FACTORS IMPACTING EXPLICIT LOCOMOTOR LEARNING POST STROKE

by

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A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

Winter 2021

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FACTORS IMPACTING EXPLICIT

LOCOMOTOR LEARNING

POST STROKE

by

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ACKNOWLEDGMENTS

Throughout my Ph.D. work, I have been lucky to be surrounded by people who have fostered my personal and professional development while making the process intellectually challenging and rewarding. Without their support, this journey would not have been as successful nor would it have been as fun.

First, thank you to my advisor and mentor, Dr. Darcy Reisman. Throughout this process, you have continually challenged and supported me so that I could succeed. You masterfully provided me the right balance of guidance and freedom to become a better researcher. Further, your advice on balancing a successful scientific career and a fulfilling personal life will continue to serve as a road map as I move forward in my career. I cannot thank you enough.

Additionally, my dissertation committee member, Drs. Matthew Cohen, Susanne Morton, and Ryan Roemmich, have provided valuable scientific and personal guidance throughout this process. Without your insights and feedback, I would not be the scientist I am today. Thank you for your time, your thoughts, and your expertise.

To my lab mates, in particular Bobby Charalambous, Xin Li, Elizabeth Thompson, Jessica Galgiani, Allison Miller, Jonathan Wood, and Soumya Bhat thank you for your support and your friendship. Without each of you, there would have been far fewer laughs over pots of crab fries at Homegrown and far more struggles. I cannot wait to see your successes moving forward.

I would also like to thank the DRI ResCore for managing the stroke registry, Tami Wright for completing clinical evaluations, and the undergraduate volunteers,

specifically Tim Gauge, who helped with data collections and data processing. Thank you all for your help, without which I would still be recruiting subjects and processing data.

I would also like to thank all of the stroke survivors and healthy adults who volunteered their time and shared their experiences with me during the completion of these studies. You were all a constant reminder of why I became a Physical Therapist and why I pursued my Ph.D. This work could not have been completed without you.

Finally, I would like to express my deepest gratitude to my family: my parents, Nancy and Steve; my siblings and their spouses, Matthew, Charlotte, Katie, and Deepak; my significant other, David; and my faithful pup, Trigger. This short blurb is not nearly enough to express my appreciation, but your unwavering love, support, and friendship have been and will continue to be a constant source of joy and stability. Thank you all.

FUNDING SOURCES

This work was supported by grants from the National Institutes of Health under grants 1R01-HD-078330-01A, S10RR028114-01, and F31NS111806 and The Foundation for Physical Therapy Research under the Florence P. Kendell scholarship and the Promotion of Doctoral Studies (PODS) Levels I and II. Lastly, this work was supported through funding from the University of Delaware, specifically the University Dissertation Fellowship Award and two Professional Development Awards.

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ABSTRACT

Stroke results in numerous physical impairments that limit functional mobility and make it the leading cause of long term disability in the United States. A primary goal for rehabilitation professionals and stroke survivors is to improve walking abilities. Despite efforts to improve walking, not every stroke survivor achieves optimal outcomes. This is in part due to our lack of understanding of the processes and factors underlying relearning to walk after stroke. The overall purpose of this work was, therefore, to expand our understanding of locomotor learning and the factors that impact locomotor learning after stroke.

To date, sensorimotor adaptation, a largely implicit and automatic form of learning, has been the primary source of our knowledge about locomotor learning; however, this is not the only type of locomotor learning. In fact, clinical practice is dominated by interventions that rely heavily on strategic learning rather than sensorimotor adaptation. Strategic learning is explicit and relies on conscious control. As a result, research focused specifically on this type of learning is needed to improve rehabilitation interventions through a broader understanding of locomotor learning. Thus, this work used a visually-guided walking paradigm to examine *explicit, strategic locomotor learning* and the factors that impact it after stroke.

In Aim 1 we found that stroke survivors were able to learn and remember a new walking as well as healthy adults. Importantly, however, there was significant variability in both stroke survivors and healthy adults. This finding is important

because it demonstrates that this type of learning may be appropriate in post-stroke rehabilitation, but optimal only for a subset of individuals.

In Aim 2, we showed that cognition explained a significant portion of variability in learning and retention of a new walking pattern. Interestingly, fluid cognition rather than visuospatial working memory, specifically, was found to be a significant predictor of learning and retention. This is important as it suggests that understanding someone's cognitive abilities may help in the design and delivery of more personalized rehabilitation interventions after stroke.

Lastly, in Aim 3 we found that exercise priming did not significantly improve retention of the newly learned walking pattern. This is in conflict with previous findings in the upper extremity; however, there are several potential reasons for this discrepancy that should be explored in future work.

In summary, this work suggests that strategic locomotor learning and retention is intact in individuals after stroke; however, there is significant intra-subject variability, part of which can be explained by cognitive abilities. This work lays the foundation for future work to further understand the role of cognition in locomotor learning and to explore interventions that can improve explicit, strategic locomotor learning after stroke.

Chapter 1

INTRODUCTION

1.1 Post-stroke Recovery.

Approximately 795,000 people in the United States experience a stroke each year, making it the leading cause of long term disability in the United States (Benjamin et al. 2017; Mozaffarian et al. 2015). In fact, two thirds of stroke survivors experience residual neurologic deficits that lead to reduced walking activity and community participation (Mayo et al. 1999; Michael et al. 2005). Additionally, only 50% of individuals regain the ability to walk independently following their stroke (Jorgensen et al. 1995). These deficits in walking are accompanied by a higher risk of secondary complications including heart disease, diabetes, depression, and recurrent stroke (Billinger et al. 2012; Mozaffarian et al. 2015). As a result, recovering and improving walking function post-stroke is a common goal of both stroke survivors and rehabilitation professionals (Bohannon et al. 1988).

Motor recovery post-stroke is often considered a two-fold process occurring spontaneously in the weeks following stroke and in response to environmental demands through neural reorganization, or neuroplasticity (Mayo et al. 1999; Michael et al. 2005; Murphy and Corbett 2009). The spontaneous recovery, which occurs primarily during the first six months after stroke, is not impacted by rehabilitation (Murphy and Corbett 2009); however, neuroplasticity that occurs in response to environmental demands is activity dependent and is thought to be facilitated by rehabilitation (Kleim 2011). The amount of neuroplasticity that occurs following

stroke impacts the amount of movement recovery; thus, post-stroke rehabilitation attempts to provide interventions that maximize neuroplasticity in order to minimize functional impairments (Dancause and Nudo 2011). In order to maximize neuroplasticity, rehabilitation interventions should be based on an understanding of motor learning, since motor learning is the process by which skills are acquired by driving neural changes. Thus, an understanding of motor learning is critical to maximizing neuroplasticity and ultimately producing optimal recovery following stroke.

In the current work, we sought to advance the field's understanding of locomotor learning in individuals after stroke. Specifically, we sought to understand the impact of stroke on locomotor learning and to determine how clinical factors and acute exercise influence locomotor learning in individuals after stroke. Completion of this work provided valuable insight into the underlying learning processes that can shape the development of rehabilitation interventions that are rooted in an understanding of motor learning thereby making them more effective.

1.2 Motor Learning Terminology.

Motor learning is a broad, generic term that refers to the set of processes associated with experience that leads to relatively permanent changes in skilled behavior (Salmoni et al. 1984). In rehabilitation, the experience that drives neuroplasticity and behavioral change occurs in the form of practice. Within the broad term of motor learning, there are several terms that are used to describe stages within the motor learning process. The first stage of motor learning is the development of a new behavior that occurs through a bout of practice or some other experience (Kantak and Winstein 2012). In some groups within the motor learning field, this stage is

referred to as “learning,” but in others it is called “acquisition” or “performance.” This inconsistence in terminology is highlighted in the work of Kantak and Winstein (2012). Those who use the term performance and acquisition, argue that learning can only be assessed through a retention or transfer test (Kantak and Winstein 2012); thus, the behavior within the practice session should not be called learning. To avoid confusion, we wish to operationally define this stage of learning. In the subsequent chapters we will measure performance (i.e., behavior during the practice bout) as a way to reflect the learning that is occurring during the practice session (i.e., within session learning). One of our primary methods for doing this will be by measuring accuracy with an error measurement. Using this metric, one would expect to observe improved performance, as indicated by a reduction of error over the course of the practice bout, if a learning process was occurring (e.g., Boyd and Winstein 2004, Boyd and Winstein 2006, Borich et al 2016, Mazzoni and Krakauer 2006, Huang et al 2011, Krakauer and Mazzoni 2011, Kitago et al 2013, Taylor et al 2014). Thus, by measuring performance we can understand the short-term or immediate within session learning that is occurring.

The second important “stage” in motor learning is retention. Retention is the ability to recall the behavior that was learned at a different time than that in which it was learned (Kantak and Winstein 2012). This serves as an indicator of long-term learning and indicates the stability of the behavior that was learned during the practice bout. In subsequent chapters, we will use a 24-hour retention test to assess the stability of the behavioral changes that occurred during the practice session. Finally, consolidation, or offline learning, is a stage of the motor learning process that occurs between the practice bout and retention. This phase of motor learning results in a more

stable memory of the task that was learned; thus, successful consolidation results in good retention (Kantak and Winstein 2012; Krakauer and Shadmehr 2006).

1.3 Forms of Motor Learning.

In addition to including multiple stages, motor learning encompasses multiple forms of learning that have unique characteristics. Understanding the unique characteristics of each form of motor learning is critical to capitalizing on motor learning principles in order to develop effective rehabilitation interventions after stroke. Sensorimotor adaptation and strategic learning are two of these specific forms of motor learning that have drawn significant attention in the upper extremity (Mazzoni and Krakauer 2006; Morehead et al. 2015; Taylor and Ivry 2014; 2011; Taylor et al. 2014) and are very different (Table 1.1). Sensorimotor adaptation is typically considered an implicit learning process, meaning that it is automatic in nature (i.e. requires minimal cognitive resources) and generates no increase in verbal knowledge about the movement (Kleynen et al. 2014; Kleynen et al. 2015). Strategic learning, on the other hand, is considered an explicit learning process, meaning that it requires cognitive resources and generates verbal knowledge of the movement (Kal et al. 2016; Kleynen et al. 2014; Kleynen et al. 2015). Both forms of learning occur in

Table 1.1: Comparison between sensorimotor adaptation and strategic learning.

Sensorimotor Adaptation	Strategic Learning
Primarily implicit	Primarily explicit
Automatic process	More consciously controlled
Largely cerebellar dependent	Largely prefrontal cortex dependent
Rapidly decaying	Can be repeated on command
Well studied in locomotion	Rarely studied in locomotion
Rarely used in clinical practice	Frequently used in clinical practice

response to errors; however, the type of error that drives these two types of learning is quite different. Sensorimotor adaptation is driven by sensory prediction errors, or a mismatch in what the central nervous system expects to occur and what actually occurs. This type of learning occurs automatically in the presence of this error signal, even if performance on the task is negatively affected (Haith and Krakauer 2013; Mazzoni and Krakauer 2006; Shadmehr et al. 2010; Taylor and Ivry 2014; 2011). In contrast, strategic learning is driven by task performance errors (i.e. whether you were successful on the task or not) and prioritizes improved performance of a task (Taylor and Ivry 2014; 2011). Further, the time course of these two forms of motor learning is different. Specifically, the new behavior is learned slowly though sensorimotor adaptation, but then decays rapidly when the error signal is removed (i.e. de-adaptation) (Bastian 2008; Haith and Krakauer 2013; Martin et al. 1996; Taylor and Ivry 2014). On the other hand, strategic learning results in fast learning, but a slower decay than implicit learning with the new behavior being able to be recalled even days later when the approach cues are present (Morehead et al. 2015; Morehead et al. 2017; Taylor and Ivry 2014). Importantly, the ability of individuals to recall things that were learned through strategic learning is dependent on verbal or visual cues, such that the cue results in the implementation of the learned strategy (Mazzoni and Krakauer 2006; Morehead et al. 2015; Taylor and Ivry 2014). This, however, does not appear to be the case for sensorimotor adaptation. Lastly, past research suggests that different regions of the brain are primarily involved during sensorimotor adaptation and strategic learning, suggesting that the neural processes underlying these forms of learning are different (Mazzoni and Krakauer 2006; Taylor and Ivry 2014). Specifically, sensorimotor adaptation is primarily controlled by the cerebellum (Maschke et al.

2004; Morton and Bastian 2006; Smith and Shadmehr 2005), while the prefrontal cortex is heavily involved in strategic learning (Slachevsky et al. 2001; Slachevsky et al. 2003; Taylor and Ivry 2014). This is supported by work showing that individuals with cerebellar damage have difficulty with sensorimotor adaptation tasks during both locomotion (Morton and Bastian 2006) and upper extremity reaching (Smith and Shadmehr 2005; Tseng et al. 2007). These differences have significant implications for how these forms of learning can be effectively applied to clinical practice.

Despite the substantial differences between implicit, sensorimotor adaptation and explicit, strategic learning, recent research suggests that these learning processes, and others, can occur together during the same task (French et al. 2018; Morehead et al. 2015; Taylor and Ivry 2011; Taylor et al. 2014; Wood et al. 2020). The visuomotor rotation task in upper extremity research is a well-studied paradigm that illustrates this. In this paradigm, subjects reach towards a target while they are unable to see their hand, but are provided with feedback about their movement from a cursor on a computer screen. During the learning portion of the task, the cursor feedback is no longer accurate and instead is rotated. This rotation results in the cursor no longer hitting the target initially; however, over time the subject changes their reaching direction so that the cursor hits the target. In early studies of this task, the learning observed was believed to be occurring through sensorimotor adaptation, but recent work suggests that the learning that occurs in this task actually occurs through a combination of strategic learning and sensorimotor adaptation. This was initially demonstrated in an experiment where neurologically intact adults were provided with an explicit strategy about how to be successful with the task (Mazzoni and Krakauer 2006). When instructed on where to reach to successfully counter the rotation, subjects

immediately corrected for the rotation (i.e. they use the strategy); however, their performance gradually declined as the obligatory process of sensorimotor adaptation continued (Mazzoni and Krakauer 2006). In subsequent work, when neurologically intact adults were given a longer learning timeframe, they adjusted their strategy so that performance improved after the initial decline in performance (i.e. they change their strategy to "account" for the ongoing process of sensorimotor adaptation) (Taylor and Ivry 2011; Taylor et al. 2010). This work demonstrates that sensorimotor adaptation and strategic learning are distinct underlying processes that occur in parallel to produce the observed behavior. Interestingly, when individuals with cerebellar damage are provided a strategy about how to complete the visuomotor rotation task, they successfully use the strategy, but there is no decline in their performance as is observed in neurologically intact adults (Taylor and Ivry 2014; Taylor et al. 2010). Conversely, in individuals with damage to the prefrontal cortex, there is a greater decline in performance, suggesting that they are unable to modify their strategy (Taylor and Ivry 2014). This illustrates that neurologic damage can result in learning deficits that are unique to specific types of learning. As a result, understanding how damage to the central nervous system impacts each motor learning process and how these learning processes work together within the same task is critical for effective rehabilitation prescription.

Although tasks often involve multiple forms of learning, tasks are typically characterized as being "more explicit" or "more implicit" based on the task and the information/feedback provided to the learner (Izadi-Najafabadi et al. 2015; Marinelli et al. 2017; Taylor and Ivry 2014). In the visuomotor adaptation paradigm described above, characteristics of the task can be manipulated to shift the task towards the

"more explicit" or "more implicit" end of the learning spectrum depending on the goals of the research. In locomotor learning, the split belt treadmill paradigm has been studied extensively and has greatly improved our understanding of learning a locomotor task (Malone and Bastian 2010; Malone et al. 2011; Reisman et al. 2013; Reisman et al. 2007; 2009; Roemmich and Bastian 2015; Roemmich et al. 2016). Importantly, this type of learning is broadly accepted as falling on the "more implicit" end of the learning spectrum with sensorimotor adaptation being the dominate form of learning in this task (Bastian 2008; Helm and Reisman 2015; Reisman et al. 2010). However, current rehabilitation techniques after stroke utilize primarily explicit learning techniques (i.e. verbal cues and visual feedback (Durham et al. 2009; Urquhart and Skidmore 2014)), which are more similar to explicit, strategic learning rather than implicit sensorimotor adaptation. This creates a mismatch between what is known about locomotor learning through research and the type of locomotor learning that is most often applied clinically.

