Using Diffusion Tensor Imaging to Identify the White Matter Correlates of Motor Skill Learning and Visuospatial Processes in Older Adults

by

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ABSTRACT

Repetitive practice of functional movement patterns during motor rehabilitation are known to drive learning (or relearning) of novel motor skills, but the learning process is highly variable between individuals such that responsiveness to task-specific training is often patient-specific. A number of neuroimaging and neurophysiological methods have been proposed to better predict a patient's responsiveness to a given type or dose of motor therapy. However, these methods are often time- and resource-intensive, and yield results that are not readily interpretable by clinicians. In contrast, standardized visuospatial tests may offer a more feasible solution. The work presented in this dissertation demonstrate that a clinical paper-and-pencil test of visuospatial function may improve predictive models of motor skill learning in older adults and individuals with stroke pathology. To further our understanding of the neuroanatomical correlates underlying this behavioral relationship, I collected diffusion-weighted magnetic resonance images from 19 nondemented older adults to determine if diffusion characteristics of white matter tracts explain shared variance in delayed visuospatial memory test scores and motor skill learning. Consistent with previous work, results indicated that the structural integrity of regions with the bilateral anterior thalamic radiations, corticospinal tracts, and superior longitudinal fasciculi are related to delayed visuospatial memory performance and one-week skill retention. Overall, results of this dissertation suggest that incorporating a clinical paper-and-pencil test of delayed visuospatial memory may prognose motor rehabilitation outcomes and support that personalized variables should be considered in standards of care. Moreover, regions within specific white matter tracts may underlie this behavioral relationship and future work should investigate these regions as potential targets for therapeutic intervention.

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TABLE OF CONTENTS

CHAPTER Page

LIST OF TABLES

Table Page

LIST OF FIGURES

Figure Page

CHAPTER 1

INTRODUCTION

Overview

Neural injury, disease, and the degenerative effects of aging are responsible for clinically diagnosed motor impairments in millions of Americans, and motor rehabilitation is an important intervention for restoring or improving function. The capacity to learn and retain motor skills is fundamental to this process; however, aging often threatens one's motor learning (defined as the amount of motor skill learned and retained after repeated practice (Schmidt, Lee, Winstein, Wulf, & Zelaznik, 2018)), such that older adults tend to learn and adapt movements to a lesser extent than younger adults for a given amount of practice (Raz, Williamson, Gunning-Dixon, Head, & Acker, 2000; Swinnen, 1998). Nearly 50% of all physical therapy patients in the United States are aged 65 years or older (Bell, 2015), and given their advancing age, may be at risk for reduced responsiveness to motor rehabilitative strategies that are not tailored to their specific needs or profiles. Since older adults have varying motor learning capacities (Harada, Natelson Love, & Triebel, 2013; Salthouse, 1985) and will therefore respond differently to the same training regimen, the one-size-fits-all approach is a critical barrier within motor rehabilitation therapy. Without a clinical 'gold standard' to estimate one's motor learning capacity, patients who will receive little to no benefit from motor rehabilitation will continue to participate in ineffective therapies, unnecessarily burdening the U.S. healthcare system.

Experimental work in individuals with neuropathology suggest that individual characteristics (such as baseline motor function, presence of a motor evoked potential, structural integrity of specific white matter tracts, etc.) may yield an accurate prognosis one's ability to improve motor function due to biological recovery (i.e., motor performance improvement is not due to repeated practice). An example of this is the Predicting Recovery Potential algorithm, which reports 88% predictive power in predicting upper-extremity function in individuals with stroke over a 12 week recovery period (Stinear, Barber, Petoe, Anwar, & Byblow, 2012). However, this algorithm requires specialized technical equipment (i.e., a magnetic resonance imaging (MRI) machine and transcranial magnetic stimulator) and is time-intensive (i.e., an estimated minimum of four hours is needed for patient data collection and analysis), making this predictive model an infeasible option during the clinical visit. Other work has supported the role of specific white matter tracts in skill retention after training (Borich, Brown, & Boyd, 2014), but again, these methods require expensive MRI referrals for data collection and specialized training to process and interpret the data.

In contrast, cognitive testing may be a low-cost alternative that can be feasibly administered within the duration of the clinical visit. Studies have shown that older adults tend to learn motor skills at a slower rate and to a lesser extent than younger adults (Raz et al., 2000; Swinnen, 1998), and given that aging populations also experience cognitive decline (Jenkins, Myerson, Hale, & Fry, 1999; Li, Hämmerer, Müller, Hommel, & Lindenberger, 2009; Ren, Wu, Chan, & Yan, 2013; Zelinski & Burnight, 1997), where one in five older adults (age>65) have some form of cognitive impairment ("Alzheimer's

& Dementia: Mild Cognitive Impairment," 2018), poorer motor learning may, in part, be linked to the presence of cognitive impairments rather than to chronological age. Thus, the scientific premise of this dissertation is that specific cognitive impairments in aging populations may underlie reduced therapeutic responsiveness in older adults. This premise has been supported by clinical studies in neurorehabilitation, yet it is unclear which cognitive impairments are most disruptive to one's capacity for motor learning (discussed further in Chapter 2).

Results from recent experimental studies have shown that visuospatial function (or, the ability to perceive and understand spatial relationships among objects and integrate visuomotor information (Jagaroo, 2009)) may be positively related to motor learning ability, where better visuospatial function is related to better skill learning (Bo, Borza, & Seidler, 2009; Fleishman & Rich, 1963; Langan & Seidler, 2011; Mayr, 1996). It is important to note, however, that these studies implemented experimenter-derived measures of visuospatial function, which are not standardized measures of visuospatial function. In contrast, I have recently reported that a widely-used, standardized paper-and-pencil test of visuospatial function predicted the amount of motor skill older adults acquired and retained over a one-week period of no practice (Lingo VanGilder, Hengge, Duff, & Schaefer, 2018). While this suggests a standard measure of visuospatial function may predict skill learning, the visuospatial domain comprises many cognitive abilities (such as memory, attention, construction, perception, etc.), such that it remains unclear which specific test is the best predictor of skill learning. Moreover, the underlying neural mechanisms of the relationship between visuospatial function and motor learning in older adults remains unclear. Filling these knowledge gaps will advance clinical practice by identifying the best predictor of rehabilitation responsiveness and a potential neural target for therapeutic intervention.

Objectives

The long-term goal of this work is to identify clinical predictors of motor learning ability in older adults. The objectives of my dissertation were to determine 1) the neuropsychological test most predictive of motor skill learning and 2) the neural basis of this phenomenon. We have recently shown that by testing older adults' visuospatial function, we can predict their motor learning capacity, and importantly, this effect remains even when we account for participant age (Chapter 4). This suggests that regardless of age, lower visuospatial abilities are associated with less motor learning. In fact, our studies show that older adults with above-normal visuospatial scores retained up to 4 times as much skill as those with below-normal visuospatial scores, regardless of baseline upper extremity motor function, age, and other impairments in language, attention, or delayed memory. These behavioral correlations have now led to the question: What is the neural basis for the relationship between visuospatial scores and motor skill learning?

My central hypothesis was that older adults' motor learning capacity can be predicted using clinical visuospatial tests. This hypothesis results from our recently published work that indicates visuospatial function may predict motor learning capacity in adults aged 65 years and older (Lingo VanGilder et al., 2018). It is still unclear, however, *which* specific visuospatial tests are most sensitive and could therefore have the most clinical utility in identifying those at risk for reduced responsiveness to motor learning-based therapies. Moreover, preliminary neuroimaging data suggest that the integrity of the superior longitudinal fasciculus (SLF), a frontoparietal white matter tract, may explain why clinical visuospatial tests are predictive of older adults' motor skill learning. Briefly, recent work from our collaborators suggested that individuals with stroke who have better SLF integrity demonstrated greater change in motor performance during a single practice session on an upper-extremity task, as compared to those with worse SLF integrity (Regan et al., 2021). Whether the SLF was related to the amount of upper-extremity motor skill retained over a period of no training in healthy older adults remained unclear; further, this previous work evaluated only a few regions-of-interest (i.e., the SLF and corticospinal tracts), such that other white matter tracts that contribute to skill retention may have been excluded. Thus, I proposed the following objectives in nondemented adults aged 65 and older:

Identify which visuospatial tests are most predictive of one-month motor skill learning in older adults. Motor skill retention was evaluated at one month as this period of time is sufficient to demonstrate relatively permanent changes in motor performance (Schmidt et al., 2018). Although we have shown that visuospatial function is related to the amount of motor skill learned and retained over one week, I previously only used a limited number of visuospatial tests to demonstrate this. Because I proposed to administer a more comprehensive battery of visuospatial tests, I used principal component analyses to identify the latent constructs among the test battery, and regression analyses to determine which test(s) were *most* predictive of the ability to learn a new motor skill. Based on our published study (Lingo VanGilder et al., 2018), I expected visual perception would be most related to the amount of motor skill learned and retained over one month.

Identify the white matter structural correlates of motor skill learning and visuospatial function. Based on pilot data, I hypothesized that the structural integrity of the SLF would underlie variance in motor skill learning and visuospatial function, such that greater SLF structural integrity would predict a greater amount of motor skill learned and retained as well as higher visuospatial test scores. Whole-brain analysis was used to evaluate all white matter tracts involved in the behavioral relationship between motor learning and visuospatial function.

Organization of studies

One of the overarching goals of this work was to identify clinical predictors of motor rehabilitation outcomes. In Chapter 2, I review recent work that suggests cognitive impairments may impact motor relearning and propose that post-stroke motor rehabilitation therapies may benefit from formal neuropsychological testing (Lingo VanGilder, Hooyman, Peterson, & Schaefer, 2020). For example, early work suggests that in neurotypical adults, cognitive function may be predictive of responsiveness to motor rehabilitation and cognitive training may improve mobility.

If we understand the mechanism between cognition and rehabilitation outcomes, we may be able to identify a target for therapeutic intervention. Given motor rehabilitation outcomes may be dependent upon motor learning processes, my next study evaluated whether a clinical test of global cognition was related to motor learning in a convenience sample of individuals with Parkinson disease (PD). In Chapter 3, I examined if scores on the Montreal Cognitive Assessment (MoCA, a brief global cognitive screen (Nasreddine et al., 2005)) were positively related to follow-up performance after training on an upper-extremity motor task (such that individuals with better cognition were faster than those with poorer cognition); specifically, baseline task performance, age, PD severity, depressive symptoms, and medication status were unrelated to follow-up performance (Lingo VanGilder et al. *in press*). The results of this analysis align with previous work that suggest cognitive impairments may interfere with motor learning in PD and support the premise that cognitive training prior to or concurrent with motor training may enhance rehabilitative outcomes for individuals with PD. Findings also suggest that assessing cognition in individuals with PD could provide prognostic information about their responsiveness to motor rehabilitation.

One drawback of using the MoCA, however, is that this quick screen only tests global cognitive function and does not thoroughly assess the function of specific cognitive domains. Results from related work suggest that specific cognitive domains may be related to motor learning ability (e.g., visuospatial working memory (Bo & Seidler, 2009), executive processes (Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011), and attention (Song, 2019)); thus, it remained unclear if a specific cognitive domain (i.e., clinical test) is most related to skill learning. The purpose of my next study was to examine which cognitive domains would best predict the amount of retention on a motor task one week after training in older adults with no known diagnosis of amnestic Mild Cognitive Impairment ((Lingo VanGilder et al., 2018), see Chapter 4). Twenty-one adults ages 65 to 84 years old were assessed with Repeatable Battery for the Assessment of Neuropsychological Status, which assesses five cognitive domains (immediate and delayed memory, visuospatial/constructional, language, and attention). Participants also completed one training session of a functional upper extremity task and were re-tested one week later. Stepwise regression indicated that the visuospatial domain was the only significant predictor of how much skill participants retained over one week, with a visual perception subtest explaining the most variance. Results from this study support previous work reporting that older adults' capacity for motor learning can be probed with visuospatial tests.

While these findings suggested that visuospatial function may be positively related to skill learning, the visuospatial domain comprises a broad swathe of cognitive abilities (e.g., visual construction, memory, reasoning, etc.). Thus, my next study tested which clinical visuospatial test was most predictive of motor learning (Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2021), see Chapter 5). Forty-five nondemented older adults completed six standardized visuospatial tests, followed by three weekly practice sessions on a functional upper-extremity motor task. Participants were re-tested one month later on the trained task and another untrained upper-extremity motor task to evaluate the durability and generalizability of motor learning, respectively. Principal component analysis first reduced the dimensions of the visuospatial battery to two principal components for inclusion in a mixed-effects model that assessed one-month follow-up performance as a function of baseline performance and the principal components. Of the two components, only one was related to one-month follow-up. Factor loadings and post hoc analyses suggested that of the six visuospatial tests, the Rey-Osterrieth test (visual construction and memory) was related to one-month follow-up of the trained and untrained tasks. Thus, it may be plausible that older adults' long-term motor learning capacity could be evaluated using the Rey-Osterrieth test, which would be feasible to administer prior to motor rehabilitation to indicate risk of non-responsiveness to therapy.

While collectively my findings add to the body of work supporting the role of delayed visuospatial memory function in motor learning, current predictive models of motor recovery of individuals with stroke generally exclude cognitive measures, thereby overlooking the potential link between motor learning and visuospatial memory. The purpose of my next study (Chapter 6) was to validate my previous findings using Rey-Osterrieth Complex Figure Delayed Recall test scores to predict motor learning and determine if this relationship generalized to a set of individuals post-stroke (Lingo VanGilder, Hooyman, Bosch, & Schaefer, 2021). Two regression models (one including Delayed Recall scores and one without) were trained using data from non-stroke older adults. To determine the extent to which Delayed Recall test scores impacted prediction accuracy of one-month skill learning in older adults, I used leave-one-out cross-validation to evaluate the prediction error between models. To test if this predictive relationship generalized to individuals with chronic ischemic stroke, I then tested each trained model on an independent stroke dataset. Results indicated that in both stroke and older adult datasets, inclusion of Delayed Recall scores explained significantly more variance of one-month skill performance than models that included age, education, and baseline motor performance alone. This proof-of-concept suggests that the relationship between delayed visuospatial memory and one-month motor skill performance generalizes to individuals with chronic stroke and supports the idea that visuospatial testing may provide prognostic insight into clinical motor rehabilitation outcomes.

Finally, to extend the clinical implications of my work, I investigated the neural mechanism for the behavioral relationship between motor skill learning and delayed visuospatial memory test scores (Chapter 7, Lingo VanGilder et al., *in review*). Previous work implicates the role of white matter in age-related and pathological cognitive decline, and frontoparietal tracts (specifically, the superior longitudinal fasciculus) may play a prominent role in upper-extremity motor skill learning (Regan et al., 2021; Steele, Scholz, Douaud, Johansen-Berg, & Penhune, 2012); these same neural structures have been implicated in visuospatial processes (Chechlacz, Gillebert, Vangkilde, Petersen, & Humphreys, 2015). To this end, I performed whole-brain analyses to determine the white matter correlates of delayed visuospatial memory and one-week motor skill retention in nondemented older adults. I hypothesized that better frontoparietal tract integrity would be positively related to better behavioral performance. Nineteen participants (age>58) completed diffusion-weighted imaging, then a clinical test of delayed visuospatial memory and 50 training trials of an upper-extremity motor task; participants were retested on the motor task one week later. Principal component analysis was used to create a composite score for each participant's behavioral data, i.e. shared variance between visuospatial capability and motor skill retention, which was then entered into a voxel-based regression analysis. Behavioral results demonstrated that participants learned and retained their skill level after a week of no practice, and their delayed visuospatial memory score was positively related to the extent of skill retention. Consistent with previous work, neuroimaging results indicated that the structural integrity of regions within the bilateral anterior thalamic radiations (ATR), corticospinal tracts (CST), and superior longitudinal fasciculi (SLF) were related to better delayed visuospatial memory and skill retention.

Overall, this body of work suggests that: 1) the simple act of testing for specific cognitive impairments prior to therapy may identify individuals who will receive little to no benefit from the motor rehabilitation regimen, and 2) regions within specific white matter tracts (namely, bilateral CST, ATR, and the SLF) may be related to skill learning and serve as potential targets for therapeutic intervention (e.g., via neuromodulation (Reis et al., 2009), etc.).

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CHAPTER 2

POST-STROKE COGNITIVE IMPAIRMENTS AND RESPONSIVENESS TO MOTOR REHABILITATION: A REVIEW

Abstract

This review discusses the prevalence of cognitive deficits following stroke and their impact on responsiveness to therapeutic intervention within a motor learning context. Clinical and experimental studies have established that post-stroke cognitive and motor deficits may impede ambulation, augment fall risk, and influence the efficacy of interventions. Recent research suggests the presence of cognitive deficits may play a larger role in motor recovery than previously understood. Considering that cognitive impairments affect motor relearning, post-stroke motor rehabilitation therapies may benefit from formal neuropsychological testing. For example, early work suggests that in neurotypical adults, cognitive function may be predictive of responsiveness to motor rehabilitation and cognitive training may improve mobility. This sets the stage for investigations probing these topics in people post-stroke. Moreover, the neural basis for and extent to which these cognitive impairments influence functional outcome remains largely unexplored and require additional investigation.

Introduction

Motor learning is important for motor rehabilitation as individuals must often relearn lost motor skills (Bastian, 2008). Evidence from clinical and experimental studies have long supported that specific cognitive abilities such as attention, working memory, and visuospatial ability are related to both performance and performance improvement on novel motor tasks (i.e., procedural learning) (Bo & Seidler, 2009; Buszard et al., 2017; Langan & Seidler, 2011a; Lingo VanGilder, Hengge, Duff, & Schaefer, 2018; Lingo VanGilder, Walter, Hengge, & Schaefer, 2020; Raw et al., 2019; Schaefer & Duff, 2017; Schweighofer et al., 2011; Song, 2019). This may be problematic for stroke survivors, as these same domains are often impacted post-stroke. While the reporting of cognitive data has become more customary in stroke rehabilitation studies, these data are often limited to global cognitive screening tools that provide only a cursory glimpse into cognitive function and are typically used only to exclude individuals with low scores. Moreover, a comprehensive understanding of specific cognitive impairments in stroke-survivors, and the extent to which they interfere with gait rehabilitation remains a critical knowledge gap.

Here, we will briefly summarize key points regarding the effects of stroke on gait and posture, and discuss a novel, less-studied area of research regarding the extent to which cognitive impairments may interfere with motor learning and rehabilitation. We first review common neuropsychological assessments used to evaluate cognition, particularly those relevant to the stroke survivor population, and discuss the limitations and broader implications of using these assessments. We then discuss the role of stroke-specific cognitive deficits in gait and postural control, and how these deficits may influence the degree of improvement in motor behaviors. Finally, we discuss our understanding of how specific cognitive deficits may impact stroke rehabilitation and propose that thorough neuropsychological evaluation be integrated in stroke protocols (rather than serve as exclusion criteria) to clarify cognition’s role in recovery and relearning of motor skills.

What are common cognitive impairments associated with stroke and how can they be measured?

While cognitive impairment following stroke is certainly linked to the lesion location and/or size (Corbetta et al., 2015; Geschwind, 1965; Teasell, Salter, Faltynek, Cotoi, & Eskes, 2018), clinical studies indicate that impairments in attention, executive function, and processing speed are the most prevalent across stroke survivors (Nys et al., 2007; Teasell et al., 2018). In fact, stroke survivors are tenfold more likely to show impaired memory, orientation, language, and attention, compared to age-matched non-stroke individuals, with prevalence rates of 35% vs 3%, respectively (Tatemichi et al., 1994). Moreover, these impairments may be differentially impacted throughout neurological recovery. For instance, attention and executive functions may be most susceptible to impairment at the time of stroke diagnosis (Al-Qazzaz, Ali, Ahmad, Islam, & Mohamad, 2014), whereas impairments in memory, executive, and visuospatial functions are notable three months post-stroke (Jokinen et al., 2015). Interestingly, these cognitive deficits persisted in patients with no apparent physical or cognitive disability as screened by the modified Rankin Scale and Mini-Mental State Exam, respectively (Jokinen et al., 2015), suggesting subtle cognitive impairments may remain undetected if evaluated with a brief global cognitive screen.

However, there is no gold standard for the diagnosis of post-stroke cognitive impairment (i.e., vascular cognitive impairment) (Teasell et al., 2018), which obfuscates the selection of clinical cognitive screening and assessments. For instance, the Mini-Mental State Exam (MMSE) has been widely used as a clinical diagnostic tool of cognitive impairment since its advent in 1975, despite its authors' warnings it cannot be used exclusively to diagnose impairment (Folstein, Folstein, & McHugh, 1975). In fact, it excludes an evaluation of executive function and has poor sensitivity in Mild Cognitive Impairment detection (Nasreddine et al., 2005). The Montreal Cognitive Assessment (MoCA) is also commonly used, and although it provides a measure of executive function and may be more reliable in Mild Cognitive Impairment detection (Nasreddine et al., 2005), it has poor sensitivity in quantifying cognitive function of the domains it asserts to evaluate (Moafmashhadi & Koski, 2013). Moreover, these brief clinical assessments do not provide standardized age-adjusted scoring (although recent work has attempted to address this limitation (Malek-Ahmadi, O'Connor, Schofield, Coon, & Zamrini, 2018)), which may be particularly important considering the preponderance of older adults among the stroke population (K. R. Lohse, Schaefer, Raikes, Boyd, & Lang, 2016).

The National Institutes of Health (NIH) developed the National Institutes of Health Stroke Scale (Ortiz & L. Sacco, 2014), a measure of activities of consciousness, movement, sensation, response and advanced neurological function in stroke patients, and is a reliable indicator of stroke severity (Zhao et al., 2018). Similar to other global cognitive screens, however, it yields a global measure of cognition that may be insensitive to cognitive deficits (Abzhandadze, Reinholdsson, & Stibrant Sunnerhagen, 2020); it is also susceptible to floor effects and biased towards hemisphere-specific lesions (Gottesman et al., 2010). The NIH has proposed a validated, standardized, robust measure of cognitive function, namely the NIH Toolbox Cognitive Battery (Weintraub et al., 2013), however, it is only appropriate for research applications and does not serve as a substitution for formal neuropsychological or other clinical testing. At present, the battery has only been validated in healthy populations while the work to validate it in traumatic brain injury, spinal cord injury, and stroke cases remains ongoing (Babakhanyan et al., 2019; Carlozzi et al., 2017; Tulsky et al., 2017). In the interim, implementing formal neuropsychological testing, specifically tests that thoroughly evaluate cognitive domains particularly relevant to motor-related outcomes (e.g., executive function and functional outcome in stroke patients (Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011); spatial working memory with procedural learning (Bo, Borza, & Seidler, 2009)), may provide critical prognostic insight into stroke rehabilitation outcomes. This aligns with the first recommendation by the Cognition Working Group, which convened as part of the second international Stroke Recovery and Rehabilitation Roundtable (McDonald et al., 2019).

How is cognition typically measured?

Global cognition broadly encompasses six domains of cognitive function, namely attention, executive function, learning and memory, language, perceptual-motor function, and social cognition, with each domain being further stratified into subdomains

(Psychiatric Association, 2013). As previously mentioned, the MoCA and MMSE are ubiquitous clinical tools used to quickly screen global cognitive status by cursorily evaluating attention, language, memory, and visuospatial/executive functions. Although these global screening tools are relatively quick (approximately 5-10 minutes) and easy to administer, they may have differential sensitivity to premorbid abilities (Psychiatric Association, 2013), and are subject to age, educational, and cultural background confounds (Gluhm et al., 2013). More extensive neuropsychological assessments that rigorously test each cognitive domain may provide a more robust estimation of cognitive status (e.g., Repeatable Battery for Neuropsychological Status (Randolph, Tierney, Mohr, & Chase, 1998), Weschler Adult Intelligence Scale (Wechsler, 1955)), yet often require costly instrumentation, appropriate licensure, and longer administration periods (approximately 30 and 75 minutes, respectively). Unlike the MoCA or MMSE (or similar), these assessments can evaluate individual domains (e.g., complex attention, language) and subdomains (e.g., long-term memory, working memory). For instance, the Repeatable Battery for Neuropsychological Status and Weschler Adult Intelligence Scale yield an age-adjusted composite score comprising multiple index scores, each validated to represent a specific cognitive domain.

If the function of a single cognitive domain is of interest to a clinician, they can utilize individual neuropsychological tests. For example, the Rey-Osterrieth Complex Figure test is a widely used paper-and-pencil examination that measures visuospatial construction, immediate visuospatial memory, and delayed visuospatial memory (Osterrieth, 1944), and has also been shown to evaluate latent constructs such as graphomotor function, object use and planning, visuo-motor transformation, and visuospatial perception (Chen et al., 2016). One major advantage of using standardized cognitive assessments is that normative data, user qualifications, administration instructions, and results reporting are generally well-documented, and reputable online databases that thoroughly review important considerations of individual neuropsychological assessments (such as cost, test/retest reliability, cutoff scores, normative data, etc.) are publicly accessible, much like many physical/motor assessments that physical and occupational therapists use (e.g., https://www.sralab.org/rehabilitation-measures Shirley Ryan AbilityLab). We take the time to summarize this point here to encourage future studies to utilize standardized, validated assessments alongside (or in place of) novel experimental methods for characterizing cognition post-stroke.

