovered is marginally correlated with performance of a visual motor task. Interestingly, cognitive tasks require more activation of the frontal lobe area while motor skill learning requires prefrontal, sensorimotor, and subcortical areas of the brain (Dayan and Cohen, 2011; Doyon and Benali, 2005; Platz et al., 2012). As we advance our understanding of the "connectome", where complicate neural networks integrate even the simplest of movements support that centers involved with motor skill learning and memory, likely involve the coordination of many centers of the brain.

Regular physical activity is purported to increase motor cortical excitability (Cirillo et al., 2009; Pearce et al., 2000; Rosenkranz et al., 2007b), which may promote the capacity to optimally "tune" the LLR to minimize error. Our findings support that young individuals, who participate in regular physical activity, showed similar error in the timeframe associated with the LLR. The active and less active young groups may not have differed because physical activity results in the greatest effect on prefrontal cognitive function (Colcombe and Kramer, 2003) and it is not necessary for young people to have prefrontal engagement during visual motor tasks (Berchicci et al., 2014). Conversely, older people require more prefrontal activity during the visual motor tasks (Berchicci et al., 2014), making the potential impact more prominent in older people.

For expected events, we discovered that active older people demonstrated less error in performing the task on the first day (Figure 3.3A, Expected). We also observed decreased user rates in both less active and active groups following the first day, but the active group showed a greater motor acquisition within the first day and a greater

motor retention on Day3, with user rates on both days closer to the gold standard, -70 degrees/second (Figure 3.3B, Expected). The underlying mechanisms for why active older people demonstrate better motor performance, motor acquisition, and motor retention during expected visual motor tasks may be due to neurological adaptations induced by the physical activity. For example, exercise increases BDNF, catecholamines, and lactate (Mang et al., 2014; Skriver et al., 2014; Winter et al., 2007), which all have been shown to correlate to motor skill acquisition and/or retention (Skriver et al., 2014). Importantly, physical activity has been shown to increase the activation of the brain in areas related to motor skill learning, including the hippocampus, premotor cortex, and the supplementary motor cortex (Schlaffke et al., 2014). In addition, motor cortical excitability is enhanced in people who are more active (Cirillo et al., 2009; Pearce et al., 2000; Rosenkranz et al., 2007b).

The most important finding, however, was that motor performance was “better” in active older people who were suddenly, under random conditions, exposed to an unexpected event (Figure 3.3B, Unexpected). This finding suggests that physical activity has the potential to offer a “global protection” that allows improved responses when exposed to something unexpected. The importance of this finding is that an injury is believed to occur when the nervous system is fooled. In this study, we analyzed the user rate at a time that implicates two parts of the nervous system after it has been fooled: The first is the trans-cortical long latency triggered responses that help correct for an unexpected perturbation. The second, is to incorporate an optimal feed forward control plan based on either life experiences or adaptations that offer a better “default” strategy to respond when and if something unexpected occurs. Because physical activity reduces the age-

related decline in proprioception (Ribeiro and Oliveira, 2007; Wright et al., 2011) and physically active elderly people have a better ability to use sensory information to maintain postural stability when experiencing sensory disturbance (Lamoth and van Heuvelen, 2012; Maitre et al., 2013; Maitre et al., 2015), it is reasonable that physically active old adults have the capacity to transmit the sudden perturbation, via muscle spindle velocity dependent afferents, to the sensory and motor cortex which allows a "correction" before the volitional reaction time.

The absolute errors during the unexpected events were not changed in both groups as a result of motor practice (Figure 3.3A). However, this could be due to the fact that the unexpected event may have propelled some older subjects closer to the target, fostering a loss of sensitivity to improvement. For this reason, we analyzed the user rate in an effort to capture the true effect of the perturbation. When examined at the Medium speed, which was the speed associated with the most prominent perturbation induced error and learning, we discovered that less active elderly had a poorer response to the unexpected perturbation, but that practice negated the impact of the reduced activity. Although motor practice decreased user rates in both groups, in real life, people rarely obtain the opportunity to "practice" an unexpected event that caused an injury. However, the more regular exposure to unexpected conditions, which do not produce an injury, may be beneficial to people who are older. It is noteworthy that physically active older people may have greater capacity to also respond to an unexpected perturbation during a volitional reaction time, but our study focused only on the 100 ms time after a perturbation. We intend to further examine the data to answer follow up questions

related to other strategies used by elderly to elucidate beneficial adaptations associate with regular physical activity.

In summary, physically active old people demonstrated better performance when exposed to an unexpected event; however, those who are less active can learn with practice, falling under the principles of specificity of training. These findings support the value of an active lifestyle with age, but also the capacity for less active people to benefit from practice and perhaps strategic neuro-rehabilitation interventions in efforts to prevent injury when and if they are exposed to an unexpected event.

Cognitive Function in Healthy Old Adults

Within the healthy elderly group, we discovered that the group with the higher cognitive function (DCCS: >75th percentile) was significantly younger than the group with the lower cognitive function (DCCS: 25th– 74th percentile); a finding that is not surprising given that executive function decreases with age (Fjell et al., 2016). The people with the higher DCCS score also had better Flanker scores, indicating that people with better cognitive flexibility may also have better inhibitory control. Cognitive flexibility and inhibitory control are two main domains in executive function and both are related to prefrontal areas (Diamond, 2013). There was a trend in our study that supported that the group with the higher DCCS scores performed better in the unexpected event and took more steps compared to the less active group, suggesting that physical activity is associated with execution function. Our result is consistent with findings from previous studies (Colcombe and Kramer, 2003; Frederiksen et al., 2015). Surprisingly, the group with higher DCCS scores weighed more than the group with lower DCCS scores (Table 3.1). Although obesity may exacerbate cognitive declines (Chan et al., 2013; Waldstein

and Katzel, 2006), none of our subjects were truly obese when examining height and body fat percentages (Table 3.1). Thus, our subjects who were “heavier”, still fell in a normal BMI range for age.

Most participants enrolled in this study had higher executive function assessed by DCCS (≥ 75th percentile: 17/29 (59%) subjects; ≥ 50th percentile: 28/29 (97%) subjects) as compared to the general population. Although we still found some differences in motor function between groups we would expect even greater differences in a more heterogeneous group demonstrating a greater range in DCCS scores.

Although older adults with lower cognitive function (DCCS: 25th -74th percentile) demonstrated higher errors, they did not lose the ability to acquire the new skill in both expected and unexpected events. Specifically, for motor performance, our results showed a between-group difference in errors, suggesting that the older people with higher executive function demonstrated better motor performance. However, for motor skill learning, both groups showed similar changes in error and user rate during expected and unexpected events as a result of motor practice, indicating that the impact of executive function on motor skill learning may not be significant. As the executive function relies on the frontal cortex especially the prefrontal area (Diamond, 2013), we suggest that the frontal area has more contribution to motor performance than motor skill learning, supported by the fact that the frontal area plays an important role in voluntary movement, motor planning, and motor programming.

Motor learning involves complex neuronal networks. The lack of between-group differences in motor learning during both events may be explained by changes in brain

recruitment pattern in people with lower DCCS score. Although the prefrontal cortex is particularly vulnerable to age-associated deterioration (Greenwood, 2000), the group with lower DCCS score could learn to recruit other areas to compensate for the deficits in the frontal area, such as premotor and supplementary motor cortex, subcortical area, and/or cerebellum. Furthermore, it is still possible that the deterioration in the frontal cortex does not have a great effect on motor learning in certain tasks because neuronal networks related to motor learning also involve other areas, including the M1, cerebellum, striatum, and medial temporal cortex (Dayan and Cohen, 2011; Doyon and Benali, 2005; Platz et al., 2012). For example, studies have shown the important role of the cerebellum in the visual motor task (Hallett and Grafman, 1997; Miall et al., 2000).

Several studies have used accelerometers to relate physical activity with cognitive function (Brown et al., 2012; Buchman et al., 2008; Hayes et al., 2015; Wilbur et al., 2012). Those findings are in line with the fact that the effects of exercise may also be attributed to changes in cognitive function including working memory and executive function (Colcombe and Kramer, 2003; Daly et al., 2014; Frederiksen et al., 2015).

In this study, a physically active lifestyle was related to higher executive function in cognitive flexibility. Specifically, time spent in light and very vigorous activity was associated with higher DCCS scores (Table 3.2). Our findings are in agreement with previous research (Brown et al., 2012; Wilbur et al., 2012), despite the discrepancy in measurement tools (Stroop vs DCCS) (Brown et al., 2012; Wilbur et al., 2012). Also, we did not observe any correlations between physical activity and inhibitory control, although previous studies have indicated that people with higher aerobic fitness demonstrate better inhibitory control (Colcombe et al., 2004). We do not know if people

who took more steps each day also had higher overall aerobic fitness. However, previous reports support our findings in that physical activity does not directly influence inhibitory control (Weng et al., 2015). In addition, our findings also showed that working memory (LSWM) was not related to step count or the time spent in each activity level. There are discrepancies in the literature as some showed that physical activity is positively associated with working memory (Hayes et al., 2015; Weng et al., 2015), others did not (Wilbur et al., 2012). The disparity is probably due to the differences in assessment tools, subjects studied, and how activity level was measured. Interestingly, certain executive function assessment tools are known to challenge various parts of the brain (Hayes et al., 2015).

Methodological Considerations and Clinical Implications

The participants in the old group enrolled in this study had levels of physical activity and executive function that are not representative of the general population. In our cohort, over 97% of the older subjects had above average DCCS scores and took in excess of 5000 steps per day. More studies are needed to investigate the extent to which motor learning occurs in people with sedentary lifestyles and significantly lower executive function consistent with those who have a higher incidence of chronic disease. However, this study develops the framework for subsequent studies to better understand the impact of activity level, cognitive skills, and age on movement control and learning. In addition, further studies are needed to investigate the mechanisms by which physical activity and executive function modulate motor function and motor learning.

SUMMARY AND CONCLUSIONS

Human motor performance to expected and unexpected events is diminished in older people who are less active. Older people with diminished motor performance demonstrate the capacity to learn, by practice, and improve to levels comparable to those who are active. However, injury typically occurs when an individual is exposed to a single unexpected event; that is there are rarely “re-takes” when a non-contact injury occurs. These findings suggest that activity level enhances the ability for elderly to respond to a random, unexpected event, before there is an opportunity to practice. Hence, by logical extension, activity level may protect against the random, unpredictable, events that cause injury in older people who attempt to increase their activity level suddenly.

TABLES

Table 3.1 Demographic Data of Participants in Groups with Different Physical Activity Levels and Executive Function

Demographic data of participants in the (A) young, (B) old, and (C) executive function groups. Value = mean ± standard deviation. M: Male, F: Female; DCCS: Dimensional Change Card Sort Test; LSWM: List Sorting Working Memory Test. *: significant.

(A) Young-Physical activity

	5-9.999K (n=20)	**10-20K** (n=17)	**P Value**
Age	25.05 ± 3.39	25.53 ± 3.34	0.956
Sex	13 M, 7 F	9 M, 8 F	0.516
Height (cm)	177.5± 11.84	175.08 ± 11.01	0.527
Weight (kg)	77.28 ± 15.75	72.91 ± 11.87	0.354
Body Fat (%)	20.12 ± 7.95	21.01 ± 7.77	0.735
Handedness	96.9 ± 8.24	97.76 ± 4.99	0.698
Step per day	8427.88 ± 990.75	12534.17 ± 2132.1	<0.001*

(B) Old-Physical activity

	5-9.999K (n=16)	**10-20K** (n=13)	**P Value**
Age	66.19 ± 5.52	63.92 ± 3.64	0.215
Sex	5 M, 11 F	8 M, 5 F	0.144
Height (cm)	168.28± 11.42	172.72 ± 10.57	0.291
Weight (kg)	77.21 ± 13.25	83.55 ± 18.86	0.298
Body Fat (%)	33.46 ± 11.16	29.93 ± 9.68	0.378
Handedness	98.75± 5	100 ± 0	0.33
MMSE	28.38 ± 1.5	29 ± 1.15	0.228
DCCS	8.24 ± 0.66	8.67 ± 0.55	0.068
Flanker	8.75 ± 0.36	8.87 ± 0.27	0.329
LSWM	16.12 ± 2.83	17 ± 1.73	0.338
Step per day	7806.69 ± 1343.44	11464.11 ± 1679.27	<0.001*

(C) Old-Executive function

	DCCS 25th-74th (n=12)	**DCCS >75th** (n=17)	**P Value**
Age	67.5 ± 5.79	63.53 ± 3.28	0.048*
Sex	4 M, 8 F	9 M, 8 F	0.452
Height (cm)	168.4± 11.4	171.6 ± 11	0.451
Weight (kg)	69.48 ± 11.59	87.52 ± 14.62	0.001*
Body Fat (%)	29.04 ± 7.41	33.88 ± 12.03	0.228
Handedness	98.33± 5.77	100 ± 0	0.339
MMSE	28.67 ± 1.3	28.65 ± 1.46	0.971
DCCS	7.83 ± 0.29	8.86 ± 0.45	<0.001*
Flanker	8.57 ± 0.3	8.97 ± 0.23	0.001*
LSWM	16.58 ± 2.91	16.47± 2.07	0.904
Step per day	8468.3 ± 1759.8	10136.5 ± 2539.8	0.06

Table 3.2 Correlation between Cognitive Function and Physical Activity

DCCS: Dimensional Change Card Sort Test; LSWM: List Sorting Working Memory Test.
*: significant.