1.4 Locomotor Learning.

As just discussed, in studies of locomotor learning, sensorimotor adaptation has been the primary form of learning examined. One learning paradigm for studying this is the split belt treadmill. Locomotor learning on the split belt treadmill has been explored in both neurologically intact adults (Malone and Bastian 2010; Malone et al. 2012; Roemmich and Bastian 2015; Roemmich et al. 2016; Torres-Oviedo et al. 2011) and stroke survivors (Helm et al. 2016; Malone and Bastian 2014; Reisman et al. 2007; 2009; Tyrell et al. 2014) extensively. In this paradigm, the treadmill has two belts that are controlled separately. The belts are either "tied" (i.e. moving at the speed) or "split" (i.e. moving at different speeds). Initially, when the belts are split,

individuals are perturbed, resulting in a change in their walking pattern; however, over time individuals, both neurologically intact and after stroke, reduce this perturbation through sensorimotor adaptation (Helm and Reisman 2015; Malone et al. 2012; Reisman et al. 2010; Reisman et al. 2005; Reisman et al. 2007; Roemmich and Bastian 2015). When the belts are then tied again, negative after effects are observed and quickly decay (i.e. deadaptation). The change in behavior that occurs with practice on the split belt treadmill is most apparent using a measure of step (a)symmetry (Malone and Bastian 2014; Reisman et al. 2005; Reisman et al. 2007). Based on past work using the split belt treadmill, we know that individuals after stroke are able to learn and retain a new walking pattern when it is learned using this paradigm (Reisman et al. 2013; Reisman et al. 2007; 2009; Tyrell et al. 2014; 2015). However, we also know that learning in this paradigm following stroke is slower than age-matched neurologically intact adults (Tyrell et al. 2014). Although split belt treadmill walking has been the primary method for studying sensorimotor adaptation during locomotion, other tasks have been examined as well. One example of another locomotor learning paradigm examining sensorimotor adaptation during locomotion in both neurologically intact adults (Savin et al. 2010) and those with stroke (Savin et al. 2013) is from Savin et al (2010, 2013). In this paradigm a force is applied to the leg to resist the advancement of the leg during swing phase. In both studies, the authors found that the swing time of the leg with the resistance was initially perturbed (i.e. swing time was increased), but over the course of learning the swing time of that leg returned to baseline. When the resistance was removed, negative affect effects that quickly de-adapted were observed (Savin et al. 2010; Savin et al. 2013). Walking with prism glasses is another sensorimotor adaptation paradigm that has been examined in

locomotion in neurologically intact adults (Alexander et al. 2011; Morton and Bastian 2004b). In this learning paradigm individuals wear glasses with prism lens that result in the visual field being shifted. While walking and stepping over obstacles with prisms, individuals change how they walk to account for the shifted visual field and demonstrate negative after effects. All three of these tasks result in sensorimotor adaptation and have provided us with valuable information about locomotor learning. From this work it is clear that the implicit process of sensorimotor adaptation can occur during locomotion in neurologically intact adults and stroke survivors.

Despite this work, there are other forms of motor learning that can occur during walking. Specifically, strategic learning has been demonstrated previously during locomotion in neurologically intact adults. This has been demonstrated by coupling visual feedback with split belt treadmill walking and using visual feedback alone. In work by Roemmich et al (2016), neurologically intact adults walked on a split belt treadmill while watching visual feedback about step length that was designed to assist with learning the new walking pattern on a split belt treadmill. The findings suggest that provision of visual feedback resulted in an explicit process (i.e. a voluntary correction or strategic process) that occurred along with the sensorimotor adaptation process (Roemmich et al. 2016). In a similarly designed paradigm, Statton et al (2016) coupled split belt treadmill walking with visual feedback about knee joint angle. During learning, neurologically intact adults changed their knee flexion angle in response to the visual feedback while changing their step symmetry in response to the split belt treadmill (Statton et al. 2016). When the belts were tied and the visual feedback removed, typical after effects were observed in step symmetry (Statton et al. 2016). Additionally, an after effect was observed in knee flexion angle. It is important

to note, however, that the size of the knee flexion after effect was significantly less than the knee flexion angle that was learned with the visual feedback. Although the authors suggest that the learning that occurred from the visual feedback of knee flexion was sensorimotor adaptation (Statton et al. 2016), the significantly smaller after effect in knee flexion angle suggests that this may in fact be more analogous to explicit, strategy based learning. Thus, this would suggest that two distinct learning processes occurred, one that is implicit (i.e., sensorimotor adaptation) and one that is explicit (i.e., strategic).

Several studies have provided visual feedback about various gait parameters to examine explicit, strategic locomotor learning without walking on a split belt treadmill. One example of this is the work of Hussain et al (2013), which found that neurologically intact adults were able to change their swing time in response to visual feedback. They also found that subjects were able to recreate this walking pattern when prompted to do so without visual feedback (Hussain et al. 2013). Additionally, Kim et al (2012, 2014, 2015) demonstrated that neurologically intact adults were able to change their step length during a distorted visual feedback paradigm and that they could retain that pattern (Kim and Krebs 2012; Kim and Mugisha 2014; Kim et al. 2015). In the distorted visual feedback paradigm, a bar graph displays real-time information about step length in the form of a bar graph. During learning phases, the feedback is distorted so that subjects have to change their step length to have the bars representing their step length hit a target line. French et al (2018) used a similar paradigm to illustrate that not only were neurologically intact adults able to learn and recall a new walking pattern with this paradigm, but the paradigm resulted in a largely strategically learned walking pattern (French et al. 2018). This was demonstrated in

part by the ability of individuals to switch between the learned walking pattern and their normal walking pattern based on a verbal cue, which is characteristic of strategic learning (French et al. 2018). While this paradigm is largely explicit, it also involves implicit learning processes (French et al. 2018; Wood et al. 2020), which makes it an ideal paradigm to understand explicit learning and to examine how implicit and explicit learning processes interact during locomotion.

From the work described above, several things are well established about locomotor learning: 1) stroke survivors can learning through implicit, sensorimotor adaptation during locomotion, 2) explicit, strategic locomotor learning is a process that is distinct from implicit, sensorimotor adaptation, and 3) explicit, strategy-based locomotor learning is possible in neurologically intact adults. It is less clear, however, if stroke survivors can learn and retain new walking patterns through explicit, strategic forms of motor learning. A recent study by Cherry-Allen et al (2018) provides some insight into this (Cherry-Allen et al. 2018). In this study, stroke survivors walked on a treadmill while they received visual feedback about their knee flexion angle, similar to the paradigm used in Statton et al (2016). They found that stroke survivors were able to change their knee flexion angle in response to the visual feedback, which the authors suggest may have an explicit, strategic component (Cherry-Allen et al. 2018). These results suggest that stroke survivors can learn new walking patterns through explicit learning; however, it does not provide insight into retention or how explicit, strategic learning after stroke compares to that of neurologically intact adults. Similarly, work exploring the use of visual feedback as a rehabilitation intervention after stroke suggest that individuals are able to change their walking pattern in response to visual feedback (Druzbicki et al. 2018; Genthe et al. 2018; Sackley and

Lincoln 1997; Sanchez and Finley 2018; van Gelder et al. 2018); however, that work provides no insight into the underlying learning processes and how they compare to neurologically intact adults. The lack of knowledge about explicit locomotor learning in stroke survivors is particularly problematic because explicit learning techniques (i.e. verbal and visual cues) dominate current clinical practice (Durham et al. 2009; Urquhart and Skidmore 2014). *Thus, **Aim 1** used the distorted visual feedback paradigm to examine the ability of individuals after stroke to learn and retain a new walking pattern compared to age-matched neurologically intact adults.* This work advanced the field's understanding of how stroke impacts strategic learning, thus, guiding the development of rehabilitation interventions rooted in an understanding of locomotor learning.

1.5 Clinical Factors Impacting Motor Learning.

It is well known that recovery following stroke is highly variable (Danielsson et al. 2014; Danks et al. 2016; Michael et al. 2005; Schmid et al. 2007; Schmid et al. 2012). Many factors, including age, genetics, depression, and cognitive impairment, have been found to predict overall recovery after stroke (Alawieh et al. 2016; 2018; Park et al. 2015; Tsouna-Hadjis et al. 2000; Watila and Balarabe 2015; Winovich et al. 2017). Variability in individual responses to rehabilitation interventions have also been observed post-stroke. This has resulted in patient's being categorized as "responders" (i.e. those who respond well to a given intervention) and "non-responders" (i.e. those who do not respond well to a given intervention) (Bowden et al. 2013; Carey et al. 2014; Dobkin et al. 2014). The existence of responders and non-responders has been found in a variety of interventions including locomotor treadmill training (Bowden et al. 2013; Dobkin et al. 2014) and repetitive transcranial magnetic

stimulation (Carey et al. 2014). Since motor learning is the foundation of rehabilitation, it is likely that differences in how well individuals can learn contribute to this variability in response to rehabilitation intervention and in recovery after stroke. In fact, variability in the ability of individuals post-stroke to learn with the split belt treadmill has been previously observed (Reisman et al. 2013; Reisman et al. 2007; Tyrell et al. 2014). This suggests the presence of "learners" and "non-learners." Although it is clear that learners and non-learns exist during post-stroke locomotor learning, it remains unclear what factors impact a stroke survivor's ability to learn. To date, demographic information (such as age) and sensorimotor impairment (such as sensation and Fugl-Meyer scores) have been explored as possible factors to explain the observed variability in locomotor learning (Reisman et al. 2013; Reisman et al. 2007; Tyrell et al. 2014). These factors, however, do not explain a significant amount of the variability observed during locomotor learning after stroke. As a result, we are still unable to determine who will learn well and who will not in any given locomotor paradigm or task.

In neurologically intact adults, cognitive capacity has been explored as a factor that explains variability in motor learning with upper extremity tasks. Cognition consists of many different domains, including visuospatial working memory, executive functions, and attention. Of these various domains of cognition, visuospatial working memory, or the temporary storage of visual and/or spatial information for short term manipulation to accomplish a goal or task (Baddeley 1992; Baddeley and Hitch 1974; Kent 2016; Matthews 2015), is the primary domain that has been examined for its role in motor learning. Visuospatial working memory is thought to be a type of short term memory that is made up of several interactive processes that allow

for the manipulation of the information that is stored (Baddeley 1992; Kent 2016). However, unlike other forms of memory, such as episodic memory, visuospatial working memory does not involve the encoding of information, rather it is only available for short-term use and manipulation (Baddeley 1992; Baddeley and Hitch 1974; Kent 2016; Matthews 2015); thus, visuospatial working memory is classified by some as an executive function (Matthews 2015; Rabinovici et al. 2015). In sequence learning (Bo et al. 2009; Bo and Seidler 2009), visuomotor rotation tasks (Anguera et al. 2010; Christou et al. 2016), and other upper extremity tasks (Lingo VanGilder et al. 2018; Schaefer and Duff 2017), poor visuospatial working memory has been found to relate to poorer performance on the motor learning task. From the work involving the visuomotor rotation task, it has been suggested that the role of visuospatial working memory is specifically related to early learning (Christou et al. 2016). This phase of visuomotor rotation learning is thought to reflect the explicit, strategic portion of visuomotor rotation learning (Anguera et al. 2010; Christou et al. 2016). The same relationship was not found during late learning; thus, the relationship between visuospatial working memory and motor learning may be isolated to explicit, strategic learning. Given the significant role of the prefrontal cortex in explicit learning and cognitive processes, including visuospatial working memory (Kolb and Whishaw 2015; Matthews 2015; Morgan and J.H. 2008), this relationship is not entirely surprising. It is not known, however, if visuospatial working memory is related to explicit, strategic learning tasks during locomotion.

Despite work suggesting visuospatial working memory relates to upper extremity motor learning, it is not clear that visuospatial working memory is the most important or the only cognitive domain affecting motor learning. One reason for this

uncertainty is that many domains of cognition overlap (D'Esposito and Postle 2015; Kent 2016). For example, visuospatial working memory is highly related to executive functions and attention, making it challenging to measure visuospatial working memory in isolation. To further the uncertainty of the relationship between visuospatial working memory and motor learning, many studies have not used standardized visuospatial working memory tests when examining this relationship. Instead much of the previous work have used tasks that the authors suggest measure visuospatial working memory (Anguera et al. 2010; 2011; Bo et al. 2009; Christou et al. 2016). While it is possible that the tasks accurately reflect visuospatial working memory, these tasks have not undergone the rigorous validation processes that standardized tests have; thus, due to the overlapping nature of cognitive domains, it is possible that the tasks previously used to measure visuospatial working memory actually reflect visuospatial working memory and other cognitive domains such as attention and executive functions. It is therefore unclear if the relationship between cognition and motor learning is isolated to visuospatial working memory.

There is limited work that suggests one's fluid cognitive abilities, or one's ability to problem solve or learn new things (Akshoomoff et al. 2013; Horn 1968), may also relate to motor learning. This is particularly the case when the task is explicit in nature (Unsworth and Engle 2005). Unsworth and Engle (2005) assessed the relationship of fluid cognitive abilities and a sequence learning task. Subjects performed the task either with detailed instructions (explicit) or without detailed instructions (implicit) (Unsworth and Engle 2005). The authors found that when the task was explicit, fluid cognitive ability was significantly related to learning; however, this was not the case when the task was performed implicitly (Unsworth and Engle

2005). This suggests that the relationship between motor learning and cognition may extend to higher levels of global cognition, such as fluid cognitive abilities. Alternatively, because fluid cognitive ability is a global measure of cognition that reflects multiple domains of cognition including working memory, executive function, attention, and episodic memory (Akshoomoff et al. 2013; Heaton et al. 2014), it is possible that specific cognitive domains other than visuospatial working memory are important.

Cognitive impairments are common following stroke (Barker-Collo and Feigin 2006). In fact, it has been suggested that 70% of individuals with a stroke have impaired information processing and more than 40% have memory and visuospatial deficits (Hochstenbach et al. 1998; Rasquin et al. 2004). Additionally, it is estimated that 50% of stroke survivors have attention deficits that persist for years after their stroke (Hochstenbach et al. 2003; Hyndman and Ashburn 2003). As highlighted by a recent review, research has largely overlooked the role of cognitive function in post-stroke motor learning despite the prevalence of cognitive impairments following stroke (Lingo VanGilder et al. 2020). One study in stroke survivors, however, found that impaired visuospatial working memory is associated with a reduced ability to learn an upper extremity motor task (Schweighofer et al. 2011). Similar to the previous work in neurologically intact adults, the motor learning task in this study was explicit in nature (i.e. used visual feedback and was able to be recreated when prompted to do so). Additionally, the only domain of cognition that was assessed was visuospatial working memory. Thus, given the existing work, it is unclear if 1) the relationship between cognition and explicit motor learning holds for locomotion in stroke survivors and 2) if visuospatial working memory is the only important domain

of cognition for motor learning. *Therefore, in **Aim 2**, we explored the relationship between explicit, strategic locomotor learning and cognition, specifically visuospatial working memory and fluid cognition broadly, in individuals after stroke.*
Understanding the relationship between cognition and locomotor learning will allow us to understand inter-subject variability so that rehabilitation interventions can be personalized based on the individual patient being treated.

1.6 Exercise Priming and Motor Learning.

Because the success of rehabilitation relies on neuroplastic changes, research has aimed to develop interventions to facilitate neuroplasticity. Exercise priming, or the coupling of a short bout of high intensity exercise with a task, is one potential intervention that may promote neuroplasticity after stroke (Mang et al. 2013; Roig and de Las Heras 2018). Early work found that a short bout of exercise coupled with cognitive learning tasks improved performance on the task (Basso et al. 2015; Chang et al. 2012; Hindin and Zelinski 2012; Roig et al. 2016); thus, researchers became interested in whether or not acute exercise could positively impact motor learning. Initial work in the upper extremity found that exercise priming improves motor learning in neurologically intact adults (Ferrer-Uris et al. 2017; Lundbye-Jensen et al. 2017; Mang et al. 2014; Neva et al. 2019; Roig et al. 2012; Snow et al. 2016; Statton et al. 2015; Thomas et al. 2016a; Thomas et al. 2016b) and stroke survivors (Nepveu et al. 2017). Although the underlying mechanism is unclear, it has been proposed that the short bout of exercise results in and increased release of neurotrophic factors and catecholamines (e.g., Brain-derived Neurotrophic Factor), which lengthens the duration of long-term potentiation during consolidation. The increased activity during

consolidation in turn allows for improved memory formation, or retention (Moriarty et al. 2019; Ostadan et al. 2016; Roig et al. 2016; Skriver et al. 2014).

Many factors related to the exercise bout may influence the effectiveness of exercise priming. Specifically in neurologically intact adults, the impact of intensity, type, and timing of the exercise on the effects of exercise priming have been examined. First, it has been found that exercise priming conducted at a high intensity is most effective at improving retention. This is largely from the work of Thomas et al (2016a), which found that a group of neurologically intact adults who exercised at 90% of their maximum power output retained an upper extremity tracing task better than the group that exercised at 45% of their maximum power output or the group that simply rested (Thomas et al. 2016b). In other work intensity has been quantified using age predicted heart rate maximum, change in lactate, and VO2 maximum. Regardless of how intensity is quantified, there is consensus that exercise priming is most effective when performed at high intensities (Mang et al. 2014; Snow et al. 2016; Statton et al. 2015; Thomas et al. 2016b). A second parameter of exercise that may impact the effect of exercise priming is the type of exercise performed. Thomas et al (2017) compared three types of high intensity exercise to resting. The authors found that all high intensity exercise, regardless of the type, had a positive effect on retention of an upper extremity tracing task (Thomas et al. 2017). This suggests that the type of exercise is not important for exercise priming, unlike intensity which appears critical for the beneficial effects of exercise priming. Another parameter that has been examined is the timing of the exercise. It has been found that exercise after learning (i.e. during the consolidation phase) produces the most positive impact on motor learning (Roig et al. 2012). Thomas et al (2016a) advanced this knowledge by

examining specifically when after learning the exercise priming should occur. In this study, they compared high intensity exercise 20 minutes, 1 hour, and 2 hours after learning an upper extremity tracing task (Thomas et al. 2016a). They found that high intensity exercise performed 20 minutes after learning resulted in better retention both 1 day and 7 days after learning, with the effect being largest at seven days after learning (Thomas et al. 2016a). Given this work, it appears that high intensity exercise of any kind that is performed 20 minutes after learning will produce the greatest positive benefits on motor retention, especially when measured seven days after learning (Lundbye-Jensen et al. 2017; Mang et al. 2014; Roig et al. 2012; Roig et al. 2016; Snow et al. 2016; Statton et al. 2015; Thomas et al. 2016a; Thomas et al. 2017; Thomas et al. 2016b).