When formal neuropsychological testing is unavailable or infeasible, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders provides a list of brief assessments that can provide insight into each subdomain. For example, to evaluate planning ability (a subdomain of executive function), the examinee should demonstrate the ability to find the exit to a maze and/or interpret a sequential picture or object arrangement (Psychiatric Association, 2013). Similarly, while researchers may develop experimental approaches that provide insight into a specific cognitive domain (e.g., (Bo et al., 2009)), one caveat to experimenter-derived assessments is that they are not necessarily standardized (i.e., generalizable), potentially complicating comparison and replication of research findings among laboratories.

We also want to briefly acknowledge a recent study demonstrated that years of education explained differences in cognitive factors such as executive function, working memory, global cognition, and alertness, as well as motor function (as measured by the modified Rankin Scale) among stroke survivors with right-hemispheric lesion (Umarova et al., 2019). Education served as a proxy for cognitive reserve (i.e., the brain's resilience to neuropathological damage (Stern, 2009)), which is a very feasible variable to collect, and may be an important factor to consider or control for in motor rehabilitation trials. Notably, results of this study also highlight the complex interplay between cognitive function, cognitive reserve, and motor behavior.

What is the effect of stroke and cognitive impairment on gait and balance?

Gait and balance deficits are common post-stroke, and directly contribute to poor mobility, increased falls, and reduced quality of life (Mackintosh, Goldie, & Hill, 2005; Schmid et al., 2013). Given that a stroke can result in heterogeneous sensory and motor deficits such as muscle weakness, altered movement selection, spasticity, and altered sensation and integration of proprioceptive signals, the severity of balance and/or gait changes observed post-stroke is largely variable among individuals. In general though, slower ambulation, increased variability (Balasubramanian, Neptune, & Kautz, 2009) and asymmetry (Lewek, Braun, Wutzke, & Giuliani, 2018), shorter, wider steps (Stimpson, Heitkamp, Embry, & Dean, 2019), and large anterior-posterior and lateral deviations of the trunk and pelvis (Van Criekinge et al., 2017), are common gait impairments following stroke. Like gait, impairments in balance are similarly broad in scope and may include asymmetric and increased sway (de Haart, Geurts, Huidekoper, Fasotti, & van Limbeek, 2004; Sackley, 1991), poor weight transfer (Rogers, Hedman, & Pai, 1993), a reduced limit of stability (Goldie, Matyas, Evans, Galea, & Bach, 1996), and poor reactive postural control (i.e., the ability to quickly react to imbalance) (de Kam, Roelofs, Bruijnes, Geurts, & Weerdesteyn, 2017). As proprioceptive capacity is typically diminished following stroke, many stroke survivors may also become more reliant on visual information to maintain appropriate postural control (de Haart et al., 2004).

Nearly 60% of older adults with cognitive impairment experience at least one fall annually (van Dijk, Meulenberg, van de Sande, & Habbema, 1993), more than twofold that of their cognitively intact peers (Burns & Kakara, 2018). Indeed, the link between cognition and motor behavior has been well-established, but to what extent do stroke-related cognitive impairments affect gait and balance? Recent research has shown that the Stroop Color Word Test (a measure of inhibition of cognitive interference) and errors made on part B of the Trail Making Test, (a measure of attention switching) predict fall risk in stroke survivors (Saverino et al., 2016). Further, when compared to age-matched controls, stroke survivors tend to have the highest levels of cognitive-motor interference (i.e., the relative cost of dual-tasking) when performing concurrent working memory and balance tasks (Bhatt, Subramaniam, & Varghese, 2016); results indicated that working memory, but not semantic memory, had a disproportionately negative impact on cognitive-motor interference for the stroke group compared to controls. Interestingly, the stroke survivors had similar cognitive scores (i.e., score >10 on the Short Orientation–Memory–Concentration Test of Cognitive Impairment (Katzman et al., 1983)) as age-matched controls, suggesting that individuals with stroke may require greater attentional resources due to their motor impairment(s), to perform as well as their age-matched counterparts. Collectively, these findings suggest that working memory, attention switching, and inhibition may be the most pertinent cognitive domains for proper balance control, and encourages future work to discern if the presence (or absence) of selective cognitive impairments following stroke may, in part, explain inter-individual differences in motor behavior (e.g., balance and gait).

Does cognitive impairment interfere with motor rehabilitation?

Given that an estimated 40-50% of all physical rehabilitation patients currently receiving care in the United States are over age 65 (Bell, 2015), it is imperative that today's therapies are effective for older adults (Gatchel, Schultz, Ray, Hanna, & Choi, 2018). And while it is difficult to precisely quantify the amount of elderly stroke survivors seeking some form of motor rehabilitation, the Centralized Open-Access Rehabilitation Database for Stroke (SCOAR) (K. R. Lohse et al., 2016) approximates that ~33% of motor rehabilitation trials for stroke have an average participant age of 65 or older. Carefully chosen rehabilitation interventions can improve mobility, even in older stroke survivors (Arienti, Lazzarini, Pollock, & Negrini, 2019; Schroder, Truijen, Van Criekinge, & Saeys, 2019). However, improvements through rehabilitation can be variable, with some survivors improving more than others or at different rates. Thus, an important factor to consider is the likelihood that many older patients may present with cognitive impairments. Rigorous assessment of cognitive capacity may improve rehabilitative care for at least two reasons. First, it can instruct the patient interaction, including the types and modalities of instructions given to the patient. Second, cognitive impairments may interfere with their ability to learn or regain motor skills after stroke or neurological injury. For example, as a proof-of-concept, we recently demonstrated that regardless of primary diagnosis, overall cognitive status affected the extent to which transitional care patients improved their gait speed over their length of stay (Schaefer, Sullivan, Peterson, & Fauth, 2020) (see also (Friedman, Baskett, & Richmond, 1989)). This trend persisted in a stroke-specific sample as well over one-year post-stroke (Sagnier et al., 2017). Importantly, this does not suggest that cognitively impaired individuals should not participate in motor therapy, given they may still experience significant gains (Poynter, Kwan, Sayer, & Vassallo, 2011; Rabadi, Rabadi, Edelstein, & Peterson, 2008; Vassallo, Poynter, Kwan, Sharma, & Allen, 2016). Instead, it advocates for 1) developing more personalized or targeted physical therapeutic interventions that are effective in cases of specific cognitive impairments post-stroke (e.g., (Fasoli & Adans-Dester, 2019)), and 2) conducting additional research that investigates which post-stroke cognitive impairments interfere most with motor skill learning. However, the field of stroke rehabilitation has only recently begun to investigate the impact of cognitive deficits on therapeutic responsiveness. In a recent meta-analysis of 215 stroke rehabilitation randomized controlled clinical trials (RCTs) from SCOAR, only 31% of the studies reported collecting cognitive information from participants (as measured by the MMSE), and nearly half of those studies used this information to *exclude* participants with cognitive deficits (K. R. Lohse et al., 2016). Overall, the use of cognitive assessments is encouraging, as it indicates that cognitive data are being collected in stroke motor rehabilitation, and could theoretically be used in retrospective, secondary analyses of clinical trial data. For example, Dobkin et al. (Dobkin et al., 2014) conducted secondary analyses on the Locomotor Experience Applied Post Stroke (LEAPS) RCT (Duncan et al., 2007) and reported that attentional switching (measured as the difference in performance on Trails A and B) at baseline predicted participants' change in gait speed in response to a partial bodyweight-supported intervention involving both treadmill and over-ground walking. These analyses occurred retrospectively, after the initial LEAPS trial reported equivalent walking outcomes for both the treadmill and over-ground walking intervention and home-based exercise (that did not emphasize walking). However, given that the most common cognitive assessments reported among stroke rehabilitation RCTs are global cognitive screens, there remains opportunity for scientific inquiry regarding which, when, and to what extent specific cognitive deficits affect the motor rehabilitative process.

Are there specific cognitive impairments that can affect motor skill learning after stroke?

As summarized above, considerable work has demonstrated the relationship between cognition and gait/posture performance. However, an equally pertinent question for clinicians is whether cognitive factors affect *responsiveness* to gait training (which is driven by mechanisms of motor learning) are less understood. Although there remains a relative dearth of information on this topic, several recent studies have begun to provide insight into this knowledge gap. For example, evidence from a small (6-study) meta-analysis by Mullick et al. (Mullick, Subramanian, & Levin, 2015) suggests that both executive function and attention deficits after stroke can affect the amount of improvement in upper-extremity motor function following training, although there may be stronger cognitive-motor learning associations when kinematic outcomes (i.e., peak velocity or endpoint accuracy (C M Cirstea, Ptito, & Levin, 2006)) are used rather than clinical scales (e.g., the Action Research Arm Test or the Wolf Motor Function Test (Boe, Pedersen, Pedersen, Nielsen, & Blicher, 2014)). Visuospatial impairments also influence how much motor task performance improves following upper extremity task-specific training (Lingo VanGilder et al., 2018; Lingo VanGilder, Walter, et al., 2020; Schaefer & Duff, 2017; P. Wang, Infurna, & Schaefer, 2019), as well as the amount and rate of functional improvement (measured with the Functional Independence Measure motor subscale) (Toglia et al., 2011). Provocative findings from Schweighofer and colleagues (S. Kim, Oh, & Schweighofer, 2015; Schweighofer et al., 2011) also implicate visuospatial working memory in upper extremity motor learning after stroke, particularly the role of contextual interference. Moreover, the post-stroke integrity of functional networks that are critical for visuospatial function (namely, frontoparietal) can predict how responsive individuals will be to upper-extremity motor training (Zhou et al., 2018).

However, it is likely that the cognitive processes underlying the learning of upper vs. lower extremity movements are distinct. For example, while evidence supports the impact of visuospatial deficits on upper-extremity motor learning, such deficits may be less detrimental to gait and/or postural training. At present, there are limited studies that investigate cognitive factors related to lower- vs. upper-extremity motor learning, and no studies that have systematically compared across cognitive domains and body effectors. Moreover, it is plausible that different types of motor learning (implicit vs. explicit, (R Schmidt, Lee, Winstein, Wulf, & Zelaznik, 2018)) are more reliant on different cognitive domains, which suggests the cognitive impairments that interfere with learning discrete upper extremity skills (like reaching, grasping, or object manipulation) would likely differ from those that interfere with adaptations of gait and posture.

McDowd et al. (McDowd, Filion, Pohl, Richards, & Stiers, 2003) suggests that attention (divided and switching, specifically) may be the most critical for determining the amount of improvement made during gait training in stroke. This has also led to an important area of research regarding whether engaging in concurrent cognitive tasks during gait training is more efficacious that simply walking (see (Silsupadol et al., 2009)). For example, gait training while solving a problem using visual feedback has been shown to improve both gait and some aspects of cognition (namely, backwards visual digit span) but not others (auditory digit span) (Chung et al., 2019). Such findings do not, however, directly address the question of whether attentional deficits post-stroke result in poorer gait relearning or slower recovery of balance, per se, although there is evidence of this in upper-extremity recovery, (see (Doron & Rand, 2019) for review). If so, therapists could use different strategies, such as internal or external loci of attention (Kal, Prosee, Winters, & van der Kamp, 2018), to enhance gait and balance rehabilitation via an attention mechanism/intervention.

Can cognitive rehabilitation improve motor rehabilitation after stroke?

The correlative relationship observed between cognition and balance suggests it is plausible that cognitive training (or, motor rehabilitation paired with a cognitive task) could enhance motor performance improvement (i.e., relearning). However, while early evidence in healthy adults suggests cognitive training may improve some aspects of mobility (Marusic, Verghese, & Mahoney, 2018), evidence in stroke survivors is limited and mixed. For example, Helm and colleagues (Helm, Pohlig, Kumar, & Reisman, 2019) had two groups of stroke survivors perform locomotor training with either constant or variable practice structure, where variable practice requires greater attentional demands compared to constant practice; results indicated there was no difference in performance or retention of the locomotor task between either group. Whereas, Liu and colleagues (Liu, Yang, Tsai, & Wang, 2017) evaluated if various dual-task training (i.e., motor-motor: tray-carrying and walking, or cognitive-motor: serial subtraction and walking) would affect different gait parameters in individuals with stroke; results indicated that each dual-task had differential effects on stride length and dual-task cost, suggesting that specific dual-task training may address selective cognitive deficits. At present, no studies have reported the effect of specialized training to target select cognitive deficits and its subsequent effect on gait in a neuropathological population (i.e., stroke). Future work is necessary to better understand if cognitive training impacts motor performance and learning.

Conclusions

Cognition is important for motor rehabilitation, particularly domains shown to underlie procedural learning such as attention, working memory, visuospatial abilities. Global cognitive testing is insensitive to subtle deficits in cognition and may only narrowly establish if an individual is cognitively intact. Neuropsychological tests that thoroughly evaluate the function of select cognitive domains may provide critical prognostic insight into rehabilitation outcomes. For example, recent work suggests that visuospatial deficits are associated with poorer upper-extremity motor recovery. Further, other studies have linked stroke-specific cognitive impairments not only with altered gait and balance performance, but with the degree to which patients improve gait with training as well. Stroke-related research studies should consider incorporating comprehensive neuropsychological testing to further our understanding of cognition's role in recovery and relearning of motor skills.

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CHAPTER 3

RELATING GLOBAL COGNITION WITH UPPER-EXTREMITY MOTOR SKILL RETENTION IN INDIVIDUALS WITH MILD-TO-MODERATE PARKISON DISEASE

Abstract

Cognition has been linked to rehabilitation outcomes in stroke populations, but this remains unexplored in individuals with Parkinson disease (PD). The purpose of this secondary data analysis from a recent clinical trial (NCT02600858) was to determine if global cognition was related to skill performance after motor training in individuals with PD. Twenty-three participants with idiopathic PD completed three days of training on an upper-extremity task. For the purposes of the original clinical trial, participants trained either “on” or “off” their dopamine replacement medication. Baseline, training, and 48-hour retention data have been previously published. Global cognition was evaluated using the Montreal Cognitive Assessment (MoCA). Linear regression examined whether MoCA score predicted longer-term retention at nine-day follow-up; baseline motor task performance, age, PD severity, depressive symptoms, and group (medication “on”/“off”) were included as covariates. Baseline and follow-up motor task performance were assessed for all participants while “on” their medication. MoCA score was positively related to follow-up motor task performance, such that individuals with better cognition were faster than those with poorer cognition. Baseline task performance, age, PD severity, depressive symptoms, and medication status were unrelated to follow-up performance. Results of this secondary analysis align with previous work that suggest

cognitive impairment may interfere with motor learning in PD and support the premise that cognitive training prior to or concurrent with motor training may enhance rehabilitative outcomes for individuals with PD. Findings also suggest that assessing cognition in individuals with PD could provide prognostic information about their responsiveness to motor rehabilitation.

Introduction

Despite clear evidence of deficits in upper extremity motor control and dexterity in Parkinson disease (PD) (Ingvarsson, Gordon, & Forssberg, 1997; Nowak & Hermsdörfer, 2006) that meaningfully impact on one's activities of daily living (Raggi et al., 2011), most rehabilitation research and clinical practice for PD focuses on gait and balance problems. When prescribed, however, motor rehabilitation can improve upper extremity movement patterns and physical function (Nackaerts et al., 2013; Vanbellingen et al., 2017), depending on one's ability to learn and retain novel motor skills. While individuals with PD may benefit from physical rehabilitation, they demonstrate slower learning rates (Nieuwboer, Rochester, Müncks, & Swinnen, 2009) and learn to a lesser extent (Felix et al., 2012) than individuals without PD, yet longer-term skill retention remains unclear (Mak, Wong-Yu, Shen, & Chung, 2017). In light of this, some people with PD show marked gains following therapeutic intervention, while others do not (e.g.(Vanbellingen et al., 2017), see also (Robinson, Dennett, & Snowdon, 2019)). The ability to predict therapeutic responsiveness could help therapists streamline and personalize treatments. However, most predictive tools or models of post-intervention motor outcomes are time- and cost-intensive (e.g., annual clinical measures (Salmanpour et al., 2020), neuroimaging (Leung et al., 2018), etc.).

In contrast, cognitive assessment may be a feasible, brief, and relatively inexpensive tool for gaining insight to an individual's motor learning capacity (see (Lingo VanGilder, Hooyman, Peterson, & Schaefer, 2020)). Global cognitive status has been shown to predict gains in walking speed following standard-of-care physical therapy independent of primary diagnosis (Friedman et al., 1989; Schaefer, Sullivan, et al., 2020), but the relationship between global cognitive measures and clinical upper-extremity outcomes in PD has not been explored. Empirically, visuospatial function has been linked with upper limb motor learning in both younger (Bo & Seidler, 2009; Jeunet, Jahanpour, & Lotte, 2016; Jeunet, Kaoua, Subramanian, Hachet, & Lotte, 2015; Langan & Seidler, 2011a) and older adults (Bo et al., 2009; Chan, Wu, Liang, & Yan, 2015; Lingo VanGilder et al., 2018; Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2020; Lingo VanGilder, Walter, et al., 2020) without PD, and since visuospatial deficits can occur with PD (Cummings, 1988; Mata et al., 2016; Sahakian et al., 1988), this may help explain why people with PD tend to learn motor skills slower and to a lesser extent than those without PD. However, the extent to which cognitive impairment (global or specific) interferes with upper extremity motor learning in individuals with PD remains unknown.

In a recent randomized clinical trial in individuals with mild-to-moderate PD (clinicaltrial.gov registration number NCT02600858) (Paul et al., 2020), motor practice while "on" dopamine replacement medication (i.e., levodopa) improved 48-hour retention of a functional upper extremity motor task compared to practice "off" dopamine replacement medication. The purpose of the present study was to perform secondary analyses of these data to evaluate whether cognition was related to skill learning in the upper extremity. Based on previous findings, it was hypothesized that cognitive functioning would be related to longer-term retention of an upper extremity motor task, where better cognition would be associated with more skill retention.

Methods

Participants

Twenty-three adults aged ≥ 50 years old with a confirmed diagnosis of PD were included in this secondary analysis of data from a previously published randomized clinical trial (clinicaltrials.gov registration number NCT02600858) (Paul et al., 2020). Exclusion criteria included prior surgical treatment of PD (e.g., deep brain stimulation), dementia (Montreal Cognitive Assessment (Nasreddine et al., 2005) (MoCA) < 18) (Hoops et al., 2009), and the presence of concomitant neurological conditions. Included participants must have been taking dopamine replacement medications. The clinical trial protocol required half the participants (n=12) to complete upper extremity motor training while continuing to take their prescribed dose of levodopa medication; the other half (n=11) skipped their first dose of medication each day of motor training such that they were “off” medication following overnight withdrawal. These participants took their remaining daily doses after they completed the motor training each morning. Details regarding dopamine medication and other participant characteristics have been previously reported (Paul et al., 2020).

Global cognition was measured using the MoCA, a brief cognitive screening tool in which scores range from zero to 30; a score of 26 (or higher) is considered to be normal cognitive functioning, as defined by the publisher (Nasreddine et al., 2005). To evaluate upper extremity dexterity, participants completed the Nine-hole peg test (Earhart et al., 2011) (a timed clinical measure of dexterity) and a timed experimental task that simulates buttoning a shirt unimanually (Lingo VanGilder, Walter, et al., 2020; Schaefer, 2015; Walter, Hengge, Lindauer, & Schaefer, 2019); for both these tasks faster trial times indicate better performance. Participants were also tested by a trained examiner with the motor subsection of the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) (total range of scores = 0-152) (Goetz et al., 2008). To evaluate depressive symptoms, participants completed the Geriatric Depression Scale (GDS) Short Form (Yesavage & Sheikh, 1986), a self-report rating tool consisting of 15 items and a score of four or lower is considered normal. Participants self-reported hand dominance. All participant characteristic data, including MoCA score, were collected in a baseline visit while the participants were "on" their prescribed dose of dopamine replacement medication, regardless of which group they were randomized to ("on" vs. "off" medication).

Upper extremity motor training

As described previously (Paul et al., 2020), the motor training protocol required participants to complete a familiarization trial, then 50 training trials each day for three consecutive days. More details regarding the motor task are provided below. Participants were then re-tested two and nine days later. Two-day follow-up was the stated primary outcome of this clinical trial and was therefore reported previously; thus, only the longer-term nine-day follow-up was included in this analysis.

The motor task used in this study was designed to mimic an activity of daily living (i.e., feeding (Katz, Downs, Cash, & Grotz, 1970)). This task has been validated against subjective and objective measures of daily functioning in a cognitively impaired sample (Schaefer, Hooyman, & Duff, 2020). The experimental apparatus was comprised of three ‘target’ cups placed 16 cm from a center ‘home’ cup at 45, 90, and 135 degrees (Fig. 3.1). Participants were asked to use a plastic spoon held in their nondominant hand to collect two raw kidney beans from the home cup and transport them to one of the three target cups. The nondominant hand was used to ensure the task was not overlearned and to avoid potential confounds of a ceiling effect (Suchy, Kraybill, & Franchow, 2011). Participants were instructed to move first to the target cup ipsilateral to the nondominant hand, then to the middle cup, then to the contralateral cup, repeating this pattern four more times. Thus, each trial consisted of 15 reaches. The primary measure of performance was *trial time*, which began when the participant picked up the spoon and ended when they completed all reaching movements and placed the spoon back onto the table; thus, lower trial times indicated better performance. Dropping beans, transporting an incorrect amount, or moving to the wrong target were counted as errors, and the participant could not continue until the error was corrected, therefore errors contributed to longer trial times. Participants were not provided with performance feedback but could explore different movement strategies to optimize performance (i.e., discovery learning (Orrell, Eves, & Masters, 2006)). As noted previously, each training session consisted of 50 trials (i.e., 750 reaches per session), and participants completed three training sessions over 3 days (1/day), totaling 2,250 reaches. This dose of training was selected based on previous feasibility and efficacy studies in other clinical and healthy populations (Schaefer, Dibble, & Duff, 2015; Schaefer, Patterson, & Lang, 2013).

Figure 3.1. Participants used their nondominant hand to complete a reaching task that simulates feeding oneself; participants use a spoon to select only two beans from the center ‘home’ cup and deposit them into target cups. One trial consisted of 15 repetitions (i.e., five arcs to each of the three target cups). This figure was adapted from “Dexterity and Reaching Motor Tasks” by MRL Laboratory is licensed under CC BY 2.0.

Statistical analysis

JMP Pro 14.0 (SAS Institute Inc., Cary NC) was used for all statistical analyses. To examine whether global cognition was related to the amount of learned motor skill, MoCA scores were included in a multiple linear regression model as a predictor of nine-day follow-up performance (α=0.05), along with baseline motor performance, age, MDS-UPDRS Motor subsection score, and GDS as covariates. The MDS-UPDRS Motor subsection score and GDS were included to control for severity of PD motor signs and depressive symptoms, respectively. Baseline motor performance was measured as the first trial of the first motor training session. Although we did not have a specific hypothesis regarding the effect of dopamine replacement medication on learning, we also included the variable of group ("on" vs. "off" medication) as a covariate to control for any confounds of dopamine replacement medication status on the primary outcome.

Results

Mean and standard deviation values for participant characteristics are provided in Table 3.1. As shown in Table 3.1, the average MoCA score was greater than 26, suggesting that the sample overall was predominantly cognitively intact; however, these scores ranged between 23 to 30, indicating some variable cognition within the sample. Participants demonstrated mild PD symptoms and disease severity (median Hoehn and Yahr stage = 2). Using their nondominant hand, participants completed the Nine-hole peg test and experimental dexterity task in 26.01 ± 3.97 and 102.81 ± 53.81 seconds (mean±SD), respectively. Results for the Nine-hole peg test were consistent with previously reported values in PD (Earhart et al., 2011). In addition, participants were bradykinetic, taking twice as long to complete the dexterity task as healthy older adults from previously reported data (Walter et al., 2019).

Table 3.1. Sample (n=23) characteristics.