Variable	Variable	R value	P value
DCCS	Steps	0.35	0.06
DCCS	Light intensity duration	-0.37	0.05*
DCCS	Moderate intensity duration	-0.11	0.57
DCCS	Vigorous intensity duration	0.03	0.89
DCCS	Very Vigorous intensity duration	0.41	0.03*
Flanker	Steps	0.1	0.6
Flanker	Light intensity duration	-0.2	0.3
Flanker	Moderate intensity duration	-0.22	0.26
Flanker	Vigorous intensity duration	-0.1	0.6
Flanker	Very Vigorous intensity duration	0.28	0.15
LSWM	Steps	0.22	0.25
LSWM	Light intensity duration	-0.27	0.16
LSWM	Moderate intensity duration	0.11	0.56
LSWM	Vigorous intensity duration	-0.06	0.75
LSWM	Very Vigorous intensity duration	-0.08	0.68

FIGURES

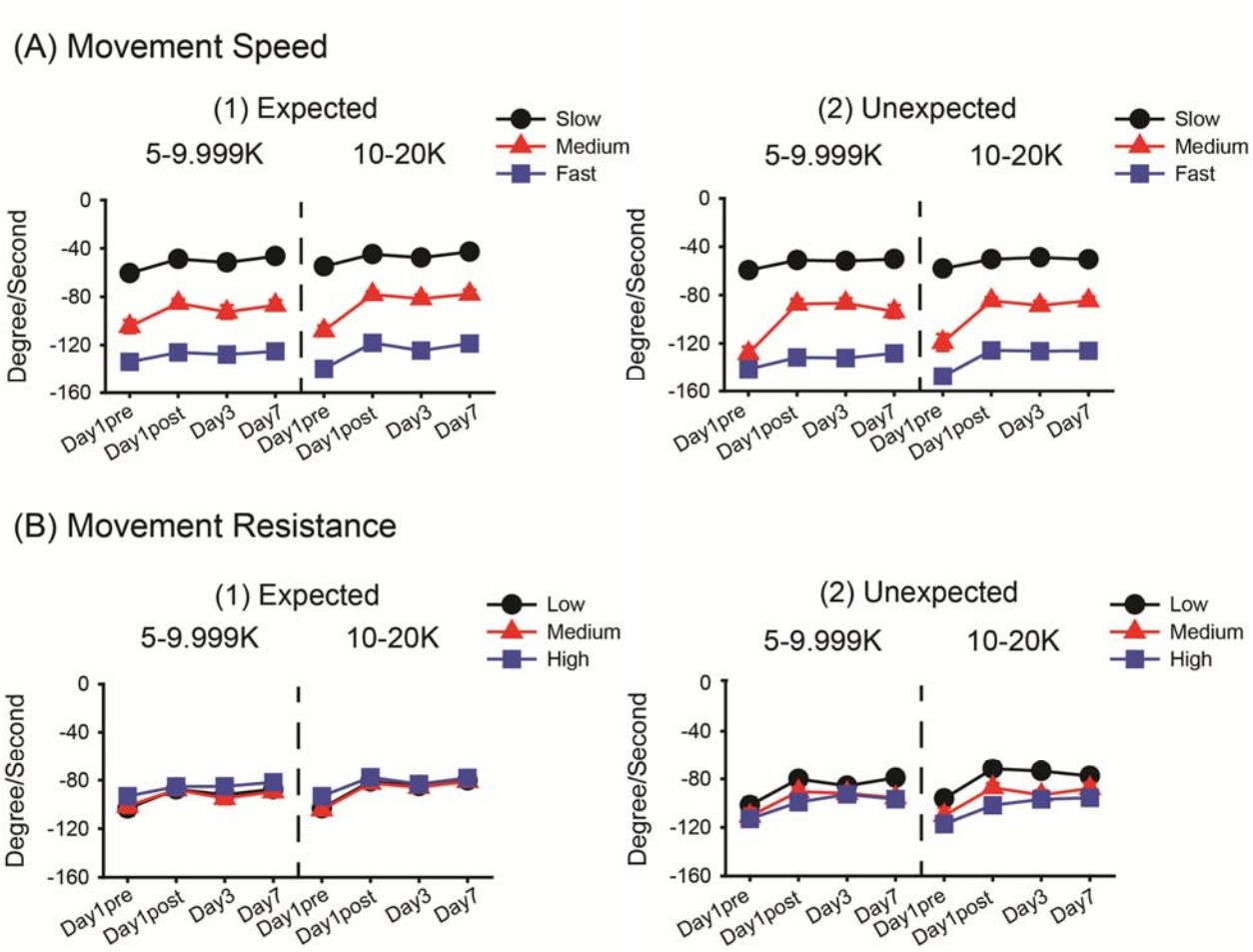

Figure 3.1 Effect of Speed and Resistance Level on User Rate

User rates during both expected (1) and unexpected (2) events with different speeds (A) and resistance levels (B) in the less active (5-9.999K steps) and active (10-20K steps) groups. Value = mean ± standard error.

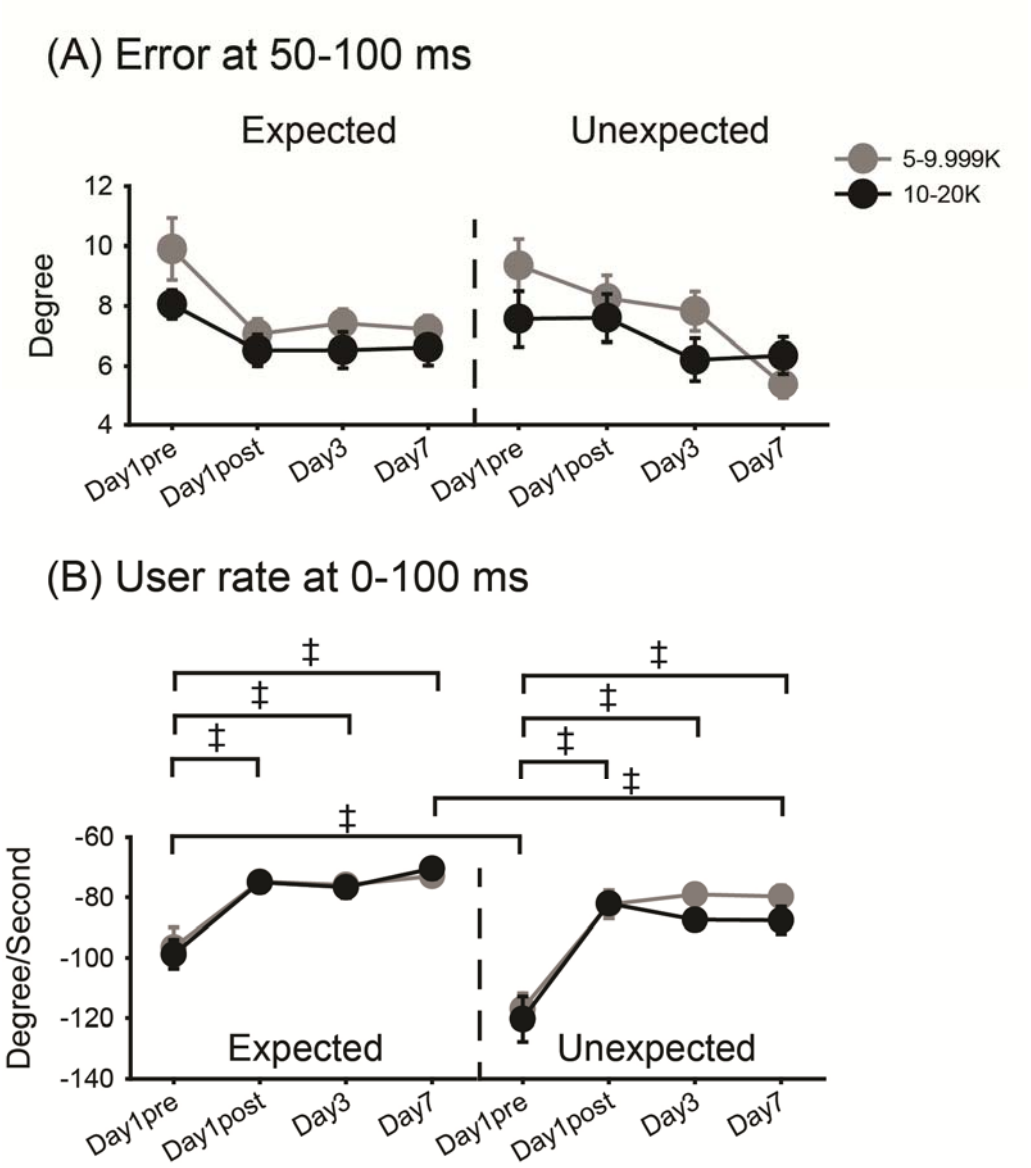

Figure 3.2 Effect of Physical Activity on Error and User Rate in the Young Group

Error at 50-100 ms (A) and user rate at 0-100 ms (B) during both expected and unexpected events in the less active (5-9.999K steps) and active (10-20K steps) young groups. Value = mean ± standard error. ǂ: P<0.05 in the post-hoc testing for TIME x PERTURBATION.

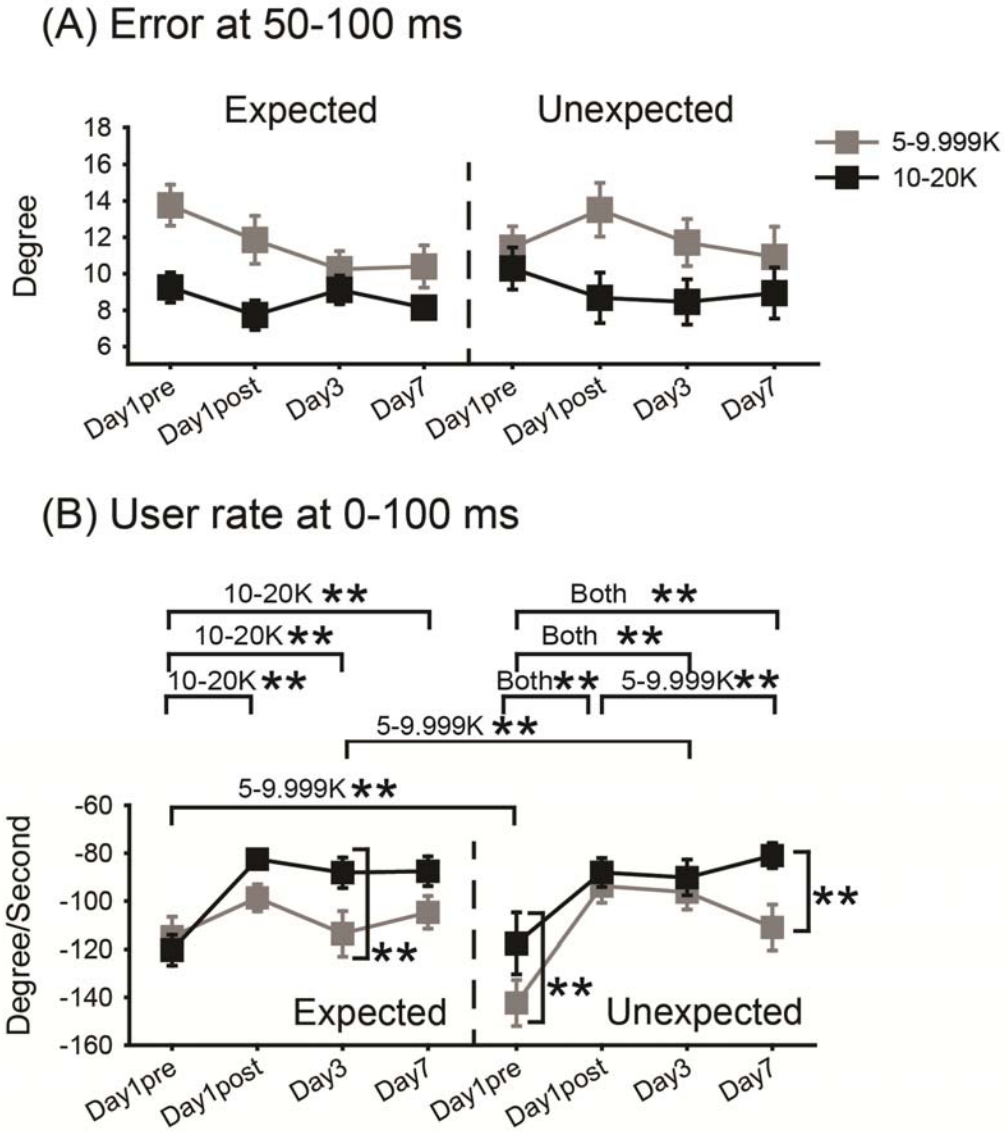

Figure 3.3 Effect of Physical Activity on Error and User Rate in the Old Group

Error at 50-100 ms (A) and user rate at 0-100 ms (B) during both expected and unexpected events in the less active (5-9.999K steps) and active (10-20K steps) old groups. Value = mean ± standard error. **: P<0.05 in the post-hoc testing for TIME x GROUP x PERTURBATION.