As stated previously, locomotor learning during sensorimotor adaptation following stroke is impaired compared to age-matched healthy adults (Savin et al. 2013; Tyrell et al. 2014); thus, exercise priming has been thought to be a promising avenue for improving locomotor learning after stroke. However, the same positive effects that have been found in memory and upper extremity tasks have not been found during locomotor learning in stroke survivors or neurologically intact adults (Charalambous et al. 2018; Helm et al. 2017; Roig and de Las Heras 2018). This was found despite the timing and intensity of exercise being performed similarly to what has been done in the upper extremity (i.e. high intensity during consolidation). This would suggest that exercise priming is not an effective method for improving locomotor learning; however, there are several potential reasons for this discrepancy. First, locomotion is a complex task that requires postural stability, multi-joint movements, and interlimb coordination. The tasks in the upper extremity research, on

the other hand, are seated, single-joint movements that require no bimanual coordination. Thus, it is possible that the impact of exercise priming is in fact dependent on the demands of the task itself (i.e. seated, upper extremity, single joint task vs locomotion) (Charalambous et al. 2018; Roig and de Las Heras 2018). Another possible explanation for the discrepancy is the duration of exercise. The studies examining the role of exercise priming on locomotor learning have included 5 minutes of exercise priming (Charalambous et al. 2018; Helm et al. 2017), while the studies in the upper extremity have included longer durations of priming (i.e. 15-30 minutes) (Nepveu et al. 2017; Snow et al. 2016; Thomas et al. 2016a; Thomas et al. 2017; Thomas et al. 2016b). It is possible that a longer duration of acute exercise is required to achieve optimal benefits. Unfortunately, the duration and structure (i.e., interval vs continuous) of the exercise bout has varied significantly across the literature and little work has examined the impact of these exercise parameters. Although this has not been thoroughly examined, recent work suggests that a five minute bout of exercise is as effective as a longer 13-minute bout of exercise (Angulo-Barroso et al. 2019). However, this remains a possible reason for the discrepancies in the effect of exercise on motor learning. Lastly, the form of motor learning may impact the effect of exercise priming (Charalambous et al. 2018; Charalambous et al. 2019; Roig and de Las Heras 2018). The tasks used in the upper extremity include visuomotor tracking tasks and motor sequencing tasks. These tasks include clear goals, detailed instructions, and online visual feedback, which makes them akin to explicit, strategic learning. This is in stark contrast to split belt treadmill walking, which has been used to examine the impact of exercise priming during locomotion and is dominated by implicit, sensorimotor adaptation (Bastian 2008; Helm and Reisman 2015; Reisman et

al. 2010). Given that exercise has been found to affect the prefrontal cortex (Basso et al. 2015) and strategic learning is primarily a prefrontal process (Slachevsky et al. 2001; Slachevsky et al. 2003; Taylor and Ivry 2014), it is possible that exercise priming positively impacts explicit, strategic learning, but not implicit, sensorimotor adaptation (Charalambous et al. 2018; Charalambous et al. 2019; Roig and de Las Heras 2018). If this is the case, exercise priming may be a viable option to improve explicit, locomotion learning. *Therefore, in **Aim 3** we examined the impact of exercise priming on locomotor learning in stroke survivors using an explicit, strategic learning paradigm (i.e., distorted visual feedback).* Understanding the effect of exercise priming on explicit locomotor learning, will provide needed insight into the use of exercise to improve locomotor learning and potentially provide clinicians with a relatively simple method to improve learning after stroke.

1.7 Summary, Specific Aims, and Hypotheses.

Stroke is the leading cause of long term disability in the United States (Mozaffarian et al. 2015). Despite significant time and money spent on post-stroke rehabilitation, many stroke survivors are left with reduced walking ability and quality of life (English et al. 2014; Mozaffarian et al. 2015; Wade et al. 1987). This is in part due to highly variable responses to interventions across individuals (Bowden et al. 2013; Carey et al. 2014; Dobkin et al. 2014). Thus, my long-term career goal is to improve the field's understanding of factors impacting post-stroke walking recovery to develop personalized rehabilitation interventions that optimize functional recovery after stroke. Because rehabilitation capitalizes on motor learning (Dancause and Nudo 2011), our lack of knowledge about motor learning and factors that impact motor learning is a major barrier to personalizing post-stroke rehabilitation. As a step

towards my long-term goal, this work examined explicit locomotor learning and determined how cognition and exercise priming impact locomotor learning after stroke.

There is a striking disconnect between clinical practice and research paradigms examining locomotor learning after stroke. Current clinical practice promotes locomotor learning through a form of learning that is mainly explicit, such as visual feedback and verbal cues (Durham et al. 2009; Urquhart and Skidmore 2014). However, locomotor learning research has focused on a form of learning that is primarily implicit (Helm and Reisman 2015; Malone and Bastian 2014; Reisman et al. 2007; 2009; Tyrell et al. 2014; 2015). Previous research suggests that these two forms of motor learning are quite different (Izawa et al. 2012; Morton and Bastian 2004; Smith and Shadmehr 2005; Taylor and Ivry 2014; Taylor et al. 2010); thus, it is likely that stroke impacts these forms of motor learning differently. However, few studies have examined explicit locomotor learning after stroke. Aim 1 addressed this critical gap in knowledge.

In both neurologically intact adults and stroke survivors there is significant variability in how well people can learn. Some individuals learn well (i.e., "learners") while others do not learn as well (i.e. "non-learners"). Identifying clinical factors that predict who learn well and those who do not learn as well is critical to providing optimal post-stroke rehabilitation. Previous research in stroke survivors has found that walking capacity and sensorimotor impairments are unable to predict who are learners and who are non-learners (Reisman et al. 2013; Reisman et al. 2007; 2009). Cognitive function, however, has been found to relate to motor learning in upper extremity tasks in younger (Anguera et al. 2010; Seidler and Carson 2017) and older adults (Anguera

et al. 2011; Lingo VanGilder et al. 2018; Schaefer and Duff 2017).This factor has largely been ignored in stroke despite the prevalence of cognitive deficits after stroke (Barker-Collo and Feigin 2006; Hochstenbach et al. 1998; Hochstenbach et al. 2003; Rasquin et al. 2004). Thus, understanding the impact of cognition on explicit, strategic locomotor learning is essential to developing individualized rehabilitation interventions to optimize post-stroke rehabilitation and was addressed in Aim 2.

Exercise priming, or a short, high intensity bout of exercise coupled with a motor learning task, has been found to improve upper extremity motor learning in healthy adults and those post-stroke when the tasks that are tested are primarily explicit upper extremity tasks (Ferrer-Uris et al. 2017; Roig et al. 2012). However, this has not been found in more implicit locomotor learning tasks (Charalambous et al. 2018; Helm et al. 2017). Because of differences in these forms of learning, it has been suggested that exercise priming may improve explicit but not implicit locomotor learning (Charalambous et al. 2018; Roig and de Las Heras 2018). Thus, Aim 3 will examine the effect of exercise priming on explicit locomotor learning post-stroke. Because exercise priming is relatively easy to implement, it is critical to understand if it can improve locomotor learning so that post-stroke outcomes can be improved through this mechanism.

This work used a primarily explicit, strategic locomotor learning paradigm that has been examined in young healthy adults (French et al. 2018; Kim and Krebs 2012; Wood et al. 2020) to complete the following objectives:

Aim 1. To examine the ability of stroke survivors to learn a new walking pattern through an explicit, strategic locomotor learning paradigm.

> ***Hypothesis 1.1***. Stroke survivors will learn a new walking pattern through an explicit locomotor learning paradigm.

Hypothesis 1.2. Stroke survivors will retain the new walking pattern learned through an explicit locomotor learning paradigm 24 hours after learning has occurred.

Hypothesis 1.3. Stroke survivors will not learn as well as neurologically intact adults.

Hypothesis 1.4. Stroke survivors will retain less than neurologically intact adults.

Aim 2. To evaluate the relationship between cognition and learning/retaining a new walking pattern through an explicit, strategic locomotor learning paradigm in individuals post stroke.

Hypothesis 2.1. Cognitive abilities will explain variance in learning above and beyond that explained by demographics and sensorimotor impairments in stroke survivors.

Hypothesis 2.2. Cognitive abilities will explain variance in retention above and beyond that explained by demographics and sensorimotor impairments in stroke survivors.

Hypothesis 2.3. Both fluid cognition and a test of visuospatial working memory specifically will be significant predictors of learning in stroke survivors.

Hypothesis 2.4. Both fluid cognition and a test of visuospatial working memory specifically will be significant predictors of retention in stroke survivors.

Aim 3. To determine if exercise priming can improve explicit, strategic locomotor learning in stroke survivors.

Hypothesis 3. Exercise priming will improve 24-hour retention of a walking pattern learned through an explicit locomotor learning paradigm in stroke survivors.

Completion of these aims will address significant gaps in our knowledge regarding locomotor learning after stroke and what factors impact locomotor learning.

The results provide critical information that can be used to optimize and individualize rehabilitation interventions to improve walking recovery after stroke.

Chapter 2

LEARNING AND RETENTION OF A NOVEL WALKING PATTERN THROUGH AN EXPLICIT, VISUALLY-GUIDED LOCOMOTOR LEARNING PARADIGM AFTER STROKE

2.1 Abstract.

Background: Locomotor sensorimotor adaptation has been studied extensively using the split-belt treadmill; however, sensorimotor adaptation is one specific form of learning that relies on particular neural processes (Morton and Bastian 2004b; Smith and Shadmehr 2005; Taylor and Ivry 2014). Explicit, strategic learning is another form of motor learning that relies on different neural processes (Taylor and Ivry 2014; Taylor et al. 2010). Sensorimotor adaptation has been well-studied in post-stroke locomotion via the split belt treadmill paradigm (Charalambous et al. 2018; Finley et al. 2015; Malone and Bastian 2014; Reisman et al. 2013; Reisman et al. 2007; 2009; Tyrell et al. 2014), yet strategic learning has rarely been studied. This represents an important gap in our knowledge as stroke may affect these forms of learning differently since distinct brain areas dominate each type of learning. Here we examine stroke survivors' ability to learn and retain new walking patterns through strategic learning and compare that to age-matched healthy adults.

Methods: Fifteen chronic stroke survivors and fifteen age-matched healthy adults participated in a 2-day treadmill study. Subjects completed Baseline, Acquisition1, Acquisition2, and Immediate Retention walking phases on Day 1 and 24-hour Retention on Day 2. During Acquisition1 and 2, we taught subjects a new walking

pattern during the acquisition phases by providing visual feedback about step length (French et al. 2018; Wood et al. 2020). Performance, or the behavior when the visual feedback was provided, was quantified by accuracy and variability of step length during the acquisition phases and retention was quantified by step length during Immediate and 24-hour Retention.

Results: Stroke survivors improved their accuracy ($p=0.02$) and reduced their variability ($p=0.01$) during the acquisition phases and remembered the pattern at Immediate and 24-hour Retention ($p=0.96$). There was no difference between groups in accuracy or variability at Early ($p=0.49$ and $p=0.54$, respectively) or Late Acquisition ($p=0.57$ and $p=0.29$, respectively). Additionally, there was no difference between groups during Immediate and 24-hour Retention ($p=0.22$).

Conclusion: Stroke survivors learn and remember new walking patterns through strategic learning as well as age-matched healthy adults; however, there is great inter-subject variability. Additional work to understand sources of this variability would be valuable.

2.2 Introduction.

Locomotor learning has been extensively studied using the split-belt treadmill. The split-belt treadmill paradigm is believed to examine a specific form of motor learning called sensorimotor adaptation. Sensorimotor adaptation occurs when a perturbation creates a sensory prediction error (Mazzoni and Krakauer 2006; Shadmehr et al. 2010; Taylor and Ivry 2014; Tseng et al. 2007). This error causes a change in motor behavior that occurs over time to accommodate the new perturbation. When the perturbation is removed, after effects are present. This has been reliably observed during locomotion in many populations, including healthy young adults

(Malone and Bastian 2010; Reisman et al. 2005; Roemmich and Bastian 2015; Torres-Oviedo and Bastian 2012) and stroke survivors (Charalambous et al. 2018; Finley et al. 2015; Malone and Bastian 2014; Reisman et al. 2013; Reisman et al. 2007; 2009; Tyrell et al. 2014). This work has found that stroke survivors can learn and retain a new walking pattern through sensorimotor adaptation, but do so slower than age-matched healthy adults (Tyrell et al. 2014). Although this work has significantly advanced the field of motor learning, sensorimotor adaptation is rarely used during post-stroke rehabilitation of walking in part because de-adaptation occurs quickly when the split-belt perturbation is removed resulting in limited retention of the new behaviors. Instead, post-stroke rehabilitation is dominated by more explicit forms of learning that use visual feedback and verbal cues (Durham et al. 2009; Urquhart and Skidmore 2014).

Explicit forms of motor learning, such as strategic learning, have gained attention in upper extremity work (Bond and Taylor 2015; Brudner et al. 2016; McDougle et al. 2015; McDougle et al. 2016; Taylor and Ivry 2014; 2011; 2012). Strategic learning is quite different from sensorimotor adaptation. Sensorimotor adaptation is primarily an implicit process that is largely dependent on cerebellar processes and occurs in response to sensory prediction errors (i.e., a mismatch between what is expected and what actually occurs) (Morton and Bastian 2004b; Smith and Shadmehr 2005; Taylor and Ivry 2014). Strategic learning, on the other hand, is a more explicit process that relies heavily on prefrontal processes and occurs in response to task performance errors (i.e., whether the task was successful or not) (Taylor and Ivry 2014; Taylor et al. 2010). Additionally, strategic learning is a highly flexible process that responds to the demands of the task (Bond and Taylor 2015).

Lastly, unlike sensorimotor adaptation, reaching and walking patterns learned through more explicit, strategic learning processes can be repeated on cue (French et al. 2018; Morehead et al. 2015). Because of these significant differences, the effects of stroke on these two types of learning (*explicit, strategic learning* and *implicit, sensorimotor adaptation*) are likely not the same. Although past work has examined the use of visual feedback as an intervention to change gait parameters after stroke (Druzbicki et al. 2018; Genthe et al. 2018; Sackley and Lincoln 1997; Sanchez and Finley 2018),the use of visual feedback to systematically examine explicit, strategic learning processes has rarely been examined in locomotion, especially after stroke.

Stemming from work in the upper extremity, locomotor learning paradigms have been developed to examine explicit, strategic learning (French et al. 2018; Hussain et al. 2013; Kim and Krebs 2012). Visual feedback paradigms, such as visually guided walking with error added to the display, is one example of this (French et al. 2018; Hussain et al. 2013; Kim and Krebs 2012; Wood et al. 2020). A study by Hussain et al (2013) found that young healthy adults could change their swing time in response to erroneous visual feedback and that they were able to recall that walking pattern 24 hours later without visual feedback when cued to do so. Additionally, Kim and colleagues (2014, 2015) found in a series of studies, that young healthy adults were able to change their step length in response to distorted visual feedback and then remember that pattern without visual feedback. Similarly, previous work from our lab showed that young healthy adults could change their step length in response to distorted visual feedback (French et al. 2018; Wood et al. 2020) and switch between the learned pattern and their normal pattern in response to a cue (French et al. 2018). The work of French et 2018 also provided evidence that this distorted visual feedback

paradigm resulted largely in explicit, strategic learning, rather than implicit forms of learning such as sensorimotor adaptation, since subjects could switch between the new walking pattern and their usual walking pattern with a simple verbal cue (French et al. 2018).

Although young healthy adults can change their walking pattern in response to visual feedback and remember it without visual feedback, we do not know if stroke survivors can do the same. Despite this lack of knowledge, explicit, strategic learning is commonly used during rehabilitation to improve walking. Thus, the purpose of this study was two-fold. First, we aimed to determine if stroke survivors could learn through strategic learning processes by assessing their ability to change their step length in response to visual feedback (i.e., acquire a new walking pattern) and then remember the new walking pattern (i.e., retain a new walking pattern). Next, we aimed to compare the ability of stroke survivors to change their walking pattern and retain the new walking pattern learned to that of age-matched healthy adults. Understanding how stroke affects strategic locomotor learning is critical for designing effective rehabilitation interventions. We hypothesized that stroke survivors would be able to change their walking pattern and remember the new pattern, but that stroke survivors would not do so as well as age-matched healthy adults.

2.3 Methods.

2.3.1 *Subjects.*

Stroke survivors were recruited from local physical therapy practices, support groups, and advertisements, while age-matched healthy adults (±5 years) were recruited from the local community through fliers and advertisements. To be included,

all subjects had to meet the following criteria: 1) age 18-85, 2) able to walk 10 meters without physical assistance, 3) resting heart rate within 40 to 100 beats per minute, and 4) resting blood pressure within 90/60 and 185/100 mmHg. Additionally, stroke survivors had to have MRI evidence of a single unilateral chronic (>6 months) stroke and healthy adults needed to be in generally good health. Subjects were excluded if they reported 1) visual changes post stroke, 2) history of coronary artery bypass graft or myocardial infarction within 3 months, 3) unexplained dizziness in the last 6 months, or 4) pain that limited walking. Stroke survivors were also excluded if any of the following criteria were met: 1) MRI evidence of a cerebellar stroke, 2) neurologic conditions other than stroke, 3) neglect, or 4) inability to communicate with or understand the investigators as measured by questions 1b and c of the NIH Stroke Scale. All participants signed an informed consent approved by the Human Subjects Review Board at the University of Delaware prior to participation.