Characteristic	Mean (±SD)	Range (Minimum-Maximum)	Std. Error	95% Confidence interval
Age (years)	71.07 (±6.88)	50.5-80.3	1.43	68.09-74.05
Education (years)	16.30 (±2.51)	12-20	0.52	15.22-17.39
GDS (0-10)^	2.76 (±3.1)	0-10	0.55	0.09-0.39
MDS-UPDRS-3 (0-152)^	30.53 (±8.84)	13-55	1.8	26.79-34.34
MoCA	26.35 (±2.04)	23-30	0.40	25.61-27.25
9 HPT-ND (seconds)^	26.01 (±3.97)	3.97	0.83	24.29-27.72
UE Dexterity Task (seconds)^	102.81 (±54.37)	54.37	11.33	79.30-126.32
Reaching task Baseline (seconds)^	64.1 (±9.4)	46.72-84.91	1.97	60.24-67.96
Reaching task 9-day Follow-up (seconds)^	55.0 (±11.8)	36.38-77.62	2.46	50.18-59.82

Abbreviations:
SD = Standard deviation
GDS = Geriatric Depression Scale
H&Y = Hoehn and Yahr
MoCA = Montreal Cognitive Assessment
MDS-UPDRS-3 = Movement Disorder Society – Unified Parkinson Disease Rating Scale Motor Portion (assessed "on" medication)
9 HPT-ND = Nine Hole Peg Test Non-Dominant Hand (prior to intervention)
UE Dexterity Task = Upper Extremity Dexterity task (nondominant hand)
^Higher scores indicate worse performance

Overall, nine-day follow-up performance on the motor task was significantly faster (better) than that of baseline (one-sample t(43)=-3.13; p=0.0016), as shown in Figure 3.2. This indicates an overall effect of motor learning in this sample. Linear regression model results indicated that only MoCA score predicted nine-day follow-up performance (β=-2.76; 95% CI [-5.11, -0.39], p=0.0248), such that higher MoCA scores were associated with faster (better) trial times nine days post-training. Participant age (β=-0.18; 95% CI [-0.89, 0.52], p=0.59), severity of PD motor signs (β=0.26; 95% CI [-0.34 0.86], p=0.37), GDS (β=0.71; 95% CI [-0.73 2.15], p=0.31) and medication status group (β=2.83; 95% CI [-2.02, 7.68], p=0.23) were not significantly related to follow-up motor performance.

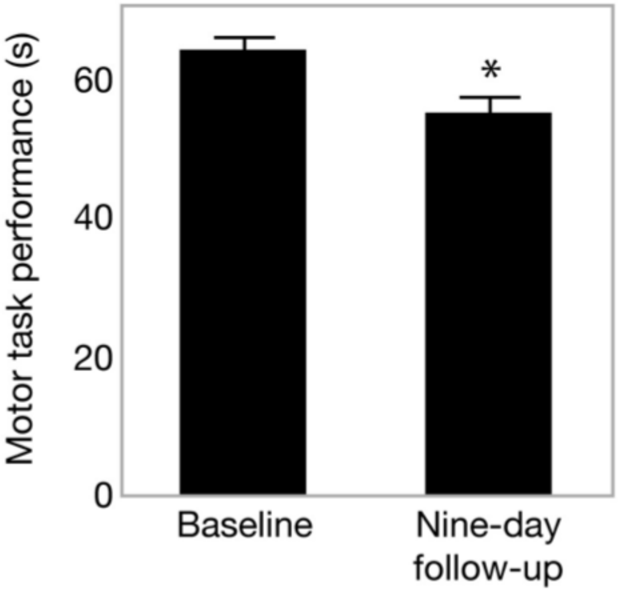

Figure 3.2. Participant motor task performance for the baseline and nine-day follow-up trials. On average, participants demonstrated significantly faster trial times (in seconds) on the follow-up trials, indicating the motor task was learned and retained over a period of nine days. * indicates p=0.0016.

Discussion

The purpose of this secondary analysis was to determine whether cognition was related to upper extremity motor skill learning in individuals with PD. Results indicated that MoCA score predicted follow-up performance of a functional upper extremity motor task nine days after the last practice session, more so than baseline performance and age (regardless of "on"/"off" medication groups). These findings align with previous work that suggest cognitive testing can be used to predict rehabilitative outcomes (Saverino et al., 2016; Toglia et al., 2011) and support that global cognition may be a useful tool to predict motor learning in clinical populations (Abzhandadze, Rafsten, Lundgren Nilsson, Palstam, & Sunnerhagen, 2019; Lim et al., 2018; Zietemann et al., 2018). Although the MoCA was used to evaluate global cognition in this study, there is existing evidence that supports the value of assessing specific cognitive domains as predictors of motor learning (Lingo VanGilder, Walter, et al., 2020; Toglia et al., 2011; P. Wang et al., 2019).

Given the high prevalence of cognitive impairment among people with PD (Aarsland, Brønnick, Larsen, Tysnes, & Alves, 2009; Hely, Reid, Adena, Halliday, & Morris, 2008), global and specific cognitive measures should be considered to identify which and to what extent various cognitive impairments interfere with learning different skills. In terms of global cognitive measures, the MoCA may be particularly sensitive to screening cognitive deficits associated with PD compared to other global cognitive measures of cognition (i.e., the Mini Mental State Examination) (Hoops et al., 2009). We acknowledge, however, that the MoCA is a rapid cognitive screen that does not thoroughly assess the function of each cognitive domain nor is it validated to measure the function of individual cognitive domains. Thus, a more comprehensive battery of cognitive assessments would determine whether specific cognitive domains (or specific cognitive deficits) more closely predict motor skill retention in this population. For example, visuospatial deficits may interfere with upper-extremity learning (Lingo VanGilder et al., 2018; Lingo VanGilder, Hooyman, Bosch, & Schaefer, 2021; Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2021; Lingo VanGilder, Walter, et al., 2020; Mullick et al., 2015), while fluid cognitive skills or executive function may interfere with lower-extremity learning (French, Cohen, Pohlig, & Reisman, 2021). While these previous studies have not focused on motor learning in PD specifically, the effects of particular cognitive deficits may not be PD-specific but instead generalize to a number of older patient populations who may be receiving motor rehabilitation for a number of reasons (e.g., stroke, joint replacement). As such, the effect of cognitive impairment on motor rehabilitation is gaining interest, within and beyond PD (Lingo VanGilder, Hooyman, et al., 2020; McDonald et al., 2019). Future studies in motor learning should consider a more comprehensive battery of cognitive tests, especially those that evaluate visuospatial and executive abilities, in order to identify evidence-based targets for adjuvant cognitive or non-invasive brain stimulation therapies (e.g., (Begemann, Brand, Ćurčić-Blake, Aleman, & Sommer, 2020; Jiang, Guo, McClure, He, & Mu, 2020; King et al., 2020)) that can be administered prior to or during motor therapy for people with PD.

In addition to providing empirical evidence as the groundwork for developing effective adjuvant therapies for motor rehabilitation in PD, this study offers clinicians a low-cost, easy-to-implement way to predict how responsive a person with PD might be to motor therapy. It is well-established that responsiveness to motor rehabilitation is often highly variable between PD patients (see 95% CIs in (Robinson et al., 2019)). As such, the findings from the current study suggest that the MoCA may be a quick (~5-10 minute) and simple way to predict how responsive a patient might be to upper-extremity training. This would inform therapists in how to streamline and tailor their treatments, and better allocate their time to activities that they know their patients will benefit from. Predictors of therapeutic responsiveness are already being explored outside PD using neuroimaging (Burke Quinlan et al., 2015; Carmen M Cirstea et al., 2018; Tozlu et al., 2020), neurophysiology (Burke Quinlan et al., 2015; Smith, Byblow, Barber, & Stinear, 2017; C. M. Stinear et al., 2017), or genotyping (E.-J. Kim et al., 2016; Pham et al., 2021; Qin et al., 2014), but these investigational methods are time- and cost-intensive, making them unfeasible for an allied health setting and out-of-pocket therapy.

In the published clinical trial (Paul et al., 2020), there was a modest effect of medication status during training (i.e., “on”/“off” medication while practicing the task) between baseline and 48-hour follow-up task performance, such that the “on” medication group performed significantly better at this short-term retention period than did the “off” medication group. These results were interpreted to indicate that being “on” dopamine replacement medications may facilitate short term retention of motor skill. However, this secondary analysis indicates that the group difference was no longer present by the ninth day of retention, likely due to the modest effect of medication status on training previously observed. Instead, global cognition (which was not originally considered in the parent clinical trial) was a significant predictor of motor task performance well after training had been completed (nine days later), regardless of whether training had occurred “on” or “off” dopamine replacement medication. Indeed, dopamine replacement may be insufficient to offset the breadth of cognitive deficits associated with PD (Kulisevsky et al., 2000), and the short duration in which participants in the “off” group were withdrawn from their medication for training (relative to the nine-day duration of retention) may explain the lack of effect of group in this secondary analysis.

A limitation of this study is that the participants in the “off” medication group resumed their regularly prescribed dopamine replacement therapy after training each day and throughout the nine-day retention period; thus, we are unable to discern potential effects of medication adherence or withdrawal on motor skill consolidation and retention. It is well-established that consolidation and retention are critical periods for motor learning, as well as acquisition (Kantak & Winstein, 2012). We also acknowledge that this study was not designed to directly test if global cognition would be predictive of clinical rehabilitation motor outcomes in individuals with PD, since it only evaluated the amount of skill retained over a period of nine days. Performance of the functional upper extremity task used in this study has, however, been associated with subjective and objective measures of daily functioning in individuals diagnosed with Mild Cognitive Impairment (Schaefer, Hooyman, et al., 2020), suggesting that the benefits of training may generalize to activities of daily living.

Conclusions

Our study supports the premise that cognitive impairments interfere with motor skill learning in PD, and provides the proof-of-principle that 1) cognitive screening may be a viable solution for personalizing motor rehabilitation for people with PD and 2) cognitive therapy and/or brain stimulation prior to, or concurrent with, motor training could enhance functional outcomes. Future mechanistic work should systematically test which specific cognitive domains are most relevant for different types of motor learning in PD to help inform targeted adjuvant cognitive or neurostimulation therapies that can enhance motor rehabilitation. For example, fluid cognition training may enhance gait adaptation, or non-invasive stimulation of parietal cortex could enhance functional upper-extremity training via visuospatial processes.

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CHAPTER 4

VISUOSPATIAL FUNCTION PREDICTS ONE-WEEK MOTOR SKILL RETENTION IN COGNITIVELY INTACT OLDER ADULTS

Abstract

Motor learning declines with aging, such that older adults retain less motor skill after practice compared to younger adults. However, it remains unclear if these motor learning declines are related to normal cognitive changes associated with aging. The purpose of this study was to examine which cognitive domains would best predict the amount of retention on a motor task one week after training in cognitively intact older adults. Twenty-one adults ages 65 to 84 years old were assessed with Repeatable Battery for the Assessment of Neuropsychological Status, which assesses five cognitive domains (immediate and delayed memory, visuospatial/constructional, language, and attention). Participants also completed one training session of a functional upper extremity task, and were re-tested one week later. Stepwise regression indicated that the visuospatial domain was the only significant predictor of how much skill participants retained over one week, with a visual perception subtest explaining the most variance. Results from this study support previous work reporting that older adults' capacity for motor learning can be probed with visuospatial tests. These tests may capture the structural or functional health of neural networks critical for skill learning within the aging brain, and provide valuable clinical insight about an individual's unique rehabilitation potential.

Introduction

Motor learning declines with aging, such that older adults tend to learn slower and retain less motor skill than younger adults (Raz, Williamson, Gunning-Dixon, Head, & Acker, 2000; Swinnen, 1998). Given the concurrence of aging and cognitive decline (Harada, Natelson Love, & Triebel, 2013; Jenkins, Myerson, Hale, & Fry, 1999; Li, Hämmerer, Müller, Hommel, & Lindenberger, 2009; Ren, Wu, Chan, & Yan, 2013; Zelinski & Burnight, 1997), poorer motor learning may, in part, be linked to normal cognitive changes associated with aging. Studies have shown that memory deficits do not account for motor learning deficits (Eslinger & Damasio, 1986; Gobel et al., 2013; Yan & Dick, 2006; Yan & Zhou, 2009), suggesting that other cognitive impairments may instead interfere with learning a motor skill. For example, in patients ages 65 to 89 diagnosed with amnestic Mild Cognitive Impairment (MCI), their ability to retain a motor skill may be related to visuospatial impairments rather than their memory impairments (Schaefer & Duff, 2017). Visuospatial function has been implicated in other types of motor learning, such as motor sequence learning (Bo et al., 2009; Bo & Seidler, 2009), but has not been explored extensively in the learning and retention of more complex motor skills in older adults. To further investigate this relationship in the absence of delayed memory impairments, cognitively intact older adults were assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). They then completed a single training session of a functional upper extremity motor task, and were re-tested on the motor task one week later. The purpose of this study was to test whether older adults' motor skill retention was related to their visuospatial function, above and beyond other cognitive domains (namely immediate and delayed memory, language, and attention). We hypothesized that better visuospatial scores would be associated with more retention of a complex motor skill from baseline to follow-up one week later.

Materials and methods

Participants

All human research procedures were approved by the university's Institutional Review Board, in accordance with the Helsinki Declaration. Twenty-one cognitively intact adults ages 65 to 84 years old (six males, 15 females) provided informed consent prior to enrollment. Participants were excluded if any cognitive test score fell 1.5 or more standard deviations below normative data, which is a common demarcation point for Mild Cognitive Impairment (Albert et al., 2011; Petersen et al., 2013). Participants were also excluded if they had any significant functional limitations, as evidenced by the Katz Inventory of Activity of Daily Living (Katz et al., 1970). Exclusion criteria also included any self-reported history of major neurological (e.g., stroke, seizure, traumatic brain injury) or psychiatric (e.g., bipolar disorder, schizophrenia) disorder. To ensure intact sensorimotor function, grip strength (Jamar hand dynamometer, (Mathiowetz et al., 1985)), functional dexterity (Grooved Pegboard, Lafayette Instruments, (Merker &

Podell, 2011)), and tactile sensation (Semmes-Weinstein monofilaments, (Bell-Krotoski, Fess, Figarola, & Hiltz, 1995)) of both hands were collected.

Neuropsychological Battery

All participants completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which is a widely-used cognitive measure that uses 12 standardized tests to assess the following five cognitive domains as Indexes: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. A Total Scale score indicating global cognition is also determined by combining all five Index scores. Index and Total scores are age-corrected standard scores (Mean=100, SD=15) based on normative information from the assessment manual; higher values indicate better function. Generally speaking, age-corrected scores represent the participant's cognitive status relative to normative values from age-matched peers, such that the age-corrected score may be interpreted as the participant's cognitive status regardless of age.

Motor skill retention

Motor skill retention was measured using a functional upper extremity motor task. This task was selected for several reasons. First, it is feasible and efficacious for motor skill learning in older adults (Schaefer et al., 2015, 2013) and is retainable (Glenberg, Goldberg, & Zhu, 2011; Schaefer & Duff, 2015). Second, it has concurrent and ecological validity with more traditional point-to-point reaching paradigms (Schaefer & Hengge, 2016) that have been used previously to quantify retention in more cognitively impaired patients (Yan & Dick, 2006) yet is more functional (Jebsen, Taylor, Trieschmann, Trotter, & Howard, 1969).

One trial of the motor task was comprised of five repetitions to three different targets placed radially around a constant start location at a distance of 16 cm; thus, each trial equaled 15 repetitions total. The start location and all three targets were cups that were 9.5 cm in diameter and 5.8 cm in height. Additional details regarding the motor task apparatus, including a schematic, have been published elsewhere (Schaefer and Hengge 2016; Schaefer and Duff 2017). For each repetition, participants used their nondominant hand to acquire and transport two raw kidney beans from the start location to one of the three target locations with a conventional plastic spoon. At the start of each trial, participants' first repetition was out to the ipsilateral target cup, next to the center target cup, and then to the contralateral cup, relative to the hand used. As noted above, participants repeated this sequence five times to complete the trial. Each trial began when the participants picked up the spoon and ended when the last two beans were dropped into the final cup, yielding a 'trial time' as the measure of performance. Time continued to elapse in the event of any unsuccessful attempts (e.g., only one bean was placed into a target cup per repetition); thus, any errors that would have occurred during a trial would be accounted for in the performance measure. Performing this task with the nondominant hand is by design to ensure that the task is under-practiced and not over-learned, particularly in older adults (Schaefer, 2015), such that participants have the potential to show practice effects without confounds of floor or ceiling effects (Suchy et al., 2011). A modified Edinburgh Handedness Inventory was used to identify participants' nondominant hand (Oldfield, 1971).

As stated above, the measure of performance was the time taken to complete the 15 repetitions (i.e., “trial time”), with lower times indicating better performance, as participants were instructed to “move as quickly yet as accurately as possible.” All trials were timed to the nearest 100th of a second via stopwatch. Participants were allowed to adopt any movement pattern during training (i.e., they were not required to move or hold the spoon in any specified manner with their nondominant hand), thereby facilitating exploratory attempts for discovering successful movement strategies for completing the task (see (Taubert et al., 2010)).

After one familiarization trial to ensure participants understood the task, they completed 10 trials. The first trial served as their baseline performance. This small dose of training has also been shown to be sufficient for determining longer-term acquisition and retention (Park & Schweighofer, 2017; Schaefer & Duff, 2015). Participants were then re-tested a week later on a follow-up trial to identify any measurable skill retention across one week.

Motor skill retention was selected as the primary dependent variable because motor learning is defined as a relatively permanent change in motor performance due to practice or experience (Richard Schmidt & Lee, 2005). The amount of motor skill retention at one week relative to baseline performance was calculated using Equation 1.

$$\text{retention (\%)} = [(\text{baseline} - \text{follow-up}) / \text{baseline}] \times 100 \quad \text{(Eq. 1)}$$

Positive values indicated more retention. Normalizing the amount of retention accounts for variations in movement speed or performance on the motor task between participants at baseline (Temprado et al., 2013).

Statistical analysis

The SAS® statistical software program JMP Pro 12 (SAS Institute Inc., Cary, NC) was used for all statistical analysis ($\alpha = 0.05$). The five individual RBANS Index scores were entered into a backwards elimination stepwise regression analysis as predictors of skill retention. This procedure was the same as in the previous study (Schaefer & Duff, 2017) in order to test the replicability of these findings, in spite of many known limitations of retrospective stepwise regression in general (e.g. (Copas, 1983)). Only Index scores that significantly contributed to the variance in the retention variable were included in the final model based on the criterion-to-remove of $p > 0.05$. Multiple linear regression was then used to determine which subtests within any significant Indexes were most related to retention. Subtests were entered in a single step into this regression model. Any correlation coefficients (r) greater than 0.59 were considered to be strong, between 0.30 and 0.59 were moderate, and below 0.30 were weak effect sizes (Cohen, 1988).

Results

Group means (and standard deviations) and medians of age, education, grip strength, functional dexterity, and all RBANS Index scores are provided in Table 4.1. All participants had intact tactile sensation in the tested hand (finest Semmes-Weinstein monofilament detectable, *n*=20; next finest detectable, *n*=1). RBANS Total and Index scores had mean and median values ~100, including that of the Delayed Memory Index, which supports that this sample was largely cognitively intact.

Table 4.1. Participant characteristics.

	Mean ± SD	Median	Range
Age (years)	72.9 ± 6.4	74	65-84
Education (years)	15.9 ± 3.2	16	12-24
Grip strength (kg)	22.7 ± 5.5	23.3	12.3-31.6
Grooved Pegboard (s)	101.4 ± 28.5	92.6	71.3-192.7
RBANS[a] Total Scale Index	105.1 ± 10.8	102	92-136
Immediate Memory Index	103.1 ± 12.0	103	85-129
Visuospatial/Constructional Index	104.4 ± 12.1	105	84-126
Language Index	100.9 ± 11.1	101	82-125
Attention Index	110.5 ± 11.7	115	85-128
Delayed Memory Index	100.1 ± 12.4	101	81-129

N = 21; 6 males and 15 females.

[a] RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. Scores are age-corrected, with a normal score of 100 and with a standard deviation of 15.

Performance on the motor task across all trials is shown in Figure 4.1. Overall, participants improved rapidly from a mean±SD baseline performance of 62.83±12.32 s to 56.71±7.34 s on trial 10, consistent with previous findings (Schaefer et al., 2015). To test the extent to which participants retained these improvements one week later, performance at the one-week follow-up was compared to that at baseline (Eq. 1). On average, retention was 3.22±20.10% (95% CI [-5.93, 12.36]). While statistically this suggests that the group, on average, showed little retention, the large standard deviation indicated a wide range of retention scores. That is, some participants retained little to no skill, while others did. Bivariate analysis indicated that the amount of retention was unrelated to Total Scale Index scores (*p*=0.11), consistent with previous findings (Schaefer & Duff, 2017). However, backwards elimination indicated that the Visuospatial/Constructional Index (standardized β=0.56; *r*=0.56; adjusted *r*=0.52; *p*=0.009) was the only significant cognitive predictor of skill retention, such that higher (better) scores were associated with more retention (Fig. 4.2A). The strength of this effect was considered moderate. All other Index scores for Immediate Memory, Language, Attention, and Delayed Memory were eliminated in the stepwise regression due to lack of significance (all *p*>0.05).

Figure 4.1. Mean ± standard error task performance for baseline, the nine remaining trials, and one-week follow-up trial. Task performance on the y-axis was measured as the time taken to complete each trial, yielding 'trial time' in which lower trial times indicate better task performance.

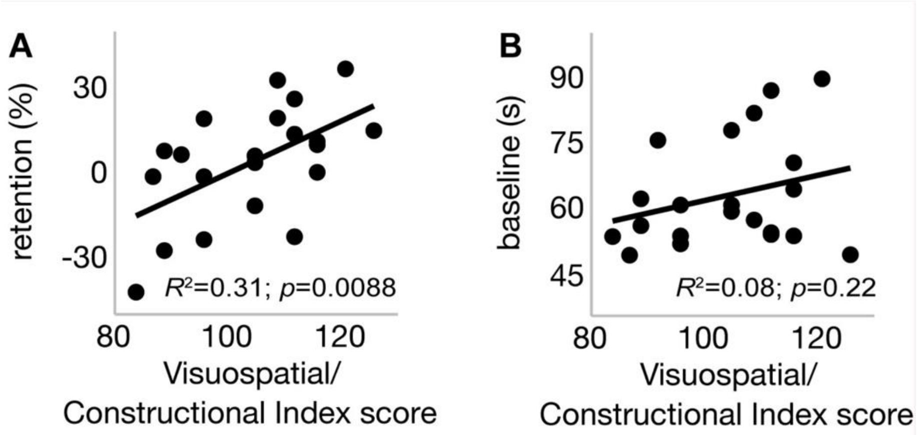

Figure 4.2. Motor task results were plotted for all participants as a function of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Visuospatial/Constructional Index score. Greater values along the x-axis indicate better Index scores. R^2 and p values are reported for reference. A: Motor skill retention at one week is expressed as a percentage of baseline performance (Eq. 1), with more positive values indicating better retention. B: Baseline performance during the initial testing session is expressed in seconds, with lower times indicating better performance.

Because the motor task itself is visuospatial in nature, requiring visually guided reaching to different spatial locations, it is plausible that participants' baseline performance could also be related to their visuospatial ability. However, baseline performance was not significantly related to Visuospatial/Constructional Index score (p=0.22) (Fig. 4.2B). This indicates that participants' change in motor skill due to practice/experience, rather than their ability to navigate the task at baseline, is dependent on visuospatial abilities.

Further analysis determined which of the two visuospatial tests that comprise the Visuospatial/Constructional Index explained the most variance in one-week skill retention: Figure Copy and Line Orientation. This was done to explore which aspects of the visuospatial domain may be most predictive of retention among older adults. Multiple linear regression showed that only the Line Orientation subtest was related to skill retention (standardized β=0.52; *p*=0.02); Figure Copy was not significant (*p*=0.15). (Assumptions of no multicollinearity were verified; VIF=1.07). For example, a participant with raw score of 20 (age-adjusted *z*-score=1.29) on Line Orientation improved by over 30% on the motor task from baseline to follow-up, whereas a participant with a raw score of 10 (*z*-score=-2.28) was ~42% worse at follow-up compared to baseline, even though both participants had similar Figure Copy scores (17 (*z*-score=-0.44) and 18 (*z*-score=-0.059), respectively).

Discussion

This study addressed whether declines in motor skill learning with aging may, in part, be linked to age-related cognitive decline. Consistent with previous findings (Schaefer & Duff, 2017), motor skill retention was related to visuospatial function in cognitively intact older adults. Furthermore, underlying motor learning processes may be more dependent on visual perception (measured with Line Orientation) than visuoconstruction (measured with Figure Copy) (Spencer et al., 2013), although other visuospatial functions not tested by the RBANS may also be important (Bo et al., 2009; Bo & Seidler, 2009; Schweighofer et al., 2011).