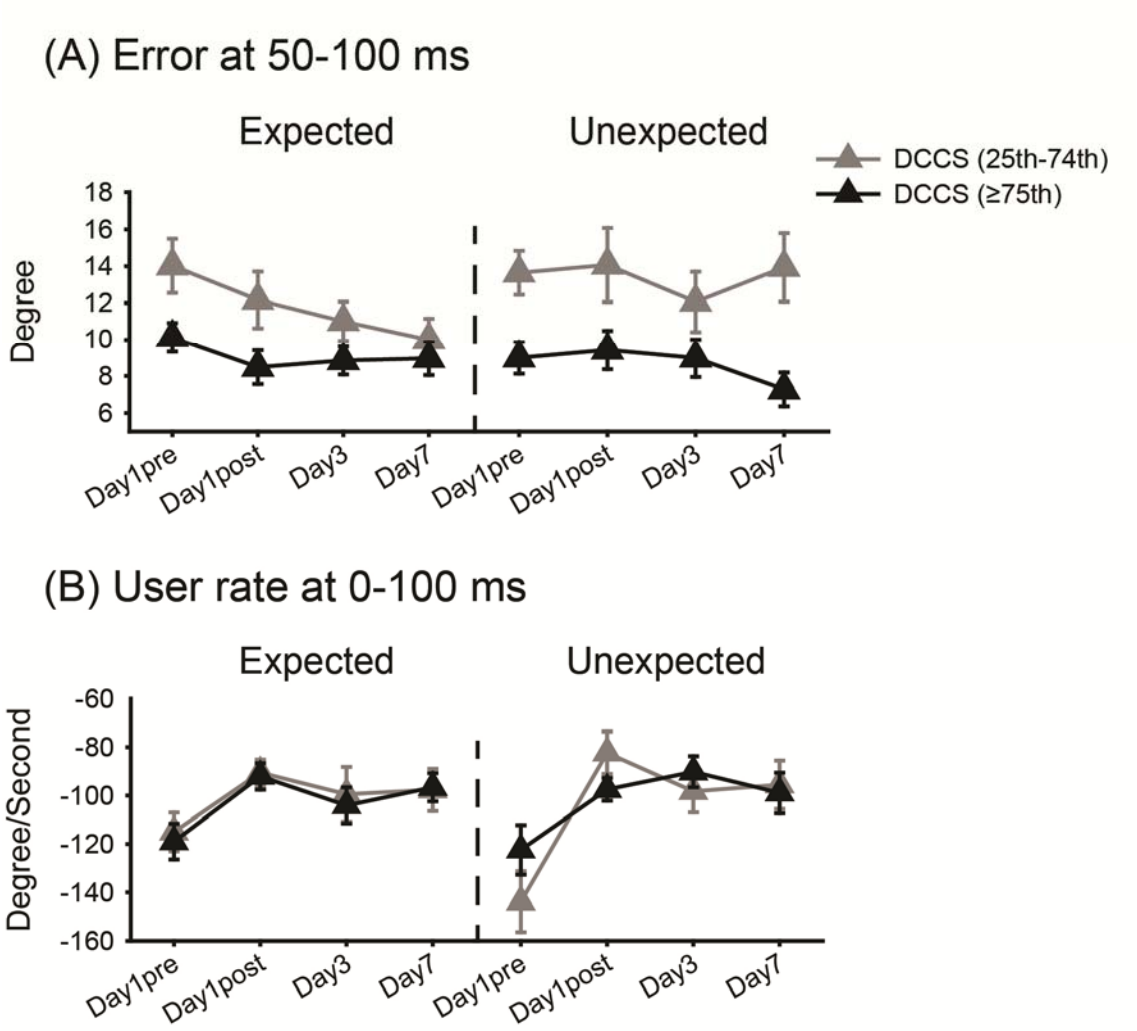

Figure 3.4 Effect of Executive Function on Error and User Rate

Error at 50-100 ms (A) and user rate at 0-100 ms (B) during both expected and unexpected events in old groups with lower (DCCS 25th-74th percentile) and higher (DCCS ≥75th percentile) cognitive function. Value = mean ± standard error.

CHAPTER 4 INCREASED MOTOR CORTICAL EXCITABILITY DISRUPTS MOTOR LEARNING DURING UNEXPECTED EVENTS IN YOUNG ADULTS

INTRODUCTION

Increasing motor cortical excitability is associated with an enhanced capacity to learn and retain a novel motor skill. One method to enhance motor cortical excitability is through paired associative stimulation (PAS), which is based on an induced spike timing-dependent plasticity in the central nervous system (Stefan et al., 2000; Stefan et al., 2002; Wolters et al., 2003). When the afferent signal elicited by peripheral nerve stimulation (PNS) reaches the motor cortex shortly before a TMS pulse that is applied over the motor cortex (M1) a resulting long-term potentiation (LTP)-like plasticity is induced. The increased cortical motor excitability by the PAS protocol has been shown to increase motor scale scores and muscle strength in people with stroke (Castel-Lacanal et al., 2007). However, it remains unclear whether the increased cortical motor excitability by PAS influences motor skill, particularly during unexpected events. To our knowledge, no previous study has assessed the effect of using PAS to enhance motor skill, over and above, that obtained through a training program (learning versus acquisition).

Enhanced motor cortical excitability has the potential to tune the motor performance in response to an unexpected event. Following a perturbation, the nervous system modulates a muscle response to allow a quick reaction to disturbances from an unexpected event. These responses are not stereotypical but frequently modulated

based on task dependency. The LLR is mediated by group Ia afferents initially (Schuurmans et al., 2009), and is tuned by a trans-cortical neural pathway (Goodin et al., 1990; Krutky et al., 2004). Areas of the CNS that have been implicated as part of this pathway include M1, sub-cortical areas, and the cerebellum (Kimura et al., 2006; Kurtzer et al., 2013; Lewis et al., 2004; Shemmell et al., 2009). Because the LLR is potentially influenced by the contralateral M1, it is reasonable that any excitability change in the contralateral M1 may modulate the motor performance during unexpected events.

All people do not respond to PAS protocols equally. TMS-induced changes in cortical motor excitability may be variable across subjects (López-Alonso et al., 2014). This presents a unique opportunity to capitalize on a pragmatic control group to determine if changes in cortical excitability truly modulate responses to unexpected events in humans. We expected that responders to the PAS protocol would show improved motor performance during both expected and unexpected conditions during the visual motor task of the wrist; consistent with previous reports that increased cortical motor excitability improves hand and wrist function (Castel-Lacanal et al., 2007).

Although a number of studies have examined the link between exercise and neural plasticity, little is known about the effect of physical activity on TMS-induced plasticity. For example, cortical PAS induces a greater increase in MEP amplitudes of the abductor pollicis brevis in physically active individuals as compared to sedentary individuals (Cirillo et al., 2009). Moreover, the effects of PAS on cortical motor excitability in the abductor pollicis brevis muscle are larger in professional musicians compared to non-musicians (Rosenkranz et al., 2007b). Taken together, these studies

suggest that physical activity level may be associated with those people who are responders to the PAS protocol. Physical activity in both upper and lower limbs have been shown to modulate TMS-induced neuroplasticity in hand muscles (Cirillo et al., 2009; Mang et al., 2014; McDonnell et al., 2013; Rosenkranz et al., 2007b; Singh et al., 2014). However, these studies often relied on self-report measures of physical activity rather than quantitative measures. Self-report activity levels have a risk of bias and lacks information regarding which limb is involved in the physical activity. Furthermore, it is unclear whether neuro-plasticity is driven primarily by “overall” physical activity or limb dependent plasticity (upper extremity vs lower extremity).

The primary aim of this study was to determine the effect of increased motor cortical excitability, using PAS, on people who demonstrated retention during both expected and unexpected conditions while performing a visual motor task of the wrist. We expected that people who were responders to PAS would demonstrate improved motor performance during both expected and unexpected conditions. Our secondary aim was to explore the relationship between motor cortical excitability level and EMGs in LLR (50-100 ms) and volitional reaction (100-300 ms) times. We expected that the motor cortical excitability would correlate to the extensor carpi radialis (ECR) in LLR and volitional reaction times. This finding would support that the LLR has a trans-cortical component in humans during upper extremity perturbations. Our third aim was to investigate the relationship between the change of motor cortical excitability level and physical activity level. We expected that the change of motor cortical excitability would be positively related to physical activity level. This finding would support that regular physical activity level would be related to the capacity to respond to PAS.

METHODS

Subjects

Sixteen young healthy right-handed individuals (between 20 and 40 years of age) participated in this study. Handedness was verified using the Edinburgh handedness inventory (Oldfield, 1971). All subjects passed the Transcranial Magnetic Stimulation Adult Safety Screen (Keel et al., 2001), and reported no history of current orthopedic or neuromuscular dysfunction, and no consumption of any substances that may alter stimulation thresholds (Rossi et al., 2009). Subjects abstained from consumption of alcohol and caffeine in the 24 hours prior to the experimental session. This study on the females was carried out between the first and the seventh day from the start of their menstrual cycles (Smith et al., 1999b; Smith et al., 2002). This study was approved by the Institutional Review Board of the University of Iowa and all subjects provided their written informed consent before participating.

Paradigm

This study was carried out on Day7, followed by the previous study. On Day7pre, subjects received the pre-measurement of motor function, including maximal voluntary isometric contraction (MVIC) of wrist extensors and flexors, as well as a visual motor manual tracking task. Here, the motor assessment on Day7pre in this study was that on Day7 in the previous study. After motor function test, motor cortical excitability was measured. Then subjects received PAS. Motor cortical excitability was measured immediately after PAS (Day7post). Motor performance in a visual motor manual tracking task was reassessed 10 min after PAS. Figure 4.1A provides a schematic of the testing paradigm.

Behavioral Testing

During all testing sessions, subjects sat in a comfortable chair in front of a computer controlled LCD panel. The right forearm was relaxed on a pillow on the lap and the left forearm was supported on a movable table of a custom-built device, allowing movements of wrist flexion and extension only (Shields RK. Patent US 7,011,605 B2). This custom-built device consisted of a force transducer, a braking system, and a potentiometer which were connected together and aligned with the same axis of rotation of the wrist (Figure 4.1B). The styloid process of the ulnar bone was aligned to the axis of rotation of the device. The resting position of the left arm was in 80 degrees of shoulder abduction, 60 degrees of shoulder flexion, 60 degrees of elbow flexion, with the forearm and wrist in a neutral position. Forearm support straps and blocks restricted unwanted movements (i.e. forearm supination/pronation). We tested the left hand because motor training results in more improvement in the non-dominant hand (Ridding and Flavel, 2006).

TMS Measurement

A MagStim 200^2 (MagStim Company, Whitland, UK) electromagnetic stimulation unit and one 70 mm figure-of-eight coil was used for the single-pulse TMS measures before and after PAS. An electric headband was worn over the subject's head to check and maintain the coil placement throughout the study. First, the vertex was identified and a standardized search technique was used to identify the "hotspot" for the left ECR muscle, which was the coil position on the head over the right M1 that elicited the greatest electrical response consistently from the ECR. Beginning at a location on the scalp that was 3 cm lateral to the vertex, the coil was positioned tangential to the scalp

and with the handle pointed backward and laterally from the midsagittal plane at an angle of ~30-45 degrees. Supra-threshold pulses were delivered while the coil was moved in 0.5 cm increments around the initial spot until the hotspot was identified. The optimal coil orientation for eliciting MEPs was recorded and monitored using a optically tracked navigation system, consisting of a camera (Polaris Vicra P6, Northern Digital, Inc., Waterloo, Ontario, Canada) with respect to a 3-D head reference marker affixed to the subject's forehead and digitized to four anatomical landmarks (ear tragic, tip of nose, and skull vertex). TMS measurement with this navigation device is reliable (Littmann et al., 2013). Next, the RMT was determined by identifying the minimum stimulus intensity which elicited a MEP in the contralateral ECR with peak-to-peak amplitude of ≥ 50 μV in at least 5 out of 10 consecutive pulses (Rossini et al., 1999).

Before PAS, single pulses of TMS was delivered over the right M1 ECR hotspot at 120% RMT and the stimulus intensity for the PAS protocol (PAS intensity) (please see PAS session). Ten pulses delivered at a frequency of 0.1 Hz and MEP amplitudes were recorded before and after PAS.

PAS

One TMS (a Magstim 200 stimulator) with one figure-of-eight coil and one PNS with the pulse duration of 200 μs (DS7A, Digitimer, Digitimer Ltd., Welwyn Garden City, Hertfortshire, UK) was used for PAS. The PAS protocol was followed by previous studies' protocol (Castel-Lacanal et al., 2007; Castel-Lacanal et al., 2009). Briefly, subjects received PAS targeted at the left ECR muscles. PAS involved 180 pairs of TMS pulses delivered over the hot spot for the left ECR and PNS pulses delivered to the motor points of left ECR with 10 Hz trains of 1 ms square wave for 500 ms. The

paired pulses were delivered every 10 seconds for 30 minutes. The stimulus intensity of TMS was either the intensity which evokes MEPs of around 0.3-1 mV or the intensity which elicited the maximal MEP amplitudes (PAS intensity). The stimulus intensity of PNS was delivered at an intensity which induces a visible muscle response. TMS pulses were delivered 25 ms after PNS pulses delivered over ECR. Figure 4.1C shows the illustration of PAS protocol. Because attention is a factor influencing PAS-induced effects (Stefan et al., 2004), subjects was asked to report the number of stimuli delivered by PNS. During PAS and motor cortical excitability testing, subjects were instructed to remain still and relax throughout the entire session.

Data Collection

We developed a task in which subjects were instructed to follow a moving target on a screen using wrist position. Labview (National Instruments Corp., Austin, TX, USA) was used to display the moving sinusoidal target, depicted by a white line on the screen. Subjects were instructed to track the sinusoidal wave by controlling a red line as precisely as possible with their wrist position, moving from wrist extension, to wrist flexion and back to wrist extension to complete one cycle. The lowest trough of the target represented wrist flexion of 37.25 degrees and the highest crest represented wrist extension of 37.25 degrees. The position of the wrist was signaled by a potentiometer. The position was sampled at 4000 Hz and stored for off-line analysis using MATLAB software.

Nine trials (3 velocities x 3 resistance levels) were used in this wrist visual motor manual task (Figure 2.1C). The velocity was set at 30 (Slow speed), 52.25 (Medium speed), and 74.5 (Fast speed) degrees/second; while the resistance was set at 10 (Low resistance),

17.5 (Medium resistance), and 25 (High resistance) % of MVIC of the left wrist extensor muscles. Each trial contained 5 cycles. Unexpected stretches were imposed to the wrist extensor muscles by releasing the resistance of the device when the participant completed the first one third of the flexion phase as determined by the initial starting location, in the 2nd, 3rd, 4th, or 5th cycle in the wrist flexion phase in each trial (stretching the wrist extensors). The cycle for the perturbation was determined randomly.