2.3.2 *Experimental Design.*

Subjects walked on a dual-belt treadmill instrumented with two 6 degrees of freedom force plates (Bertec Corporation, Columbus, OH) during the 2-day study. Day 1 consisted of 5 phases: Baseline, Orientation, Acquisition1, Acquisition2, and Immediate Retention, while Day 2 consisted of 24-hour Retention (Figure 2.1a). During all bouts of walking, stroke survivors walked at a comfortable, self-selected walking speed and age- matched healthy adults walked at the same speed as their corresponding stroke survivor. Throughout the protocol, a 20-inch computer monitor was positioned in front of the treadmill (Figure 2.1b). This computer monitor was blank during Baseline, Immediate Retention, and 24-hr Retention and showed a bar graph during Orientation, Acquisition1, and Acquisition2 (Figure 2.1a).

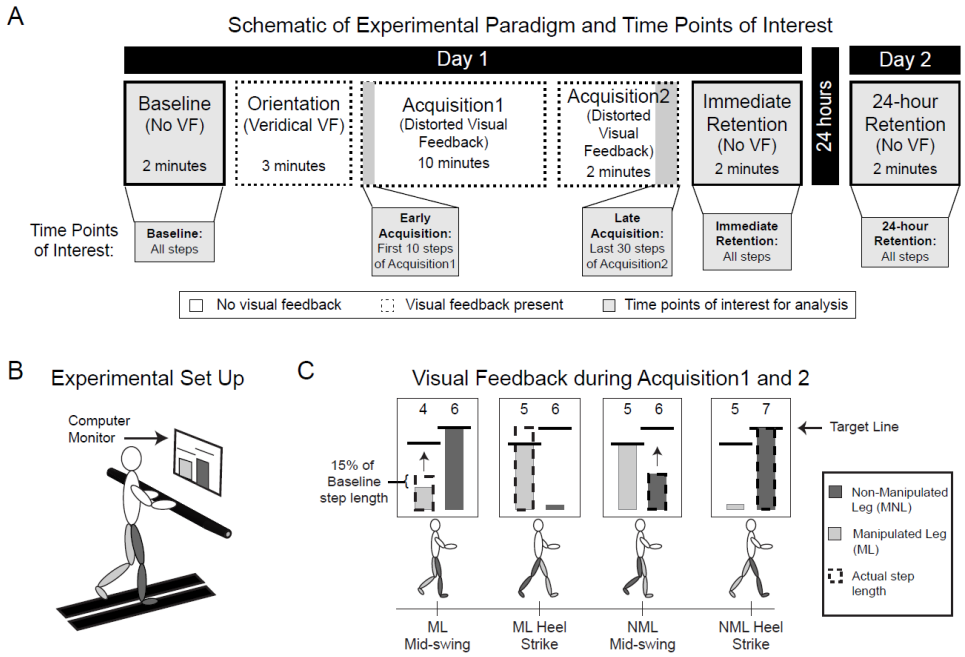

Figure 2.1: Experimental Set up and Paradigm. A) Subjects participated in a 2 day treadmill walking study. Day 1 consisted of 5 phases of walking, while Day 2 consisted of 1 phase of walking. During Orientation, Acquisition1, and Acquisition2 (dotted boxes), visual feedback about step length was displayed. For statistical analysis 5 time points were use and are highlighted in grey. B) During treadmill walking a computer monitor was positioned in front of the treadmill. This display presented real-time feedback about step length during Orientation, Acquisition1, and Acquisition2. C) During Acquisition1 and 2, visual feedback of the Manipulated Leg (ML) was distorted such that the bar looked shorter than the actual step being taken (dotted line represents actual step length); thus, a longer step with the ML was needed to hit the target line. The bar of the Non-Manipulated Leg (NML) was accurate. Each time the bars high the target line the counter increased.

No visual feedback was displayed during Baseline. During this phase, we calculated the average step length for each leg and identified the leg that took a shorter step. This leg will be called the Manipulated Leg (ML), while the other leg will be called the Non-Manipulated Leg. Additionally, the average baseline step length was

used to create a bar graph that was displayed on a computer monitor during Orientation, Acquisition1, and Acquisition2.

During Orientation, Acquisition1, and Acquisition2, a bar graph was shown on the computer monitor. This graph displayed real-time information about step length, similar to that described in French et al 2018 and Wood et al 2020. Briefly, this display had two bars, one representing the left leg and one representing the right leg (Figure 2.1b). Each bar grew during the swing phase of that leg until heel strike was identified, at which point the bar maintained its height until the next swing phase was initiated on that side (Figure 2.1c). Additionally, two horizontal target lines, representing the subject's baseline step lengths, were positioned two-thirds of the way up the screen (Figure 2.1b and c). Orientation was 3 minutes long and included several short bouts of walking that ensured that subjects understood the display and were physically able to change their step length enough to succeed with the task. Prior to the first portion of Orientation, subjects were told, "*You are going to see a bar graph on the screen in front of you. Each bar will represent your step length. Step length is the distance from one heel to the other when the front heel hits the ground. On the graph, the green bar will represent your right leg and the blue bar will represent your left leg. You will also see 2 pink horizontal lines across the screen. These lines represent your baseline step length and will serve as a target line later. Please watch the display and walk normally.*" Subjects were asked to verbalize what step length meant to confirm understanding. Next, during Orientation, subjects were instructed to "*take the longest possible step*" with the ML to make the corresponding bar "*go above the pink line*." Throughout this bout of walking, the visual feedback was accurate.

During Acquisition1 and Acquisition2, we added error to the visual feedback to teach subjects a new walking pattern (French et al. 2018; Wood et al. 2020). In this paradigm, the bar representing the ML was distorted such that it appeared that subjects were taking a shorter step with the ML than they actually were (Figure 2.1c). Thus, in order to get the bar of the ML to hit the target line, subjects needed to increase the step length on the ML. The bar was distorted by 15% of the baseline step length of the ML for all subjects (Figure 2.1c). The bar representing the Non-Manipulated Leg was accurate. During the acquisition phases, there were also numbers above the bar that increased when each leg's bar was within ± 2% of the target line. Prior to Acquisition1, subjects were told, "*You are now going to walk while watching the same graph. This time there will be numbers above each bar. These numbers will increase each time the bar hits the pink line. Your goal is to get both of those numbers as high as possible by getting the bars to hit the pink line; not go above or below it, but right on the line. The bars will not be completely accurate, so you will have to change your walking to do this.*" Subjects were then specifically told which leg to take a longer step with (i.e., the ML) and which to keep the same (i.e., the Non-Manipulated Leg). This was done to make the learning paradigm as explicit as possible since we were interested in explicit, strategic learning. Prior to Acquisition2, subjects were reminded of the goal and which leg to change. They were also told to *"try and remember exactly what you are doing to get the bars to match the pink line, because later I will ask you to repeat this learned pattern without the visual feedback.*" These instructions are similar to those used in previous studies (French et al. 2018; Hussain et al. 2013).

During Immediate Retention and 24-hour Retention, no visual feedback was provided, and subjects were told, "*You will not see anything on the display, but I want*

you to walk how you were walking while you watched the display. So, whatever you were doing to get the bars to hit the pink line, I want you to recreate that." Behavior during these periods were used to examine retention of the learned walking pattern.

2.3.3 *Data and Statistical Analysis.*

Motion capture data were collected from six markers placed on bilateral heels, lateral malleoli, and fifth metatarsal heads. Kinematic data were collected at 100 Hz using an eight-camera Vicon Motion Capture system (Vicon MX, Los Angeles, CA), while kinetic data were collected at 1000 Hz. Heel strike and toe offs were identified using kinetic data with a 20 N threshold via a custom written Matlab script (MathWorks, Natick, MA). Our primary outcome was step length of the ML (SL_{ML}), since subjects were specifically taught to change the step length of only this leg. Our secondary measure was step symmetry index (SSI), which was defined as the difference between the SL_{ML} and step length of the non-manipulated leg normalized to stride length (i.e., the sum of the two). We opted to include this measure, even though subjects were not asked to change their step length on the Non-Manipulated Leg, since this has been used extensively in past locomotor learning work (Charalambous et al. 2018; French et al. 2018; Malone and Bastian 2010; Reisman et al. 2007; Tyrell et al. 2014).

All statistical analyses were performed in SPSS v25 (IBM, Chicago, IL) with alpha set at 0.05. Outliers were screened for and identified as individuals who exceeded three standard deviations. Sensitivity analyses were performed when outliers were identified as detailed in the results section. Additionally, Shapiro-Wilks and Levene's test were used to assess normality and homogeneity, respectively. If normality or homogeneity was violated, non-parametric tests were used, otherwise

parametric tests were used as outlined below. As detailed in the results section, when a repeated measures ANOVA was planned but parametric statistics could not be used, we performed Wilcoxon signed-rank tests for ***within*** group comparisons at specific time points and Mann Whitney U tests for ***between*** group comparisons with the appropriate Bonferroni corrections.

2.3.3.1 *Measures of Performance.*

To examine performance, we used two metrics. First, we used SL_{ML} at two specific time points, Baseline and Late Acquisition (Figure 2.1a), to determine if subjects changed their step length. For Baseline, we averaged SL_{ML} throughout the Baseline walking bout to reflect the subjects' normal walking pattern. For Late Acquisition, we averaged SL_{ML} over the last 30 steps of Acquisition2 to reflect the extent of learning. With these time points, we first performed a paired t-test to compare the average SL_{ML} at these time points ***within*** stroke survivors. If the walking pattern was acquired, we would expect to see an increase in SL_{ML} during Late Acquisition compared to Baseline. Although performance within the healthy adult group was not related to a specific hypothesis, we conducted the same analysis within the healthy adult groups before performing between group comparisons for completeness. Lastly, we compared SL_{ML} ***between*** groups using a 2 x 2 repeated measures ANOVA with time (Baseline and Late Acquisition) and group as factors.

As our second measure of performance, we used SL_{ML} to calculate Percent Error of the Manipulated Leg (PE). PE reflected the accuracy of performance during the acquisition phases and was calculated as follows:

$$PE_n = \frac{|SL_{ML-n} - SL_{Target}|}{SL_{ML-BL}} * 100,$$

where SL_{ML-n} is the SL_{ML} on step *n* of Acquisition1 and 2, SL_{Target} is the step length of the ML that would result from hitting the target every step (i.e., 15% longer than the baseline SL_{ML}), and SL_{ML-BL} is the average step length of the ML during Baseline. This measure expresses error as a percentage of their baseline step length, since this is also how the amount of distortion was determined. The metric reflects how far away each step was from the target during the acquisition phases. The absolute value was used in the calculation of this metric to prevent group averages being close to zero. Since there were individuals who over and under shot the target taking the average would result in both groups being close to zero; thus, the absolute value was needed to reflect the behavior of the groups most accurately. For this measure, a smaller value indicates less error and more accurate acquisition of the walking pattern. We calculated this metric throughout the acquisition phases to qualitatively observe performance. However, we were specifically interested in several times points to quantitatively measure performance. In particular, we were interested in the first 10 steps of Acquisition1 (i.e., Early Acquisition; Figure 2.1a) to quantify initial performance and the last 30 steps of Acquisition2 (i.e., Late Acquisition; Figure 2.1a) to measure to extent of their learning.

To examine accuracy ***within*** stroke survivors, we compared PE during Early Acquisition and Late Acquisition using a paired t-test. If learning occurred, we would expect to see a reduction in PE from Early to Late Acquisition. Again, although performance within the healthy adults was not a primary question, we performed the same analysis within healthy adults for completeness. To compare accuracy ***between*** groups (i.e., between healthy adults and individuals with stroke), we compared

average PE during Early Acquisition and Late Acquisition with a 2 x 2 repeated measures ANOVA with time and group as our factors. As a secondary analysis, we performed the same analyses with accuracy defined by SSI. In these analyses, PE was calculated using SSI rather than SL_{ML} during the acquisition phases and then averaged over the same time points. Lastly, there are metrics other than accuracy that could be used to examine performance. These metrics include variability in performance and rate of learning. For simplicity, these metrics are not presented here; however, for completeness they are included in the Supplemental Analyses (see section 2.8).

2.3.3.2 *Measures of Retention.*

To quantify retention, we used two metrics. First, we compared the average SL_{ML} at specific time points to quantify retention. The time points of interest were Late Acquisition (i.e., the last 30 steps of Acquisition2), Immediate Retention, and 24-hour Retention (Figure 2.1a). The SL_{ML} was averaged during these time points and then we performed a repeated-measures ANOVA to compare the SL_{ML} ***within*** stroke survivors. If the walking pattern was retained, we would expect to see no difference between these time points. Prior to performing the between group analysis, we performed the same analysis within the healthy adults for completeness. We also compared SL_{ML} ***between*** groups using a 3 x 2 repeated measures ANOVA with time (Late Acquisition, Immediate Retention, and 24-hour Retention) and group as factors. The same comparisons were performed for SSI. All post hoc tests were performed using Bonferroni corrections.

Our second measure of retention was the Percent Forgotten (%Forgot), which represented the amount of the walking behavior that was forgotten relative to what was learned. We calculated %Forgot as follows:

$$\%Forgot = \frac{|\overline{SL}_{Imm} - \overline{SL}_{24}|}{\overline{SL}_{LA}} \; x \; 100.$$

The numerator was the absolute value of the difference between $\overline{SL}_{Imm}$, the average SL_{ML} during Immediate Retention, and $\overline{SL}_{24}$, the average SL_{ML} during 24-hour Retention; thus, representing the change in walking pattern from Day 1 to Day 2. The denominator, $\overline{SL}_{LA}$, was the average SL_{ML} during Late Acquisition (i.e., the last 30 strides of Acquistion2), thus, accounting for how much each individual learned. With this metric, a lower value indicates better retention or less forgetting. We compared %Forgot ***between*** groups using an independent t-test. Again the same comparison was made when %Forgot was calculated using SSI at the time points outlined above.

2.4 Results.

2.4.1 *Subjects.*

Fifteen stroke survivors (65.6 ± 9.5 yo; 7F) and fifteen age-matched healthy adults (66.5 ± 8.2 yo; 10 F) were included in this study. Additional characteristics of the subjects are presented in Table 1. When asked to take the longest possible step with ML during Orientation, all subjects exceeded 15% of their baseline SL_{ML} (Stroke Survivors 26.4 ± 13.5%, Healthy Adults 42.4 ± 23.3%); thus, no subjects were excluded based on ability to increase their step length.

Table 2.1: Demographic and Clinical Characteristics of Subjects.

	Stroke Survivors (n=15)	**Healthy Adults (n=15)**
Age (yrs; mean ± SD)	65.6 ± 9.5	66.5 ± 8.2
Sex	7F; 8M	10 F; 5M
Manipulated Leg	8R; 7L	7R; 8L
Time Since Stroke (months; mean ± SD)	60.0 ± 30.7	
Side of Lesion	11R; 4L	
SSWS (m/s; mean ± SD)	0.92 ± 0.3	
FMLE (mean ± SD)	24.5 ± 5.8	

2.4.2 *Performance within Groups.*

When comparing SL_{ML} during Baseline and Late Acquisition, no outliers were identified and normality was met. The paired t-test showed that the SL_{ML} used at Late Acquisition was significantly longer than Baseline ($t_{(14)}$=-9.1, p<0.001; Figure 2.2a), suggesting that subjects acquired a new walking pattern. Next, we assessed accuracy using PE. One outlier was identified within the group of stroke survivors; however, a sensitivity analysis showed that the results were the same whether this individual was included or not. Thus, the outlier has been removed from the results presented here to meet the assumption of normality. A paired t-test showed that PE significantly decreased from Early Acquisition to Late Acquisition in stroke survivors ($t_{(13)}$=3.2, p=0.007; Figure 2.2b and c).

The same analysis comparing SSI at Baseline and Late Acquisition showed that stroke survivors learned a new walking pattern; however, the comparison of accuracy at Early and Late Acquisition when calculated with SSI did not show a

significant result, although it approached significance (Z=-1.82, p=0.06). Together this suggests that stroke survivors were able to acquire a walking pattern through the distorted visual feedback paradigm that was different than their normal walking pattern. Further, learning occurred in order to acquire this pattern as evident by improved accuracy over the course of the acquisition phases.

For completeness, the same analyses were performed within healthy adults. The results of these comparisons within healthy adults mirrored the results of those described above for comparisons within the stroke survivor group. Specifically, the SL_{ML} used at Late Acquisition was significantly longer than Baseline ($t_{(14)}$=-10.8, p<0.001; Figure 2.2a) and performance improved over time as measured by PE ($t_{(13)}$=3.8, p=0.002; Figure 2.2b and c). Again when these within healthy adult analyses were completed with SSI rather than SL_{ML} the results were the same.

2.4.3 *Performance between Groups.*

When comparing SL_{ML} during Baseline and Late Acquisition between groups, no outliers were identified and the assumptions of normality were met. The results of the 2 x 2 ANOVA showed an effect of time ($F(1, 28)=202.2$, $p<0.001$), but no effect of group ($F(1, 28)=1.2$, $p=0.29$) and no interaction ($F(1, 28)=0.01$, $p=0.91$; Figure 2.2a). These results suggest that there was no difference in how well each group increased their step length from Baseline to Late Acquisition.