Although the motor task in this study requires participants to use vision to guide their movements to different spatial locations, it is important to note that the RBANS

Visuospatial/Constructional Index was unrelated to participants' baseline performance on this motor task, consistent with previous studies (Langlois et al., 2015; Schaefer & Duff, 2017). Because the Visuospatial/Constructional Index correlated with changes in performance (Fig. 4.2A) rather than to baseline performance (Fig. 4.2B), it suggests that visuospatial tests may probe the neural processes that are more crucial to *learning* a movement over time than to the execution of a given movement at a given time. In other studies, visuospatial assessments have been shown to predict rates and amounts of motor skill learning (Bo & Seidler, 2009; Hammer, Sloutsky, & Grill-Spector, 2015; Jeunet et al., 2016, 2015) even in older adults (Baweja et al., 2015; Bo et al., 2009; Schaffert, Lee, Neill, & Bo, 2017). For example, surgeons with higher visuospatial ability typically learn complex surgical procedures better and faster than those with lower visuospatial abilities (Brandt & Davies, 2006; Duce et al., 2016; Roach, Mistry, & Wilson, 2014). As in our study, visuospatial abilities also tend to not predict baseline surgical performance prior to any training (Langlois et al., 2015), but rather predict the amount of skill learning (Maan, Maan, Darzi, & Aggarwal, 2012). One explanation is that visuospatial tests may probe the structural or functional health of critical neural structures or networks for skill learning. Structural neuroimaging has shown that various types of motor learning (e.g., sequencing, force production) is correlated with the integrity of white matter tracts connecting premotor and visual cortex and the cerebellum (Steele, Scholz, Douaud, Johansen-Berg, & Penhune, 2012; Tomassini et al., 2011; Zhang et al., 2016) as well as with the functional activation of premotor, prefrontal, and parietal regions (Tomassini et al., 2011). Moreover, these frontal-parietal networks may be lateralized for processing information and/or learning different aspects of a complex motor skill (i.e., reaching, grasping, and object manipulation) (Budisavljevic et al., 2017; Mutha, Haaland, & Sainburg, n.d.). Future work is needed to determine how older adults' scores on specific visuospatial tests are related to specific white or gray matter regions of interests that have been implicated in motor learning (Biesbroek et al., 2014a).

The Visuospatial/Constructional Index of the RBANS is comprised of only two visuospatial tests: Line Orientation (for visual perception) and Complex Figure Copy (for visuoconstruction). In reality, however, the visuospatial domain is much broader. Future research is therefore needed to determine which tests of visuospatial function, such as visual perception, visual attention, visuospatial working memory, and/or visuoconstruction, are most predictive of older adults' capacity for learning and retaining a motor skill. Determining older adults' capacity for motor learning has significant rehabilitative implications, given that motor learning (also referred to as *procedural* or *errorless* learning (Lekeu, Wojtasik, Van der Linden, & Salmon, 2002; White, Ford, Brown, Peel, & Triebel, 2014)), has great rehabilitative potential for older adults with dementia (Van Halteren-Van Tilborg, Scherder, & Hulstijn, 2007; Voigt-Radloff et al., 2017; Vreese, Neri, Fioravanti, Belloi, & Zanetti, 2001; Zanetti et al., 2001). This and previous studies suggest, however, that the effectiveness of such approaches may depend on the extent of any concomitant visuospatial impairment in these patients (Mayr, 1996), and that visuospatial testing may be a viable way for clinicians to screen for 'non-responders' who may not benefit as much from more procedurally-based therapies.

The purpose of this study was to test whether older adults' motor skill retention was related to their visuospatial function, above and beyond other cognitive domains (namely immediate and delayed memory, language, and attention). Stepwise regression indicated that visuospatial function was the only significant predictor of how much skill participants retained over one week, with a visual perception subtest explaining the most variance. These findings suggest these visuospatial tests may capture the structural or functional health of neural networks critical for skill learning within the aging brain, and provide valuable clinical insight about cognitive therapeutic responsiveness.

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CHAPTER 5

EVIDENCE FOR ASSOCIATIONS BETWEEN REY-OSTERRIETH COMPLEX FIGURE TEST AND MOTOR SKILL LEARNING IN OLDER ADULTS

Abstract

Age-related declines in motor learning may be related to poor visuospatial function. Thus, visuospatial testing could evaluate older adults' potential for motor learning, which has implications for geriatric motor rehabilitation. To this end, the purpose of this study was to identify which visuospatial test is most predictive of motor learning within older adults. Forty-five nondemented older adults completed six standardized visuospatial tests, followed by three weekly practice sessions on a functional upper-extremity motor task. Participants were re-tested one month later on the trained task and another untrained upper-extremity motor task to evaluate the durability and generalizability of motor learning, respectively. Principal component analysis first reduced the dimensions of the visuospatial battery to two principal components for inclusion in a mixed-effects model that assessed one-month follow-up performance as a function of baseline performance and the principal components. Of the two components, only one was related to one-month follow-up. Factor loadings and post hoc analyses suggested that of the six visuospatial tests, the Rey-Osterrieth test (visual construction and memory) was related to one-month follow-up of the trained and untrained tasks. Thus, it may be plausible that older adults' long-term motor learning capacity could be evaluated using the Rey-Osterrieth test, which would be feasible to administer prior to motor rehabilitation to indicate risk of non-responsiveness to therapy.

Introduction

Motor rehabilitation is important for recovering lost motor function and/or training compensatory movement patterns central for activities of daily life in older adults. While the capacity to learn and generalize motor skills is fundamental to the rehabilitative process, numerous studies indicate that aging negatively impacts motor learning (i.e., the extent to which one can achieve relatively-permanent changes in motor performance due to repeated practice (R Schmidt et al., 2018)), such that older adults tend to learn and adapt movements to a reduced degree compared to younger adults (Raz et al., 2000; Swinnen, 1998; Verwey, 2010; S. Wang, Williams, & Wilmut, 2020). As such, age-related motor learning impairments may in part explain why older adults tend to be less responsive to motor therapy than younger adults (e.g., Dobkin et al., 2014; Schaefer et al., 2019)).

A recent series of experimental studies has suggested that age-related declines in motor learning may be specifically associated with reduced visuospatial function (Bo et al., 2009; Langan & Seidler, 2011b; Lingo VanGilder et al., 2018; Lingo VanGilder, Walter, et al., 2020); *visuospatial function* refers to the broad spatial processes related to high-level vision and visuomotor integration (Jagaroo, 2009) and tends to decline across the adult lifespan sooner and at a faster rate than other cognitive functions (Murre, Janssen, Rouw, & Meeter, 2013). Indeed, visuospatial cognition may uniquely predict motor learning capacity in older adults, while the function of other cognitive domains (such as attention, language, delayed memory, etc.) may not (Lingo VanGilder et al., 2018; Toglia et al., 2011). These findings build on the seminal work of Fleishman and

Rich (1963), who observed that early improvements in visuomotor task performance were dependent upon visuospatial perception in a group of healthy young adult men. More recent work highlights the role of visuospatial working memory in other forms of motor learning, namely sensorimotor adaptation (Langan & Seidler, 2011b; Schaffert et al., 2017) and sequence learning (Bo et al., 2009; Bo & Seidler, 2009; Chan et al., 2015) in both young and older adults. Similarly, an analogous effect was reported from experimental paradigms that trained participants on select activities of daily living, whereby the extent of improvement was related to visuospatial/executive function in stroke survivors (Toglia et al., 2011) and nondemented older adults (Lingo VanGilder, Walter, et al., 2020).

It is therefore plausible that visuospatial assessment may have clinical utility in predicting responsiveness to motor therapy as a means to identify individuals who may need more intensive or targeted training. However, despite the myriad of studies supporting the functional relationship between visuospatial and motor cognition in nondemented older adults (e.g., Emerson et al., 2012), there are critical knowledge gaps that preclude translation of these findings into the clinic. First, as the visuospatial domain broadly encompasses cognitive constructs of perception, memory, construction, among others (described in further detail below), and previous work evaluated disparate aspects of visuospatial cognition, it remains unclear which visuospatial construct(s) is most predictive of motor learning ability in older adults. Second, previous studies relating visuospatial function and motor learning have not consistently used any given visuospatial test, and some have even used unvalidated, experimenter-derived assessments to attempt to quantify visuospatial function. No studies to date have directly compared how well one visuospatial assessment predicts motor learning relative to another. Thus, there is currently no clear candidate for which visuospatial assessment is best, despite there being a number of standardized visuospatial tests that may have merit (see Methods). Third, these previous studies measured motor learning as the amount of motor skill learned within one session or retained over consolidation periods of one day to one week, yet longer retention periods are arguably required based on the widely-accepted definition of ‘motor learning’ involving relatively permanent changes in performance due to experience (R Schmidt et al., 2018).

To address these knowledge gaps, the present study was designed to directly compare multiple standardized visuospatial tests to identify which was most predictive of long-term motor learning outcomes (i.e., skill retention and transfer) in older adults. Based on previous work from our lab and others’, we hypothesized that tests of visuospatial perception and memory would positively correlate with the degree of motor skill retained and transferred one month after extensive training. Results of this study will advance our understanding of human visuospatial and motor cognition, and serve as a critical step towards implementing prognostic testing within motor therapy treatment plans.

Methods

All experimental procedures were approved by Arizona State University's Institutional Review Board prior to participant recruitment. Forty-five right-handed participants (28 female) with a mean ± SD age of 70.38 ± 6.77 years with no self-reported history of a previous neurological or psychiatric condition (e.g., stroke, schizophrenia, etc.) participated in this study. Participants completed a series of examinations to characterize sensory, motor, daily functioning, and mood. Bilateral index finger sensation (Semmes-Weinstein monofilaments) and grip strength (hand dynamometer (Jamar Technologies)) were collected. Participant handedness was determined using the Edinburgh Questionnaire (Oldfield, 1971) and dexterity of the nondominant hand was evaluated using the Grooved Pegboard test. Participants also completed the Activities of Daily Living Questionnaire (Katz et al., 1970) to determine the extent they independently perform six common physical activities, where the best possible score of 6 indicates full independence. The Geriatric Depression Scale was completed at the beginning of each visit. Participant data for all measures are provided in Table 5.1.

Visuospatial and other cognitive tests

To address the purpose of this study, participants completed a battery of standardized cognitive tests that were selected in consultation with a licensed clinical neuropsychologist (KD) prior to the start of the study to comprehensively evaluate the visuospatial domain:

- Benton Judgment of Line Orientation (Benton et al., 1994): This 30-item test is a validated measure of visual perception in which the participant selects a line from an array that is in the same direction and orientation as a test line shown above the array. Correct answers receive points, with a maximum score of 30 points.
- Rey-Osterrieth Complex Figure Test (Osterrieth, 1944): The Copy trial is a validated measure of visual construction in which the participant copies a complex image on a separate sheet of paper as accurately as possible. Correctly copied elements receive points, with a maximum score of 36 points. The Delayed Recall trial is a validated measure of visual memory in which the participant is asked to redraw the complex image from memory after a 30-minute period. Scores are identical to the Copy trial.
- Visual Puzzles: This 26-item validated measure of visual reasoning within the Wechsler Adult Intelligence Scale, 4th edition (Wechsler, 1955) (WAIS-IV). The participant is presented with a visual design and asked to select three constituent images that, when combined, reconstruct the completed puzzle. Correct answers receive points, with a maximum score of 26 points.
- Matrix Reasoning: This 26-item validated measure of visual abstract-problem solving, also within the WAIS-IV. The participant is presented with an incomplete visual matrix or series of images and is asked to select an option that completes the matrix or series. Correct answers receive points, with a maximum score of 26 points.

- Block Design: This 14-item validated measure of visual (object) construction, also within the WAIS-IV. The participant is presented with a 2- or 3-dimensional model and is asked to use red-and-white blocks to recreate the model. Correct recreations receive points, with bonus points for quicker responses, with a maximum score of 48 points.

It is noted that these tests may also require executive function or multiple aspects of visuospatial cognition (as is the case for Rey Complex Figure Copy, in which performance relies on planning and organization (executive function) as well as visuospatial construction and perception (Fillit, Rockwood, & Young, 2016). Again, the purpose of this study is to identify the clinical visuospatial test most predictive of one-month motor learning outcomes in older adults, and *not* to isolate the cognitive mechanism (i.e., which constructs) underlying motor learning. Additional WAIS-IV tests were used to exclude and characterize language development (Vocabulary), processing speed (Coding and Symbol Search), working memory (Arithmetic), and auditory attention (Digit Span); any score ≤ 5th percentile was considered a cutoff for study exclusion to minimize the likelihood of enrolling participants with dementia. These WAIS-IV test scores were not evaluated as predictors of motor learning, however, based on their lack of association in previous studies. All raw neuropsychological test scores were age-adjusted according to the test instructions (e.g., WAIS-IV) or published methods (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002; Ivnik, Malec, Smith, Tangalos, & Petersen, 1996). In all cases, higher scores indicated better performance on these cognitive tests.

Motor tasks

After completing all sensorimotor and cognitive assessments, baseline performance was collected for participants on two motor tasks designed to mimic important activities of daily living: functional reaching and functional dexterity. (Justification of the selection of these tasks are provided below). The functional reaching task involved upper extremity movements similar to self-feeding (i.e., using a spoon to acquire and transport objects from one location to another), whereas the functional dexterity task involved upper extremity movements necessary for self-dressing (i.e., fastening buttons). For the functional reaching task, participants used a conventional plastic spoon with their nondominant hand to acquire and transport two raw pinto beans at a time from a central cup (centered at their midline) to one of three target cups located radially about the center cup at a distance of 16 cm. All cups had a 9.5 cm diameter and were 5.8 cm tall. Participants first reached towards the ipsilateral cup, then the middle cup, and then the contralateral cup; this sequence was repeated until the last two beans from the center cup were deposited into the last target cup. Trial time began when the participant picked up the spoon, which was located next to the cup. The measure of performance on this task was trial time (i.e., the time it took to complete 15 reaches), with lower values indicating better performance. The functional dexterity task involved a wooden board (61 cm x 34 cm) with a piece of heavyweight linen fabric adhered to the back; the fabric folded around the front of the board to form a placket down its center. One side of the fabric contained 10 one-inch buttons sewn along its edge, 5.3 cm apart, while the opposing piece contained 10 complementary buttonholes. The board was placed at the participant's midline at the beginning of each trial. Participants were instructed to use their nondominant hand to fasten the buttons sequentially as fast as possible. Trial time began when the participant flipped over the button-side piece of fabric and ended when the last button was fastened. Again, lower trial times indicate better performance. Schematics for each task are provided in Figure 5.1, while additional details regarding experimental apparatus and administration (for both motor tasks) have been previously published (Lingo VanGilder, Walter, et al., 2020; Schaefer & Hengge, 2016) and are publicly available on Open Science Framework (https://osf.io/phs57/wiki/Functional_reaching_task/).

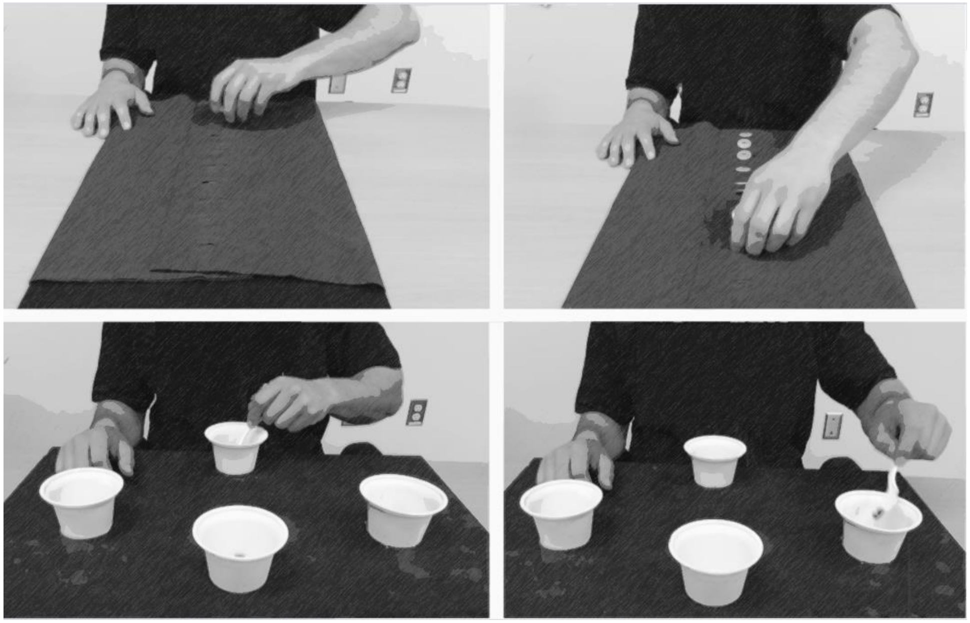

Figure 5.1. Participants used their nondominant hand to complete two functional motor tasks: A functional dexterity task (top panel) and a functional reaching task (bottom panel). "Dexterity and Reaching Motor Tasks" by MRL Laboratory is licensed under CC BY 2.0.

Motor training protocol

On Day 1, participants were evaluated on all sensory, motor, and cognitive (including all visuospatial) assessments, and baseline performance of the functional upper extremity motor tasks. On Days 8, 15, and 22 (i.e., one, two, and three weeks after baseline), participants completed 50 training trials of just the functional reaching task, thereby simulating task-specific training. Participants received no training on the functional dexterity task, which was used as the transfer task in this study. Thus, participants underwent three 50-trial functional reaching training sessions, one week apart. One month after the last training session, participants were re-tested on both the functional reaching and functional dexterity tasks to evaluate long-term skill retention and transfer, respectively. These particular motor tasks were selected for this study because this training paradigm has previously shown transfer of learning in both stroke (Schaefer et al., 2013) and cognitively-intact adult (Lingo VanGilder, Walter, et al., 2020; Schaefer & Lang, 2012) populations. In other words, there is previous evidence that transfer occurs from the functional reaching task to the functional dexterity task. Furthermore, the dose and timing of motor training was based on previous work demonstrating their efficacy in promoting lasting training effects (retention and transfer) (e.g., Schaefer et al., 2015; Walter et al., 2019). The training in this study was *not* intended to mimic the delivery of motor therapy in standard care (as the dose of training here exceeds that of clinical motor therapy) (Kimberley, Samargia, Moore, Shakya, & Lang, 2010; Lang, MacDonald, & Gnip, 2007; Lang et al., 2009).

Statistical analysis

Statistical analyses were performed using JMP Pro 13.1 software (SAS Institute Inc., Cary, NC) and R 3.6.1 (R Core Team). Wilcoxon signed-ranked tests were used to first verify that there was a significant amount of improvement in the trained functional reaching (i.e., retention) and untrained dexterity (i.e., transfer) tasks from baseline to one-month follow-up. Because visuospatial tests do not evaluate a unitary visual construct (e.g., a test may be a validated measure of visual construction, yet performance on that test may also engage other aspects of visuospatial cognition, such as perception, reasoning, etc.), it is likely that the visuospatial tests used in this study may overlap in the visuospatial constructs they test (i.e., they are not independent of each other). To account for collinearity among these visuospatial tests, all age-adjusted visuospatial scores (Benton Judgment of Line Orientation, Rey Complex Figure Copy and Delayed Recall, Visual Puzzles, Matrix Reasoning, and Block Design) were subjected to an *a priori* principal component analysis to reduce dimensionality for inclusion in regression analysis. This step serves two important purposes: (1) it isolates the shared variance between tests that would be excluded if all of the visuospatial scores were put into the same multivariable regression in parallel, and (2) it reduces the number of statistical tests that would need to be run if each visuospatial score was tested in serial (i.e., six different statistical tests, one for each visuospatial measure), thereby controlling for Type-I error. Loading matrices were used to identify which visuospatial tests loaded on to which principal component (PC). The Kaiser-Meyer-Olkin measure of sampling adequacy was calculated to confirm our sample size provided appropriate stability for principal component analysis (Kaiser, 1974).

All PCs with Eigenvalues > 1.00 were then carried forward to a mixed-effects regression model that also used baseline performance and task (reaching vs. dexterity) as predictor variables of one-month follow-up performance. As we had six candidate visuospatial tests to consider rather than a single ‘gold standard’ visuospatial test, a family-wise error correction could have been imposed, but being cognizant of the cost of Type-II errors in this exploratory study was also important; we reasoned Type-II errors to be more costly.

Mixed-effects regression models included factors of task, baseline performance, and all PCs. To follow-up statistically interesting effects of PCs (or Task x PC interactions), the age-adjusted scores from the tests that loaded on that PC were then entered back into the mixed-effects model in place of the PC, one test at a time. This post hoc analysis determined if an individual test (i.e., Line Orientation, Figure Copy, etc.) could in fact be used to predict skill retention or transfer.

Results

Participant characteristics are provided in Table 5.1.

Table 5.1. Participant characteristics and neuropsychological data.

	Mean ± SD	Median	Range
Age (years)	70.4 ± 6.8	70	56-87
Education (years)	16.2 ± 2.8	16	12-24
Tactile sensation (NDH)	3.3 ± 0.5	3.6	2.8-4.3
Grip strength (kg)	26.5 ± 10.5	24.7	10.7-50
Grooved Pegboard (s)	107.6 ± 50.2	88.63	64.6-335.6
Activities of Daily Living	6.02 ± 0.15	6	6-7
Geriatric Depression Scale	0.61 ± 1.57	0	0-8.2
Line Orientation	11.6 ± 2.9	13	5-16
Rey Figure Copy	33.3 ± 3.7	34.5	21.3-37.4
Rey Delayed Recall	18.2 ± 6.5	17.6	5.1-33.7
Visual Puzzles	11.2 ± 3.6	10	5-18
Matrix Reasoning	11.8 ± 2.7	12	7-17
Block Design	11.4 ± 2.9	11	7-18
Vocabulary	12.5 ± 2.4	13	8-17
Digit Span	11.3 ± 2.3	11.5	7-17
Symbol Search	12.3 ± 3.2	12	7-18
Coding	12.9 ± 2.2	13	9-19
Arithmetic	11.7 ± 3.0	12	7-17

Note. N=45; 17 males and 28 females. A subset of participants completed non-visuospatial WAIS-IV tests and the Geriatric Depression Scale (GDS) (n=33; female=21); GDS scores were averaged across all visits. Neuropsychological test scores are age-adjusted.

NDH = nondominant hand.

Results from the Wilcoxon signed-rank tests indicated that participants significantly improved their performance from baseline to one-month follow-up on both motor tasks. For the functional reaching task, participants improved by a mean of 14.7 seconds from baseline to follow-up (Z = -261, $p < 0.0001$), and for the functional dexterity task, participants improved by 6.6 seconds despite no training (Z = -110, $p < 0.018$). These values are reported simply to confirm that both tasks showed significant improvement; given that the tasks themselves are functionally quite different (Schaefer et al., 2013), the magnitude of improvement for one task is not meant to be compared to that for the other task. Mean values for baseline and one-month follow-up across participants are shown in Figure 5.2 for both tasks, as well as the overall training data (Fig. 5.2). This demonstrates the feasibility and efficacy of the motor training paradigm in this sample.

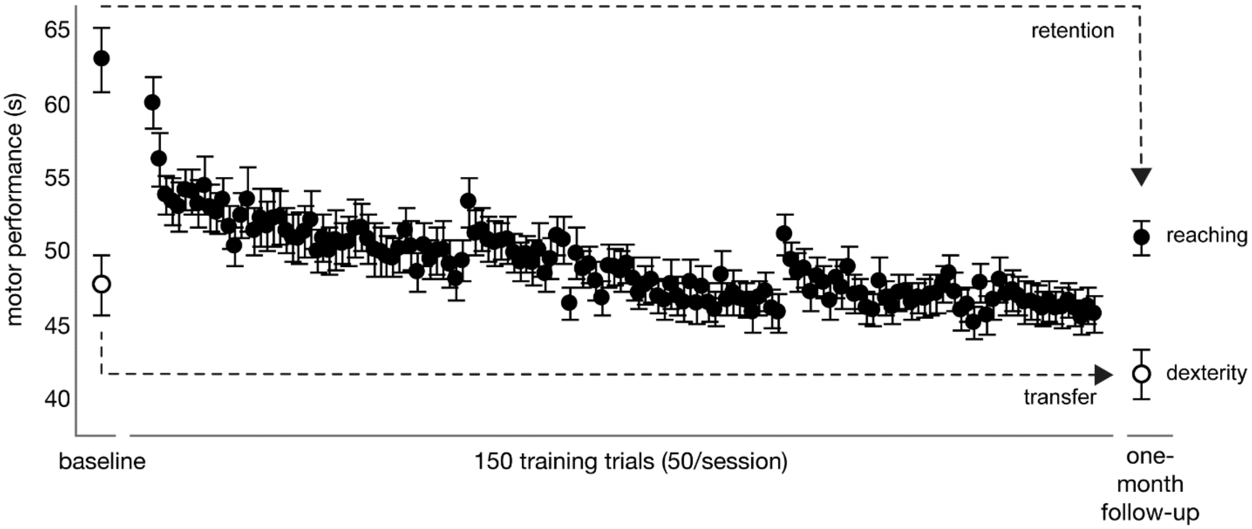

Figure 5.2. Participants completed a baseline trial of the reaching and dexterity motor tasks, then completed 50 training trials on the reaching task during three weekly sessions (totaling 150 trials). Participants were retested on the trained (reaching) and untrained (dexterity) task one month later to determine skill retention and transfer, respectively. Mean motor performance (trial time in seconds) is plotted on the y-axis, where lower values indicate better performance. ● = trained reaching task; ○ = untrained dexterity task. Error bars indicate standard error.