EMG Recording

Two bipolar electromyographic (EMG) electrodes (Therapeutics Unlimited, Iowa City, IA), each with an inter-electrode distance of 2 cm, were placed over the muscle bellies of the left ECR and flexor carpi radialis (FCR) muscles after prepping the skin with light abrasion and an alcohol swab. The electrode for ECR was placed over one third of the distance from the lateral epicondyle of the humerus on a line connecting the lateral epicondyle of the humerus and the styloid process of the radius, whereas the electrode for FCR was placed over one third of the distance from the medial epicondyle of the humerus on a line connecting the medial epicondyle of the humerus and the styloid process of the radius (Chow et al., 1999). The reference electrode was placed over the left lateral epicondyle of the humerus. EMG signals were pre-amplified with a gain of 35 and further amplified by a GCS 67 differential amplifier (Therapeutics Unlimited, Iowa City, IA) with a gain of 1000-5000. The differential amplifier had an input impedance of 15 MΩ at 100 Hz, a frequency response of 15–1000 Hz, a common mode rejection ratio of 87 dB at 60 Hz, and a bandwidth of 20–400 Hz. EMG was sampled at 4000 Hz and stored for off-line analyses using MATLAB software (The MathWorks, Natick, MA).

Physical Activity Measure

Participants securely wore adjustable bands containing WGT3X-BT (Actigraph wGT3X-BT, Pensacola, FL, USA) around left wrist and left ankle for 7 days. The wrist one was positioned at the line connecting styloid process of ulna and styloid process of radius bone, whereas the ankle one was positioned above medial and lateral malleolus. The WGT3X-BT is portable light weight accelerometer and record acceleration ranging from - 8 to 8 g. The data was collected at a sample rate of 30 Hz, stored on the flash memory, and then downloaded to a computer for processing in the ActiLife software (Actigraph, Pensacola, FL, USA).

Data Analysis

All MEP amplitude data was analyzed using MATLAB (The MathWorks, Natick, MA) software. All signals were demeaned and the gain removed. EMG signals over a 50 ms window prior to the stimulus was analyzed to determine if the background EMG signal from either muscle ever exceeded 10 μV. All trials in which this occurred were discarded from the analysis. Next, peak to peak MEP amplitudes were calculated within a 50 ms window from 10-60 ms post-stimulus. For each subject, the 10 MEP amplitudes at 2 stimulus intensities were averaged separately. The effect of PAS on MEP amplitude was expressed as percentage difference compared with baseline MEP amplitudes. We defined responders by an MEP increase (ratio of mean post-test MEP to pre-test MEP >1.0), and non-responders by an MEP decrease (ratio of post-test MEP to pre-test MEP<1.0).

Motor performance, measured as absolute error, was determined by calculating the absolute difference during the flexion phase between the target and wrist displacements

at each time point. This study focused on the motor performance during the flexion phase because the perturbations were delivered during the wrist flexion phase. The averaged absolute errors during the flexion phase (from the highest crest to the lowest trough) in both expected and unexpected events were calculated separately. Absolute errors in unexpected cycles were defined as absolute errors in unexpected cycles, whereas absolute errors in expected events were defined as the average of absolute errors in the 3rd to 5th expected cycles.

For unexpected cycles, the averaged absolute errors from 50 ms before the perturbation, and at 0-50 ms, at 50-100 ms, and at 100-300 ms after the perturbation were calculated. In addition, the RMS EMG response for the ECR and FCR at 0-50 ms, at 50-100 ms, and at 100-300 ms after the perturbation was calculated. For expected cycles, the RMS EMG response over the same period of time in each cycle was calculated and averaged as the EMG in the expected events, where “time-zero” was defined as the time at which wrist was at the first one third of the flexion phase. For each trial, the RMS EMG in the unexpected events was normalized to that in the expected events.

For each subject, the absolute errors and the RMS EMG from 9 conditions (3 speeds and 3 resistance levels) were averaged as the overall error. Furthermore, the absolute errors and the RMS EMG from conditions with the same speed (Slow, Medium, and Fast speed) or resistance (Low, Medium, and High resistance levels) on both Day7pre and Day7post were averaged separately.

The physical activity data was analyzed by using ActiLife 6.11.5 software (Actigraph, Pensacola, FL, USA). The step count was calculated based on the stored information from the ankle sensors. We also used wrist and ankle vector amplitudes as the primary independent variables. We calculated the averaged step count and vector amplitude per day.

Statistical Analysis

SAS 9.3 (SAS, Cary, NC) software was used for all statistical analyses. Independent t tests were used to test for differences in continuous variables (age, height, weight, body fat, handedness, RMT, PAS intensity, baseline MEPs, errors in counting, wrist and ankle vector magnitudes, and step count) between groups. T-test corrected values were used when equal variances were not assumed. A chi-square test was used to test the sex differences between groups.

Two-way repeated-measures mixed-model ANOVAs (the between-group factor “group” had levels responders and non-responders; the within-group factor “time” had levels Day7pre, Day7post) were used to determine if there were any differences in averaged absolute errors and EMG of 9 conditions between responders and non-responders across time points. In addition, two-way repeated-measures mixed-model ANOVAs were used to determine if there were any differences between responders and non-responders across time points in each condition with the same speeds or resistance levels. If any of these ANOVAs revealed a significant effect, Tukey’s HSD test was used for post-hoc comparisons.

Pearson correlations were used to explore associations between errors and EMG changes, between MEP amplitude and EMG changes, and between the MEP amplitude change and physical activity levels (steps, wrist and ankle vector magnitudes). For the correlations related to error, MEP, and EMG variables, we assessed the variables on Day7post normalized to their respective baseline levels on Day7pre. For all, the significance level was set at $p<0.05$.

RESULTS

None of the individuals had any adverse effects during TMS or PAS sessions. Among the 16 subjects tested, 8 subjects showed the expected facilitation PAS effect (responders), while the remaining 8 subjects showed no facilitation in corticomotor excitability (non-responders). Closer inspection revealed that PAS responders and non-responders did not differ with respect to demographic and baseline neurophysiologic characteristics (Table 4.1).

Corticospinal Excitability

Figure 4.2A shows raw MEP traces from a representative non-responder and responder, illustrating the changes observed on after the PAS protocol. The non-responder showed very little change in MEP amplitudes (Figure 4.2A(1)), whereas the responder showed an increase in MEP amplitudes after the PAS (Figure 4.2A(2)).

The MEP was 30% and 96% increased at an intensity of 120% RMT and the PAS intensity, respectively, for responders, whereas the MEP was 22% and 15% decreased at an intensity of 120% RMT and the PAS intensity, respectively, for non-responders. There was a significant TIME main effect (P=0.0018) and a significant TIME x GROUP

interaction (P<0.0001), but there was no significant main effect for GROUP (P=0.646). Post-hoc testing for the interaction showed similar MEP amplitudes between groups on Day7pre (P=0.563). However, following PAS, MEP amplitudes were increased in responders (P<0.0001) but not non-responders (P=0.075; trend for a decrease) (Figure 4.2B). For the MEP at the PAS intensity, there was a significant TIME x GROUP interaction (P=0.0002), but there were no significant main effects for TIME or GROUP (P>0.426). Post hoc testing of the interaction showed similar MEP amplitudes between groups on Day7pre (Post-hoc, P=0.599). However, following PAS, MEP amplitudes were increased in responders (P=0.002) and decreased in non-responders (P=0.007) (Figure 4.2B). These findings support that non-responders and responders demonstrated opposite effects of the PAS.

Absolute Errors

Expected Events (Unperturbed) Error Analysis

The mean absolute flexion errors in the expected events on Day7pre were 6.48 and 6.53 degrees for the non-responders and responders, respectively. The percent changes in errors from Day7pre to Day7post were -11.11 and -11.64, for non-responders and responders, respectively. (Figure 4.3A). There was a significant TIME main effect (P=0.0005) but there was no GROUP effect (P=0.968) or the TIME x GROUP interaction (P=0.897). This supports that both non-responders and responders decreased overall errors following PAS and there were no differences between groups.

The percent changes in error for the non-responders from Day7pre to Day7post were -15.05, -9.55, and -10.15, for the Slow, Medium, and Fast speed, respectively. The

percent changes in error for the responders from Day7pre to Day7post were -20.64, -17.52, and -1.83, for the Slow, Medium, and Fast speed, respectively. For each speed condition, there were no significant main effects for GROUP (P>0.222) and TIME x GROUP interaction (P>0.229). This supports that the non-responders and responders were similar. There was a significant main effect for TIME in Slow and Medium speed conditions (P<0.0049), but not in the Fast condition (P=0.273). The average errors are shown for all speed levels in Figure 4.3B.

The percent changes in error for the non-responders from Day7pre to Day7post were 5.73, -19.23, and -16.97, for the Low, Medium, and High resistance level, respectively. The percent changes in error for the responders from Day7pre to Day7post were -4.45, -21.04, and -8.71, for the Low, Medium, and High resistance level, respectively. For each resistance level condition, there were no significant main effects for GROUP (All: P>0.678) and TIME x GROUP interaction (All: P>0.393). This supports that both groups demonstrated similar error changes following PAS in conditions with each resistance level. There was a significant main effect for TIME in Medium and High resistance level conditions (P<0.034), but not in the Low resistance level condition (P=0.930). The average errors are shown for all resistance levels in Figure 4.3C.

Unexpected Events (Perturbed) Error Analysis

The mean absolute flexion errors in unexpected events on Day7pre were 6.54 and 6.72 degrees for the non-responders and responders, respectively. The percent changes for errors from Day7pre to Day7post were -4.74 and 11.76, for non-responders and responders, respectively (Figure 4.4A). There was a significant TIME x GROUP interaction (P=0.024) but there were no significant main effects for TIME (P=0.289) and

GROUP (P=0.190). Post-hoc testing for TIME x GROUP revealed no difference in errors between groups on Day7pre (P=0.765). In non-responders, the error was unchanged (P=0.331), whereas in responders, the error was significantly increased on Day7post (P=0.023). Error was smaller in the non-responders on Day7post (P=0.042). These results support that PAS decreased motor performance in responders, but not in the non-responders.

The percent changes in error for the non-responders from Day7pre to Day7post were -1.25, 18.35, and -22.26, for the Slow, Medium, and Fast speed, respectively. The percent changes in error for the responders from Day7pre to Day7post were 2.9, 32.57, and 2.93, for the Slow, Medium, and Fast speed, respectively. This suggests that errors were increased in responders following PAS, especially in the Medium speed condition. For each speed condition, there was no significant main effect for GROUP (P>0.126) and no TIME x GROUP interaction (P>0.056). This supports that non-responders and responders were similar from Day7pre to Day7post. There was a significant main effect for TIME in Medium speed conditions (P=0.004), but not in the Slow and Fast condition (P>0.12). The average errors are shown for all speed levels in Figure 4.4B.

The percent changes in error for the non-responders from Day7pre to Day7post were -15.44, 1.73, and -2.08, for the Low, Medium, and High resistance level, respectively. The percent changes in error for the responders from Day7pre to Day7post were 14.1, -0.14, and 21.59, for the Low, Medium, and High resistance levels, respectively. For the Low resistance level, there was a significant TIME x GROUP interaction (P=0.046). Post-hoc testing reveals no difference between groups in each time point. For the Medium resistance level, there was no significant main effects for TIME and GROUP or

TIME x GROUP interaction (P>0.799). For the High resistance level, there was a significant main effect for GROUP (P=0.022), but there was no main TIME effect or TIME x GROUP interaction (P>0.095). The average errors are shown for all resistance levels in Figure 4.4C.

Unexpected Events in the Condition with High Resistance

Because there was a between group difference in the High resistance condition and across the average of all 9 conditions, we will focus the error and EMG analysis on these conditions.

Absolute Errors Analysis at Each Timeframe

The changes in error for the non-responders from Day7pre to Day7post were 0.04, 0.09, 0.16, and 0.48 degrees, for 50-0 ms before perturbations, 0-50 ms, 50-100 ms, and 100-300 ms after perturbations, respectively. The changes in error for the responders from Day7pre to Day7post were 1.86, 1.79, 1.23, and 0.44 degrees, for the 50 ms before perturbations, 0-50 ms, 50-100 ms, and 100-300 ms after perturbations, respectively. This suggests that errors were increased from Day7pre to Day7post in responders, especially from 50 ms before perturbations to 100 ms after perturbations. However, there were no significant main effects for TIME and GROUP and no TIME x GROUP interaction (P>0.101). This supports that both groups were similar and errors were unchanged in each timeframe in both groups. The average errors at different timeframes for non-responders and responders on Day7pre and Day7post are presented in Figure 4.5.

ECR Analysis at Each Timeframe

The averaged normalized ECR response at 50-0 ms before perturbations from Day7pre to Day7post was from 1.08 to 1.01 and from 1.01 to 0.99, for non-responders and responders, respectively. The averaged normalized ECR response at 0-50 ms after perturbations from Day7pre to Day7post was from 1.02 to 0.94 and from 0.87 to 1.09, for non-responders and responders, respectively. The averaged normalized ECR response at 50-100 ms after perturbations from Day7pre to Day7post was from 1.24 to 1.12 and from 1.03 to 1.3, for non-responders and responders, respectively. The averaged normalized ECR response at 100-300 ms after perturbations from Day7pre to Day7post was from 1.85 to 1.63 and from 2.25 to 2.66, for non-responders and responders, respectively. This suggests that following PAS, the normalized ECR at the timeframes following perturbations was increased in responders, but not in non-responders. For the ECR response at 50 ms before perturbations and 0-50 ms after perturbations, there were no significant main effects for TIME and GROUP, and the TIME x GROUP interaction ($P>0.113$) (Figure 4.6A & B). This supports that ECR was not changed in the feed-forward and monosynaptic timeframe in each group. However, for the ECR response at 50-100 ms and 100-300 ms following perturbations, there was a significant TIME x GROUP interaction ($P<0.029$) but there were no main effects for TIME and GROUP ($P>0.128$). This supports that PAS induced different effects between groups. Post-hoc testing for the interaction showed that before PAS the ECR response at 50-100 ms and 100-300 ms was similar between responders and non-responders ($P>0.288$). However, at both at 50-100 ms and 100-300 ms following perturbations, the ECR response was increased in responders ($P<0.041$), but not in non-responders ($P>0.227$) (Figure 4.6C & D). Responders demonstrated more ECR activation at 100-

300 ms on Day7post compared to non-responders (P=0.042) (Figure 4.6D). These findings suggest that the increased motor cortical excitability enhanced the ECR activation in the trans-cortical and volitional reaction timeframes.