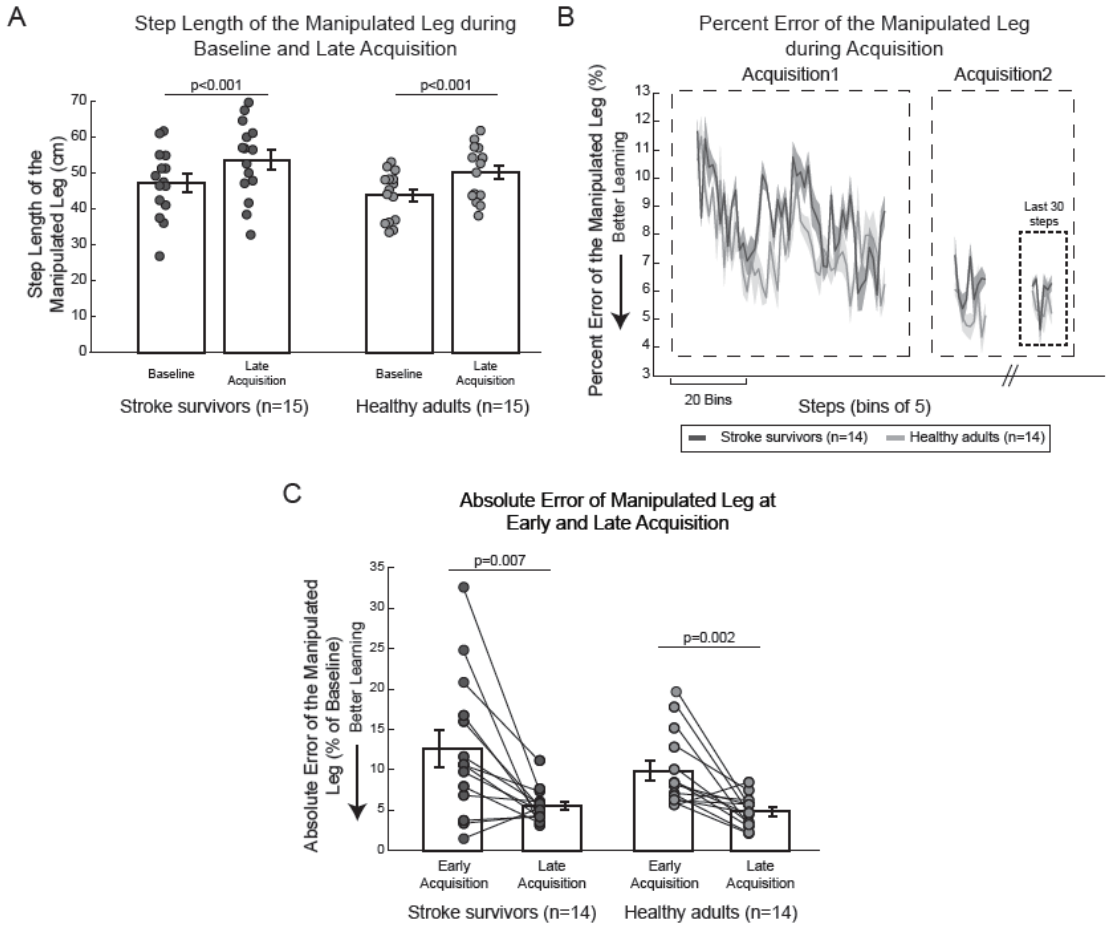

Figure 2.2: Performance in Stroke Survivors and Age-Matched Healthy Adults. A) Within the stroke survivor and healthy adult group, there was a significant increase in step length of the Manipulated Leg from Baseline to Late Acquisition ($p<0.001$ for both groups). When comparing between groups with a 2 x 2 ANOVA, there was not significant effect of group ($p=0.29$), but there was a significant effect of time ($p<0.001$). B) Percent Error for both stroke survivors (dark grey) and healthy adults (light grey) during Acquisition1 and 2decreased over the acquisition phases. C) In individuals after stroke and healthy adults, there was a significant decrease in Absolute Error from Early Acquisition to Late Acquisition ($p=0.007$ and $p=0.002$, respectively). A 2 x 2 ANOVA showed a significant effect of time ($p<0.001$), but no effect of group and no interaction ($p=0.44$ and $p=0.24$, respectively). Individual dots represent individual subjects and error bars indicate standard error.

Next, we examined accuracy by comparing PE between groups. One outlier was identified in the age-matched healthy control group in addition to the outlier described in the stroke survivor group. Sensitivity analysis shows that the results were the same if the outliers were or weren't included; thus, to meet the assumptions of normality, the outliers are removed from the presented results. The 2 x 2 repeated measures ANOVA showed a significant effect of time ($F_{(1,26)}$=22.4, p<0.001) and no effect of group ($F_{(1,26)}$=0.6, p=0.44) or interaction ($F_{(1,26)}$=1.4, p=0.24; Figure 2.2c). When this analyses was performed with SSI and with PE being calculated by SSI, the results were the same, indicating that both groups acquired a new pattern and reduced their error over the course of the acquisition phases.

2.4.4 *Retention within Groups.*

First, we assessed retention by comparing SL_{ML} at three time points: Late Acquisition, Immediate Retention, and 24-hour Retention. No outliers were identified and assumptions of normality were met. Results of a repeated-measures ANOVA showed no significant effect of time on SL_{ML} ($F_{(2,28)}$=0.07, p=0.94; Figure 2.3a). These results suggest that stroke survivors were able to remember the pattern they acquired immediately and 24 hours after learning the new pattern. The analyses of retention using SSI also showed no effect of time on retention, also indicating that stroke survivors were able to retain the walking pattern.

For completeness, the same analysis was performed within healthy adults. The comparison of SL_{ML} at these three time points within healthy adults show no significant effect of time ($F_{(2,28)}$=0.66, p=0.52; Figure 2.3a), suggesting that the group of healthy adults were able to retain the new walking pattern. When this analysis was performed with SSI the results were similar.

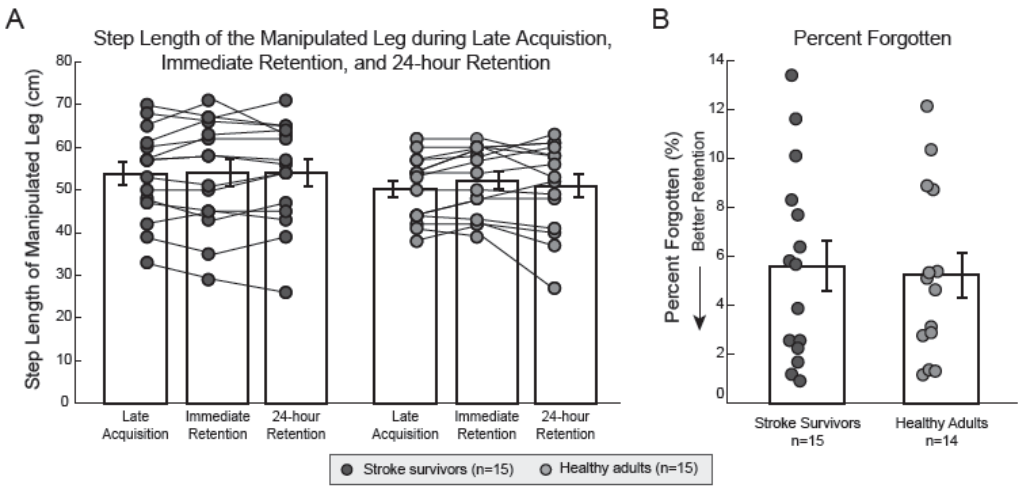

Figure 2.3: Retention in Stroke Survivors and Age-Matched Healthy Adults. A) Within the stroke survivor and healthy adult group, there was no effect of time on step length of the Manipulated Leg during Late Acquisition, Immediate Retention, and 24-hour Retention in stroke survivors (p=0.96). Additionally, when comparing step length between groups at these time points, there was no effect of group (p=0.46) or time (p=0.22) and not interaction (p=0.71). B) There was no significant difference between Percent Forgotten (p=0.79). Individual dots represent individual subjects and error bars indicate standard error.

2.4.5 *Retention between Groups.*

To examine retention between groups, we performed a 3 x 2 ANOVA with SL_{ML} during Late Acquisition, Immediate Retention, and 24-hour Retention. No outliers were identified. These results showed no significant main effect of Time ($F_{(2, 28)}$=1.6, p=0.22) or Group ($F_{(2, 28)}$=0.56, p=0.46) and no significant interaction ($F_{(2, 28)}$=.35, p=0.71; Figure 2.3a). When this analysis was performed with SSI, no significant differences between groups were found.

Lastly, when comparing %Forgot, we identified one outlier in the age-matched healthy control group. Sensitivity analysis showed that the results were not different whether this individual was included or removed; thus, to meet the assumption of

normality, this subject is removed from the results. An independent t-test showed no difference between groups ($t_{(27)}$=0.8, p=0.79; Figure 2.3b). When SSI was used to calculate %Forgot, again there was no significant difference between groups.

2.4.6 *Exploring Inter-subject Variability.*

Due to the observation of substantial inter-subject variability during performance and retention for the stroke survivors, we performed an exploratory analysis to see if physical impairment, as measured by Fugl-Meyer Lower Extremity (FMLE), explained the observed variability in performance and retention. Although, past work has not found a relationship between physical impairment and locomotor learning (Reisman et al. 2007; Tyrell et al. 2014), this has not been examined with this task. First, we examined the relationship between FMLE and PE at Late Acquisition with a Pearson's correlation. This did not show a significant relationship (r=-0.08, p=0.79). Similarly, a Pearson's correlation between FMLE and %Forgot was not significant (r=-0.3, p=0.28). When these correlations were examined using SSI to calculate the performance and retention metric, again there was not a significant relationship with FMLE.

2.5 Discussion.

In this study we sought 1) to determine if stroke survivors could acquire a new walking pattern and retain that walking pattern through this explicit, visually-guided walking task and 2) to compare performance and retention between stroke survivors and age-matched healthy adults. In agreement with our hypothesis, stroke survivors were able to acquire the new walking pattern and retain it through this explicit learning task; however, contrary to our hypothesis, stroke survivors and age-matched

healthy adults acquired and retained this walking pattern similarly. This finding was consistent regardless of whether SL_{ML} or SSI was used to determine our measures of performance and retention. These results have important implications for the study of locomotor learning and for rehabilitation because explicit, strategic forms of learning are commonly used in rehabilitation of persons with stroke (Durham et al. 2009; Urquhart and Skidmore 2014).

A vast majority of the work in locomotor learning has examined sensorimotor adaptation through the split-belt treadmill. Through that work, it is clear that sensorimotor adaptation learning processes are intact following cerebral stroke (Finley et al. 2015; Malone and Bastian 2014; Reisman et al. 2007; 2009; Savin et al. 2013), although learning is slowed compared to age-matched healthy adults (Tyrell et al. 2014). Based on those results, it appears that damage to the brain outside of the cerebellum, the region primarily responsible for sensorimotor adaptation (Morton and Bastian 2006; Taylor and Ivry 2014), resulted in grossly intact ability to learn through sensorimotor adaptation. Thus, we hypothesized that cerebral stroke could impact forms of learning that are dominated by more cerebral neural pathways. Strategic learning provided a framework with which to examine this, since it relies heavily on cerebral, specifically prefrontal, processes. Prior to this work, however, the ability of stroke survivors to acquire and retain new walking patterns through forms of learning other than sensorimotor adaptation had been rarely studied, despite the differences in the neural processes.

One study by Cherry-Allen et al (2018) examined the ability of stroke survivors to learn and immediately remember a new knee flexion angle during walking through visual feedback (Cherry-Allen et al. 2018). They found that stroke

survivors could acquire a new walking pattern with a new knee flexion angle while the visual feedback was present. Similarly, our results suggest that stroke survivors can acquire a new walking pattern through a visually guided explicit task as well as age-matched healthy adults. However, in Cherry-Allen et al (2018) stroke survivors showed little retention of the new walking pattern when visual feedback was removed, suggesting that stroke survivors were unable to retain the new, explicitly learned walking pattern. Importantly, in that work, subjects were not given a cue to continue using the newly learned walking pattern during the retention portion of the study. Because, retention of behaviors learned through strategic learning are believed to be revealed when a visual or verbal cue is provided (French et al. 2018; Mazzoni and Krakauer 2006; Morehead et al. 2015; Taylor and Ivry 2014), it was possible that subjects did retain the newly acquired walking pattern, but did not utilize the new walking pattern because they were not prompted to do so. In fact, in the current work, we found that stroke survivors were able to remember the newly acquired walking pattern both immediately and 24 hours later when they were provided a verbal cue. Thus, based on our work, it appears that stroke survivors maintain the ability to acquire new walking patterns and retain those walking pattern through explicit, strategic processes.

We also hypothesized that stroke survivors with cerebral lesions would not learn or retain a new pattern as well as age-matched healthy adults. Instead, however, this work provides evidence that explicit, strategic learning and retention is similar in stroke survivors and healthy adults. While this finding was surprising, it is possible that the form of learning directly contributes to this. Sensorimotor adaptation is an automatic process that is relatively stereotyped across individuals (Morehead et al.

2017; Taylor and Ivry 2014). Strategic learning, on the other hand, requires more conscious control and is inherently more flexible than sensorimotor adaptation (Bond and Taylor 2015; Taylor and Ivry 2011). For example, explicit, strategic learning requires more cognitive resources than sensorimotor adaptation (Taylor and Ivry 2014). Therefore, it is possible that the cognitive abilities of individuals may be critical to this form of learning. If this were the case, then it is possible that the cognitive changes that are normal as people age could also impair explicit, strategic learning in normally aging adults. The implication of this for the current study is that it is possible that we did not observe a difference between groups because our control group, the age-matched healthy adults, may have had age-related cognitive changes that could have impacted the explicit locomotor learning performed in this study. In other words, it is possible that at least some individuals in both groups had learning impairments due to age-related or stroke-related cognitive changes. Future work should examine the relationship between cognitive abilities and explicit, strategic locomotor learning as well as compare this type of learning in healthy older adults with that in young healthy adults. This will be examined in Aim 2 of this dissertation project. Additionally, Tyrell et al 2014 looked at rate of learning over multiple days; thus, it is possible that differences in rate may emerge in a multiday study with this or other primarily explicit, strategic learning paradigms. Future work should examine the impact of repeated exposure to this learning paradigm to determine the impact of prolonged training in stroke survivors compared to healthy adults.

One feature of explicit, strategic learning is that it requires the presence of a cue to produce recall of the learned walking pattern (French et al. 2018; Mazzoni and Krakauer 2006; Morehead et al. 2015; Taylor and Ivry 2014). In our study we used a

verbal cue similar to other studies to elicit the use of a strategy (French et al. 2018; Hussain et al. 2013; Mazzoni and Krakauer 2006); however, environmental cues have also been used (Morehead et al. 2015). Because of the need for a cue or change in context to engage a given strategy and the prefrontal pathways involved in strategic learning, this type of learning requires greater cognitive demands than other forms of more implicit learning (Taylor and Ivry 2014). The cognitive demand of strategic learning is a limitation to the application of this form of learning to rehabilitation practice. Previous work, however, has found that practice can make behaviors learned through strategic learning more automatic, i.e., less cognitively demanding (Haith and Krakauer 2018; Huberdeau et al. 2019). As a result, future work examining the impact of continued practice with this visual-guided learning task on the automaticity of the new walking pattern would be beneficial to the translation this knowledge into rehabilitation applications.

While the overarching conclusion from our analysis is that stroke survivors maintain the ability to acquire and retain walking patterns through a learning paradigm dominated by explicit, strategic learning as well as age-matched healthy adults, it is critical to acknowledge that there was large variability across subjects. In all of our measures of performance, including accuracy, there is significant variability in how well both stroke survivors and age-matched healthy adults acquire the task (Figure 2.2). Specifically, there are individuals who improve their accuracy, while others maintain their initial level of accuracy. This individual variability is also observed during retention (Figure 2.3). As a result, a more appropriate interpretation of our data is that, while as a group both stroke survivors and age-matched healthy adults can acquire and retain a new walking pattern through this visually-guided, explicit

learning task some individuals do so well and others do not do so as well. Understanding the source of this variability is critical in the translation of motor learning studies into real-world practice. Based on our exploratory analyses, the observed variability in both performance and retention within the stroke survivors does not appear to be explained by physical impairment as measured by FMLE. This is consistent with work in the split-belt treadmill which has found that physical impairment does not relate to stroke survivors' performances on the split-belt treadmill (Reisman et al. 2013; Reisman et al. 2007). Thus, future work exploring other sources of variability, such as cognitive abilities and genetics, is warranted.

In summary, stroke survivors can acquire and retain new walking patterns through explicit, strategic learning paradigms, such as this visually guided walking task, as well as age-matched healthy adults. This provides the potential to utilize this form of learning in post-stroke rehabilitation; however, a better understanding of the effect of long-term practice and individual variability is required to make this translation.

2.6 Acknowledgements.

The authors would like to thank the participants of this study as well as the undergraduate research assistants for their assistance with data processing and analysis.

2.7 Funding.

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by the National Institutes of Health [grant numbers 1R01-HD-078330-01A, S10RR028114-

01, and F31NS111806]; and The Foundation for Physical Therapy Research [2016 Florence P. Kendell Doctoral Scholarship, 2018-2019 Promotion for Doctoral Studies (PODS) Level I Award, and 2019-2020 Promotion for Doctoral Studies (PODS) Level II Award].

2.8 Supplemental Analyses.

In the main body of this chapter we only quantify performance by examining SL_{ML} and accuracy; however, other metrics are useful to fully understand performance. Thus, here we use variability during the acquisition phases and learning rate over the course of the acquisition phases to more completely characterize performance during the task.

2.8.1 *Variability.*

First, we calculated variability as the standard deviation of SL_{ML} at specific time points. Similar to the times points used when examining accuracy, we calculated variability at Early Acquisition and Late Acquisition (Figure 2.1a). We also calculated variability throughout the Baseline phase to more thoroughly understand how behavior changed during the acquisition phases relative to subjects' normal variability.