Principal component analysis was used to reduce the dimensionality across the age-adjusted scores from the six visuospatial tests and account for shared variance among them. To confirm our sample size provided appropriate stability for principal component analysis, we computed the measure of sampling adequacy (MSA = 0.77), which indicates the sample size was reasonable and our component loadings would be moderately stable. Two PCs emerged with Eigenvalues > 1.00, and when combined accounted for 69.7% of the variance. The visuospatial tests and corresponding factor loadings for each PC are provided in Table 5.2. Results indicated that Block Design and Matrix Reasoning primarily loaded on PC1, whereas Rey-Osterrieth Complex Figure Copy and Delayed Recall primarily loaded on PC2.

Table 5.2 Factor loadings for principal components.

	Component 1	Component 2
Line Orientation	0.63	0.41
Rey Figure Copy	0.07	**0.88**
Rey Delayed Recall	0.23	**0.81**
Visual Puzzles	0.67	0.43
Matrix Reasoning	**0.85**	-0.16
Block Design	**0.81**	0.33

Note. Light grey and bold typeface fonts indicate the lowest and highest factor loadings, respectively.

To determine which PC(s) predicted motor skill retention and transfer, PC1 and PC2 were entered in a mixed-effects model as predictors of one-month follow-up motor performance, along with baseline motor performance, a ‘task’ factor (functional reaching vs. functional dexterity), and task interactions (see Table 5.3).

Table 5.3. Parameters from the mixed-effect regression model explaining one-month follow-up performance.

Random-Effects					
Name	*Variance*	*SD*			
Participant	1.70	1.31			
Residual	38.76	6.23			
Based on 90 observations from 45 participants.					
Fixed-Effects					
Name	*Estimate (β)*	*SE*	*df*	*t-value*	*p-value*
Intercept	46.96	0.78	60.02	59.85	<0.001*
Baseline	0.49	0.05	78.14	9.62	<0.001*
Task	-0.88	0.76	60.82	-1.16	0.251
PC1	-0.09	0.40	43.45	-0.22	0.828
PC2	-1.08	0.66	44.17	-1.63	0.110
Baseline x Task	0.09	0.05	73.97	1.76	0.083
PC1 x Task	-0.07	0.39	43.45	-0.19	0.850
PC2 x Task	-1.27	0.64	44.13	-1.99	0.053

Note. Baseline was mean-centered and Task was contrast coded with Untrained = +1 and Trained = -1. Degrees of freedom were estimated based on the Welch-Satterthwaite approximation (Satterthwaite, 1946; Welch, 1947). Further, a covariate interaction was controlled for to get the most unbalanced estimate of the interaction of interest (Yzerbyt, Muller, & Judd, 2004). PC = principal component.

As expected, regression analysis revealed a statistically significant relationship between baseline and one-month follow-up performances for both motor tasks ($p < 0.001$). This relationship was slightly stronger for the untrained dexterity task than the trained reaching task, but the Baseline × Task interaction was not statistically significant ($p = 0.083$). There was not a significant main effect of PC1 ($p = 0.83$), nor was there a significant PC1 × Task interaction ($p = 0.85$), suggesting that PC1 (i.e., the shared variance between tests that loaded on this PC) has a minimal relationship with one-month follow-up performance and that this relationship does not change as a function of task. While there was not a significant main effect of PC2 ($p = 0.11$), there was evidence for a

PC2 × Task interaction ($p = 0.053$), suggesting PC2 (namely, the Rey-Osterrieth test) may be related to follow-up performance, particularly for the untrained task (i.e., skill transfer).

When considering 95% confidence intervals for each effect rather than their statistical significance in isolation (Wasserstein, Schirm, & Lazar, 2019), there was again little evidence to suggest that PC1 was related to one-month follow-up performance (main-effect $\beta = -0.09$, CI = [-0.90, 0.73]), or changed as a function of task (interaction $\beta = -0.07$, CI = [-0.85, 0.71]). In contrast, PC2 appeared to have a stronger relationship with one-month follow-up performance overall (main-effect $\beta = -1.08$, CI = [-2.41, 0.25]), which was potentially stronger for the untrained task (i.e., skill transfer) compared to the trained task (i.e., skill retention) (interaction $\beta = -1.27$, CI = [-2.55, 0.01]). Given the history of past work showing that (various) visuospatial tests correlate with individual differences in motor learning outcomes, we decided to investigate this interaction further.

Because the Rey-Osterrieth Complex Figure test primarily loaded on to PC2, and there was evidence that PC2 was related to motor skill transfer, additional analyses evaluated whether this relationship was predicated upon the performance of the Figure Copy or Delayed Recall trial. Individual mixed-effects models analogous to those shown in Table 5.1 were independently conducted for the Figure Copy and Delayed Recall trials of the Rey-Osterrieth Test, in place of PC2 (all other variables remained in the model) (Tables 5.4 and 5.5, respectively).

Table 5.4. Parameters from the mixed-effect regression model using Figure Copy to explain one-month follow-up performance.

Random-Effects		
Name	*Variance*	*SD*
Participant	3.07	1.75
Residual	37.67	6.14
Based on 90 observations from 45 subjects.		

Fixed-Effects					
Name	*Estimate (β)*	*SE*	*df*	*t-value*	*p-value*
Intercept	27.34	9.35	51.56	2.92	0.005*
Baseline	0.49	0.05	80.45	9.55	<0.001*
Task	-5.11	2.88	72.25	-1.77	0.081
PC1	0.23	0.51	41.38	0.45	0.657
FC	-0.23	0.25	43.72	-0.94	0.352
Baseline x Task	0.08	0.05	72.90	1.53	0.130
PC1 x Task	0.62	0.47	41.39	1.31	0.199
FC x Task	-0.54	0.23	43.58	-2.35	0.023*

Note. Baseline was mean-centered and Task was contrast coded with Untrained = +1 and Trained = -1. Degrees of freedom were estimated based on the Welsh-Satterthwaite approximation. PC1 = Principal component 1; FC = Figure Copy.

Table 5.5. Parameters from the mixed-effect regression model using Delayed Recall to explain one-month follow-up performance.

Random-Effects					
Name	*Variance*	*SD*			
Participant	0.00	0.00			
Residual	40.97	6.40			
Based on 90 observations from 45 subjects.					
Fixed-Effects					
Name	*Estimate (β)*	*SE*	*df*	*t-value*	*p-value*
Intercept	26.89	4.33	90.00	6.21	<0.001*
Baseline	0.48	0.05	90.00	9.55	<0.001*
Task	-6.81	2.89	90.00	-2.35	0.021*
PC1	0.79	0.54	90.00	1.47	0.146
DR	-0.35	0.15	90.00	-2.36	0.020*
Baseline x Task	0.11	0.05	90.00	2.10	0.039*
PC1 x Task	0.08	0.54	90.00	0.15	0.885
DR x Task	-0.05	0.15	90.00	-0.31	0.756

Note. Baseline was mean-centered and Task was contrast coded with Untrained = +1 and Trained = -1. Degrees of freedom were estimated based on the Welsh-Satterthwaite approximation. PC1 = Principal component 1; DR = Delayed Recall.

Results indicated that Figure Copy scores were not reliably related to one-month follow-up performance overall (main-effect $\beta = -0.23$, CI = [-0.72, 0.26], $p = 0.35$), but showed a statistically more negative relationship to one-month follow-up performance on the untrained task (i.e., skill transfer) than that for the trained task (interaction $\beta = -0.54$, CI = [-0.07, 0.26], $p = 0.02$). Again, lower trial times correspond to better performance in our tasks; thus, results indicate that better Figure Copy scores predicted more skill transfer at one-month follow-up. Conversely, Delayed Recall scores were negatively related to performance overall (main-effect $\beta = -0.35$, CI = [-0.65, -0.05], $p = 0.02$) and this relationship was not statistically different between the trained and untrained tasks (interaction $\beta = -0.05$, CI = [-0.35, -0.25], $p = 0.76$), indicating higher Delayed Recall scores predicted better skill retention and transfer at one-month follow-up. Collectively, these findings suggest that of all the visuospatial tests administered in this study, the Rey-Osterrieth Complex Figure test is the most predictive of motor skill learning.

In the absence of an *a priori* power analysis, we used Monte Carlo simulation (Green & MacLeod, 2016) to test the sensitivity we achieved for the PC2 x Test interaction. These simulations assume that other aspects of the model are held constant (e.g., random-effects, variance explained by other parameters, etc.), but return the estimated power to detect a fixed effect at different magnitudes. At our sample size (N=45), we had only marginal power to actually detect what we observed (~60%). We do have some confidence in this effect as it conceptually replicated past work, but future studies seeking to replicate this effect should use larger samples.

Discussion

The purpose of this study was to identify which visuospatial test(s) was most predictive of skill retention and transfer one-month after extensive motor training in nondemented older adults. Results indicated that older adults learned both functional upper extremity motor tasks (i.e., skill retention and transfer), and provided new evidence showing that among the visuospatial cognitive abilities evaluated, only construction and delayed visuospatial memory (i.e., Rey-Osterrieth Complex Figure test) predicted long-term learning. These findings are consistent with experimental studies that demonstrated figure drawing performance partially explained short-term skill transfer in normative aging (Lingo VanGilder, Walter, et al., 2020) and individuals with stroke (Toglia et al., 2011). Overall, results support that visuospatial testing could be implemented in geriatric rehabilitation to estimate long-term motor learning potential.

Why might Rey-Osterrieth Complex Figure Tests be related to motor skill transfer?

A possible explanation for the observed relationship between transfer of motor learning and the Rey-Osterrieth test score is that the cognitive processes underlying these behaviors use a shared neural network. The strongest effect observed in our model comparison was Figure Copy performance (i.e., visuospatial construction), specifically. Visuospatial construction represents the ability to reconstruct a visual percept (e.g., an image or object) using its constituent parts (Mervis, Robinson, & Pani, 1999). Figure Copy performance is a function of graphomotor ability and may also rely on interplay between parallel cognitive networks underlying high-level motor control, visuomotor transformation, and multistep object use (Chen et al., 2016). Human clinical studies of dementia have shown that in addition to visuospatial construction, Figure Copy performance is also associated with multifaceted spatial constructs such as perception and working memory (Biesbroek et al., 2014b; Freeman et al., 2000; Possin, Laluz, Alcantar, Miller, & Kramer, 2011). While the primary cognitive processes of skill transfer are less understood, it has been suggested that transfer of learning depends upon both short- and long-term memory. For instance, motor control theory suggests that transfer exploits abstract motor memories of the learned skill (R Schmidt et al., 2018), and experimental studies indicate the degree of motor transfer in both young and healthy older adults is associated with spatial working memory (Langan & Seidler, 2011b). It seems reasonable then, that Figure Copy performance may predict motor skill transfer as both behaviors rely on spatial working memory. It is noted, however, that although previous studies reported Figure Copy performance was related to working memory, Rey-Osterrieth Complex Figure Copy has not been validated for this purpose.

This theoretical framework is supported by neuroanatomical findings that indicate skill transfer and Rey-Osterrieth performance have similar structural and functional neural correlates as those with spatial memory. For example, functional and structural magnetic resonance imaging studies have implicated the role of the right inferior parietal lobule in the degree of skill transfer (Seidler, 2010), spatial working memory (Haley et al., 2008), and Figure Copy (Biesbroek et al., 2014b). Moreover, cortical activations within the middle occipital gyri (Seidler, 2010) and dorsolateral prefrontal cortex (Kantak & Winstein, 2012) have been observed during both skill transfer and Figure Copy performance (Biesbroek et al., 2014b; Possin et al., 2011). While collectively these findings suggest a common neural substrate may underlie skill transfer and visuospatial construction behavior, future work will examine the neuroanatomical correlates of this behavioral relationship within a homogeneous sample, and evaluate causal mechanisms (i.e., does the parietal, occipital, and/or frontal cortices mediate the relationship between transfer of motor learning and visuospatial construction ability?).

The Delayed Recall trial was also related to motor skill retention and transfer. Delayed Recall performance relies on the integration of perceptual-motor and planning-related executive abilities (González Viéitez, 2019), and has been used clinically to measure nonverbal episodic memory (Wong, Flanagan, Savage, Hodges, & Hornberger, 2014). Structural neuroimaging studies that evaluated episodic memory using Delayed Recall suggest that the mnemonic constructs required to reconstruct the figure primarily depend upon prefrontal networks (Wong et al., 2014), and that there may exist a left-hemispheric bias (Ostby, Tamnes, Fjell, & Walhovd, 2012). Indeed, a seminal neuroimaging study that evaluated visuospatial episodic memory recall in healthy adults observed increased cerebral blood flow to the left dorsolateral prefrontal cortex (among other regions) during task performance (Schacter et al., 1995). Consistent with these findings, experimental studies evaluating the structural neural correlates of long-term motor skill retention (e.g., a retention period > four weeks) reported increased cortical volume within primary motor and dorsoparietal (Sampaio-Baptista et al., 2014) and left prefrontal (Taubert et al., 2010) regions were positively correlated with greater amounts of skill retention. While collectively these studies may implicate left prefrontal networks in episodic and motor skill recall, the neural basis for the predictive relationship between Delayed Recall test scores and one-month skill retention remains unexplored.

Limitations and future directions

Although all training was completed with the nondominant (left) hand, the question emerges as to whether our findings are limited to right-hemispheric networks, or if they generalize to motor learning processes overall. While data from the current study do not directly resolve this issue, we hypothesize our results are generalizable based on previous work by Jeunet et al. (Jeunet et al., 2016, 2015). Visuospatial ability has been shown to predict learning of a motor-imagery task controlled by an electroencephalography-based brain-computer interface, a task that involves no effector (hand) at all. Further, visuospatial working memory has been associated with sensorimotor adaptation (Langan & Seidler, 2011b; Schaffert et al., 2017) and motor sequence learning (Bo et al., 2009; Bo & Seidler, 2009; Chan et al., 2015) in studies that typically utilized the dominant hand. However, future work will include efforts to replicate the effects in the current study in other effectors.

We also acknowledge the high level of education in this sample, which may influence the nature or generalizability of our findings. And while the emergence of two principal components is interesting from a neuropsychological perspective by demonstrating that, at least in older adults, some visuospatial tests are similar to each other while others are very different and independent from one another, another limitation of this study is related to the clinical interpretability of the principal components themselves. For instance, our interpretation focused on the primary factor loadings for each principal component (i.e., tests that exceeded 0.80), yet all visuospatial tests loaded onto each component (albeit some more than others) and therefore contributed to the regression results in some manner. Moreover, Block Design and Figure Copy are both tests of visual construction and primarily loaded onto principal components 1 and 2, respectively. Since tests of visual construction loaded onto both principal components nearly equally, this may suggest that visual construction did not drive the relationship with one-month motor learning. Future work will disentangle if graphomotor function or visual construction/memory (or both) explains why the Rey-Osterrieth Complex Figure test scores predict one-month motor learning outcomes.

While performance on many of these visuospatial tests involves executive function, it is important to note that two principal components emerged from our analysis, with PC2 primarily comprising the Rey-Osterrieth tests. It is likely that PC2 represents the psychological processes unique to the Rey-Osterrieth tests rather than a measure of executive cognition; otherwise, more visuospatial tests would have loaded on it. While we are unable to discern the latent constructs that PC1 and PC2 represent (and is outside the scope of the purpose of this study), it is clear that PC2 has a relationship with motor skill learning while PC1 does not. We acknowledge the principal component approach has limited clinical interpretability, yet it is necessary to control for statistical confounds and minimize Type-I error rate.

It is also noted that the present study did not replicate previous correlations between the Benton Judgement of Line Orientation test and motor skill retention (Lingo VanGilder et al., 2018). A major distinction between these studies is the retention period over which the trained skill was retested (i.e., one week versus one month). A theoretical model of early-and-late stages of motor learning (Doyon & Benali, 2005) posits that skill improvement during early learning relies upon higher-order cognitive processes (e.g., visuospatial function), whereas improvement during later stages (e.g., automaticity has been achieved) shifts dependence from cognitive to specialized sensorimotor networks (such as cortico-striatal and -cerebellar circuits). Seminal work by Fleishman and Rich (1963) demonstrated this by showing that within a cohort of young adult males, the degree of motor skill improvement during early trials of a joystick-coordination task was correlated with visuospatial perception, whereas improvement during later stages of learning became less so (skill improvement during later trials were correlated with proprioceptive ability). Thus, the one-month retention period in the present study may indeed be a measure of late-stage motor learning in which the motor skill could be readily executed with negligible cognitive effort (Fitts & Posner, 1967). To further explore the reproducibility of previous findings, future work will evaluate if visuospatial perception and proprioception predict skill improvement during early and late stages of motor learning (i.e., one-week and one-month retention), respectively.

Due to its sensitivity and specificity to visuoconstructional deficits, the Rey-Osterrieth Complex Figure test has high clinical utility, such as diagnostic testing for i) numerous neurological pathologies like prodromal Alzheimer's Disease (Han et al., 2015) and William's syndrome (Hoeft et al., 2007; Mervis et al., 1999); ii) distinguishing dementias like Alzheimer's and Parkinson's Disease (Freeman et al., 2000; Possin et al., 2011); and iii) localizing nonverbal memory in patients with epilepsy (Frank & Landeira-Fernandez, 2008). Findings from the present study suggest that an older adult's performance on the Rey-Osterrieth Complex Figure test is predictive of their motor learning capacity; future work will evaluate if this test may also be prognostic of an older adult's capacity to benefit from motor rehabilitation, particularly when task-specific training is used as a therapeutic intervention. (In a sense, this is similar to the use of visuospatial and other cognitive tests to predict disease progression in more cognitively impaired adults, as summarized in Prado et al. (2019)). In other words, there is a clinical expectation that the learned motor skill will generalize to other motor tasks outside of therapy (i.e., skill transfer), thereby maximizing the benefit of training (Babulal, Foster,

& Wolf, 2016). Thus, administration of the Rey-Osterrieth test prior to therapy may provide critical insight into an older adult's ability to transfer motor skills learned during task-specific training. While administration of Delayed Recall is more time-intensive, results also indicate that these scores may uniquely estimate the durability of task-specific training (i.e., the amount of motor skill individuals learn and retain over a one-month period of no practice). To determine if the Rey-Osterrieth Complex Figure test can be used to predict motor rehabilitation response, future studies will evaluate if the observed behavioral relationship persists within a clinical population (e.g., stroke survivors) and the feasibility of implementing these tests to prognosticate an individual's progression through motor rehabilitation.

Conclusions

Results of the present study indicated that among older adults, the degree of skill transferred one month after extensive upper extremity motor training may be explained, in part, by performance on the Rey-Osterrieth Complex Figure test. Results also suggest the neural pathways underlying visuospatial construction may be necessary for the generalizability of motor learning, rather than its durability in response to extensive training. Future studies will evaluate if this test can be administered prior to motor training to relate to risk of non-responsiveness in therapy and determine the structural neural correlates of this predictive relationship.

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CHAPTER 6

GENERALIZING THE PREDICTIVE RELATIONSHIP BETWEEN ONE-MONTH MOTOR SKILL RETENTION AND REY-OSTERRIETH DELAYED RECALL SCORES FROM NONDEMENTED OLDER ADULTS TO INDIVIDUALS WITH CHRONIC STROKE: A SHORT REPORT

Abstract

Motor learning is fundamental to motor rehabilitation outcomes. There is growing evidence from non-neurological populations supporting the role of visuospatial memory function in motor learning, but current predictive models of motor recovery of individuals with stroke generally exclude cognitive measures, thereby overlooking the potential link between motor learning and visuospatial memory. Recent work has demonstrated that a clinical test of visuospatial memory (Rey-Osterrieth Complex Figure Delayed Recall) may predict one-month skill learning in older adults; however, whether this relationship persists in individuals with chronic stroke remains unknown. The purpose of this short report was to validate previous findings using Rey-Osterrieth Complex Figure Delayed Recall test scores to predict motor learning and determine if this relationship generalized to a set of individuals post-stroke. Two regression models (one including Delayed Recall scores and one without) were trained using data from non-stroke older adults. To determine the extent to which Delayed Recall test scores impacted prediction accuracy of one-month skill learning in older adults, we used leave-one-out cross-validation to evaluate the prediction error between models. To test if this predictive relationship generalized to individuals with chronic ischemic stroke, we then tested each trained model on an independent stroke dataset. Results indicated that in both stroke and older adult datasets, inclusion of Delayed Recall scores explained significantly more variance of one-month skill performance than models that included age, education, and baseline motor performance alone. This proof-of-concept suggests that the relationship between delayed visuospatial memory and one-month motor skill performance generalizes to individuals with chronic stroke, and supports the idea that visuospatial testing may provide prognostic insight into clinical motor rehabilitation outcomes.

Introduction

Motor learning processes are fundamental to clinical motor rehabilitation. In other words, the benefits of motor therapy are theoretically predicated upon an individual's capacity for skill reacquisition and long-term retention (Bastian, 2008). Because the effects of stroke can vary greatly between individuals, responsiveness to motor therapy can be difficult to predict. There are already several models that have been developed to predict biological motor recovery post-stroke (e.g., the Predicting REcovery Potential algorithm (C. Stinear, 2010)) that include personalized variables such as baseline motor function, age, severity of stroke, and white matter integrity. However, when attempting to predict changes in post-stroke upper-extremity impairment following therapy (i.e., responsiveness to motor therapy), recent work in machine learning has shown that the inclusion of sophisticated neuroimaging measures does not improve prediction accuracy beyond basic clinical measures (i.e., baseline Fugl-Meyer score) (Tozlu et al., 2020).

To our knowledge, no predictive models of therapeutic responsiveness include cognitive variables, despite growing evidence that they may explain significant amounts of variance in motor learning (Lingo VanGilder, Hooyman, et al., 2020; Lipp et al., 2020; Schaefer, Sullivan, et al., 2020). For example, attention, executive function, and visuospatial memory underlie crucial stages of motor learning and are also among the most common cognitive deficits reported following stroke. Furthermore, a number of studies have shown that advancing age is associated with less improvement in motor therapy following stroke (Dobkin et al., 2014) and other musculoskeletal conditions. Since cognitive status often declines with age, it is plausible that responsiveness to motor therapy can, at least in part, be predicted by cognitive factors.

Empirically, there is a longstanding line of experimental motor learning studies that have shown that visuospatial function (i.e., of or relating to visual perception and spatial relationships between objects) is positively correlated with motor learning in both young and older adults (Bo et al., 2009; Fleishman & Rich, 1963; Jeunet et al., 2016; Langan & Seidler, 2011b; P. Wang et al., 2019). Our more recent work has begun to bridge the gap between empirical and clinical studies by showing that neuropsychological tests of visuospatial function may predict upper-extremity motor learning following task-specific training in older cohorts that are age-matched to a number of clinical stroke samples (e.g., (Lingo VanGilder, Lohse, et al., 2021)), whereas other clinical tests of attention, language, memory, etc., do not (Lingo VanGilder et al., 2018; Lingo VanGilder, Walter, et al., 2020). This line of work has also highlighted that not all visuospatial tests are created equal, so to speak, since different visuospatial tests such as the Benton Judgement of Line Orientation (Benton et al., 1994) and the Wechsler Adult Intelligence Scale Block Design (Wechsler, 1955) probe different aspects of visuospatial function. By systematically comparing a battery of clinical visuospatial tests (including memory, perception, problem-solving, reasoning, and construction), we have demonstrated that only the Rey-Osterrieth Complex Figure Delayed Recall test (Osterrieth, 1944), which measures visuospatial memory, uniquely predicted long-term skill retention of task-specific training in older adults without a history of stroke (Lingo VanGilder, Lohse, et al., 2021). This work strongly supports the premise that the same assessment (i.e., Delayed Recall) may also be a predictor of motor learning after stroke.

Thus, the purpose of this short report was to determine if the previously observed relationship between Delayed Recall test scores and one-month post-training skill performance in older adults persisted in individuals with a history of stroke, and to evaluate the extent these test scores impacted prediction accuracy. This hypothesis-driven approach generated predictive models from a training dataset and then tested the generalizability of these models to an untrained dataset to test whether models that included visuospatial memory tests scores resulted in better predictive accuracy than models that did not.