FCR Analysis at Each Timeframe

The averaged normalized FCR response before perturbations from Day7pre to Day7post was from 1.19 to 1.17 and from 1.17 to 1.17, for non-responders and responders, respectively. The averaged normalized FCR response at 0-50 ms after perturbations from Day7pre to Day7post was from 1.18 to 1.1 and from 1.2 to 1.19, for non-responders and responders, respectively. The averaged normalized FCR response at 50-100 ms after perturbations from Day7pre to Day7post was from 1.06 to 0.93 and from 0.99 to 1.03, for non-responders and responders, respectively. The averaged normalized FCR response at 100-300 ms after perturbations from Day7pre to Day7post was from 0.79 to 0.72 and from 0.81 to 0.67, for non-responders and responders, respectively. For each timeframe, there was no significant main effect for GROUP or the TIME x GROUP interaction (P>0.133). This supports that the two groups were similar before and after PAS. There was no significant main effect for TIME at each timeframe (P>0.425), with the exception of 100-300 ms (P=0.005)(Figure 4.7). This supports that the FCR response was decreased in both groups following PAS.

Absolute Errors and EMGs (ECR, FCR)

There were no correlations between errors and EMG (ECR, FCR) in each timeframe on either Day7pre or Day7post (P>0.15). There were also no significant correlations between error and EMG changes from Day7pre to Day7post (P>0.15).

Corticospinal Excitability and EMG at 50-100 ms (LLR) and 100-300 ms (Volitional Reaction)

In order to investigate whether the LLR has a trans-cortical component in humans during upper extremity perturbations, we correlated the changes of MEP amplitudes and EMG. There were no significant relationships between the MEP and EMG changes for all 9 conditions (P>0.09). However, when closely inspecting the relationship in the condition with High resistance, MEP changes were correlated to ECR. Specifically, at 50-100 ms, a potential positive relationship was shown between MEP at the PAS intensity and ECR changes (R=0.53, P=0.03) (Figure 4.8A(1)). There was no correlation between MEP at the PAS intensity and FCR changes (R=0.15, P=0.57) (Figure 4.8A(2)). A similar trend was shown in the volitional reaction time, at 100-300 ms after perturbations. MEP changes were positively correlated to ECR changes (R=0.58, P=0.02) (Figure 4.8B(1)). There was no correlation between MEP and FCR changes (R=0.33, P=0.21) (Figure 4.8B(2)).

Corticospinal Excitability and Physical Activity Level

Despite no difference in physical activity measures (step count and vector magnitudes) (Table 4.1) between nonresponders and responders, MEP changes at the PAS intensity were positively related to step count (R=0.57, P=0.02) (Figure 4.9A) and ankle vector magnitude (R=0.68, P=0.004) (Figure 4.9C). A trend for a positive relationship was shown between MEP changes at the PAS intensity and wrist vector magnitude (R=0.446, P=0.06) (Figure 4.9B). In addition, there were no relationships between changes of MEP amplitude at 120% RMT and any of the physical activity measures (all P>0.43).

Summary of the Results

The MEP amplitudes were facilitated after PAS in the responders, but not in the non-responders, and, following PAS, both non-responders and responders improved motor performance during the flexion phase of the expected events. Both groups demonstrated similar motor performance in each condition. PAS deteriorated the motor performance during the flexion phase of the unexpected events in responders, but not in the non-responders. In the High resistance condition, PAS enhanced the ECR response at 50-100 ms, and 100-300 ms after the perturbation in responders, but did not impact the non-responders. Changes of cortical motor excitability were positively related to ECR changes from Day7pre to Day7post. There was no correlation between cortical motor excitability and FCR changes, and between error and EMG changes in the condition with High resistance. However, changes of motor cortical excitability were positively related to activity level (step count and ankle vector magnitude).

DISCUSSION

The purpose of this study was to examine the effects of PAS on corticomotor excitability and motor performance in responders versus non-responders to PAS. There were several major findings in this study. PAS did not improve motor performance during the expected events of the flexion phase, but PAS deteriorated the motor performance during the unexpected events only in the responders. PAS enhanced the ECR response at 50-100 ms, and 100-300 ms after perturbations in responders, but not in the non-responders (High resistance). The changes in cortical motor excitability induced by PAS were positively related to these ECR changes, however, there were no correlations

between cortical motor excitability and FCR changes. Finally, we discovered that changes of motor cortical excitability were positively related to subject activity levels.

PAS Effect on Corticospinal Excitability

Our experimental protocol induced a facilitation of corticospinal excitability in responders. These findings confirmed that our protocol was effective and similar to other PAS protocols applied over hand or wrist muscles (Castel-Lacanal et al., 2007; Castel-Lacanal et al., 2009; Vallence et al., 2013). Consistent with previous studies (Vallence et al., 2013; Voytovych et al., 2012), the facilitation of corticospinal excitability after PAS was not obtained in all subjects and our responder rate was 50%. We report a 64% average increase in MEP amplitude following PAS in responders, which is within the range of PAS-induced LTP-like plasticity reported in previous studies (Fratello et al., 2006; Quartarone et al., 2003).

TMS-induced changes in cortical motor excitability is variable across subjects (López-Alonso et al., 2014). The plastic effect in M1 has been shown to be dependent on many factors, such as age, hormones, attention, and genotypes (Fathi et al., 2010; Missitzi et al., 2011; Müller-Dahlhaus et al., 2008; Smith et al., 1999b; Smith et al., 2002; Stefan et al., 2004). We controlled for these factors by recruiting young healthy adults and testing in the early follicular phase for female subjects. Also, both groups showed similar errors in counting PAS pulses (Table 4.1), indicating that attention was not a moderating factor to induce the difference in MEP amplitudes between groups. Other factors, including genotype may regulate motor cortical excitability. Previous studies have shown that individuals with val66met polymorphism in the BDNF gene show less reluctance to increase in MEP amplitude after PAS (Missitzi et al., 2011). These individuals also

demonstrate greater errors during motor learning compared to individuals without val66met polymorphism (McHughen et al., 2010). We cannot fully rule out that our MEP results between responders and non-responders were not dependent on genetic factors. However, we showed that non-responders seemed to be better learners in the visual motor task, which may not be the typical characteristic in individuals with val66met polymorphism (McHughen et al., 2010). Because other studies indicate no association of val66met polymorphism with motor learning (Cardenas-Morales et al., 2014; Freundlieb et al., 2012; Morin-Moncet et al., 2014), we do not believe the BDNF genotype factor impacted our results.

PAS Effect on Motor Performance

We hypothesized that PAS would improve motor performance in the novel visuomotor manual tracking task. Out hypothesis was not supported by the results of the present study. We showed that in expected events PAS induced a similar effect between non-responders and responders (Figure 4.3A). Conversely, in unexpected events, PAS resulted in a poorer performance only in the responders (Figure 4.4A). Responders demonstrated greater errors than non-responders following PAS. These findings are novel when compared to previous studies (Frantseva et al., 2008; Rajji et al., 2011). Several reasons may contribute to the different response induced in our study. First, Frantseva et al and Rajji et al used a rotary pursuit task, whereas we used a novel visuomotor manual tracking task. Second, PAS was applied to the subjects on the Day7pre, in the retention stage of an extensive motor learning experience, whereas previous studies employed naïve subjects who had not saturated the learning curve. As PAS and motor learning interact in a homeostatic manner, it seems reasonable that

enhancing cortical excitability may have disrupted a natural balance that was attained through the extensive practice paradigm (Frantseva et al., 2008; Rajji et al., 2011).

The interaction between motor learning and PAS-induced plasticity may contribute to our unexpected results. Both motor learning and PAS increases synaptic plasticity. Synaptic plasticity tends to follow the Bienenstock-Cooper-Munro (BCM) mechanism (Bienenstock et al., 1982), which indicates that the threshold to induce LTP or LTD is dynamically adjusted in the postsynaptic neuron based on the history of previous excitation. In this study, when corticospinal excitability in M1 was increased by a preceding session of motor learning, such as in the non-responders, the threshold for induction of LTP was raised and the “normal” facilitation effect of PAS on MEP amplitude could be blocked. Conversely, in responders, the LTP plasticity was not saturated, which then may allow further PAS-induced plasticity. This is supported by previous studies showing that a ballistic thumb training session attenuates subsequent PAS-induced LTP-like plasticity (Rosenkranz et al., 2007a; Stefan et al., 2006; Ziemann et al., 2004), and other studies indicating an association between the occlusion of anodal tDCS LTP-like aftereffect and skill retention (Cantarero et al., 2013a; Cantarero et al., 2013b). The homeostatic plasticity is also confirmed by previous work with two consecutive applications of TMS protocols applied to M1 (Delvendahl et al., 2010; Müller et al., 2007), as well as a period of motor learning followed by another brain stimulation protocol (Amadi et al., 2015). Together, these results indicate that the change in motor cortex excitability, either by brain stimulation or motor learning, triggered a BCM-like homeostatic mechanism that influences the plastic change in corticomotor excitability.

Interestingly, the homeostatic plasticity was only apparent during the unexpected events. Few studies have included unexpected events, which may explain the novelty of this finding in our research. A plausible explanation for why the expected errors were not disrupted by TMS is because they are relatively easy. Accordingly, subjects could use other brain areas, such as prefrontal areas, to offset the interference created in M1 by TMS. Another alternative explanation is that ECR activations may not have a greater impact on motor performance during the flexion phase of expected events but has a significant impact during unexpected events.

The greatest between-group differences occurred in the condition with High resistance, which is reasonable considering the High resistance condition often is associated with greater perturbations (Schuurmans et al., 2009). Also, although responders had greater overall flexor errors following PAS in unexpected events (Figure 4.4A), closer inspection revealed that in the condition with High resistance the PAS induced errors from 50 ms before the perturbation all the way to the volitional reaction time (300 ms). (Figure 4.5). Hence, the responders demonstrated greater errors during the entire flexion phase.

PAS Effect on ECR and FCR Activations Following Perturbations

While FCR activation did not differ between responders and responders (Figure 4.7), ECR activations were significantly increased at 50-100 ms and 100-300 ms after perturbations in responders (Figure 4.6) compared to non-responders. These changes of ECR were further correlated to motor cortical excitability changes (Figure 4.8). These results suggest that the increased motor cortical excitability is able to increase the muscle activation during trans-cortical and volitional reaction timeframes, and the motor

cortex excitability contributes to the amplitude of the LLR, consistent with previous human (Goodin et al., 1990; Krutky et al., 2004) and animal studies (Bawa et al., 1979; Cheney and Fetz, 1984).

PAS-induced LTP-like Plasticity and Physical Activity

Previous associations between physical activity level and synaptic plasticity have been purported (Cirillo et al., 2009; Mang et al., 2014; McDonnell et al., 2013; Rosenkranz et al., 2007b; Singh et al., 2014), however, to the best of our knowledge, this is the first study to measure the relationship recorded step activity and cortical excitability. We found a positive relationship between MEP changes and step count (Figure 4.9A), between MEP changes and ankle vector (Figure 4.9C), suggesting that regular lifestyle activity enhances synaptic plasticity capacity, in line with previous findings (Cirillo et al., 2009; Rosenkranz et al., 2007b). The mechanisms underlying TMS induced plasticity in physically active people are not exactly known, however, they likely reflect a neurophysiologic adaptation in the brain and/or along the corticospinal tract. Exercise regulates AMPA-type receptor in M1 (Real et al., 2010). Exercise increases BDNF and catecholamines (Mang et al., 2014; Skriver et al., 2014; Winter et al., 2007), all involved with the LTP process (Bekinschtein et al., 2008; Jay, 2003; Korchounov and Ziemann, 2011; Suzuki et al., 2011). Physically active people have increased synaptic connectivity which results in the increase of recruitment following PAS. Surprisingly, we did not observe any relationship between changes of MEP amplitude at 120% RMT and any of the physical activity measures. This may reflect that we did not use high enough stimulus intensities (Cirillo et al., 2009; Rosenkranz et al., 2007b).

We found that MEP changes were significantly correlated to ankle vector magnitudes, but only a non-significant trend relationship between MEP changes and wrist vector magnitudes (Figure 4.9B). Our results are in line with previous findings that both upper and lower extremity-driven physical activity are able to modulate TMS-induced plasticity (Cirillo et al., 2009; Mang et al., 2014; McDonnell et al., 2013; Rosenkranz et al., 2007b; Singh et al., 2014). However, we suggest that physical activity in the upper extremity is not necessary to induce a stronger plastic effect in the upper extremity muscles as compared to physical activity in the lower extremity muscles. Physical activity probably induces its signaling through a non-task-specific systemic adaptation along the corticospinal tract.

Methodological Considerations

There are several considerations one should consider when interpreting the findings of this study. First, the sample size used was relatively small. Thus, some of the effects of PAS may have been underestimated. However, our effect size calculations were 1.2 for the averaged flexion errors in the unexpected events, indicating high differences between responders and non-responders would be detectable. For the condition with High resistance, the effect sizes were 1.4, and 1.2, for normalized ECR at 50-100 ms and 100-300 ms following perturbations. Taken together, we believe the findings would be minimally influenced with greater numbers. Second, we did not re-measure the RMT after the rTMS protocol in order to have sufficient time to collect MEPs post PAS. Therefore, we do not know if the threshold changed after the PAS; an unlikely possibility based on previous studies (Castel-Lacanal et al., 2009). Third, we did not perform the full input-output recruitment curve for motor cortical excitability; however, we used two

stimulus intensities, 120% RMT and the PAS intensity. Although we could not calculate the slope, we were still able to detect increased MEPs at the two stimulus intensities in responders. Finally, we did not assess any neurophysiologic measures, such as intracortical inhibitory or facilitory responses after the PAS. Further studies are needed to better understand the mechanisms that influence motor cortical excitability and subsequent influence on motor performance during unexpected events.