To examine variability ***within*** stroke survivors, we compared variability during Baseline, Early Acquisition, and Late Acquisition using a repeated-measures ANOVA. If learning occurred, we would expect to see an increase in variability at Early Acquisition compared to Baseline, followed by a reduction in variability towards Baseline at Late Acquisition; thus, preplanned comparisons were performed between 1) Baseline and Early Acquisition, 2) Early Acquisition and Late Acquisition, and 3) Baseline and Late Acquisition. Prior to conducting between group comparisons,

we performed the same analysis within healthy adults. To compare variability ***between*** groups, we performed a 3 x 2 repeated-measures ANOVA with time (i.e., Baseline, Early Acquisition, and Late Acquisition) and group as factors. All post hoc tests were completed with a Bonferroni correction. As a secondary analysis, we also performed these analyses using SSI rather than SL_{ML} to determine variability.

Prior to conducting the *within* group analysis, we identified one outlier at the Early Acquisition time point. Sensitivity analysis revealed that the results were unchanged regardless of this subject's inclusion; however, when this subject was removed the assumption of normality was met. Therefore, the results presented meet the assumptions of normality and do not include the outlier. The repeated-measures ANOVA showed that time had a significant effect on variability ($F_{(2,26)}$=8.9, p=0.001; Figure S2.1a). Post hoc paired t-tests showed that variability of SL_{ML} during Early Acquisition was significantly greater than that at Baseline (t(13)=-4.1, p=0.001) and the variability of SL_{ML} during Late Acquisition was significantly less than that at Early Acquisition (t(13)=2.7, p=0.02), which is a typical pattern of change observed with learning (Muller and Sternad 2009). Finally, the step length variability of SL_{ML} decreased during Late Acquisition so that it was not significantly different than Baseline (t(13)=-1.1, p=0.30).

The results of *within* group comparisons in the healthy adult group were similar to those within the group of stroke survivors. Specifically, there was a significant effect of time ($F_{(2,26)}$=13.8, p=0.001; Figure S2.1a). Post hoc paired t-tests showed that variability of SL_{ML} during Early Acquisition was significantly greater than that at Baseline (t(13)=-5.2, p=0.001) and the variability of SL_{ML} during Late Acquisition was significantly less than that at Early Acquisition (t(13)=3.4, p=0.004).

Step length variability of SL_{ML} decreased during Late Acquisition so that it was not significantly different than Baseline (t(14)=-1.8, p=0.10).

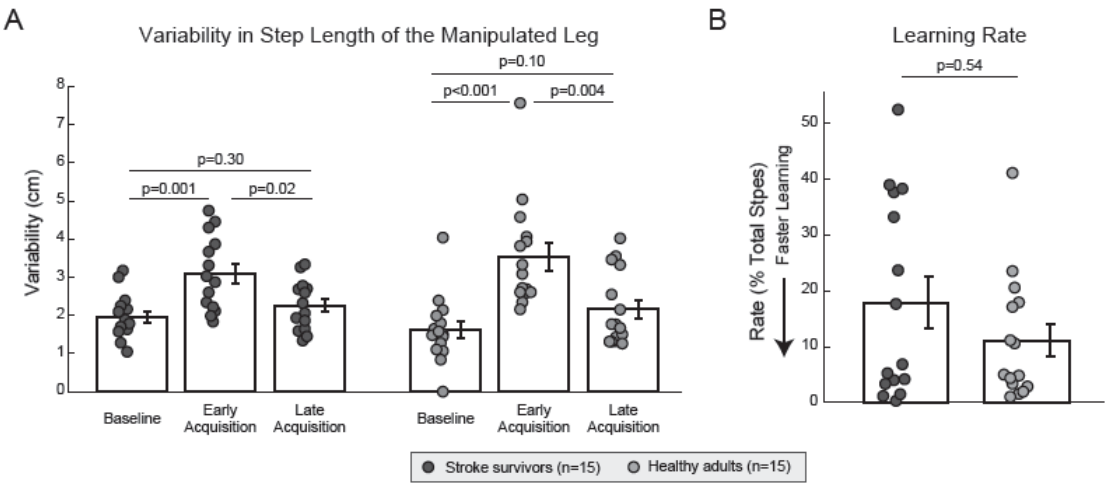

Figure 2.4: Supplemental Measures of Performance. A) In stroke survivors and healthy adults, subjects were significantly more variable at Early Acquisition compared to Baseline (p=0.001 and p<0.001, respectively) and Late Acquisition (p=0.02 and p-0.004, respectively); however, there was not significant difference between Baseline and Late Acquisition (p=0.30 and p=0.1, respectively). Additionally, there was no difference in step length variability between groups at Baseline (p=0.27), Early Acquisition (p=0.54), or Late Acquisition (p=0.29). B) There was no significant difference in rate of learning between groups (p=0.54). Individual dots represent individual subjects and error bars indicate standard error.

When comparing variability *between* groups, we identified one outlier in the age-matched healthy adult group during the Early Acquisition period. Sensitivity analysis showed no impact of removing this subject. Upon removal of this outlier, the assumptions of normality were still violated; thus, we included the outliers and compared variability between groups using Mann-Whitney U tests at the three specific

time points of interest. These results showed no difference between groups at Baseline (Z=-1.14, p=0.27), Early Acquisition (Z=-0.64, p=0.54), or Late Acquisition (Z=-1.1, p=0.29; Figure S2.1a). When the same analysis was conducted with variability of SSI, the results were unchanged for both within and between group comparisons.

2.8.2 *Learning Rate.*

As our final measure of performance, we determined learning rate using PE over the course of the acquisition phases through a previously established method (Charalambous et al. 2018; Malone and Bastian 2010). First, we smoothed the data with a moving average of three. Then we determined the number of steps required to fall within the plateau, which was defined as the average PE during the last 30 steps of Acquisition2 (i.e., Late Acquisition; Figure 2.1a). The point at which 5 consecutive steps fell within the plateau was normalized to the total number of steps to account for varied number of steps due to different walking speeds. As a result, learning rate is measured as the percent of total strides required to reach plateau, where a lower value indicates a faster rate. To compare learning rate *between* groups, we used an independent t-test. Again, we performed a secondary analysis were learning rate was calculated with SSI rather than SL_{ML}.

When comparing learning rate between groups, we found no outliers; however, the assumptions of normality were violated. As a result, we performed a Mann Whitney U test. This showed no difference between groups (Z=-0.6, p=0.54; Figure S2.1b). When we conducted the same analyses with SSI, the results were the same, showing no significant differences in learning rate between groups.

Chapter 3

USE OF EXPLICIT PROCESSES DURING A VISUALLY GUIDED LOCOMOTOR LEARNING TASK PREDICTS 24-HOUR RETENTION AFTER STROKE

3.1 Preface.

Upon completing the analysis for Aim 1 as described in Chapter 2, we were particularly interested in the inter-subject variability. As a result, we performed further analysis with data from stroke survivors and healthy adults. While not originally outlined as a question within my dissertation proposal (and therefore not outlined in my specific aims page in Chapter 1 section 1.7), we felt it was important to include this data here to provide a more comprehensive assessment of the ability of individuals after stroke to learn through explicit, strategic learning compared to age-matched healthy adults. Thus, this chapter provides additional analysis that aimed to understand the underlying learning processes occurring during this task. To do this, we adapted an approach from the visuomotor rotation literature to determine how much of the observed behavioral change was due to implicit and explicit learning processes. Then we examined how the learning process used related to performance and retention in order to better understand the inter-subject variability that we observed.

Of note, the metrics of retention used in this chapter differ from the metrics of retention used in the other chapters. This is because this manuscript was the first to be submitted for publication. Since submission, our thinking has evolved and we believe that accounting for the change in context caused by the removal of visual feedback on

Day1 should be accounted for *within* the measure of 24-hour retention. Thus, in all other chapters we utilize a measure of retention that does just that and have called it Percent Forgotten. For consistency, we have added a supplemental section to this chapter that uses Percent Forgotten, which we believe to be the more accurate metric of retention, to examine the relationship between the type of learning process and retention.

Additionally, in this chapter and subsequent chapters, we use Step Length of the Manipulated Leg to calculate our metrics of performance and retention and do not include Step Symmetry Index as we did in Aim 1 (Chapter 2). This was intentionally done since the results in Aim 1 did not differ based on which measure (i.e., Step Length of the Manipulated Leg or Step Symmetry Index) was used to calculate of learning metrics. Thus, because the visual feedback was only manipulated on one leg, we believe that using Step Length of the Manipulated Leg to quantify behavior most accurately represents the behavior that was taught.

Lastly, with the exception of this section and the supplemental analyses presented in section 3.11, this chapter has been accepted and is in press at *Journal of Neurophysiology*. Per journal policy, this work can be reproduced as part of this dissertation document without charge and without permission. The citation is as follows: French MA, Morton SM, Reisman DS. Use of explicit processes during a visually guided locomotor learning task predicts 24-hour retention after stroke. *Journal of neurophysiology.* 2020.

3.2 Abstract.

Implicit and explicit processes can occur within a single locomotor learning task. The combination of these learning processes may impact how individuals

acquire/retain the task. Because these learning processes rely on distinct neural pathways, neurologic conditions may selectively impact the processes that occur, thus, impacting learning and retention. Thus, our purpose was to examine the contribution of implicit and explicit processes during a visually guided walking task and characterize the relationship between explicit processes and performance/retention in stroke survivors and age-matched healthy adults. Twenty chronic stroke survivors and twenty healthy adults participated in a 2-day treadmill study. Day 1 included Baseline, Acquisition1, Catch, Acquisition2, and Immediate Retention phases and Day 2 included 24-hour Retention. During acquisition phases, subjects learned to take a longer step with one leg through distorted visual feedback. During Catch and retention phases, visual feedback was removed and subjects were instructed to walk normally (Catch) or how they walked during the acquisition phases (retention). Change in step length from Baseline to Catch represented implicit processes. Change in step length from Catch to the end of Acquisition2 represented explicit processes. A mixed ANOVA found no difference in the type of learning between groups (p=0.74). There was a significant relationship between explicit processes and 24-hour retention in stroke survivors (r=0.47, p=0.04), but not in healthy adults (r=0.34, p=0.15). These results suggest that stroke may not affect the underlying learning mechanisms used during locomotor learning, but that these mechanisms impact how well stroke survivors retain the new walking pattern.

3.3 New and Noteworthy.

This study found that stroke survivors used implicit and explicit processes similarly to age-matched healthy adults during a visually guided locomotion learning task. The amount of explicit processes was related to how well stroke survivors

retained the new walking pattern, but not to how well they performed during the task. This work illustrates the importance of understanding the underlying learning mechanisms in order to maximize retention of a newly learned motor behavior.

3.4 Introduction.

Locomotor learning has primarily been studied using the split belt treadmill paradigm in both young healthy adults (Leech et al. 2018; Malone and Bastian 2010; Reisman et al. 2005; Torres-Oviedo and Bastian 2010) and stroke survivors (Finley et al. 2015; Reisman et al. 2007; 2009; Tyrell et al. 2014). Traditionally, changes in behavior during split belt treadmill walking are believed to result from sensorimotor adaptation (Bastian 2008). Sensorimotor adaptation is a specific form of motor learning that is an implicit (i.e., automatic), primarily cerebellar process that occurs in response to sensory prediction errors (i.e., a mismatch between what is expected and what actually occurs) (Morton and Bastian 2004b; Smith and Shadmehr 2005; Taylor and Ivry 2014). However, there are other types of learning that are distinctly different from sensorimotor adaptation, such as use-dependent plasticity and strategic learning, that have rarely been studied during locomotion. For example, use-dependent plasticity is an implicit process that may involve the primary motor cortex and occurs in response to repetitive practice (Classen et al. 1998; Diedrichsen et al. 2010; Haith and Krakauer 2013; Mawase et al. 2017; Verstynen and Sabes 2011). Strategic learning, on the other hand, is explicit in nature and can be thought of as intentional changes to behavior that occur in response to a perturbation (Schween et al. 2020). This type of learning is thought to rely heavily on prefrontal and cognitive processes, and occurs in response to task performance error (i.e., if you were successful at the task) (Haith and Krakauer 2013; Taylor and Ivry 2014; 2011). Despite the unique

characteristics of these learning processes, they rarely occur in isolation and most often occur together during a single learning task (Diedrichsen et al. 2010; French et al. 2018; Huang et al. 2011; McDougle et al. 2015; Morehead et al. 2015; Wood et al. 2020). In other words, the behavior observed during learning tasks usually reflects multiple underlying learning processes that occur in parallel. Therefore, understanding how these learning processes work together within a single task is critical to developing a comprehensive understanding of locomotor learning (i.e., both the acquisition of a new behavior and retention of that behavior). This is particularly important when developing rehabilitation interventions targeting locomotion, because damage to different neural pathways due to stroke and other neurologic conditions likely impact each of these specific learning processes differently.

Despite the importance of understanding underlying learning mechanisms and how they work together during locomotion and after stroke, the learning processes that occur within a single locomotor learning task have not been examined. This is in contrast to visuomotor rotation reaching tasks for which learning processes have been well characterized, making it a useful task to illustrate the importance of understanding underlying learning mechanisms. Historically, the visuomotor rotation task was believed to involve primarily sensorimotor adaptation; however, recent work has demonstrated that explicit, strategic learning processes contribute significantly to the behavior that is observed during acquisition of the new behavior, while sensorimotor adaptation and use-dependent plasticity (i.e., implicit learning processes) have a smaller role (Bond and Taylor 2015; Brudner et al. 2016; McDougle et al. 2015; McDougle et al. 2016; Taylor and Ivry 2014; 2011; 2012; Taylor et al. 2010). The combination of these distinct learning processes produces the observed reaching

behavior and impacts how individuals perform and retain the task. Additionally, because these learning processes rely on distinct neural pathways, neurologic conditions selectively impact the learning processes that occur, thus, having direct implications for learning and retention. For example, individuals with cerebellar damage have difficulty with sensorimotor adaptation, while individuals with damage to the prefrontal cortex have difficulty with explicit, strategic learning. Damage to these different regions of the brain (i.e., the cerebellum and prefrontal cortex) results in different observed behavior during extended practice of a visuomotor rotation task when an aiming target is provided because of impairments to specific learning processes based on lesion location (Taylor and Ivry 2014; Taylor et al. 2010). These results suggest that in individuals with cerebellar damage, tasks that are dominated by sensorimotor adaption may be more impaired, while tasks that are dominated by explicit, strategic learning may be more affected in individuals with prefrontal damage. This knowledge can then be leveraged to develop effective, motor-learning based rehabilitation interventions.

In locomotor learning research, little work has sought to understand how these different learning processes work together during the same task or how stroke impacts these parallel processes. Work in young healthy adults and one study in those with stroke have used dual task walking, often by combining split belt treadmill walking with some form of visual feedback (Cherry-Allen et al. 2018; Day and Bastian 2019; Long et al. 2016; Malone and Bastian 2010; Roemmich et al. 2016; Statton et al. 2016), to provide evidence that multiple learning processes can occur during different tasks that are occurring simultaneously. Of particular interest is the work of Roemmich et al. (2016) which found that young healthy adults made a conscious

correction related to step length when visual feedback was provided during split belt treadmill walking, indicating that implicit and explicit processes were occurring together during this task. This was supported by the successful application of the dual-rate state space model. Additionally, Cherry-Allen et al. (2018) found that stroke survivors were able to use visual feedback to learn to walk with more knee flexion while learning a new step length on a split belt treadmill, again indicating that multiple learning processes can occur together during locomotion. Despite evidence that multiple learning processes can occur simultaneously during locomotion in healthy adults and in stroke survivors past work has not investigated how different learning processes *operate together within the same locomotor task* after stroke. Further, it is unknown how the learning processes used during a locomotor learning task impacts the acquisition of the new walking behavior and retention of that behavior. Understanding how stroke impacts parallel learning processes within a single task and how the learning processes used relates to performance and retention will guide the development of more effective locomotor rehabilitation interventions that promote efficient learning processes in individuals after stroke.

As a result, the purpose of this work is two-fold. First, we wanted to understand whether the contributions of implicit and explicit processes differed between stroke and age-matched neurologically intact subjects during a locomotor task known to involve both forms of learning. To do this, we used a distorted visual feedback (DVF) locomotor learning task previously described by our lab (French et al. 2018; Wood et al. 2020) and shown to involve both implicit and explicit processes. The contribution of each type of learning was estimated using walking behavior while visual feedback is provided (i.e., during the acquisition of the new walking pattern).

Because explicit, strategic learning relies on cognitive processes (Taylor and Ivry 2014), which are often impaired after stroke (Barker-Collo and Feigin 2006; Hochstenbach et al. 1998; Hochstenbach et al. 2003), we hypothesized that explicit, strategic processes would contribute less to the acquisition of the new walking pattern in stroke survivors than in age-matched healthy adults. We also hypothesized that implicit processes would contribute similarly in stroke survivors and age-matched healthy adults as past work has suggested that implicit processes are intact after cerebral stroke (Lewek et al. 2018; Malone and Bastian 2014; Reisman et al. 2007; 2009; Savin et al. 2013; Yen et al. 2015). Second, we wanted to understand the relationship between the amount of explicit, strategic processes and locomotor learning in stroke survivors and age-matched healthy adults. Here locomotor learning refers to 1) performance (i.e., behavior while visual feedback is present), which reflects the change in behavior that occurs during the practice session and 2) retention (i.e., behavior when the visual feedback is removed), which reflects longer term storage of the new walking pattern. Based on upper extremity work suggesting that the amount of implicit and explicit processes do not impact performance of a task (Taylor and Ivry 2012), we hypothesized that the contribution of explicit processes would not be related to how well stroke survivors *or* age-matched healthy adults performed while acquiring the a new walking pattern. We also hypothesized that the amount of explicit processes would relate to how well the new walking pattern was retained (i.e., recalled at a later time when the visual feedback was removed). This hypothesis was based on past work in upper extremity reaching showing that aftereffects are smaller (i.e., retention is decreased) when a task is more explicit (Kagerer et al. 1997; Taylor and Ivry 2012).