Methods

All experimental procedures were approved by Arizona State University's Institutional Review Board and adhered to the Declaration of Helsinki. Forty-seven adults ages 56 to 87 years old (29 female/18 male) without a history of stroke comprised the training dataset, and seven adults with a history of ischemic stroke ages 33 to 81 (3 female/4 male) comprised the testing dataset. All participants provided informed consent prior study enrollment. A subset of data in the non-stroke older adult cohort (n=45) has been published previously (Lingo VanGilder, Lohse, et al., 2021) and is included in the present study to model the predictive relationship described below. All participants were right-hand dominant (premorbidly if post-stroke), and were non-demented based on established cut-off scores for neuropsychological assessments (see (Lingo VanGilder, Lohse, et al., 2021)). Participants with a history of ischemic stroke were also evaluated for motor deficits in their more-affected arm using the Upper Extremity Fugl-Meyer Assessment and the Action Research Arm Test. Post-stroke spasticity of the elbow flexors was evaluated using the Modified Ashworth Scale. Participants were excluded if they had hemispatial neglect, as determined by the Mesulam Cancellation Test. One participant had a right thalamic infarct, one had multifocal infarcts to the left middle cerebral artery related to high grade stenosis, one had a vertebral artery dissection, and one had a thrombotic ischemic stroke at the base of the cerebellum. Lesion location information was not available for three participants.

Rey-Osterrieth Complex Figure Delayed Recall

This standardized complex figure drawing test comprises two separate trials: A Figure Copy (measures visual construction) and a Delayed Recall (measures delayed visuospatial memory) trial; the Figure Copy and Delayed Recall trials each take 1-2 minutes and are separated by 30 minutes. Participants were first asked to draw a replicate of a complex image as precisely as possible; once finished, all visual stimuli were removed from the testing area. Thirty minutes later, participants were asked to redraw the figure from memory (Fig. 6.1). To reduce interrater variability, a single rater scored each test using established testing guidelines. It is of note that the Delayed Recall score is independent of the Copy trial score (i.e., a high score on the Copy trial does not indicate the participant will achieve similar performance on the delayed memory trial). Based on our previous work using principal component analysis (Lingo VanGilder, Lohse, et al., 2021), only the Delayed Recall test scores were evaluated in this short report.

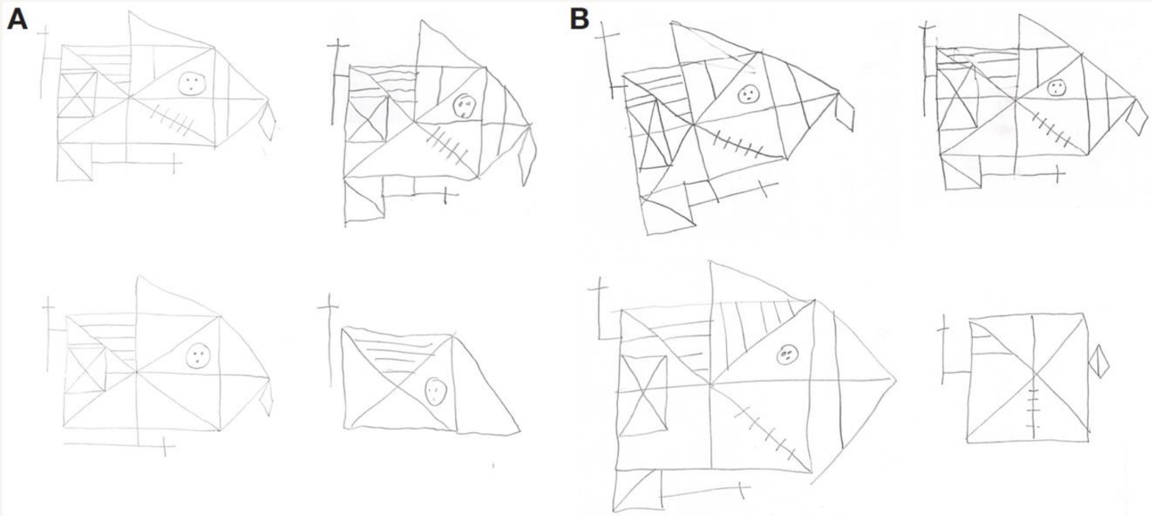

Figure 6.1. Participants completed the Rey-Osterrieth Complex Figure Copy (measures visual construction; on the top row) and Delayed Recall (measures visuospatial memory; on the bottom row); only the Delayed Recall trial was analyzed in this study. The Copy and Delayed Recall trials are scored independently from each other. Panels A and B show example drawings from older adults and individuals with a history of stroke, respectively. Note both groups demonstrated high performance on the Copy trial but marked variability in Delayed Recall performance.

Task-specific motor training

Task-specific training included three sessions of 50 practice trials of a functional upper-extremity motor task over three consecutive weeks (one session/week). More details regarding the motor task are provided below. Participants were then re-tested one month after training to evaluate the amount of motor skill retained following a period of no practice; thus, our paradigm was designed with key principles of motor learning in mind, such as repetition and distributed practice. Furthermore, our paradigm is consistent with the goal of task-specific training, whereby participants practiced a functional task that simulated the basic activity of daily living of feeding oneself (Jebsen et al., 1969; Katz et al., 1970). To ensure the task was not overlearned, the older adult cohort used their nondominant hand; individuals in the stroke cohort used their more-affected hand. Given that all participants regardless of group were right-hand dominant, the older adult group performed all assessments and training with their left hand while most individuals in the stroke group did so with their right hand (one participant experienced left hemiplegia and used this hand accordingly).

The motor task used an experimental apparatus consisting of a wooden board (43 x 61 cm) with three different target cups placed radially around a constant ‘home’ cup at a distance of 16 cm (Fig. 6.2); each cup was 9.5 cm in diameter and 5.8 cm in height. Each trial began with thirty raw kidney beans in the home cup. The participant was instructed to pick up a standard plastic spoon located on the ipsilateral side of the home cup and use it to scoop two beans at a time from the home cup to the following sequence of target cups: ipsilateral, middle, then contralateral. This sequence was repeated until the last pair of beans were placed in the contralateral target cup, completing the trial. Errors such as transporting the wrong number of beans, dropping beans, or reaching in the wrong direction were recorded; error rates for both groups were modest (11.4% and 9.5% for stroke and older adult, respectively) and not included in our analyses. Participants were timed and instructed to move as quickly and as accurately as possible while freely exploring postural techniques to enhance performance (i.e., discovery learning). Trial time began when the participant picked up the spoon, with lower trial times indicating better performance. Since each trial consisted of 15 reaching movements, participants complete 750 reaches per training session. The targeted training dose was 2,250 across the entire training paradigm, although due to scheduling issues three stroke participants only completed 1,500 reaches (2 training sessions) before their one-month follow-up. This task has ecological and construct validity (Schaefer & Hengge, 2016) and instructional videos are available on Open Science Framework (Schaefer, 2019).

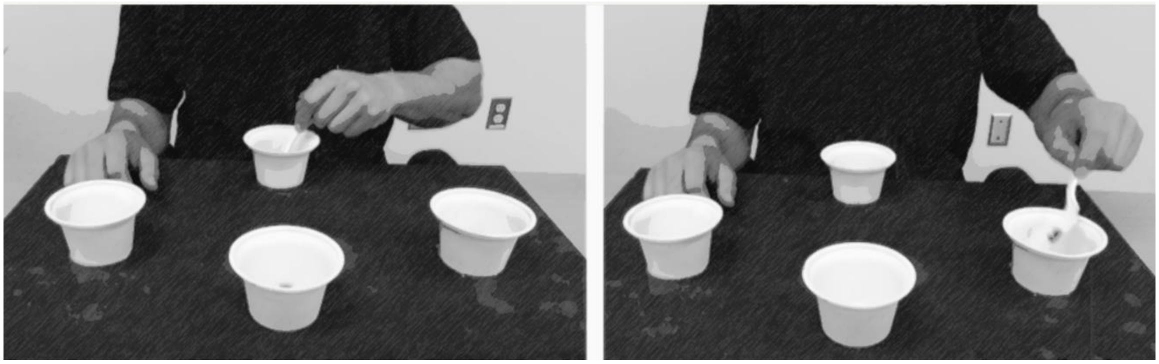

Figure 6.2. Participants used their nondominant hand to perform the motor task that mimicked the upper extremity movements required to feed oneself. This image is adapted from the “Dexterity and Reaching Motor Tasks” by MRL Laboratory that is licensed under CC BY 2.0.

Statistical Analysis

Analyses were performed in JMP Pro 14.0 (SAS) and R Core Team 4.0.0 (2020) statistical software. To model the extent to which visuospatial memory test scores predicted one-month skill learning in the older adult cohort, multivariable regression was performed using covariates of age, education, Delayed Recall score, and baseline motor performance. Education was included to serve as a proxy for cognitive reserve (i.e., the brain's resilience to neuropathological damage), which may explain differences in cognitive factors such as executive function, working memory, global cognition, and general arousal, as well as motor function following stroke (Umarova et al., 2019). A separate model was then generated that excluded Delayed Recall scores to measure prediction accuracy without these visuospatial test scores, also in the older adult cohort. Analysis of variance (ANOVA) was then used to statistically compare prediction accuracy between both models. To test the robustness of this relationship, we performed two separate analyses: both models (Delayed Recall vs. no Delayed Recall) were 1) cross-validated in the older adult cohort using a leave-one-out approach (Shao, 1993) and 2) 'trained' using data from the older adult cohort and 'tested' on the independent stroke dataset. In leave-one-out cross-validation, the model is trained on all data except that of a single participant and a prediction is made for that participant's data; this process repeats for every participant (i.e., 47 times), thus all data are used for training the model but are used for prediction only once. This approach was chosen because it provides a method of generating unbiased prediction error to better estimate model fit. The mean squared error (MSE) between predicted versus observed values was calculated to compare accuracy among predictive models. This approach was designed to evaluate the extent to which visuospatial memory test scores can improve the prediction of long-term motor learning (i.e., comparison of MSE between Delayed Recall and no Delayed Recall models) and if this relationship generalizes to individuals with a history of stroke (i.e., comparison of MSE between older adult and stroke datasets).

The proposed approach has several strengths regarding rigor and reproducibility. First, by validating our model using data from our previous experiment (i.e., from a non-stroke cohort of older adults), bias is minimized. Second, by testing this validated model on an independent stroke dataset, the generalizability of this previously identified relationship can be examined within an independent clinical sample while minimizing the likelihood of statistical issues that are common in small sample sizes (e.g., a lack of statistical power, etc. (K. Lohse, Buchanan, & Miller, 2016)).

Results

Participant characteristics, sensory and motor data are presented in Table 6.1. The age range for participants with a history of stroke was 33 to 81 years, with three being older than age 65. Overall, participants with a history of ischemic stroke had mild motor impairment, as indicated by their Upper Extremity Fugl-Meyer scores and their Action Research Arm Test scores. We acknowledge that the group had minimal motor deficits based on these stroke-specific assessments, but we point out, however, that participants with a history of ischemic stroke performed worse on the Grooved Pegboard Test than the older adult group (# drops, *p*=0.014; time to complete, *p*=0.093) even when performing it with their affected dominant (right) hand while the older adult group performed it with their nondominant (left) hand. Furthermore, the stroke group's baseline performance on the motor task was worse than the older adult group's performance with the same (right) hand (*p*=0.059) (Fig. 6.3, dashed line). Collectively, these data indicate that the stroke group did in fact have some degree of motor impairment, and that both groups improved on the task from the baseline to the retention trial.

Table 6.1. Participant characteristics.

	Older Adult (Control)	*Stroke*
Age[a]	69.7±6.5 (56-87)	58.4±16.5 (33-81)
Education[b]	16.3±2.7 (12-24)	15.9±2.0 (14-19)
Sex	29 female 18 male	3 female 4 male
Grip strength[c]	29.1±11.1 (9.3-51.7)	29.6±14.4 (11-56)
Grooved Pegboard Test[d]	104.6±49.6 (64.6-335.6)	138.7±48.8 (50.2-200.5)
Rey-Osterrieth Delayed Recall	16.1±6.7 (2-31.5)	12.3±8.3 (5-25)
Time post-stroke[e]		3.8 ± 2.8 (1.1-9.7)
Upper extremity Fugl-Meyer[f]		63 ± 3.5 (58-66)
Action Research Arm Test[g]		52.7 ± 6.9 (38-57)
Modified Ashworth Scale[h]		0.7 ± 1.1 (0-3)

[a]in years; [b]in years; [c]in kilograms (dominant hand); [d]time, in seconds; [e]in years; [f]out of 66; [g]out of 57; [h]scale of 0-4, measuring elbow flexors

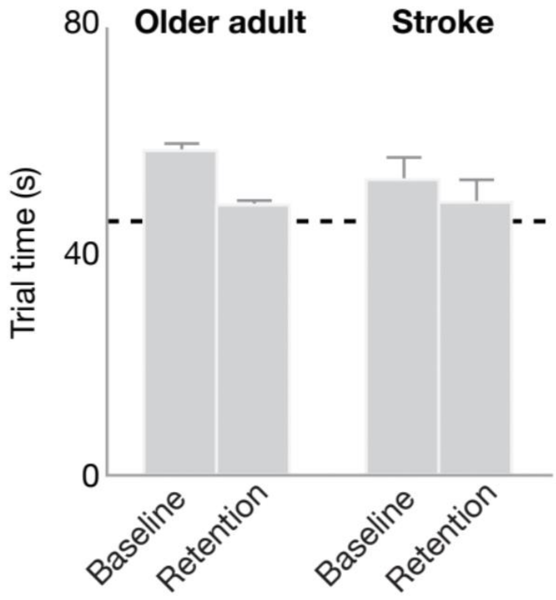

Figure 6.3 Mean and standard error performance at baseline and one-month follow-up for the older adult and stroke groups. Note: The affected hand was the pre-morbid dominant hand for all participants with stroke. Dashed line indicates older adult group's mean dominant hand performance for reference.

Baseline and retention motor performance for the older adult and stroke groups are presented in Figure 6.3. Motor training data for participants with a history of stroke are presented in Figure 6.4 (it is noted that training data for older adult cohort have been published previously (Lingo VanGilder, Lohse, et al., 2021)). On average, they improved performance from the baseline trial (mean±SD=53.09±11.31 seconds; 95% CI [44.72, 61.46]) to one-month follow-up (mean±SD=49.01±11.46 seconds; 95% CI [40.52, 57.50]), indicating that some participants improved more than others.

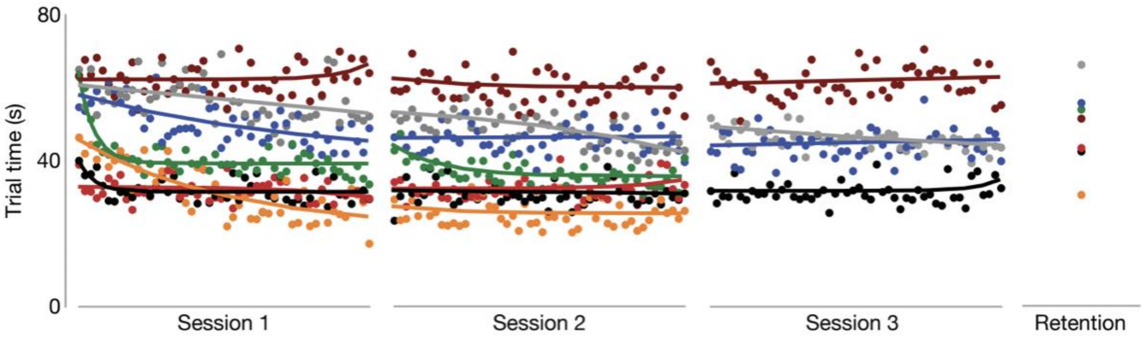

Figure 6.4. Motor task performance curves of the affected hand for each participant with stroke, fitted with three-parameter exponential decay line. Each participant is represented by a different color. Note that this was the pre-morbid dominant hand for all participants. Three participants did not complete the third training session (trials 101-150) but did return for the one-month follow-up.

To model the extent to which visuospatial memory predicted motor performance at one-month follow-up in the older adult cohort, multivariable regression included covariates of age, education, Delayed Recall score, and baseline motor performance (Table 6.2). Delayed Recall scores (*p*=0.025, β=-0.31; 95% CI [-0.59, -0.04]) and baseline motor performance (*p*=0.002, β=0.31; 95% CI [0.12, 0.50]) demonstrated a similar effect size with one-month follow-up performance, where better scores predicted better performance at one-month follow-up. Age (*p*=0.22, β=0.19; 95% CI [-0.12, 0.51]) and education (*p*=0.67, β=0.13; 95% CI [-0.54, 0.83]) did not predict follow-up. In the comparison model that excluded Delayed Recall scores, only baseline performance (*p*<0.0001, β=0.36; 95% CI [0.17, 0.55]) predicted one-month follow-up performance (Table 6.3). ANOVA confirmed a significant difference between both models (*p*<0.05, Akaike information criterion of 305.4 vs. 308.4 and R^2 of 0.41 vs. 0.35, for Delayed Recall vs. no Delayed Recall respectively, indicating that the inclusion of Delayed Recall test scores explained more variance in motor performance at one-month follow-up than baseline, age and education alone, and improved the model's overall goodness-of-fit.

Table 6.2. Parameters from the least-squares regression model including Delayed Recall that explain one-month follow-up performance.

Parameter Estimates					
Name	*Estimate (β)*	*SE*	*df*	*t-value*	*p-value*
Intercept	19.47	12.39	0	1.57	0.124
Delayed Recall	-0.31	0.13	1	-2.33	0.025*
Age	0.19	0.16	1	1.24	0.222
Education	0.13	0.34	1	0.43	0.673
Baseline	0.31	0.09	1	3.35	0.002*

Based on 47 Observations

Degrees of freedom (4,42)

Table 6.3. Parameters from the least-squares regression model excluding Delayed Recall that explain one-month follow-up performance.

Parameter Estimates					
Name	*Estimate (β)*	*SE*	*df*	*t-value*	*p-value*
Intercept	15.57	12.89	0	1.21	0.234
Age	0.19	0.16	1	1.14	0.260
Education	-0.07	0.34	1	-0.20	0.842
Baseline	0.36	0.10	1	3.76	<0.000*

Based on 47 Observations

Degrees of freedom (3,43)

To test the robustness of this relationship, both models (Delayed Recall vs. no Delayed Recall) were validated in the older adult cohort using a leave-one-out cross-validation approach. The mean squared error (MSE) between predicted and observed values for each model was 36.29 and 39.11 seconds, respectively (Fig. 6.5A). To test the generalizability of each model, both linear models (Delayed Recall vs. no Delayed Recall) were trained and then tested on the independent stroke dataset. The MSE between predicted and observed values for each model was 74.85 and 77.77 seconds, respectively (Fig. 6.5B). A null model that comprised the average one-month follow-up trial time for the older adult cohort was generated to serve as a benchmark for the models that included participant-specific data (i.e., Delayed Recall score, age, education, baseline motor performance). Overall, inclusion of Delayed Recall test scores reduced MSE, albeit modestly, in both models of one-month skill learning in older adult and stroke samples. However, these results from individual predictors are still of interest, given that the null model predicted participants would demonstrate one-month skill performance equivalent to that of the group average and performed much worse than models that included participant-specific data. The resulting MSE was 87.24 seconds and 112.61 seconds for older adult and stroke groups, respectively. Figure 6.6 shows the prediction accuracy for the highest performing model in stroke (i.e., Delayed Recall model).

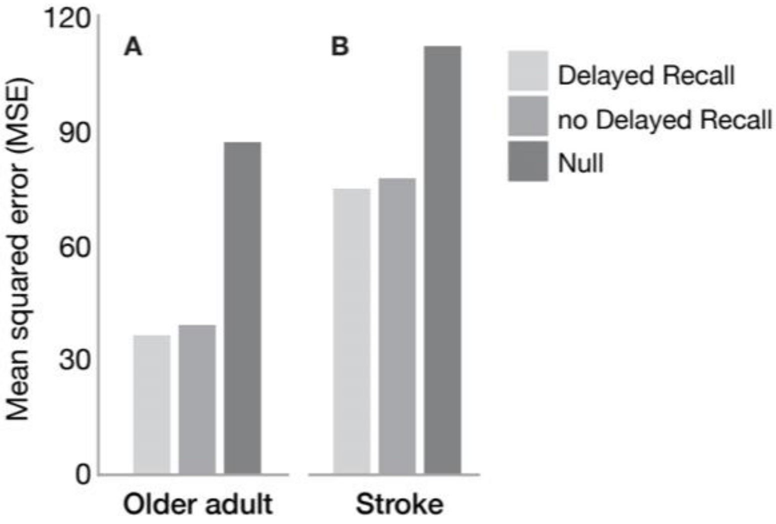

Figure 6.5. The mean squared error (MSE) for each model is presented for older adults and individuals with a history of stroke. A) Each model (Delayed Recall, no Delayed Recall, Null) was trained and tested on older adult data using a leave-one-out cross-validation approach; B) Each model was trained on older adult data and tested on individuals with stroke using a linear regression approach. Results indicate that in both groups, the inclusion of Delayed Recall test scores improved MSE.

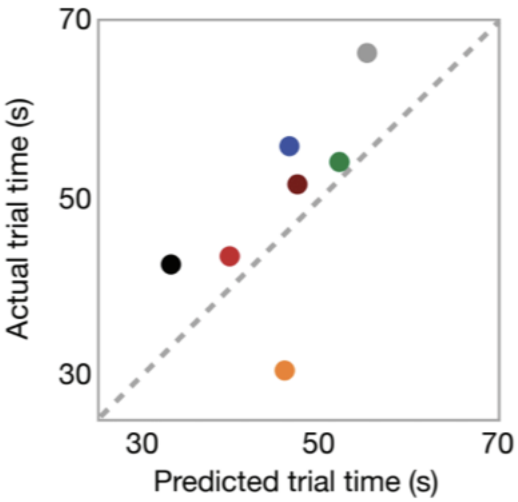

Figure 6.6. Actual vs. predicted one-month skill performance results of the Delayed Recall model for participants with stroke. The dashed diagonal line is for reference, indicating 100% accuracy. Each color represents the corresponding participant in Figure 4.

Discussion

The purpose of this short report was to determine the generalizability of the Rey-Osterrieth Complex Figure Delayed Recall test as a predictor of motor learning in a post-stroke cohort based on our previous findings, and to evaluate the extent to which adding these test scores as a predictor variable improved prediction accuracy. To address these hypothesis-driven questions, we trained two regression models (with and without Delayed Recall) using older adult data and tested them using leave-one-out cross-validation as well as on an independent stroke dataset using linear regression. Consistent with our hypothesis, results indicated that inclusion of Delayed Recall scores explained more variance in motor performance at one-month follow-up as compared to models that just included age, education, and baseline motor performance. This was consistent across both stroke and older adult datasets. These findings support the concept that visuospatial memory testing may provide prognostic insight into motor rehabilitation outcomes, and that cognitive rehabilitation could play a significant role in priming successful motor rehabilitation outcomes.

Despite the putative association between visuospatial memory and motor learning, cognitive variables are not currently considered in predictive models of upper-extremity motor recovery. This could be due to conflicting reports from clinical studies that evaluated the relationship between cognitive testing and motor rehabilitation outcomes. For example, change in motor outcomes has been linked to memory (C M Cirstea et al., 2006), executive (Dancause, Ptito, & Levin, 2002), and visuospatial (Hawe, Kuczynski, Kirton, & Dukelow, 2020; Toglia et al., 2011) functions, while other studies report no relationship between these cognitive domains and motor improvement (Boe et al., 2014). Comparison between reports is further confounded by differences in severity of impairment between groups, and more importantly, the lack of specificity in the cognitive tasks used. Often times global measures like the Montreal Cognitive Assessment or the Mini-Mental Status Exam are used to quantify cognition, but these tests insufficiently measure the function of specific cognitive domains especially pertinent to motor learning abilities and are often used as exclusion criteria (K. Lohse et al., 2016).

A plausible mechanism underlying the association between visuospatial and motor learning is variation in structural integrity of specific white matter tracts among older adults and individuals with stroke. Structural neuroimaging studies in healthy aging (Ge et al., 2002) and stroke (Y. Wang et al., 2016) demonstrate that white matter is particularly susceptible to the degenerative effects of normal aging and lesions. While the structural characteristics of frontoparietal white matter tracts have been linked to visuospatial function (Budisavljevic et al., 2017) and motor skill learning (Steele et al., 2012), it remains unknown if frontoparietal white matter microstructure explains variance in this behavioral relationship. Notably, the non-stroke older adult group in this study used their left hand to complete the motor training, while the stroke group used their more affected hand. The fact that we observed a behavioral relationship between delayed visuospatial memory and one-month skill retention independent of which hand was used suggests that this effect is generalizable.

As with neural structures, motor learning and visuospatial function typically decline across the lifespan (Bendayan et al., 2017; Grady et al., 1994; Muniz-Terrera et al., 2019; Shea & Jin-Hoon, 2006; Walter et al., 2019), yet one unexpected finding from the present study was that age did not demonstrate a significant effect on one-month follow-up performance. As a quality check, only participant age was included in the regression models of one-month follow-up, and results indicated that indeed age was related to follow-up performance (results not reported); we interpret this to suggest that behavioral factors such as baseline motor performance and delayed visuospatial memory are more sensitive predictors of one-month motor performance than chronological age (i.e., which explains why age is nonsignificant when these variables are included in the models). Moreover, our results indicate that visuospatial memory may explain variance beyond that of age, education, and baseline performance alone.