SUMMARY AND CONCLUSIONS

PAS induced similar effects on motor performance during the flexion phase of unexpected events between non-responders and responders in this study. However, PAS deteriorated motor performance during the flexion phase of perturbed events in responders, but not non-responders. Furthermore, changes of cortical motor excitability were positively related to ECR changes, the step count, and ankle vector magnitude. These findings provide important information regarding possible strategies used to regulate motor learning and human performance. Future studies are needed in people with CNS pathology in order to better understand potential rehabilitation methods to enhance movement control, especially during unexpected events.

TABLES

Table 4.1 Demographic Data of Participants

Demographic and neurophysiologic characteristics in non-responders and responders. Value = mean ± standard deviation. M: Male, F: Female

	Non-responder (n=8)	**Responder** (n=8)	**P Value**
Age	25.88 ± 3.04	26.37 ± 4.31	0.793
Sex	5 M, 3 F	4 M, 4 F	0.614
Height (cm)	179.1± 14.73	170.9 ± 11.05	0.230
Weight (kg)	77.60 ± 15.22	67.45 ± 10.36	0.142
Body Fat (%)	20.58 ± 8.77	19.93 ± 6.48	0.869
Handedness	100 ± 0	96.75 ± 6.04	0.172
Resting motor threshold (RMT) (%)	47.86 ± 11.5	38.13 ± 7.99	0.052
PAS intensity (%)	75 ± 14.64	70.63 ± 10.50	0.503
Error in counting (PAS pulse)	2.2 ± 2.95	0.67 ± 0.58	0.421
Wrist vector magnitude (K/day)	2165.12 ± 625.08	2372.32 ± 410.87	0.446
Ankle vector magnitude (K/day)	1359.46 ± 215.75	1554.75 ± 399.01	0.243
Step count per day	9909.6 ± 1960.6	11937.5 ± 3129	0.143

FIGURES

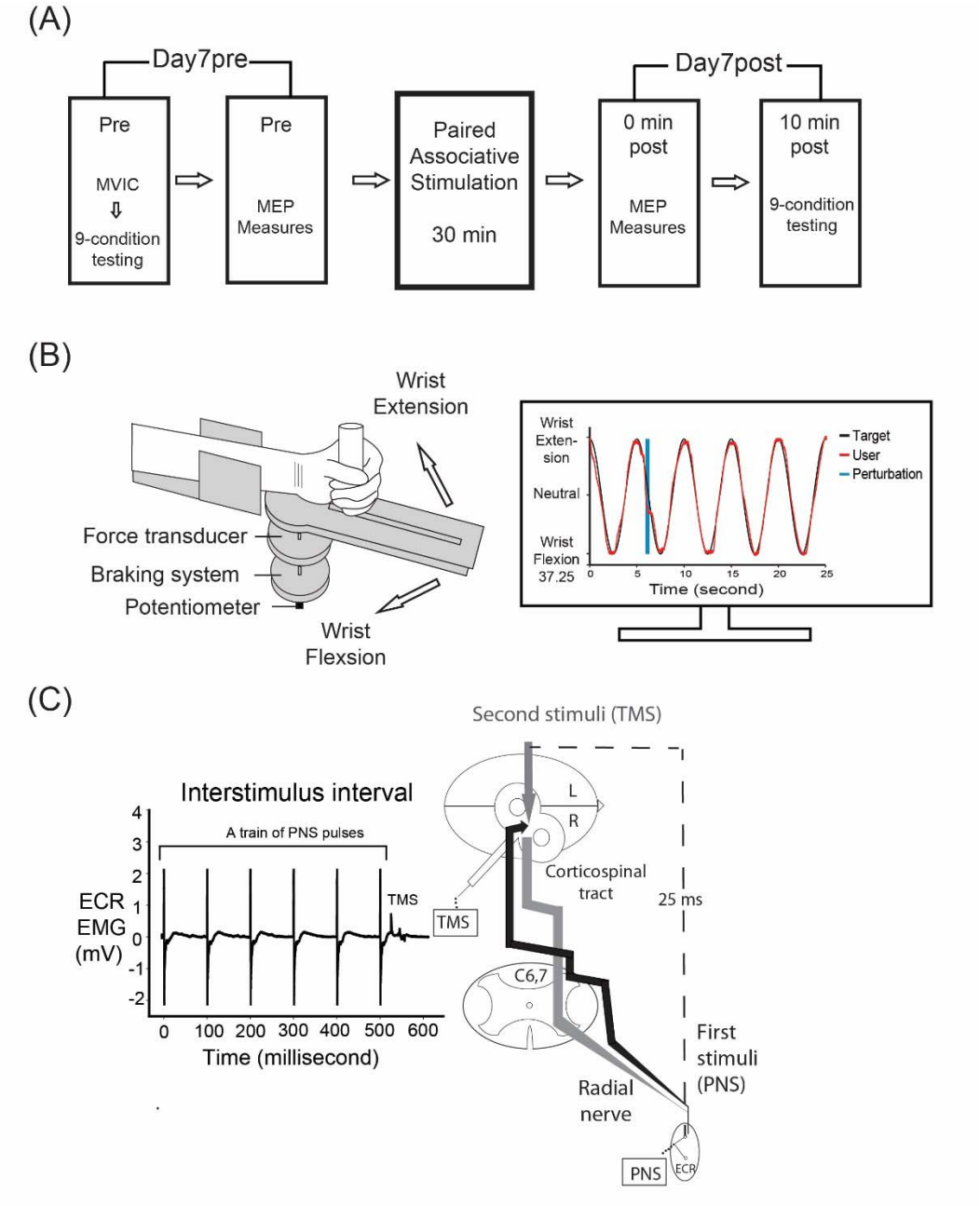

Figure 4.1 Study Paradigm

(A) Schematic overview of the experimental design. (B) Schematic diagram of the device used in the wrist visual motor manual tracking task. (C) Illustration of PAS protocol.

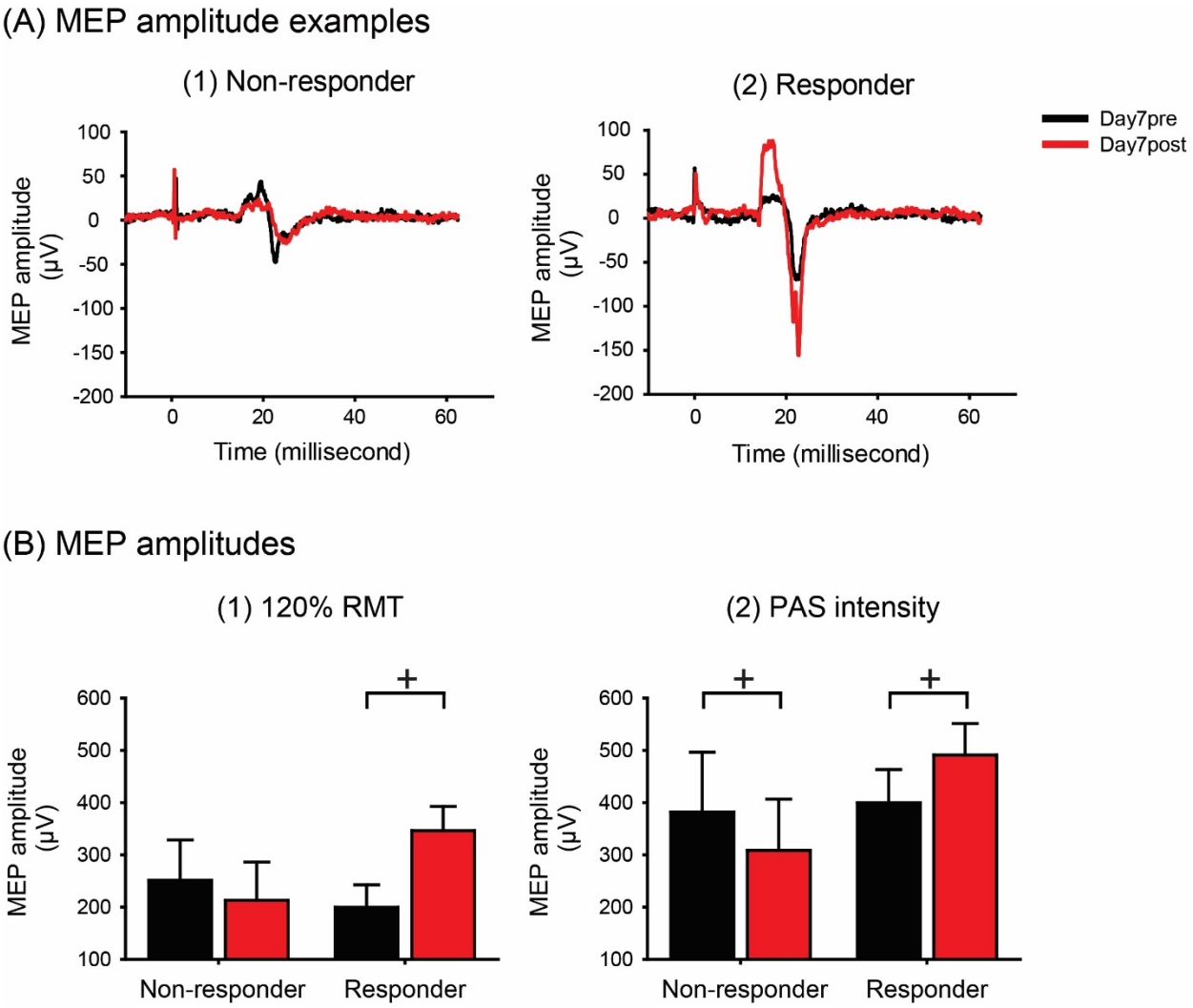

Figure 4.2 MEP Amplitudes in Non-responders and Responders

MEP amplitude examples in one (1) non-responder and one (2) responder. (B) MEP amplitudes at (1) the stimulus intensity of 120% resting motor threshold (RMT) and (2) the stimulus intensity used during the PAS protocol. Value = mean ± standard error. +: P<0.05 in the post-hoc testing for the TIME x GROUP interaction.

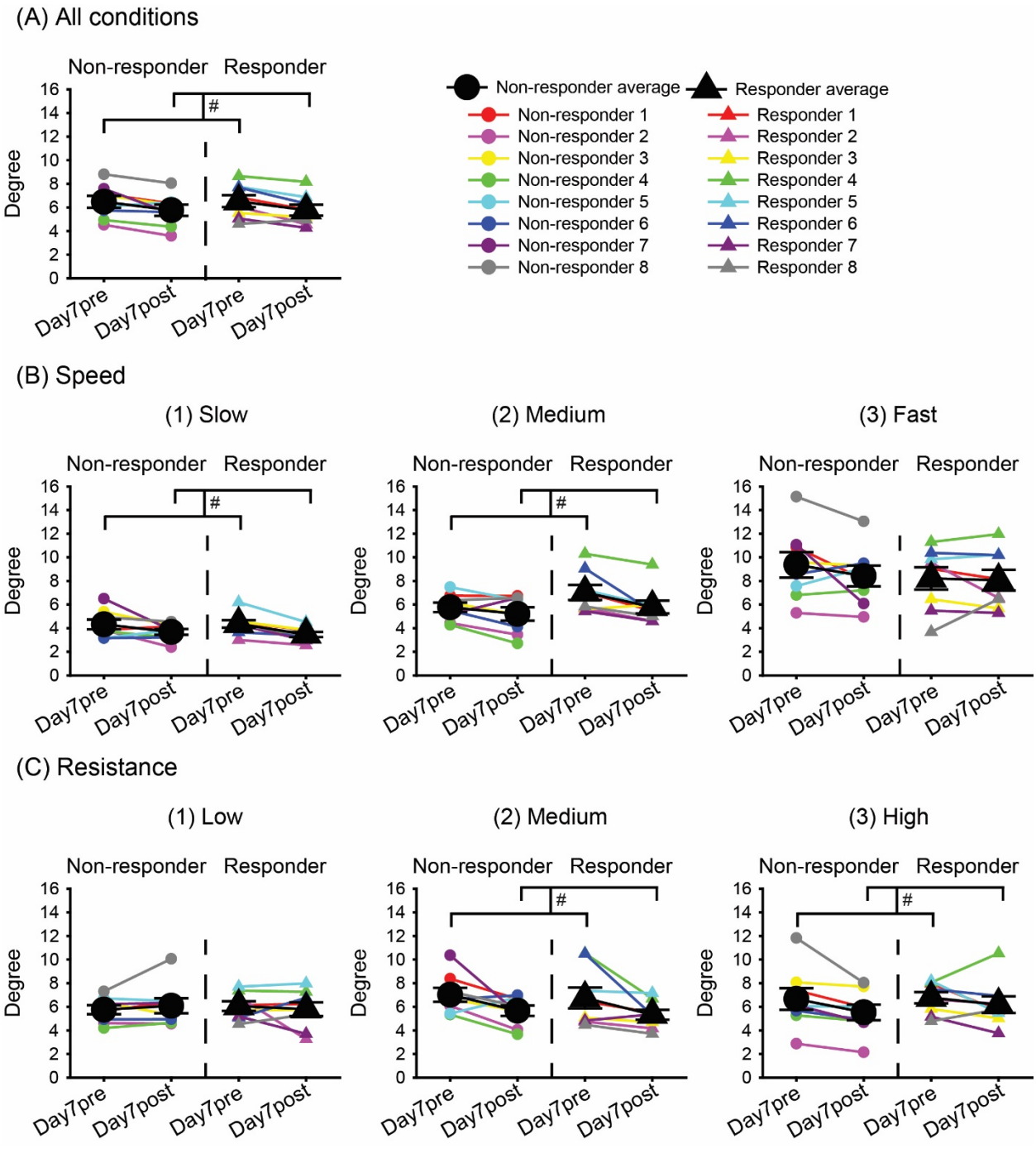

Figure 4.3 Effect of PAS on Absolute Error in Expected Events

Absolute errors during the whole flexion phase of expected events in the non-responders and responders. (A) The average of 9 conditions. (B) Conditions with Slow, Medium, and Fast speeds. (C) Conditions with Low, Medium, and High resistance levels. For group data (black circles and triangles): Value = mean ± standard error. #: P<0.05 in the post-hoc testing for TIME.