3.5 Materials and Methods.

3.5.1 *Subjects.*

Stroke survivors were recruited from local physical therapy practices, support groups, and advertisements, while age-matched healthy adults (±5 years) were recruited from the local community through fliers and advertisements. To be included, all subjects had to meet the following criteria: 1) age 18-85, 2) able to walk 10 meters without physical assistance, 3) resting heart rate within 40 to 100 beats per minute, and 4) resting blood pressure within 90/60 and 185/100 mmHg. Additionally, stroke survivors had to have MRI evidence of a single unilateral chronic (>6 months) stroke and healthy adults needed to be in generally good health. Subjects were excluded if they reported 1) visual changes post stroke, 2) history of coronary artery bypass graft or myocardial infarction within 3 months, 3) unexplained dizziness in the last 6 months, or 4) pain that limited walking. Stroke survivors were also excluded if any of the following criteria were met: 1) MRI evidence of a cerebellar stroke, 2) neurologic conditions other than stroke, 3) neglect, or 4) inability to communicate with or understand investigators. All subjects signed an informed consent approved by the Human Subjects Review Board at the University of Delaware prior to participation.

3.5.2 *Experimental Design.*

Subjects walked on a dual-belt treadmill instrumented with two 6 degrees of freedom force plates (Bertec Corporation, Columbus, OH) during the 2-day study. Day 1 consisted of 5 phases: Baseline, Orientation, Acquisition1, Catch Trial, Acquisition2, and Immediate Retention, while Day 2 consisted of 24-hour Retention (Figure 3.1a). During all bouts of walking, stroke survivors walked at a comfortable, self-selected walking speed with a 20-inch computer monitor positioned in front of the

treadmill (Figure 3.1b). As detailed below, a visual feedback display created with The Motion Monitor Toolbox (Innovative Sports Training Inc., Chicago, IL) was presented on this monitor during specific walking bouts of the study. Age-matched healthy adults walked at the same speed as their corresponding stroke survivor.

No visual feedback was displayed during Baseline. During this phase, we calculated the average step length for each leg and identified the leg that took a shorter step. This leg will be called the Manipulated Leg (ML), while the other leg will be called the Non-Manipulated Leg (NML). This information was used during the next phases to create a visual feedback display.

During Orientation, Acquisition1, and Acquisition2, the computer monitor had a bar graph that displayed real-time information about step length as described in French et al 2018. Briefly, this display had two bars, one representing the left leg and one representing the right leg (Figure 3.1b). Each bar grew in real-time during the swing phase until heel strike was identified, at which point the bar maintained its height until the next swing phase was initiated on that side (Figure 3.1c). Additionally, two horizontal target lines were positioned two-thirds of the way up the screen (Figure 3.1b and c). These target lines represented the subject's baseline step lengths and were scaled such that they were positioned two-thirds of the way up the screen for all subjects (Figure 3.1b and c). The height of these line remained the same throughout these three phases. Orientation was included to ensure that subjects understood the display. Prior to the first portion of Orientation, subjects were told, "*You are going to see a bar graph on the screen in front of you. Each bar will represent your step length. Step length is the distance from one heel to the other when the front heel hits the ground. On the graph, the green bar will represent your right leg and the blue bar will*

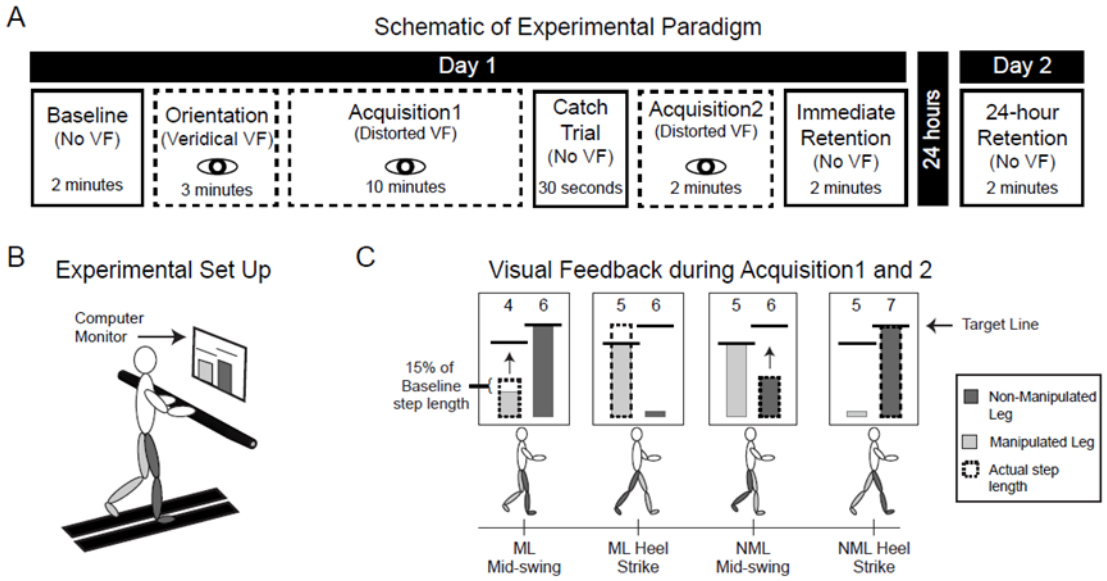

Figure 3.1: Experimental Set up and Paradigm. A) Subjects participated in a 2 day treadmill walking study. Day 1 consisted of 6 phases of walking, while Day 2 consisted of 1 phase of walking. During Baseline, Catch Trial, Immediate and 24-hour Retention, no visual feedback was provided. During Orientation, Acquisition1, and Acquisition2 (dotted boxes), visual feedback about step length was displayed. During Catch Trial, subjects were instructed to walk normally. During Immediate and 24-hour Retention, subjects were instructed to use the walking pattern they had learned during the acquisition phases. B) During treadmill walking a computer monitor was positioned in front of the treadmill. This display presented real-time feedback about step length during Orientation, Acquisition1, and Acquisition2; otherwise, the display was blank. C) During Acquisition1 and 2, visual feedback of the Manipulated Leg was distorted such that the bar looked shorter than the actual step being taken (dotted line represents actual step length); thus, a longer step with the Manipulated Leg was needed to hit the target line. The bar of the Non-Manipulated Leg was accurate. Each time the bars high the target line the counter increased. *Abbreviations: ML- Manipulated Leg, NML-Non-Manipulated Leg.*

represent your left leg. You will also see 2 pink horizontal lines across the screen. These lines represent your baseline step length and will serve as a target line later. Please watch the display and walk normally." Subjects were asked to verbalize what step length meant to confirm understanding. During a portion of this phase, subjects were instructed to "take the longest possible step" with the ML to make the corresponding bar "go above the pink line." This portion of Orientation was used to ensure that subjects were physically able to change their step length enough to succeed with the task.

During Acquisition1 and Acquistion2, we used DVF to teach subjects a new walking pattern (French et al. 2018). During these phases, the target lines remained the same, but the bar representing the ML was distorted such that it appeared that subjects were taking a shorter step with the ML than they actually were (Figure 3.1c). Thus, in order to get the bar of the ML to hit the target line, subjects needed to increase the step length on the ML. The bar was distorted by 15% of the baseline step length of the ML for all subjects (Figure 3.1c). The bar representing the NML was accurate. During the Learning phases, there were numbers above the bar that increased when each leg's bar was within ± 2% of the target line. Prior to Acquisition1, subjects were told, "*You are now going to walk while watching the same graph. This time there will be numbers above each bar. These numbers will increase each time the bar hits the pink line. Your goal is to get both of those numbers as high as possible by getting the bars to hit the pink line; not go above or below it, but right on the line. The bars will not be completely accurate, so you will have to change your walking to do this.*" Subjects were then specifically told which leg to take a longer step with (i.e., the ML) and which to keep the same (i.e., the NML). This was done to make the learning paradigm

as explicit as possible since we were interested in explicit, strategic learning. Prior to Acquisition2, subjects were reminded of the goal and which leg to change. They were also told to *"try and remember exactly what you are doing to get the bars to match the pink line, because later I will ask you to repeat this learned pattern without the visual feedback.*" These instructions are similar to those used in previous studies (French et al. 2018; Hussain et al. 2013). These phases were used to teach subjects a new walking pattern and to quantify performance.

Between Acquisition1 and Acquisition2, subjects completed a 30 second Catch Trial, where visual feedback was removed (Figure 3.1a). During this bout, subjects were told, "*You will not see anything on the display. During this time please walk normally*." This phase will be used to quantify the contribution of each type of learning process (i.e., implicit and explicit). Specifically, the instructions to walk normally were provided to remove the contribution of explicit, strategic processes; thus, allowing us to estimate the implicit processes by observing the aftereffects. This approach is commonly used to examine storage of implicit processes in both upper extremity (Benson et al. 2011; Morehead et al. 2015; Tseng et al. 2007) and walking tasks (French et al. 2018; Long et al. 2016; Reisman et al. 2009; Torres-Oviedo and Bastian 2010); however, it is possible that subjects continued to use some explicit strategy during the Catch Trial. Additionally, subjects were excluded if they were not able to understand the investigators; thus, we assumed that subjects stopped using whatever strategy they developed and used the Catch Trial to estimate the contribution of implicit processes.

Finally, during Immediate Retention and 24-hour Retention, no visual feedback was provided, and subjects were told, "*You will not see anything on the*

display, but I want you to walk how you were walking while you watched the display. So, whatever you were doing to get the bars to hit the pink line, I want you to recreate that." Consistent with previous work (Codol et al. 2018; Genthe et al. 2018; Hasson et al. 2015; Holland et al. 2018; Hussain et al. 2013; Krishnan et al. 2018), we used these phases, when visual feedback was removed and subjects are asked to recall the pattern, to quantify retention.

3.5.3 *Data Analysis.*

Motion capture data were collected from six markers placed on bilateral heels, lateral malleoli, and fifth metatarsal heads. Kinematic data were collected at 100 Hz using an eight-camera Vicon Motion Capture system (Vicon MX, Los Angeles, CA), while kinetic data were collected at 1000 Hz. Heel strike was determine as the first frame when the ground reaction force exceeded 20 N and were visually inspected to accuracy. After identifying gait events, we calculated step length of the ML (SL_{ML}) using a custom written Matlab script (MathWorks, Natick, MA). SL_{ML} was then used to calculate the amount of implicit and explicit, strategic learning processes and our measures of performance and retention.

To determine the contribution of implicit and explicit, strategic processes that occurred during the task we adapted a method used during visuomotor rotation tasks to measure contributions from specific learning mechanisms. In visuomotor rotation tasks, subjects report the specific location to which they were aiming prior to the reach to represent the amount of explicit, strategic learning. The difference then between that reported aim and the observed behavior reflects the implicit processes (McDougle et al. 2015; Morehead et al. 2015; Taylor et al. 2014). Since locomotion is a continuous task, a similar reporting method to quantify the explicit, strategic learning

process is not practical. However, catch trials have been commonly used during locomotion to quantify implicit processes (French et al. 2018; Long et al. 2016; Reisman et al. 2009; Sombric et al. 2017). Thus, rather than measuring the contribution of explicit, strategic processes as done in visuomotor rotation tasks, we first estimated the amount of implicit processes and then estimated the contribution of explicit, strategic processes. The amount of implicit processes was defined as the difference between the average SL_{ML} during Catch Trial and the average SL_{ML} during Baseline (i.e., the aftereffects) and, therefore, was measured in cm (Figure 3.2). The instructions to "*walk normally*" were designed to remove the contribution of strategy to behavior. This approach of removing the contribution of strategy with a cue has been used previously (French et al. 2018; Morehead et al. 2015; Wood et al. 2020); however, it does assume that subjects follow this instruction. The contribution of explicit, strategic processes was then estimated as the difference between the average SL_{ML} during Late Acquisition (i.e., the last 30 steps of Acquition2) and the average SL_{ML} during the Catch Trial and was also measured in cm (Figure 3.2). Late Acquisition was used to quantify the contribution of explicit processes as past work has used the acquisition phase to understand the ongoing learning mechanisms (McDougle et al. 2015; Morehead et al. 2015; Taylor et al. 2014). For these metrics of implicit and explicit processes, a higher value indicates a larger change in behavior due to that specific learning processes.

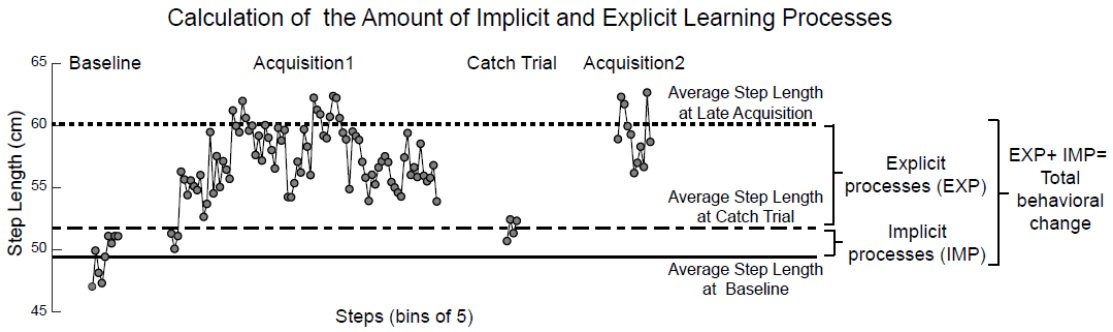

Figure 3.2: Calculation of the amount of implicit and explicit, strategic processes. The amount of implicit learning was calculated as the difference between the average step length during the Catch Trial (dashed line) and Baseline (solid line). The amount of explicit, strategic processes was calculated as the difference between the average step length at Late Acquisition (dotted line) and Catch Trial. The observed behavior at Late Acquisition is the sum of these two types of learning processes.

To quantify performance while visual feedback was present, we used Absolute Error (AE) to capture improvements in accuracy. This measure was calculated as follows:

$$AE_n = \frac{|ASL_n - SL_{Target}|}{SL_{BL}} * 100,$$

where ASL_n is the step length of the ML on step *n* during Acquision1 and 2, SL_{Target} is the step length of the ML that would result from hitting the target every step (i.e., 15% longer than the baseline SL_{ML}), and SL_{BL} is the average step length of the ML during Baseline. This metric represents how far the subject was from the target line during acquisition phases. This metric is expressed as a percentage of the subjects' baseline step length, since the amount of distortion was based on subjects' baseline step length; thus, to accurately compare error between subjects the amount of error must be relative to baseline step length. For this metric a smaller value indicates less

error or better performance while acquiring the new walking pattern. We would expect performance to improve as indicated by a reduction in error if learning was occurring.

To quantify retention, we calculated two measures of forgetting, one for Immediate Retention ($FORGET_{Imm}$) and one for 24-hour Retention ($FORGET_{24hr}$). These metrics were calculated as the absolute difference between SL_{ML} at Late Acquisition (i.e., the last 30 steps of Acquisition2) and the average SL_{ML} during Immediate or 24-hour Retention (Figure 3.1a). The average SL_{ML} was calculated across the entire two minutes of the retention phases, as we do not expect behavior to change over this time. However, to confirm that this did not impact our results, we calculated the measures of $FORGETt_{Imm}$ and $FORGET_{24hr}$ with the average of the first 30 steps as well and found no impact of using different number of steps to represent the retention phases; thus, we only present the results using the entire retention bout here to calculate $FORGET_{Imm}$ and $FORGET_{24hr}$. For this metric a smaller value indicates less forgetting or better retention.

3.5.4 *Statistical Analysis.*

All statistical analyses were performed in SPSS v25 (IBM, Chicago, IL) with alpha set at 0.05. All measures described below were screened for outliers (i.e., data greater than two standard deviations above/below the mean) and if identified were removed from the subsequent analysis. We performed Shapiro-Wilks and Levene's tests to assess normality and homogeneity, respectively. If normality or homogeneity were violated, non-parametric tests were used, otherwise parametric tests were used as outlined below. Additionally, Mauchly's Test of Sphericity was used to assess sphericity of the data during ANOVAs and if violated a Greenhouse-Geisser

correction was used. When a repeated measures ANOVA was planned but parametric statistics could not be used, we performed Mann Whitney U tests.

Prior to conducting our primary analyses, we examined if stroke survivors and healthy adults performed and retained similarly on this task, as differences in these measures could impact subsequent analyses. To do this, we compared the average AE during the first 10 steps of Acquisition1 (i.e., Early Acquisition) and the last 30 steps of Acquisition2 (i.e., Late Acquisition) between groups with a 2 x 2 mixed ANOVA. Additionally, we used a 2 x 2 mixed ANOVA to compare $FORGET_{Imm}$ and $FORGET_{24hr}$ between groups.

Next, we began our primary analyses by comparing the contribution of implicit and explicit processes between groups using a 2 x 2 mixed ANOVA, with learning process and group as factors. Finally, we examined the relationship between the contribution of explicit processes and performance and retention within each group. AE served as our measure of performance, while $FORGET_{IMM}$ was our measure of immediate retention and $FORGET_{24hr}$ was our measure of 24 hour retention. Thus, we performed Pearson's correlations (or Spearman's correlation if data were not normal) between the contribution of explicit processes and 1) AE at Late Acquisition, 2) $FORGET_{Imm}$, and 3) $FORGET_{24hr}$. All three of these correlations were performed in the group of stroke survivors and age-matched healthy adults separately.