In regard to predicting spontaneous stroke recovery, this and other studies do not suggest that visuospatial memory scores can or should replace predictor variables used in current algorithms, or that the models presented here are valid recovery prediction tools; rather, the purpose of this short report was to demonstrate the predictive relationship between visuospatial memory and motor learning persists in individuals with a history of stroke, and to empirically support the premise that visuospatial memory testing may be an overlooked consideration for understanding why responsiveness to motor rehabilitation can be so varied.

Previous research has shown that effect sizes and beta values derived from a small sample group are highly prone to inflation and therefore may be unreliable (K. Lohse et al., 2016). To avoid this pitfall in our analyses, we first evaluated the reliability of the behavioral relationship in a moderately large older adult group using leave-one-out cross validation; results indicated beta values in this dataset were reliable. This validated model was then used to test if the behavioral relationship also generalizes to individuals with a history of stroke. In other words, while the stroke cohort in this study was small, our analyses were not wholly dependent upon its sample size and the potential limitations associated with it. Another limitation to this short report is that all participants were in the chronic stage of stroke (>1 year), had various lesion locations, and exhibited very mild motor impairment. It is possible that individuals with more moderate-to-severe motor impairment (had we been able to recruit them prior to the COVID-19 shutdown) would have also had more impaired visuospatial ability (Kalra, Perez, Gupta, & Wittink, 1997), which would support previous findings of less motor learning with higher stroke severity (Boyd, Quaney, Pohl, & Winstein, 2007) based on our working hypothesis and regression model. However, as noted above, a larger, more acute, and more impaired sample has not been recruited due to COVID-19, preventing us from directly testing whether this model would retain comparable prediction accuracy in more acute or more impaired individuals. This is not a trivial question, since different cognitive deficits tend to emerge throughout the recovery process (e.g., attention deficits during acute (Al-Qazzaz et al., 2014) and visuospatial and memory deficits present at three months post-stroke (Jokinen et al., 2015)). Thus, the current study cannot discern if the presence of other cognitive impairments (or the effect of lesion location) will impact this behavioral relationship. However, since the Rey-Osterrieth Complex Figure Delayed Recall test is a validated measure of nonverbal memory, executive function, and graphomotor skills, it likely captures the breadth of cognitive impairments most common following stroke. To address these limitations, future work will involve recruiting a larger and more impaired sample and evaluating if Delayed Recall scores, and other specific neuropsychological tests, can be used to improve prediction in models involving individuals with stroke during the acute stage. In addition, the feasibility of administering the standardized Delayed Recall test within a motor rehabilitation setting remains unexplored. Therapists typically see patients in 45- to 60-minute blocks of time, and the Copy trial could feasibly be administered at the start of a therapy session and the Delayed Recall trial 30 minutes into the session, with routine therapy exercises or other data collection done in between. We see this as much more realistic within the standard of care than other proposed prognostic approaches (that require collecting kinematic, EEG, or brain imaging data), and future work will evaluate the feasibility of administering this test within that timeframe.

Conclusions

In summary, the inclusion of Delayed Recall test scores modestly improved the accuracy in predictive models of one-month skill learning in individuals with and without stroke. These findings support the concept that visuospatial memory testing may provide prognostic insight into upper extremity motor learning and encourage future work to examine the role of cognitive testing in predictive models of motor recovery.

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CHAPTER 7

A PRELIMINARY STUDY TO EVALUATE WHITE MATTER STRUCTURAL CORRELATES OF DELAYED VISUOSPATIAL MEMORY AND ONE-WEEK MOTOR SKILL RETENTION IN NONDEMENTED OLDER ADULTS

Abstract

Skill retention is important for motor rehabilitation outcomes. Recent work has demonstrated that delayed visuospatial memory performance may predict motor skill retention in older and neuropathological populations. White matter integrity between parietal and frontal cortices may explain variance in upper-extremity motor learning tasks and visuospatial processes. We performed a whole-brain analysis to determine the white matter correlates of delayed visuospatial memory and one-week motor skill retention in nondemented older adults. We hypothesized that better frontoparietal tract integrity would be positively related to better behavioral performance. Nineteen participants (age>58) completed diffusion-weighted imaging, then a clinical test of delayed visuospatial memory and 50 training trials of an upper-extremity motor task; participants were retested on the motor task one week later. Principal component analysis was used to create a composite score for each participant's behavioral data, i.e. shared variance between delayed visuospatial memory and motor skill retention, which was then entered into a voxel-based regression analysis. Behavioral results demonstrated that participants learned and retained their skill level after a week of no practice, and their delayed visuospatial memory score was positively related to the extent of skill retention. Consistent with previous work, neuroimaging results indicated that regions within

bilateral anterior thalamic radiations, corticospinal tracts, and superior longitudinal fasciculi were related to better delayed visuospatial memory and skill retention. Results of this study suggest that the simple act of testing for specific cognitive impairments prior to therapy may identify older adults who will receive little to no benefit from the motor rehabilitation regimen, and that these neural regions may be potential targets for therapeutic intervention.

Introduction

Repetitive practice of functional movement patterns during motor rehabilitation are known to drive learning (or relearning) of novel motor skills, but the learning process is highly variable between individuals, such that responsiveness to task-specific training is often patient-specific. A number of neuroimaging and neurophysiological methods have been proposed to better predict a patient's responsiveness to a given type or dose of motor therapy. However, these methods are often time- and resource-intensive, and yield results that are not readily interpretable by clinicians. In light of this, standardized visuospatial tests may offer a more feasible solution. Visuospatial function has been linked to upper-extremity motor improvement (i.e., learning) in older adults (Bo & Seidler, 2009; Langan & Seidler, 2011) and individuals with stroke pathology (Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011). Although these prior studies used experimenter-derived (i.e., unstandardized) measures of visuospatial function, a recent study demonstrated that the Rey-Osterrieth Complex Figure Delayed Recall (a clinical test of delayed visuospatial memory) predicted upper-extremity skill learning in older adults and individuals with stroke pathology (Lingo VanGilder, Hooyman, Bosch, & Schaefer, 2021), suggesting a clinical paper-and-pencil test could aid in predicting motor rehabilitation responsiveness.

Because cognitive and motor functions have historically been evaluated and studied separately, the neural mechanism of this behavioral relationship is currently unclear. It is plausible that visuospatial tests have predictive value because they probe the health of critical neural structures for motor skill learning. Classic neuropsychological studies have long supported the role of parietal cortex in visuospatial function (Mishkin, Ungerleider, & Macko, 1983; Newcombe, Ratcliff, & Damasio, 1987; Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Ungerleider & Haxby, 1994) and more recent neuroimaging studies have shown that the structural integrity of white matter tracts between parietal and frontal cortices is related to motor skill learning (Sampaio-Baptista et al., 2014; Steele, Scholz, Douaud, Johansen-Berg, & Penhune, 2012; Taubert et al., 2010; Tomassini et al., 2011). Specifically, the superior longitudinal fasciculus (SLF) has been implicated in both visuospatial processes (Chechlacz, Gillebert, Vangkilde, Petersen, & W Humphreys, 2015; McGrath et al., 2013) and skill learning (Steele et al., 2012), suggesting it may be a candidate neural pathway for explaining our earlier behavioral findings and for predicting motor skill learning in older adults.

Further evidence of this mechanism is provided in a recent preliminary study that evaluated within-session practice effects in a small cohort of individuals with stroke pathology. The structural characteristics of the SLF (e.g., fractional anisotropy, FA) were positively correlated with the amount of skill acquired after a brief practice session on a novel upper-extremity motor task (Regan et al., 2021). However, delayed visuospatial memory assessment and skill retention (i.e., the long-term retainment of acquired motor skill performance through repeated practice (Schmidt, Lee, Winstein, Wulf, & Zelaznik, 2018)) were not measured, which prevented us from fully resolving the white matter correlates of this behavioral relationship with this previous study. A retention period (otherwise known as consolidation) is important to consider when applying motor learning principles to motor rehabilitation (Bastian, 2008). Moreover, the previous study used a region-of-interest (ROI) approach, which effectively limits analyses to a specific neural structure. But since motor learning processes involve a vast neural network including frontal, parietal, and subcortical structures (Ghilardi et al., 2000; Seidler, 2010; Taubert et al., 2010), it is possible this approach did not reveal other critical pathways for skill learning.

Thus, the purpose of this exploratory whole-brain analysis was to determine whether white matter microstructure was associated with one-week motor skill retention and delayed visuospatial memory test scores in nondemented older adults. By moving beyond a specific neurologic condition (e.g., stroke), findings from this study will more broadly generalize across geriatric populations who may be undergoing motor rehabilitation for a variety of reasons (e.g., hip/knee replacement, Parkinson’s disease). Since an estimated 30-45% of physical therapy caseloads in the United States are adults over age 65 (Bell, 2015), it is critical to consider broad biological mechanisms of motor rehabilitation that are independent of diagnosis. Based on previous findings, we hypothesized that better frontoparietal tract diffusion metrics (e.g., FA and radial diffusivity), including those of the SLF specifically, would positively correlate with both motor skill retention and delayed visuospatial memory test scores.

Methods

Informed consent was obtained before participation and all experimental procedures were approved by the university's Institutional Review Board. Nineteen community-dwelling adults (age (mean±standard deviation) = 68.4±6.8 years, 13 females) were included in this neuroimaging analysis, which was a sub-study of a larger observational experiment in which participants completed a battery of clinical visuospatial tests and 50 weekly training trials of a motor task using their nondominant (left) hand for three consecutive weeks and returned one month later to retest their skill level (Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2021). One-week skill retention was not reported in the previous study, which instead focused on longer-term retention (one-month); the Wechsler Adult Intelligence Scale-Fourth Edition (Wechsler, 1955) was administered and established cutoff scores were used to screen all participants for nondemented status. The present study includes a subset of those participants who also completed diffusion-weighted neuroimaging (n=19) prior to behavioral testing.

All participants were right-handed, as determined by a modified Edinburgh Inventory (Oldfield, 1971). The nondominant hand was evaluated using grip dynamometry (i.e., maximal grip strength), Purdue Grooved Pegboard (i.e., dexterity) (Merker & Podell, 2011), and Semmes monofilaments (Bell-Krotoski, Fess, Figarola, & Hiltz, 1995) tests to characterize sensory function, respectively. Participants also completed the Short-Form Geriatric Depression Scale (Yesavage & Sheikh, 1986) and Katz Activities of Daily Living questionnaire (Katz, Downs, Cash, & Grotz, 1970) to measure for depressive symptoms and ability to independently complete motor tasks at home, respectively. Participants used their dominant hand to complete the Rey-Osterrieth Complex Figure Test (Osterrieth, 1944), a standardized complex figure drawing test that measures visuoconstruction (Figure Copy) and delayed visuospatial memory (Delayed Recall). Participants were first asked to draw a replicate of a complex image as precisely as possible; once finished, all visual stimuli were removed from the testing area. Thirty minutes later, participants were asked to redraw the figure from memory (Fig. 7.1A). A single rater scored each test using established testing guidelines to reduce interrater variability; higher scores indicate better delayed visuospatial memory.

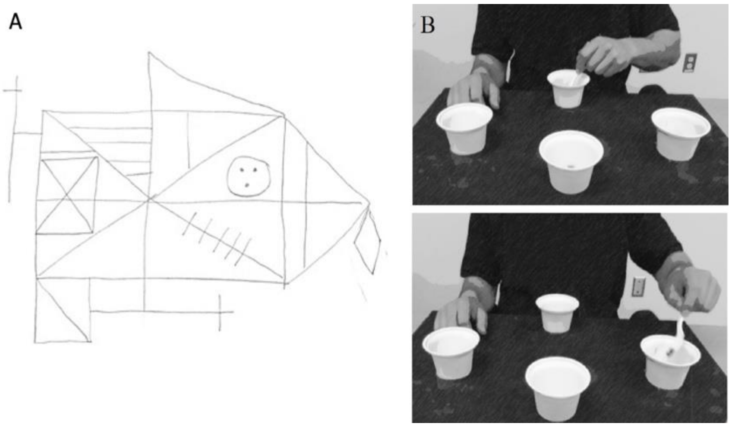

Figure 7.1. A. Participants completed the Rey-Osterrieth Complex Figure Delayed Recall test (measures delayed visuospatial memory). An example drawing from one of the participants is shown. B. Participants used their nondominant hand to perform the motor task that mimicked the upper extremity movements required to feed oneself. This image is adapted from the "Dexterity and Reaching Motor Tasks" by MRL Laboratory that is licensed under CC BY 2.0.

Motor skill retention

As described previously (Lingo VanGilder, Lohse, et al., 2021), the functional motor task used for training and retention simulated the reaching and dexterity movements required to feed oneself with a utensil (Fig. 7.1B) yet has also been validated against a more commonly used motor learning paradigm (Schaefer & Hengge, 2016). Briefly, the experimental apparatus is comprised of four plastic cups adhered to a board; three of the cups are ‘target’ cups that are located radially around a center ‘home’ cup that is aligned with the participant’s midline. The participant must use a standard plastic spoon with their nondominant hand to acquire two beans at a time from the ‘home’ cup and transport them to one of the target cups. The participants are instructed to transport the beans first to the target cup located ipsilateral to the participant’s nondominant hand. They then scoop two more beans from the ‘home’ cup and transport them to the middle target cup, then another two beans to the contralateral cup. The home cup contains 30 beans, resulting in 15 total reaches (5 target cycles) per trial. Trial time is the measure of performance, which is the elapsed time from when the participant picks up the spoon until the last of the beans are deposited into the last target cup.

Participants completed 50 training trials (i.e., a total of 750 reaches) and trial times were averaged across five trials to comprise a ‘block’ (thus, participants completed 10 blocks of five trials each across the training session). One-week skill retention was measured as the difference in performance between the last training block and a retest block that was completed one week later.

Neuroimaging acquisition

Participants underwent diffusion magnetic resonance imaging at the Keller Center for Imaging Innovation at Barrow Neurological Institute, Phoenix, Arizona. A 3-Tesla Philips Ingenia MRI (Philips, Healthcare) was used to acquire data using single-shell diffusion weighted acquisitions with the following parameters: 32 diffusion-encoding directions (b-value: 2500 s/mm^2. TR/TE: 7065/119 ms; flip-angle = 90°; matrix: 92 × 90; voxel size: 3.0 mm × 3.0 mm; slice thickness: 3.0 mm; number of averages = 1) and one B0 image at the beginning of the acquisition. All MR images were screened for neuropathology by a licensed neuroradiologist prior analysis.

Neuroimaging preprocessing

DICOM images were converted to NIFTI using dcm2niix and were preprocessed using MRtrix 3.0 (Tournier et al., 2019) and FSL 6.0.0 (FMRIB, Oxford, UK). The raw diffusion-weighted images were denoised (dwidenoise) and Gibbs ringing artifacts were removed (mrdegibbs). A whole brain mask was created to extract brain from non-brain tissues (dwi2mask). Data were then corrected for motion and eddy currents by eddy (FSL). To account for the rotational component of registration, the b-vector files were compensated after motion correction and prior to calculating the b matrices. B1-field inhomogeneity was corrected for (dwibiascorrect), and all images were upsampled to 1.25 mm (mrgrid) to improve coregistration with the MNI-ICBM152 template from the Montreal Neurological Institute (MNI). For each acquisition, a diffusion tensor model was fit at each voxel to calculate fractional anisotropy (FA) and radial diffusivity (RD) maps (dtifit, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki).

Using the B0 images from all subjects (n = 19), a group template was created using buildtemplateparallel.sh included in the advanced normalization tools (ANTs, http://stnava.github.io/ANTs/). Maps were then nonlinearly coregistered to this template using WarpImageMultiTransform (ANTs) and were spatially smoothed (FSL) using a Gaussian kernel (sigma, 2 mm). The group template was transformed from template space to MNI space using antsResistrationSyN.sh (ANTs).

Statistical analysis

JMP Pro 15.0 (SAS) was used to process participant behavioral data. To reduce the dimensionality of our statistical model and address collinearity among model predictors (i.e., mitigate the effect of reduced statistical significance due to collinearity between skill retention and visuospatial test scores), principal component analysis (PC) was used to create a ‘composite score’ that represented the shared variance of skill retention and Delayed Recall score for each participant. Since our previous work has shown a relationship between these two variables (Lingo VanGilder, Hooyman, et al., 2021; Lingo VanGilder, Lohse, et al., 2021), the PC analysis allowed for consideration of only the shared variance between them as an independent variable. Only PCs with an eigenvalue greater than one were carried forward in subsequent analyses.

Using MATLAB 2020 (MathWorks, Inc.), significant PCs and age (a covariate of noninterest) were entered into a general linear model that was applied at each voxel for each diffusion map and an FDR-correction was applied to account for multiple statistical tests. Clusters were defined as at least 100 contiguous voxels where the FDR corrected p-value was < 0.01; clusters were transformed from template space to MNI using antsApplyTransforms (ANTs) and the Johns Hopkins University JHU atlas (Hua et al., 2008; Wakana et al., 2007) was used to identify the neuroanatomical location of each cluster.

Results

Participant characteristics, motor and sensory data are presented in Table 1. Overall, participants demonstrated normal tactile sensation, grip strength, and dexterity performance consistent with that of established normative values (Bell-Krotoski et al., 1995; Earhart et al., 2011; Mathiowetz et al., 1985).

Table 7.1. Participant characteristics.

	Mean ± SD	Median	Range
Age (years)	68.4 ± 6.8	66	58-87
Education (years)	17.1 ± 1.9	18	14-20
Tactile sensation	3.4 ± 0.5	3.6	2.8-4.3
Grip strength (kg)	24.9 ± 9.4	23.3	10.7-40
Grooved Pegboard (s)	97.1 ± 38.7	84.5	65.9-206.5
Activities of Daily Living	6 ± 0	6	6-6
Geriatric Depression Scale	0.86 ± 2.10	0	0-8.2
Rey Delayed Recall	15.20 ± 5.67	16	2-25

Note. N=19; 6 males and 13 females. A subset of participants completed the Geriatric Depression Scale (n=15; male=5); scores were averaged across all visits.

Motor training data are presented in Figure 7.2A; we observed a significant difference between the baseline and final training blocks (p=0.0087, 95% CI [-9.68, -0.99]) and no difference between the final training and retest blocks (p=0.1823, 95% CI [-1.48, 7.45]), indicating that overall participants learned the motor task across the training trials and retained the skill over a period of one week without practice. Figure 7.2B demonstrates that Delayed Recall and motor skill retention scores were positively correlated (R^2=0.35; p=0.0079, 95% CI [0.18, 0.82]). These values are reported to simply confirm that participants did indeed learn the motor task (as indicated by one-week retention) and that the amount of motor skill retention was positively related to Delayed Recall scores.

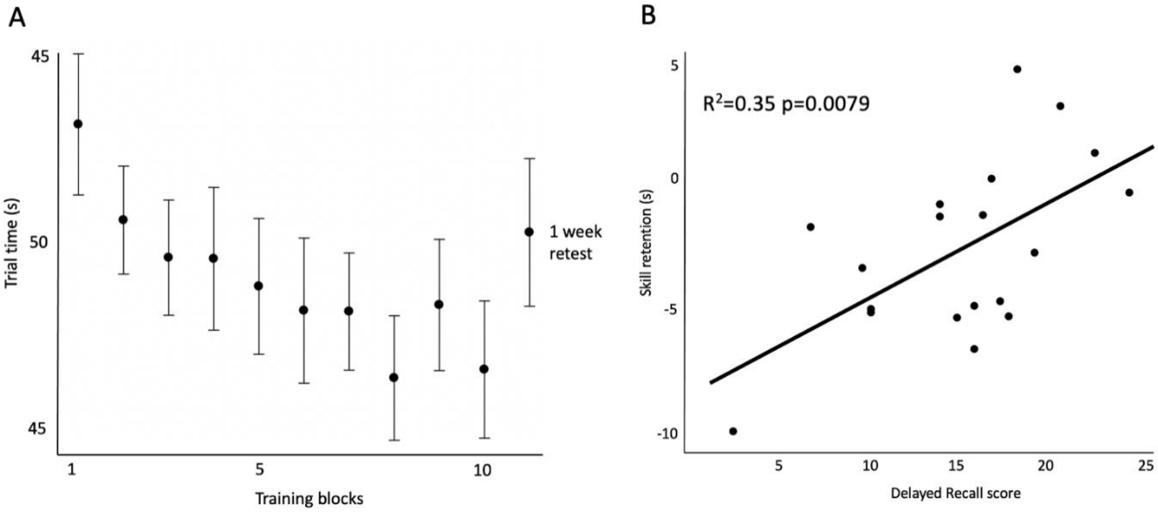

Figure 7.2. A. Participants completed 50 training trials of the reaching task and were retested one week later to determine skill retention. Trials were consolidated into blocks of five trials each. Mean motor performance (trial time in seconds) is plotted on the y-axis, where lower values indicate better performance; vertical error bars show standard deviation. B. Skill retention was measured as the last block of the training session subtracted by the retest block (one week later). Participants' skill retention is on the y-axis and Delayed Recall scores are on the x-axis; the figure illustrates that skill retention and Delayed Recall scores are positively correlated, where higher Delayed Recall scores predict better skill retention.

Only one principal component emerged from the PC analysis with an eigenvalue > 1, which accounted for 79.49% of the variance among one-week skill retention and Delayed Recall scores; factor analysis results showed that both variables equally loaded onto the PC at 0.79 (where values closer to 1 indicate that each variable's variance is wholly explained by the PC). Figure 7.3 illustrates that the PC was positively correlated with one-week skill retention and Delayed Recall scores, illustrating that the PC did indeed quantitatively represent the shared variance of both participant motor skill retention and Delayed Recall scores.

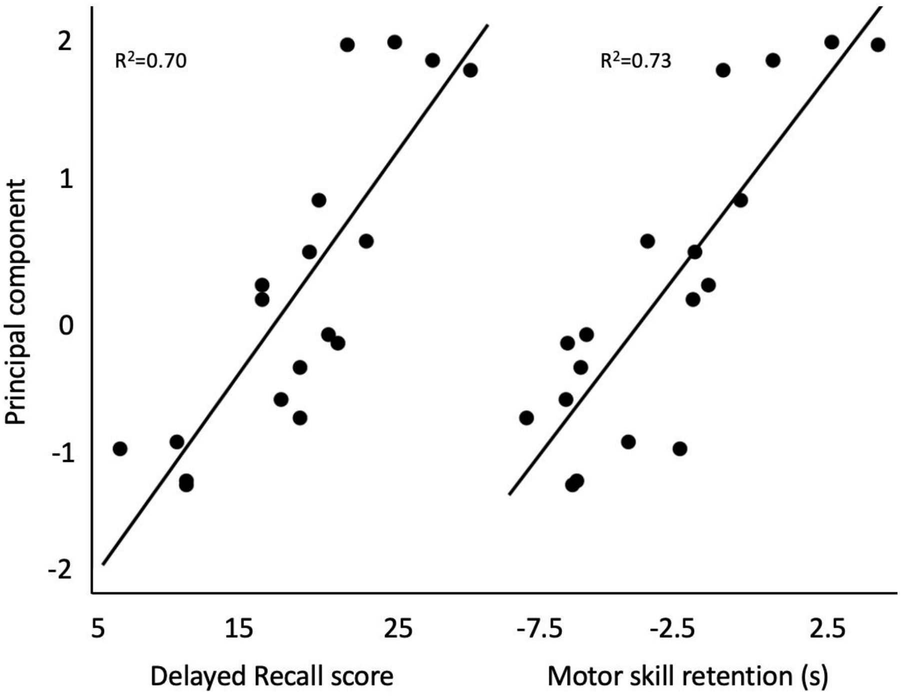

Figure 7.3. Principal component values (y-axis) for each participant was highly correlated with their one-week skill retention and Delayed Recall scores (x-axes), demonstrating that it was indeed a good representation of the shared variance of both behaviors.

Results of the voxel-based analysis are provided in Table 7.2. For FA, positive correlations were found in bilateral anterior thalamic radiations (ATR), corticospinal tracts (CST; in brainstem), and the right superior longitudinal fasciculus (SLF); a negative cluster was observed in the left hemisphere that comprised atlas regions of the SLF, ATR, and (superior) CST (Fig. 7.4A). For RD, a positive cluster was observed in this same region and negative clusters were found in the right ATR, bilateral CST (in brainstem), and left SLF (Figure 7.4B). Overall, these results indicate that the integrity of regions within the SLF, ATR, and CST were positively related to one-week skill retention and delayed visuospatial memory; the anatomical overlap between the negative and positive FA and RD clusters, respectively, may be due to well-known model limitations (Alexander, Hasan, Lazar, Tsuruda, & Parker, 2001; Hirsch, Bock, Essig, & Schad, 1999; Jones & Cercignani, 2010) and is discussed further.