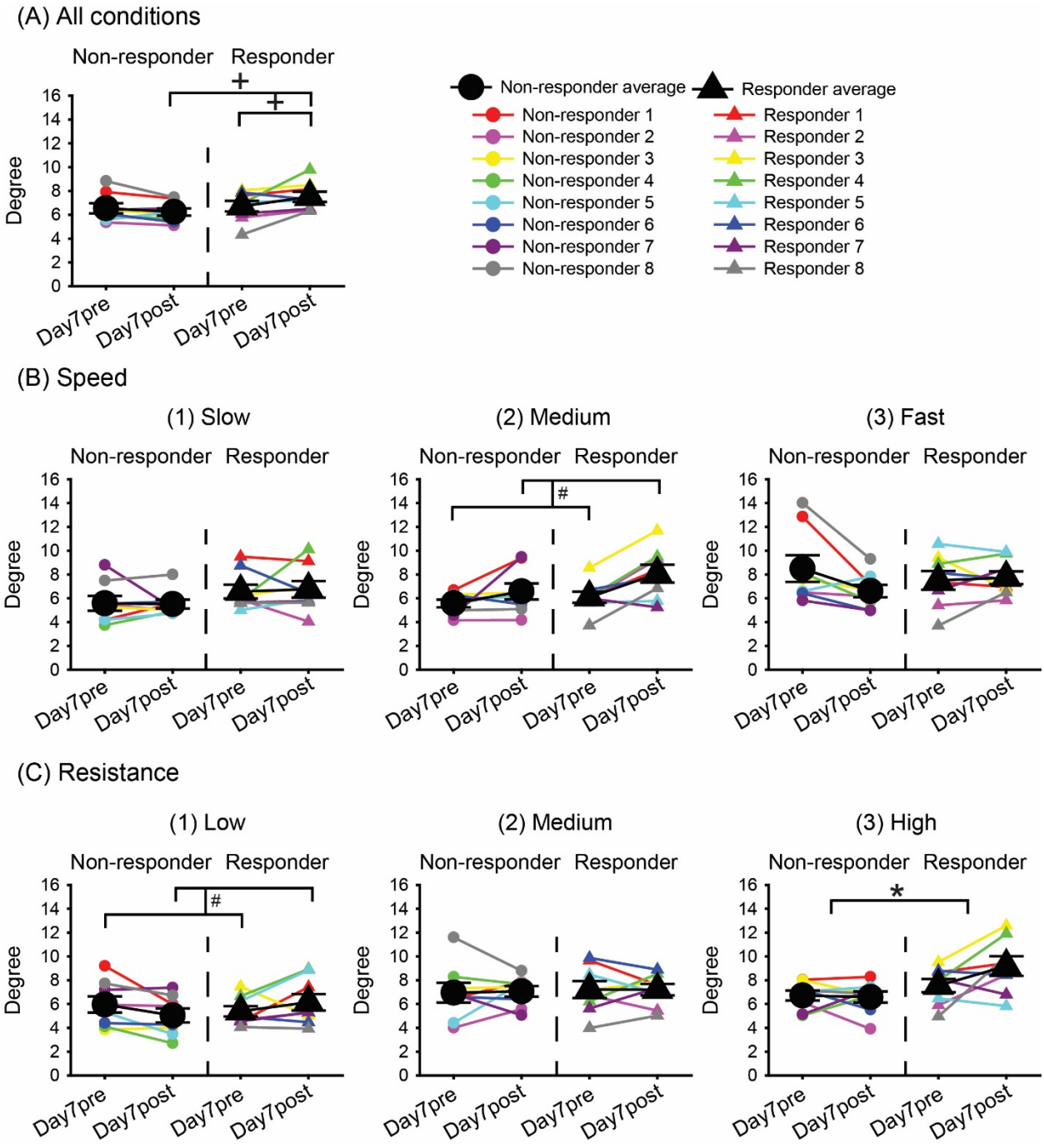

Figure 4.4 Effect of PAS on Absolute Error in Unexpected Events

Absolute errors during the whole flexion phase of unexpected events in the non-responders and responders. (A) The average of 9 conditions. (B) Conditions with Slow, Medium, and Fast speeds. (C) Conditions with Low, Medium, and High resistance levels. For group data (black circles and triangles): Value = mean ± standard error. +: P<0.05 in the post-hoc testing for the TIME x GROUP interaction. #: P<0.05 in the post-hoc testing for TIME. *: P<0.05 in the post-hoc testing for GROUP.

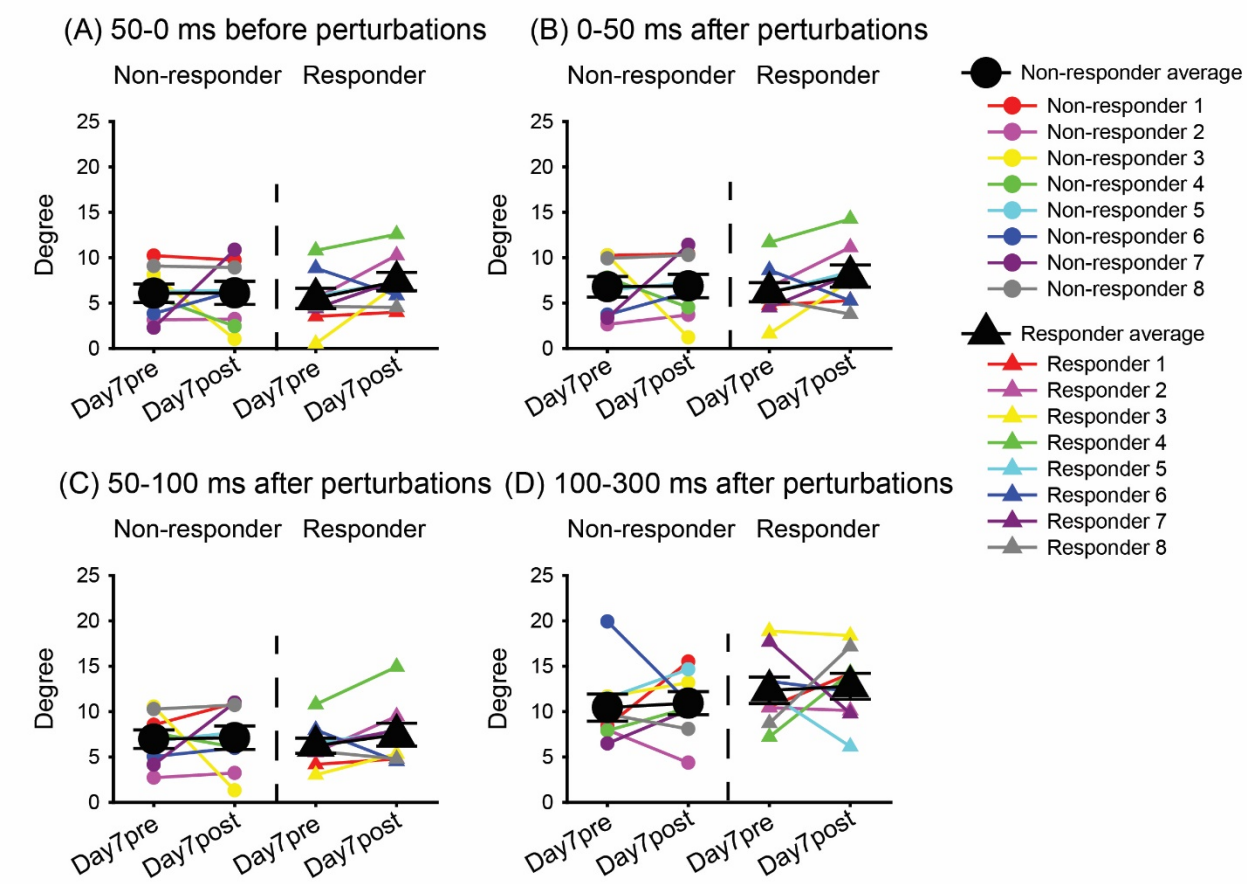

Figure 4.5 Effect of PAS on Absolute Error in the Condition with High Resistance Level

Absolute errors (A) from 50 ms before perturbations to the start of the perturbations, (B) at 0-50 ms after perturbations, (C) at 50-100 ms after perturbations, and (D) at 100-300 ms after perturbations. For group data (black circles and triangles): Value = mean ± standard error.

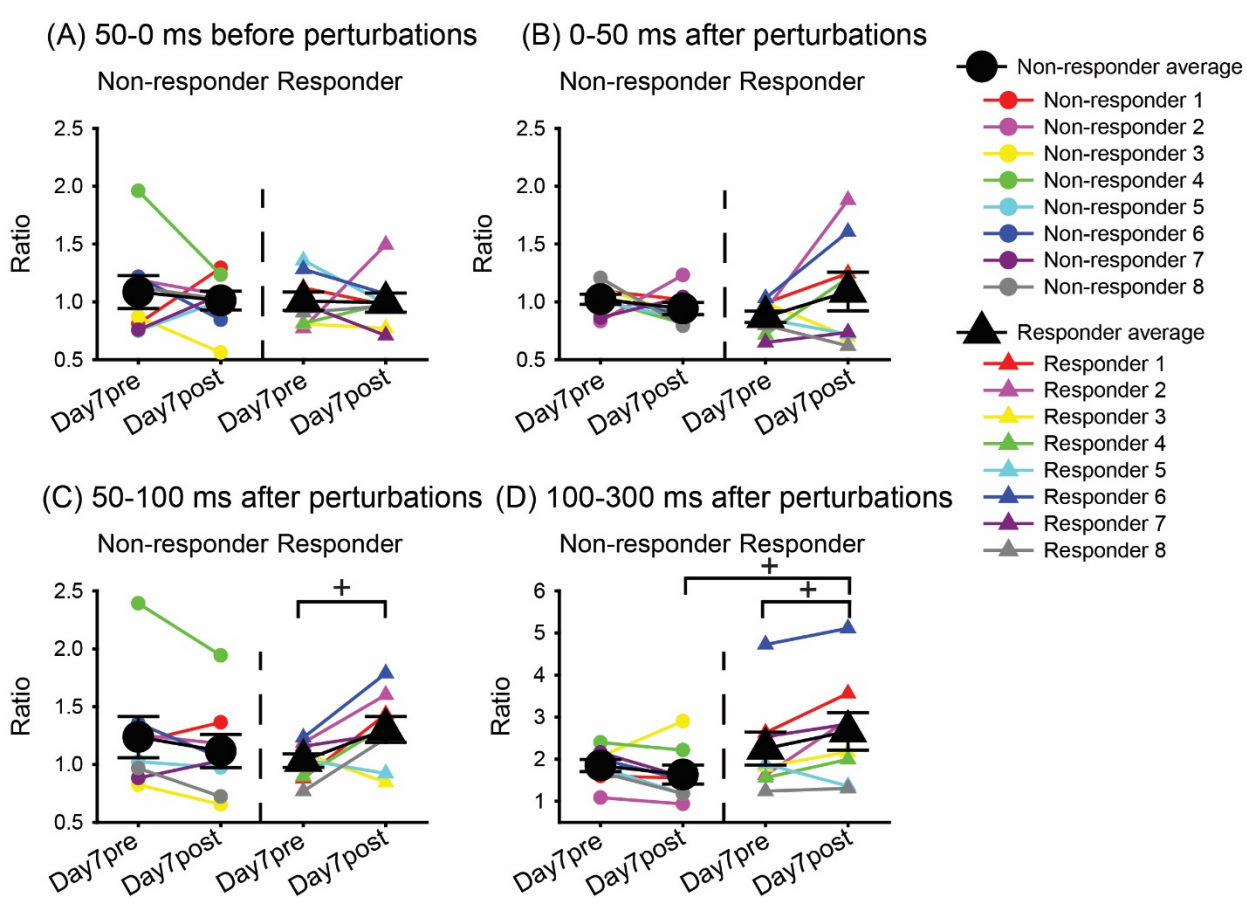

Figure 4.6 Effect of PAS on ECR Activation in the Condition with High Resistance Level

Normalized ECR (unexpected/expected) (A) from 50 ms before perturbations to the start of the perturbations, (B) at 0-50 ms after perturbations, (C) at 50-100 ms after perturbations, and (D) at 100-300 ms after perturbations. For group data (black circles and triangles): Value = mean ± standard error. +: P<0.05 in the post-hoc testing for the TIME x GROUP interaction.