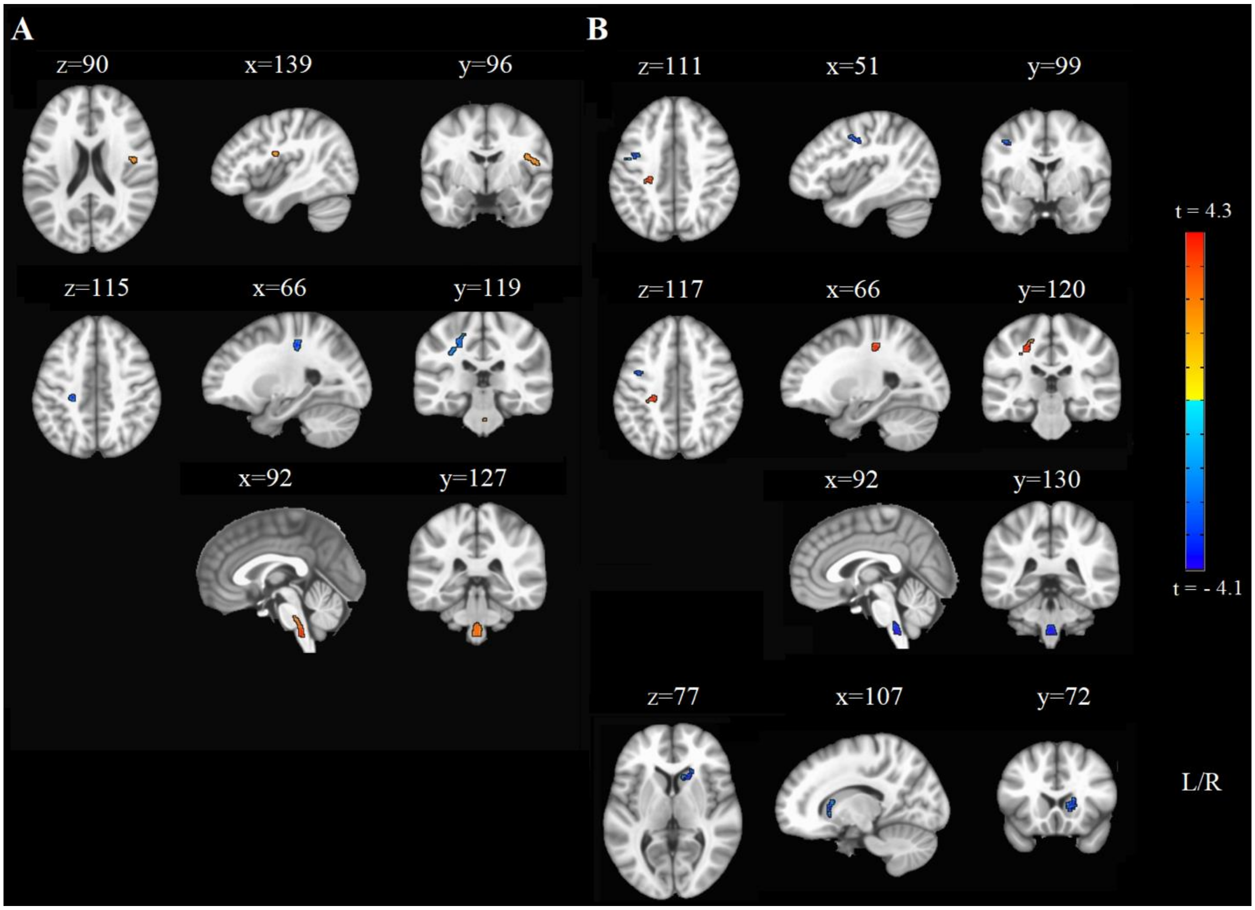

Figure 7.4. Whole-brain A) fractional anisotropy and B) radial diffusivity results are shown. In Panel A, the first row illustrates the large positive cluster in the right SLF (orange), the second row illustrates the negative cluster in the left CST/ATR/SLF, and the third row illustrates the positive cluster in bilateral CST in the brainstem. In Panel B, the first row shows the negative cluster in the left SLF, the second row shows the positive cluster in the ATR/CST, and the third row illustrates the negative cluster in the bilateral CST in the brainstem. The last row shows the negative cluster in the right ATR.

Table 7.2. Whole-brain fractional anisotropy and radial diffusivity results.

JHU (tractography)	**POSITIVE**			**NEGATIVE**		
	Fractional anisotropy					
	% volume	**t-value**	**COG (mm)**	**% volume**	**t-value**	**COG (mm)**
ATR (L)	0.12	3.894	-0.52 -34.4 -44.5	0.13	4.122	-23.4 -27.2 42.3
ATR (R)	0.15	3.926	1.6 -35.0 -45.6	-	-	-
CST (L)	0.40	4.060	-1.9 -35.6 -48.0	0.67	3.507	-23.3 -28.1 43.3
CST (R)	0.60	4.271	2.3 -35.1 -47.5	-	-	-
SLF (L)	-	-	-	0.13	3.225	-28.5 -28.1 38.8
SLF (R)	0.32	3.236	48.5 -4.6 18.0	-	-	-
SLF (temporal, L)	-	-	-	0.11	2.935	-31.6 -28.9 34.3
	Radial diffusivity					
	% volume	**t-value**	**COG (mm)**	**% volume**	**t-value**	**COG (mm)**
ATR (L)	0.09	3.847	-23.0 -27.7 44.2	-	-	-
ATR (R)	-	-	-	0.68	2.829	15.0 12.8 0.4
CST (L)	0.72	3.332	-23.1 -28.3 45.9	0.16	3.130	-1.8 -36.7 -50.5
CST (R)	-	-	-	0.22	3.723	2.8 -37.6 -52.7
SLF (L)	0.11	3.222	-27.6 -28.1 42.0	0.37	3.036	-40.5 -8.9 38.2
SLF (R)	-	-	-	-	-	-
SLF (temporal, L)	-	-	-	0.44	3.062	-42.8 -10.2 37.4

Note. Center of gravity coordinates (X, Y, Z) are in MNI space. ‘% volume’ is the percentage of voxels from each atlas region of interest that overlap with each cluster.

L = left.

R = right.

ATR = anterior thalamic radiation.

CST = corticospinal tract.

SLF = superior longitudinal fasciculus.

COG = center of gravity.

Discussion

This study aimed to extend our previous work that reported the SLF was related to within-session practice effects in a small sample of individuals with stroke pathology (Regan et al., 2021). Here, we used whole-brain analyses to determine the white matter correlates of the behavioral relationship between one-week motor skill retention and delayed visuospatial memory test scores in nondemented older adults. Results indicated that regions within the bilateral CST, SLF, and ATR were associated with one-week motor skill retention and delayed visuospatial memory performance independently of age and support that clinical visuospatial testing may prognose motor training responsiveness and the integrity of specific white matter tracts.

A possible explanation for the observed behavioral relationship between Delayed Recall scores and one-week motor skill retention is that visuospatial memory and motor learning engage overlapping neural pathways. Our results are consistent with reports from neuroanatomical and neurophysiological studies implicating the CST (Bleyenheuft et al., 2020; Christiansen et al., 2020; Song, Sharma, Buch, & Cohen, 2011) and SLF (Budisavljevic et al., 2017; Regan et al., 2021; Steele et al., 2012) in motor learning behaviors, and the SLF (Chechlacz, Gillebert, Vangkilde, Petersen, & Humphreys, 2015; Hoeft et al., 2007; Mayer & Vuong, 2014; Multani et al., 2016; Shinoura et al., 2009) and anterior thalamic nuclei (Aggleton & Nelson, 2015; O‘Mara, 2013; Peyrache, Lacroix, Petersen, & Buzsáki, 2015; Sutherland & Hoesing, 1993; Taube, 1995; Winter, Clark, & Taube, 2015) in visuospatial processing and memory. In line with this, a recent study collected resting state functional MRI from older adults to test functional connectivity of neural networks associated with Rey-Osterrieth Complex Figure Test performance; notably, the authors reported significant connections between both motor-parietal and motor-hippocampal regions (Suri et al., 2017). Moreover, the ATR is thought to relay motor signals via the thalamocortical pathway and has been linked to spatial memory in nonhuman primates (Parker & Gaffan, 1997; Spets & Slotnick, 2020), further implicating the role of motor networks in visuospatial memory.

In our previous study (Regan et al., 2021), results indicated diffusion metrics of the SLF were related to the amount of upper-extremity motor skill acquired within a training session, whereas those of the CST did not. Results of the present study suggest that fractional anisotropy and radial diffusivity of the CST, SLF, and ATR were related to one-week skill retention on this same motor task. A potential reason for our different results could be due to the methodological approaches applied to analyze the neuroimaging data and phase of motor skill learning (i.e. acquisition versus retention). Regan et al. (2020) conducted a ROI-based approach that targeted the diffusion metrics of the SLF, whereas the whole-brain approach used here applied the general linear model at each voxel containing white matter. In addition, separate phases of motor skill learning engage distinct neural networks (Doyon & Benali, 2005; K.R., K., L.A., & N.J., 2014), thus, it is plausible that the difference in timescales at which motor behavior was measured explains the discrepancy between the significant white matter regions reported. Regan et al. (2020) evaluated within-session practice effects, which was measured by calculating the change score between baseline and final performances; therefore, this metric included baseline performance and skill acquisition (in contrast to skill *retention*).

Similarly, Borich and colleagues examined the white matter correlates of motor learning on a 2-D visuomotor pursuit task by measuring the difference in performance between baseline and a delayed retention trials; they collected diffusion-weighted images from a small group of individuals with stroke pathology after participants completed five separate training sessions. Using whole-brain analyses, their group reported that regions within the posterior limb of the internal capsule were related to better skill retention (Borich, Brown, & Boyd, 2014). Again, the purpose of the present study was to identify the structural white matter correlates of one-week motor skill retention and delayed visuospatial memory, thus, our neuroimaging results reflect this behavioral relationship rather than that of motor behavior alone.

One limitation of this study regards the diffusion-weighted image acquisition protocol. Recent work has shown that free-water correction improves the accuracy and sensitivity of white matter analyses (Bergamino, Pasternak, Farmer, Shenton, & Hamilton, 2016; Bergamino, Walsh, & Stokes, 2021) by fitting a bi-tensor model to each voxel to account for partial volume effects (i.e., voxels that contain brain tissue and free-water such as cerebrospinal fluid); however, it is advised to apply this technique to single-shell diffusion-weighted images that were acquired with b-values less than 1000 s/mm^2 (Pasternak, Shenton, & Westin, 2012). Our data were acquired with b-value = 2500 s/mm^2, therefore we were unable to apply free-water correction due to our imaging acquisition. Moreover, positive and negative correlations among a single region of interest emerged from our whole-brain analyses; for example, results indicated several significant clusters present along the CST: a negative correlation in the left superior part of the tract and positive correlation in the brainstem. We observed anatomical overlap between negative and positive FA and RD clusters, respectively, in this region and interpret this finding was likely due to partial volume effects (i.e., crossing fibers as significant clusters in the SLF and ATR were also observed in this region); this interpretation is consistent with other work (Steele et al., 2012). It is prudent to mention that results may also be susceptible to artifact due to image smoothing and/or normalization registration during the preprocessing methodology; to address this potential limitation, we visually inspected all images to ensure satisfactory coregistrations. While this study design allowed us to test if pre-existing neuroanatomical measures of white matter tracts were associated with one-week skill retention and Delayed Recall test scores, a future study that involves pre- and post-training neuroimaging will allow us to test the robustness of these findings (i.e., Will we observe microstructural changes in these same tracts?).

Results of this study have several potential clinical implications. First, visuospatial testing may be a more feasible biomarker of motor therapy responsiveness than measures derived from neuroimaging or neurophysiological data (e.g., presence of a motor-evoked potential). For example, while previous studies have shown that whole-brain volume metrics (e.g., T1 scanning, etc.) may predict motor therapy outcomes (Wang et al., 2018), a visuospatial test is quick and easy to administer during the duration of a typical clinical visit, making it a more feasible alternative in terms of predicting motor rehabilitation responsiveness. Second, we have previously observed the behavioral relationship between cognitive testing and upper-extremity skill retention across patient populations (Lingo VanGilder, Hooyman, et al., 2021; VanGilder et al., 2021), suggesting this relationship is not disease-specific and is broadly generalizable across geriatric populations. Given the prevalence of cognitive impairment even in community-dwelling older adults (Burke Quinlan et al., 2015; Quinlan et al., 2018; Tozlu et al., 2020), it is plausible that older adults seeking physical therapy for a variety of reasons could have subtle underlying visuospatial impairments that may impede their responsiveness to therapy, regardless of the etiology (i.e., white matter hyperintensities (Fleischman et al., 2015), stroke, etc.). Third, our results open new avenues of research as we have begun to explore motor learning paradigms to better understand AD progression (Schaefer, Duff, Hooyman, & Hoffman, 2021; Schaefer, Malek-Ahmadi, Hooyman, King, & Duff, 2021). Research has shown that accelerated decline in visuospatial function may be an early biomarker of prodromal AD (Johnson, Storandt, Morris, & Galvin, 2009; Mitolo et al., 2013; Rizzo, Anderson, Dawson, Myers, & Ball, 2000). Given that ATR degeneration is associated with AD progression (Torso et al., 2015; Zhu et al., 2015) and that the complex figure copy/recall tests may predict AD onset (up to 20 years before clinical AD) (Caselli et al., 2020), results from this study suggest that an assessment of motor learning could help better identify disease progression in asymptomatic stages (Schaefer, Hooyman, & Duff, 2020; Schaefer, Malek-Ahmadi, et al., 2021).

Conclusions

In summary, nondemented older adults learned an upper-extremity motor task and retained the skill one week later. The amount of skill retained was related to performance on a clinical test of delayed visuospatial memory; this behavioral relationship was related to the integrity of bilateral corticospinal tracts, anterior thalamic radiations, and the superior longitudinal fasciculi, consistent with previous work. Clinical visuospatial memory testing may provide prognostic insight for one's potential to benefit from a given dose and type of motor rehabilitation as well as a target for therapeutic intervention.

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CHAPTER 8

DISCUSSION

Summary and key takeaways

Cognitive function is not currently incorporated into standard of care to prognose motor rehabilitation outcomes, despite evidence that suggests cognition and motor skill learning abilities are positively related. One objective of this body of work was to identify cognitive predictors of upper-extremity skill learning within the context of motor rehabilitation. Overall, results indicated that performance on a delayed visuospatial memory clinical test may predict short- and long-term motor skill retention in older adults and individuals with neuropathology, suggesting that clinical visuospatial memory testing may provide prognostic insight for one's potential to benefit from a given dose and type of motor rehabilitation.

Studies have shown that white matter structure is particularly susceptible to degeneration due to normal cognitive aging and neurological pathology (Ge et al., 2002; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Wang et al., 2016; Werden et al., 2017); moreover, the integrity of specific white matter tracts connecting motor (frontal and parietal) and visuospatial (parietal) cortical regions have been implicated in various forms of learning (Ripollés et al., 2017; Takeuchi et al., 2010) and the functional connectivity of these same regions were related to performance on a delayed visuospatial memory test, independent of cortical grey matter volume (Suri et al., 2017). Collectively, this led to the hypothesis that variance in white matter structure may underlie the variance in the behavioral relationship between motor skill learning and delayed visuospatial memory performance. Thus, a secondary objective of this work aimed to identify the neuroanatomical white matter correlates that contribute to the predictive relationship between skill learning and cognitive function. Neuroimaging results indicated that this behavioral relationship was positively related to the integrity of bilateral corticospinal tracts, anterior thalamic radiations, and the superior longitudinal fasciculi, consistent with previous work. These results suggest that clinical visuospatial testing may localize a neuroanatomical target for therapeutic intervention.

Remaining questions, limitations, and future work

Visuospatial function is required to adequately execute upper-extremity movements; however, the finding that visuospatial function is related to the *change* in motor performance, i.e., learning, is less intuitive. Theoretical models of motor skill learning posit that early motor skill learning is dependent on executive processes (although there remains ambiguity as to which cognitive domains are most relevant: attention (Song, 2019), working memory (Buszard et al., 2017), visuospatial working memory (Bo & Seidler, 2009; Langan & Seidler, 2011), etc.), whereas later stages of learning are dependent upon the neural structures within the corticostriatal circuit (e.g., cerebellum, striatum, frontal and parietal regions) (Doyon & Benali, 2005). As cognition is foundational for motor learning and clinical populations often present with concomitant motor and cognitive deficits (Cengić, Vuletić, Karlić, Dikanović, & Demarin, 2011; Goldman et al., 2018; Müller-Oehring et al., 2021), this dissertation supports this theoretical framework and extends it within the context of clinical motor rehabilitation by emphasizing the value of assessing cognition to prognose motor training outcomes. This work should be replicated in more severe clinical populations to determine if we can model a patient's progression through motor rehabilitation using their cognitive data.

Another remaining question is why I did not observe a relationship between one-month motor skill retention and delayed visuospatial memory (in Chapters 5 and 6) in the subpopulation of participants (n=19) that underwent neuroimaging (in Chapter 7). In Lingo et al. 2021 (Lingo VanGilder, Lohse, Duff, Wang, & Schaefer, 2021) and Lingo et al. 2021 (Lingo VanGilder, Hooyman, Bosch, & Schaefer, 2021), baseline performance was included in the regression model as a predictor of one-month follow-up performance (this model was designed to avoid statistical confounds that would exist if baseline performance was included as a predictor of the change score that would include baseline performance in its calculation). In Lingo et al. (in review, Chapter 7), only 19 of the 45 participants underwent neuroimaging and the subsequent analyses required that motor skill learning be represented by one predictor variable, i.e., a change score (for inclusion in the regression model that predicted white matter tract integrity) (Lingo VanGilder, Bergamino, et al., 2021). I observed a weak behavioral relationship between the one-month motor skill change score and delayed visuospatial memory performance in this subpopulation. In contrast, the relationship between one-week skill retention demonstrated a strong relationship with delayed visuospatial memory scores, consistent with my previous work ((Lingo VanGilder, Hengge, Duff, & Schaefer, 2018), Chapter 4) as well as Doyon and Benali's theoretical framework. While the sub-study may have been underpowered (at n=19) to observe significant behavioral effects of one-month motor performance, I think this discrepancy in findings may also highlight that the calculation used to measure motor learning should be carefully considered. In Lingo et al. 2021 and Lingo et al. 2021 (Chapters 5 and 6), baseline performance was a model predictor of one-month performance, therefore this model was unable to evaluate the degree of learning at different stages (i.e., acquisition, consolidation, and retention), which would influence one's one-month follow-up performance; thus it is plausible that the observed behavioral relationship between delayed visuospatial memory and one-month skill performance was due to *earlier changes in performance during the acquisition phase*. A future study that replicates this experimental protocol in a larger population would clarify if the discrepancy was due to sample size limitations. Nevertheless, the objective of my neuroimaging study was to extend our collaborator's findings that indicated within-session practice effects on an upper-extremity motor task were related to the integrity of specific white matter tracts in individuals with stroke (Regan et al., 2021); thus, assessing motor skill at one-week was a more appropriate measure to accomplish that.

There is evidence that cognitive training prior to or concurrent with, may yield better motor training outcomes (see Chapter 2 for review), although the nature of this relationship still remains unstudied. Future work that investigates if motor skill learning is mediated by (or simply correlated with) visuospatial function is needed (i.e., does visuospatial training improve motor performance?). A recent study reported that visuomotor training (i.e., videogame play) improved proficiency of specific surgical techniques in young surgeons, which suggests that improving visuospatial function may improve performance of [unrelated] motor skills (Datta et al., 2020; Rosser et al., 2007). Similarly, whether specific white matter regions mediate the behavioral relationship between visuospatial and motor learning still remains unknown. Future work that investigates if neuromodulatory techniques can exploit the neuroplasticity of specific white matter tracts (or cortical regions involved in visuospatial function, visuomotor control, etc.) may improve clinical neurorehabilitation outcomes.

Final thoughts

In general, this dissertation supports that clinical practice needs to move towards implementing more personalized approaches in standards of care. Since older adults have varying motor learning capacities and will therefore respond differently to the same training regimen, the one-size-fits-all approach is a critical barrier within motor rehabilitation therapy. Collectively, results of this dissertation support that clinical visuospatial testing may predict motor learning ability and that this behavioral relationship persists in individuals across the lifespan and spectrum of neuropathology. I emphasize that the results of this work do not suggest that individuals with visuospatial deficits should be filtered out of the motor rehabilitation regimen. The dose of training (extent, duration, and interval) was largely constant in these studies, such that all participants experienced the same amount of practice, and within that amount of practice, some participants learned while some did not. It is plausible that individuals with visuospatial deficits likely need a higher dose of motor practice (therapy) and/or concurrent cognitive training (such as visuospatial training).

While there is abundant research that attempts to predict changes in post-stroke upper-extremity impairment following therapy, the methodology involved are time- and cost-intensive (e.g., neuroimaging and neurophysiological signal analyses, etc.) and recent work in machine learning has shown that the inclusion of sophisticated measures may not improve prediction accuracy beyond basic clinical measures (i.e., baseline Fugl-Meyer score). Although inclusion of tests of delayed visuospatial memory performance may improve prediction of motor learning ability, there are several important remaining questions that should be addressed to determine if it is worth a therapist's time and effort to administer these tests during the clinical visit, namely: Can Delayed Recall test scores be used to predict a patient's motor rehabilitation outcome? Our work thus far has evaluated motor training responsiveness using a specific motor task; therefore, it remains unknown if the predictive relationship will persist using other measures of motor learning or motor rehabilitation outcomes (e.g., change in Fugl-Meyer scores). Perhaps an equally important question is: If the predictive relationship does persist- is the extent of *improved prediction* clinically significant (i.e., what is the effect-size of the Delayed Recall test score and is it clinically meaningful)? If inclusion of Delayed Recall scores improves prediction by only several units - is that gain in predictive accuracy worth the time and expertise required to appropriately administer, grade, and interpret the test? While these considerations are outside the scope of this dissertation, future work should address these questions to evaluate the potential clinical utility of cognitive testing to prognose motor rehabilitation outcomes.

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APPENDIX A

PERMISSIONS

PERMISSION FROM CO-AUTHORS

Chapters 2-7 are adapted from published (including *in press* and *under review*) articles and have been modified to best fit the formatting requirements of this document; the analyses, results interpretations and discussions remain unchanged. All co-authors have granted permission for the reproduction of each respective manuscript within this document. The full citation for each article is provided below:

Chapter 2: Lingo VanGilder, J., Hooyman, A., Peterson, D. S., & Schaefer, S. Y. (2020). Post-Stroke Cognitive Impairments and Responsiveness to Motor Rehabilitation: A Review. *Current Physical Medicine and Rehabilitation Reports*. https://doi.org/10.1007/s40141-020-00283-3

Chapter 3: Lingo VanGilder, J., Lennon-Lopez, C., Paul, S. S., Dibble, L. E., Duff, K., Schaefer, S.Y. (in press). Relating Global Cognition with Upper-Extremity Motor Skill Retention in Individuals with Mild-to-Moderate Parkinson Disease. *Frontiers Rehabilitation Sciences.*

Chapter 4: Lingo VanGilder, J., Hengge, C. R., Duff, K., & Schaefer, S. Y. (2018). Visuospatial function predicts one-week motor skill retention in cognitively intact older adults. *Neuroscience Letters*, *664*, 139–143. https://doi.org/https://doi.org/10.1016/j.neulet.2017.11.032

Chapter 5: Lingo VanGilder, J., Lohse, K. R., Duff, K., Wang, P., & Schaefer, S. Y. (2021). Evidence for associations between Rey-Osterrieth Complex Figure test and motor skill learning in older adults. *Acta Psychologica*, *214*, 103261. https://doi.org/10.1016/j.actpsy.2021.103261

Chapter 6: Lingo VanGilder, J., Hooyman, A., Bosch, P. R., & Schaefer, S. Y. (2021). Generalizing the predictive relationship between 1-month motor skill retention and Rey-Osterrieth Delayed Recall scores from nondemented older adults to individuals with chronic stroke: a short report. *Journal of Neuroengineering and Rehabilitation*, *18*(1), 94. https://doi.org/10.1186/s12984-021-00886-4

Chapter 7: Lingo VanGilder, J., Bergamino, M., Hooyman, A., Fitzhugh, M., Rogalsky, C., Stewart, J. C., Beeman S.C., Schaefer, S.Y. (under review). A Preliminary Study to Evaluate White Matter Structural Correlates of Delayed Visuospatial Memory and One-Week Motor Skill Retention in Nondemented Older Adults. *PLOS ONE.*