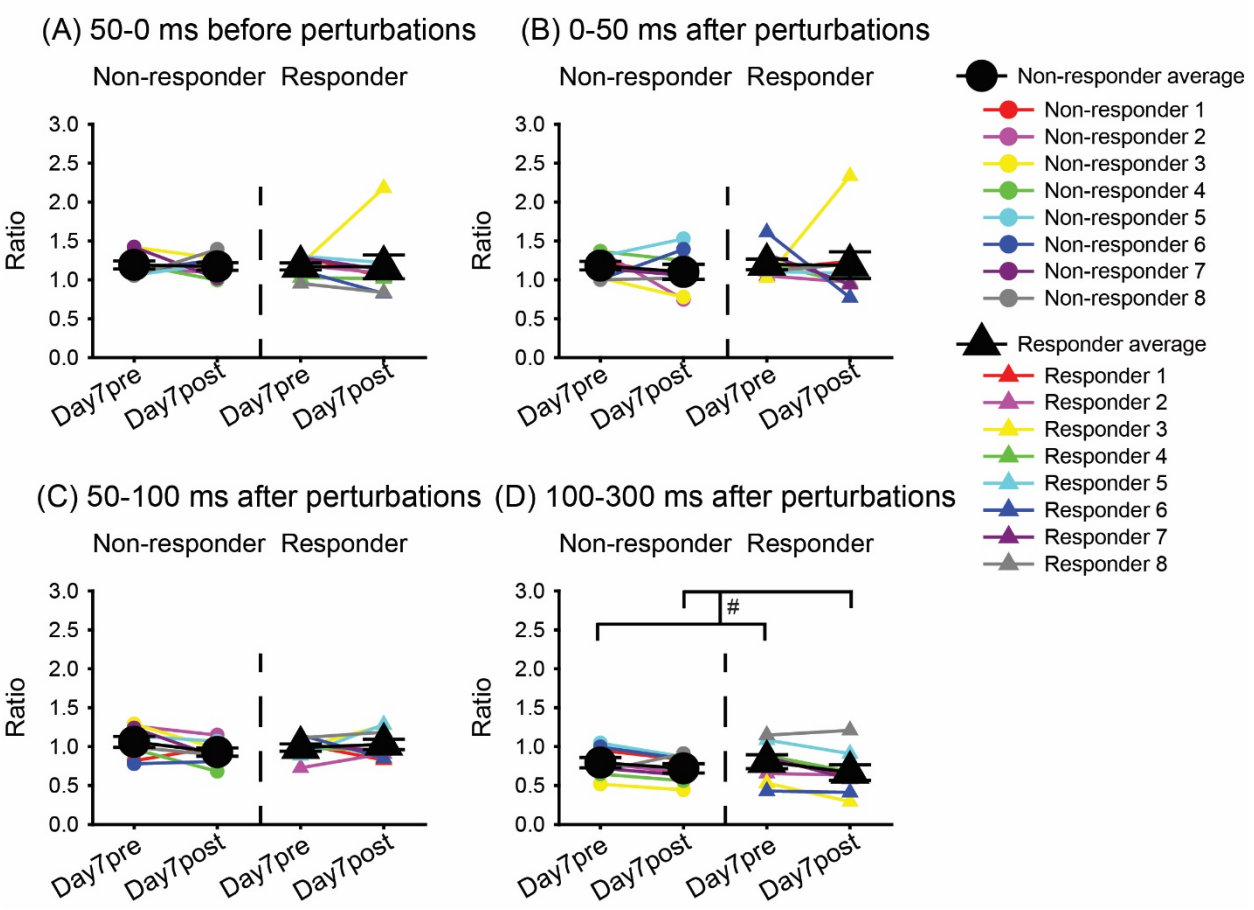

Figure 4.7 Effect of PAS on FCR Activation in the Condition with High Resistance Level

Normalized FCR (unexpected/expected) (A) from 50 ms before perturbations to the start of the perturbations, (B) at 0-50 ms after perturbations, (C) at 50-100 ms after perturbations, and (D) at 100-300 ms after perturbations. For group data (black circles and triangles): Value = mean ± standard error. #: P<0.05 in the post-hoc testing for TIME.

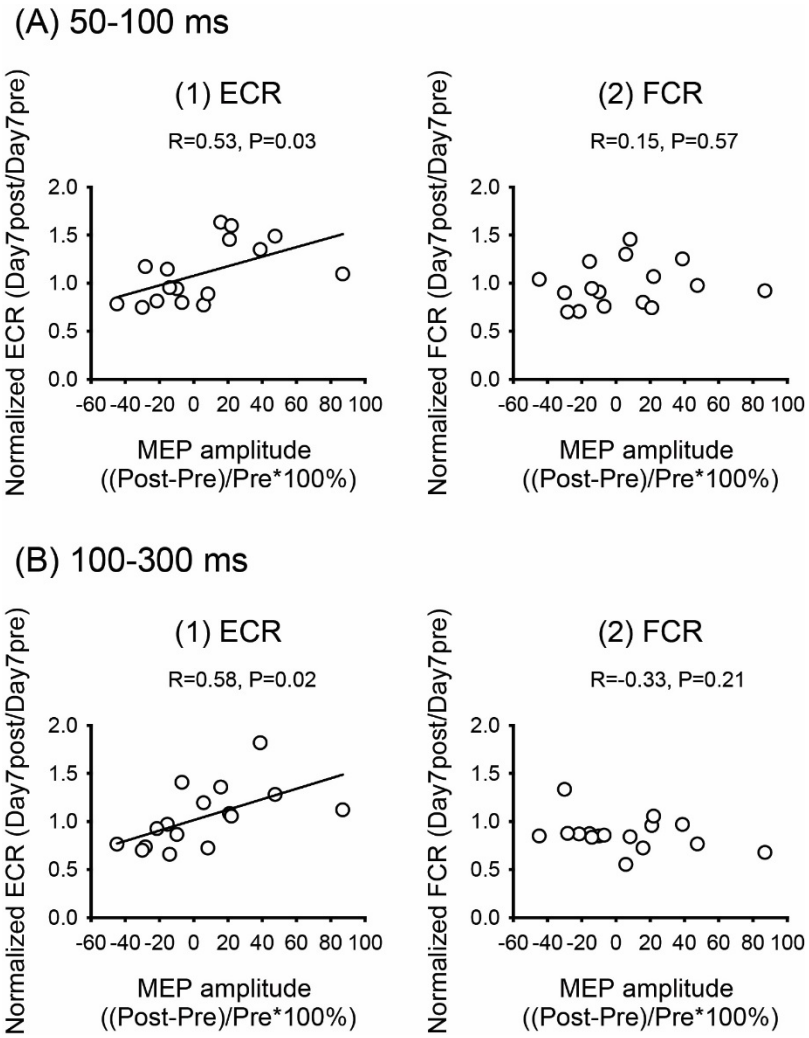

Figure 4.8 Correlation between MEP and EMG changes in the Condition with High Resistance Level

Correlation between the change of MEP amplitude at the PAS intensity and EMG (ECR, FCR) changes at (A) 50-100 ms and (B) 100-300 ms after perturbations from Day7pre to Day7post.

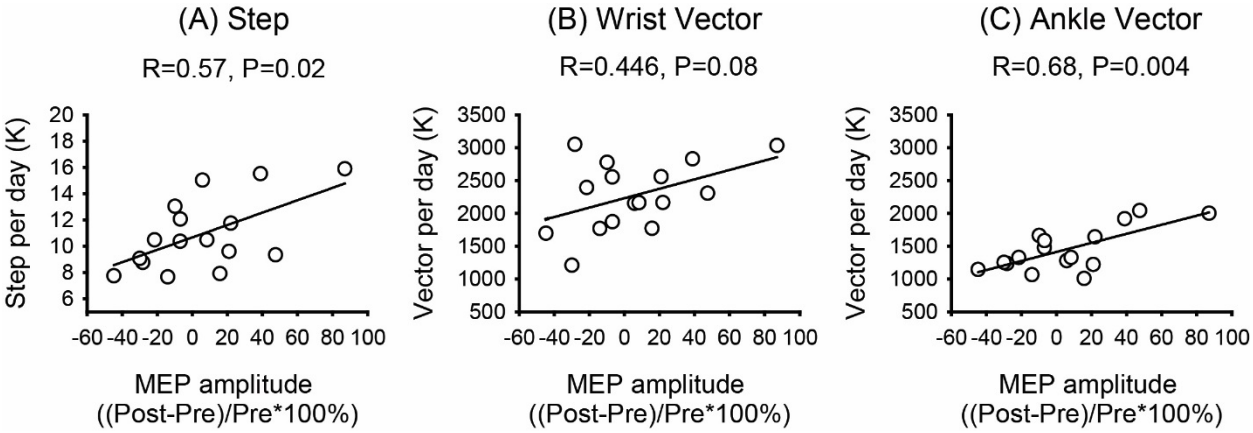

Figure 4.9 Correlation between MEP change and Physical Activity

Correlation between the change of MEP amplitude at the PAS intensity and physical activity variables. (A) Step count. (B) Wrist vector amplitude. (C). Ankle vector amplitude.

CHAPTER 5 CONCLUSIONS

Neuromuscular control of the wrist is crucial to gaining functional control of the hand. The ability to respond to expected and unexpected events during motor skill acquisition and retention is critical in daily life and this ability is influenced by several moderators. The purpose of this research was to investigate the impact of 1) age, 2) physical activity, 3) cognitive function, and 4) the increased motor cortical excitability on motor performance and motor learning during both expected and unexpected events while performing a visual motor task of the wrist.

Chapter 2

Primary Aim 1a

To determine the effect of age on motor skill acquisition (Day1) and retention (Day3; Day7) during both expected and unexpected conditions while performing a visual motor task of the wrist (3 speeds; 3 levels of resistance).

Hypothesis 1a

We expect that the young group will show less error and will demonstrate a greater capacity to acquire (Day1) and retain skill (Day3; Day7) as compared to the older group. We also expect that elderly will have a decreased ability to learn to respond to unexpected events in a timeframe prior to volitional reaction time as compared to a younger cohort. Finally, we expect that the attenuated ability to learn to respond to unexpected events with age will be the greatest in faster movements as compared to slower movements; and greatest in high resistance as compared to low resistance.

Not supported: The older people showed more errors but did not have a decreased ability to acquire and retain skill as compared to the young people. The young and old people demonstrated similar capacity to learn to respond to unexpected events with each speed and resistance level in the trans-cortical timeframe.

Secondary Aim 1b

To explore the strategy used by the young and the old to respond to unexpected events using the extensor carpi radialis (ECR) and flexor carpi radialis (FCR) EMG, triggered at 50-100 ms, following an unexpected perturbation during a visual motor task of the wrist.

Hypothesis 1b

We expect that the older group will use both feed-forward and feedback strategies whereas the young group will use the feed-forward strategy during learning the visual motor task at the wrist.

Supported: The older group modulated FCR activations both during the period before the perturbation (feed-forward) and in the trans-cortical timeframe after the perturbation (feedback), whereas the young group modulated FCR activations during the period before the perturbation (feed-forward) during learning the visual motor unexpected task.

Chapter 3

Primary Aim 2a

To determine the effect of physical activity on motor skill acquisition (Day1) and retention (Day3; Day7) during both expected and unexpected conditions while

performing a visual motor task of the wrist (3 speeds; 3 levels of resistance) in older and younger adults.

Hypothesis 2a

We expect that the young and old adults will show less error and will demonstrate a greater capacity to acquire (Day1) and retain skill (Day3;Day7) if they have a higher overall physical activity level (10-20K steps/day vs 5-9.999K steps/day). We expect that activity level will improve the overall capacity for people, young or old, to learn to respond to unexpected events in the trans-cortical timeframe.

Not supported: Young adults with higher (10-20K steps/day) and lower (5-9.999K steps/day) physical activity level showed similar amount of errors and demonstrated similar ability to acquire and retain skill. In young adults, activity level did not improve the capacity to learn to respond to unexpected events in the transcortical timeframe. Conversely, old adults with higher (10-20K steps/day) physical activity level showed less error and demonstrated a greater capacity to acquire and retain skill than those with lower (5-9.999K steps/day) physical activity level. In old adults, activity level improved the capacity to learn to respond to unexpected events in the transcortical timeframe.

Secondary Aim 2b

To determine the effect of cognitive function on motor skill acquisition (Day1) and retention (Day3; Day7) during both expected and unexpected conditions while performing a visual motor task of the wrist in older adults.

Hypothesis 2b

We expect that the old adults with higher cognitive function will show less error and will demonstrate a greater capacity to acquire (Day1) and retain skill (Day3 and Day7) than those with lower cognitive function. We expect that old adults with higher cognitive function will demonstrate a greater capacity to learn to respond to unexpected events in the trans-cortical timeframe than those with lower cognitive function.

Not supported: Old adults with lower cognitive function showed more errors but did not have a decreased ability to acquire and retain skill as compared to those with higher cognitive function. Old adults with higher and lower cognitive function demonstrated similar capacity to learn to respond to unexpected events in the trans-cortical timeframe.

Chapter 4

Primary Aim 3a

To determine the effect of increased cortical motor excitability using paired associated stimulation (PAS) on motor skill performance (Day7) during both expected and unexpected conditions while performing a visual motor task of the wrist.

Hypothesis 3a

We expect that people who show that PAS increases cortical excitability will demonstrate improved motor performance during both expected and unexpected conditions during the visual motor task of the wrist.

Not supported: People who showed that PAS increased cortical excitability demonstrated similar performance in expected conditions but poorer performance in unexpected conditions.

Secondary Aim 3b

To determine the association between increased motor cortical excitability using PAS on the extensor carpi radialis (ECR) and the flexor carpi radialis (FCR) EMG, triggered at 50-100 ms following an unexpected perturbation.

Hypothesis 3b

We expect a positive relationship between the ECR LLR and motor evoked potentials induced by the PAS protocol. We expect that there will be no correlation between FCR LLR and motor evoked potentials induced by the PAS protocol.

Supported: ECR LLR changes were positively correlated to MEP changes induced by the PAS protocol. FCR LLR changes were not correlated to MEP changes induced by the PAS protocol.

Secondary Aim 3c

To determine the relationship between increased motor cortical excitability using PAS and physical activity level.

Hypothesis 3c

We expect that physical activity level will be associated with the level of motor cortical excitability induced.

Supported: Physical activity level was positively correlated to MEP changes induced by the PAS protocol.

Summary

Motor cortical excitability plays an important role in motor skill learning. In this manuscript we used naturally occurring events (age and physical activity) and PAS to naturally or artificially change the motor cortical excitability in order to study motor skill learning of the wrist during expected and unexpected events. The first project demonstrated that age did not lose the capacity to learn during both expected and unexpected events, probably by utilizing both feed-forward and feedback strategies. The second project demonstrated that physically active old people had better performance when exposed to an unexpected event. However, by motor practice less active old people were able to improve their motor performance and achieve a skill level similar to physically active old people. Moreover, physical activity was positively related to cognitive function. These findings support the value of an active lifestyle in old people. Finally, the last project demonstrated that increased motor cortical excitability deteriorated the motor performance during unexpected events, in the retention stage of an extensive motor learning experience. Furthermore, changes of motor cortical excitability were positively related to ECR changes, and physical activity levels. These findings provide important information regarding possible strategies used to regulate motor learning and human performance. Future studies will investigate the mechanisms by which age, physical activity and increased motor cortical excitability modulate motor function and motor learning as well as potential rehabilitation methods to enhance movement control, especially during unexpected events, in people with neuromuscular control problems.

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