3.6 Results.

Twenty stroke survivors (64.2 ± 8.9 yo; 10 F) and twenty age-matched healthy adults (64.8 ± 8.5 yo; 13 F) were included in this study. Additional characteristics of the subjects are presented in Table 1. When asked to take the longest possible step with the ML during Orientation, all subjects exceeded 15% of their SL_{ML} during

Baseline (Stroke Survivors 26.4 ± 13.5%, Healthy Adults 42.4 ± 23.3%), indicating that all subjects were physically able to walk with the pattern we were trying to teach them; thus, no subjects were excluded from the analysis due to inability to complete the desired task. We identified one outlier in the age-matched healthy adult group for AE at Late Acquisition and one outlier in the age-matched healthy adult group for $FORGET_{24hr}$; thus, data for that specific measure for these individuals were removed from the analysis.

Table 3.1: Demographic and Clinical Characteristics of Subjects.

	Stroke Survivors (n=20)	**Healthy Adults (n=20)**
Age (yrs; mean ± SD)	64.2 ± 8.9	64.8 ± 8.5
Sex	10F; 10M	13 F; 7M
Manipulated Leg	10R; 10L	10R; 10L
Time Since Stroke (months; mean ± SD)	51.1 ± 29.2	
Side of Lesion	16R; 4L	
SSWS (m/s; mean ± SD)	0.93 ± 0.2	
FMLE (mean ± SD)	25.9 ± 5.8	

Abbreviations: SSWS- self-elected walking speed; FMLE- Fugl-Meyer: Lower Extremity

Prior to performing our primary analyses, we compared performance and retention between groups. Due to non-normal data, we compared AE during Early Acquisition and Late Acquisition between groups with Mann Whitney U tests to examine performance. This showed no significant difference between groups during both Early Acquisition (Z=-0.54, p=0.60) and Late Acquisition (Z=-0.98, p=0.34; Figure 3.3a and b). This suggests that both groups improved their performance

similarly during the acquisition phases. To examine retention, we compared $FORGET_{Imm}$ and $FORGET_{24hr}$ between groups using a 2 x 2 mixed ANOVA (Figure 3.3c). We found an effect of time ($F(1, 37)=4.82$, $p=0.04$), but no effect of group ($F(1, 37)=.50$, $p=0.48$) and no interaction ($F(1, 37)=2.03$, $p=0.16$). This suggests that subjects forget more 24 hours later; however, the groups forgot similarly. Because these metrics of performance and retention were not different between groups, we were able to examine the contribution of implicit and explicit processes between groups without the quality of performance or magnitude of retention influencing the results.

3.6.1 *Contribution of implicit and explicit processes.*

As the first part of our primary analysis, we used the aftereffects during the Catch Trial to quantify implicit and explicit processes. Both groups used implicit and explicit processes. However, a 2 x 2 mixed ANOVA did not find a main effect of type of learning process (i.e., implicit or explicit) ($F(1, 38)=1.45$, $p=0.24$) or group ($F(1, 38)=0.11$, $p=0.74$; Figure 3.4). Additionally, we did not find a significant interaction ($F(1, 38)=0.04$, $p=0.85$; Figure 3.4). These results suggest that the types of learning processes were not different between groups and that similar amounts of implicit and explicit processes occurred during the task in both groups. Despite these results, it is important to note the significant inter-subject variability in implicit and explicit processes in both groups (Figure 3.4).

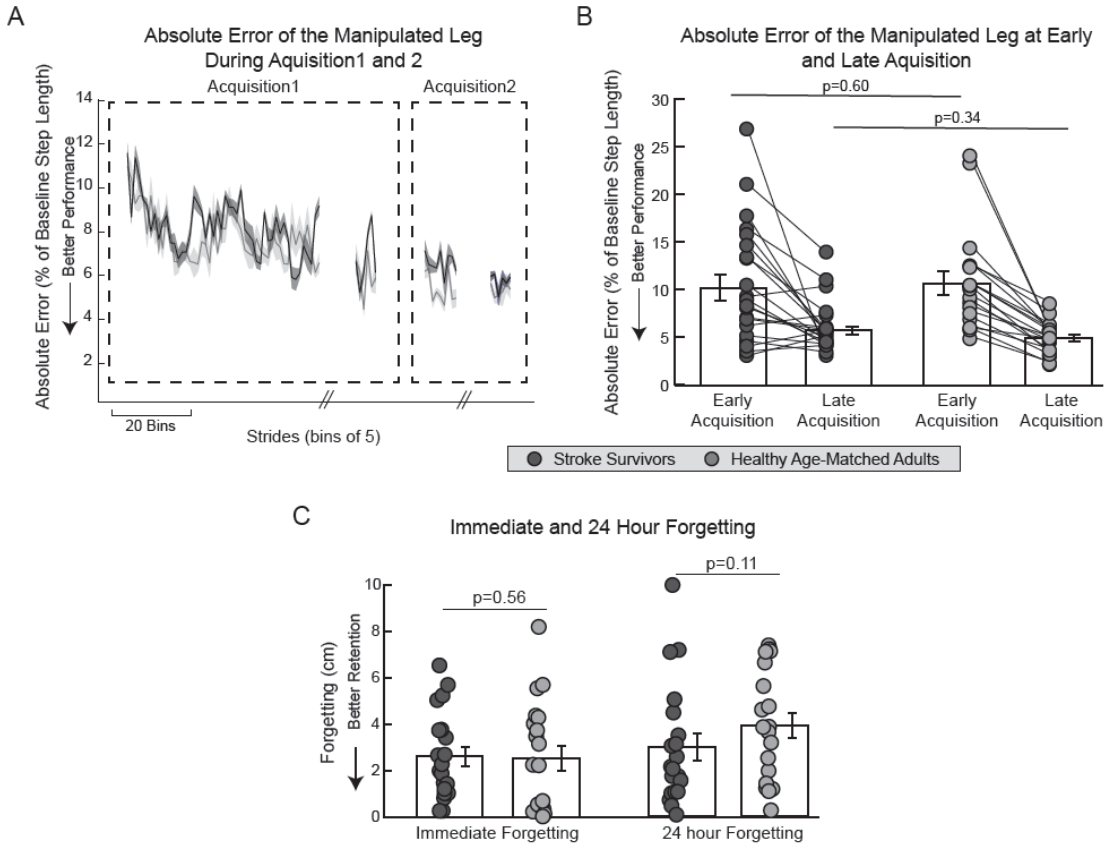

Figure 3.3: Performance and Retention in Stroke Survivors and Age-Matched Healthy Adults. A) Mean Absolute Error for stroke survivors (dark grey) and healthy adults (light grey) during Acquisition1 and 2 in bins of 5 steps with the shaded region indicating the standard error. Data are truncated to the shortest number of steps taken by a single subject with the mean and standard error of the last 30 steps for each subject shown at the end of each Acquisition1 and 2. A reduction in error over the course of the acquisition phases is observed in both groups, suggesting that performance improved over this time. B) Absolute Error, our measure of performance, was not different between groups at Early Acquisition ($p=0.70$) or Late Acquisition ($p=0.34$). As shown by the individual lines, most subjects demonstrated a reduction in error from Early to Late Acquisition. C) Forgetting, our measure of retention, was not significantly different between stroke survivors and healthy adults at immediate ($p=0.56$) or 24-hour retention ($p=0.11$). The dots represent each subject and error bars indicate standard error in B and C.

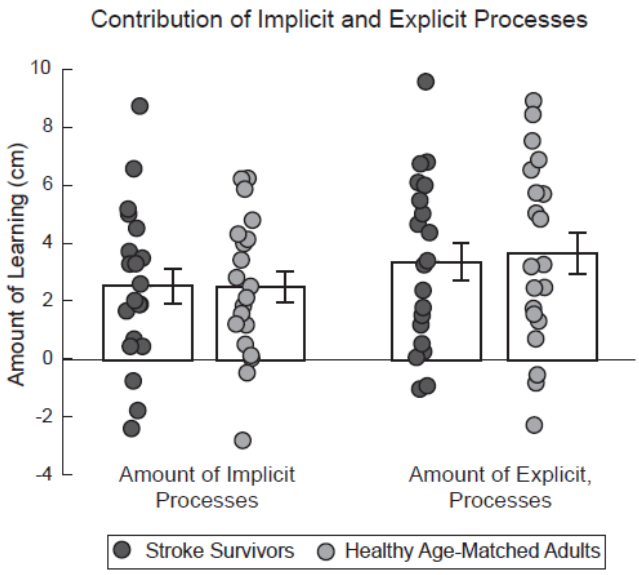

Figure 3.4: Amount of Implicit and Explicit, Strategic Processes in Stroke Survivors and Age-matched Healthy Adults. Both implicit and explicit processes contributed to the acquisition of a new walking pattern in stroke survivors (dark grey) and age-matched healthy adults (light grey). A 2 x 2 mixed ANOVA showed no main effect of type of learning ($F(1, 38)=1.45$, $p=0.24$) or group ($F(1, 38)=0.11$, $p=0.74$) and no interaction ($F(1, 38)=0.04$, $p=0.85$). Individual dots represent subjects and illustrate the significant amount of variability in both groups. Error bars reflect standard error.

3.6.2 *Relationship between the contribution of explicit processes and performance/retention.*

Lastly, we examined the relationship between the amount of explicit processes and 1) AE, 2) $FORGET_{Imm}$, and 3) $FORGET_{24hr}$ in stroke survivors and age-matched healthy adults. Due to non-normality, we used Spearman's correlation to assess the relationship between the contribution of explicit processes and performance, as measured by AE at Late Acquisition, in both groups. In stroke survivors, we found no relationship between the amount of explicit processes and AE at Late Acquisition (ρ= 0.18, p=0.43; Figure 3.5a). Similarly, in age-matched healthy adults, we found no

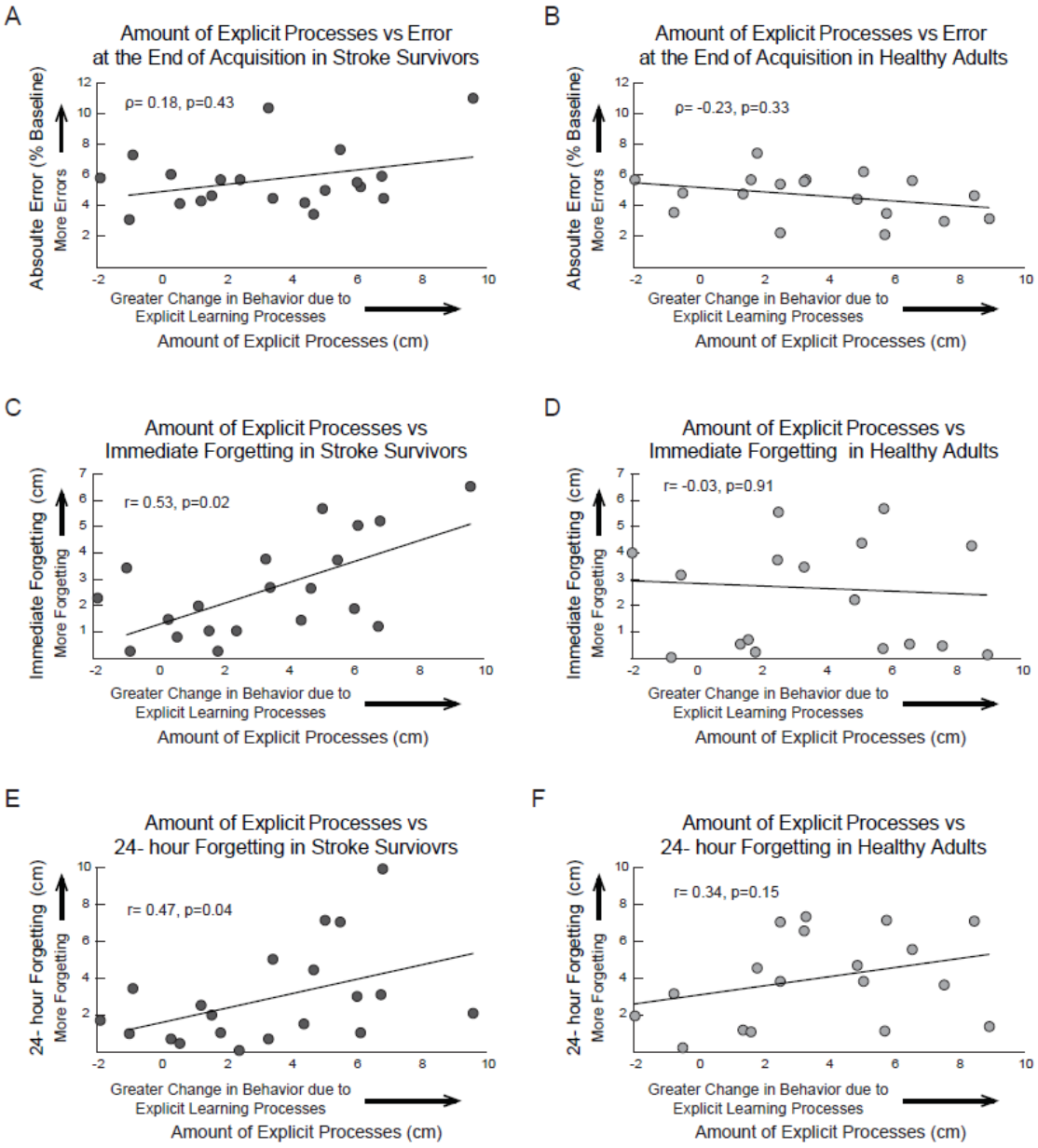

Figure 3.5: Relationship between the amount of explicit, strategic processes and locomotor learning. There was no significant relationship between the amount of explicit processes and performance in stroke survivors (a) and healthy adults (b). There was a moderate and significant relationship between the amount of explicit processes and same day forgetting (c) and 24-hour forgetting (e) in stroke survivors. However, in age-matched healthy adults, there were no significant relationships between the amount of explicit processes and same day (d) and 24-hour forgetting (f).

relationship between the contribution of explicit processes and AE at Late Acquisition (ρ= -0.23, p=0.33; Figure 3.5b). These results suggest that the amount of explicit, strategic processes did not have a significant impact on performance.

In stroke survivors, we found moderate relationships between the contribution of explicit processes and $FORGET_{Imm}$ (r=0.53, p=0.02; Figure 3.5c) and $FORGET_{24hr}$ (r=0.47, p=0.04; Figure 3.5e). In age-matched healthy adults, we found no relationship between the contribution of explicit processes and $FORGET_{Imm}$ (r= -0.03, p=0.91; Figure 3.5d) or between the contribution of explicit processes and $FORGET_{24hr}$ (r=0.34, p=0.15; Figure 3.5f). These results suggest that stroke survivors who had higher amounts of explicit, strategic learning processes forgot more (i.e., did not retain as well); but, this is not the case in age-matched healthy adults.

As an additional analysis we also examined the relationship between performance and immediate and 24-hour retention in both groups. In stroke survivors and in age matched subjects, there was no relationship between AE at Late Acquisition and $FORGET_{Imm}$ (ρ= 0.07, p=0.76; ρ= 0.15, p=0.56, respectively) or between AE at Late Acquisition and $FORGET_{24hr}$ (ρ= -0.03, p=0.90; ρ= 0.17, p=0.51, respectively). This suggests that stroke survivors and healthy adults who learned the new walking pattern well did not necessarily retain the pattern well.

3.7 Discussion.

In this study we sought to examine the contribution of implicit and explicit processes during a locomotor learning task and to understand how these underlying mechanisms impacted performance and retention in stroke survivors and age-matched healthy adults. We found that the amount of explicit, strategic processes was related to how well the newly learned walking pattern was retained both immediately and 24

hours later in individuals after stroke. Additionally, we found no relationship between the amount of explicit, strategic learning and performance and no difference in performance or retention between stroke survivors and age-matched healthy adults. The implications of these results are discussed in the following sections.

3.7.1 *Relationship between explicit, strategic processes and retention.*

Our results suggest that stroke survivors who used a greater amount of explicit, strategic processes did not retain the walking pattern as well. It is possible that this is because explicit, strategic learning processes decay quicker than implicit processes; thus, individuals who used more explicit, strategic processes would have difficulty remembering the new walking pattern long term. This is supported by evidence from the dual-rate state space model which suggests that explicit processes, represented by the fast phase in the dual-rate state space model, decays quickly (Keisler and Shadmehr 2010; McDougle et al. 2015).

However, there are likely other factors that impact this relationship such as age and cognition. Trewartha et al (2014) suggested that forgetting of the fast learning phase (i.e., explicit, strategic learning) during a force field reaching task was impacted by age. This would suggest that the relationship between explicit processes and forgetting could be mediated by age. If this was the case, we would have expected he relationship to be similar in the group of stroke survivors and healthy adults, since they were matched on age. However, we only observed a relationship between the amount of explicit processes and forgetting in individuals with stroke, not in age-matched healthy adults. Trewartha et al (2014) also suggested that cognition, rather than age, may be important in understanding the relationship between explicit processes and retention (Trewartha et al. 2014). Similarly, cognitive abilities have

been found to relate to retention of new, functional upper extremity tasks (Lingo VanGilder et al. 2018; Schaefer and Duff 2017). Thus, it is possible that the relationship between the use of explicit processes and retention is mediated by cognitive capacity. In other words, individuals who have higher cognitive capacity and use large amounts of explicit processes may retain better than individuals who use similar amounts of explicit processes but have lower cognitive capacity. Due to normal variability in cognitive capacity and potential changes to cognition due to stroke and age, we are unable to make a hypothesis regarding how cognitive capacity directly impacted our results. However, it is possible that cognition may serve as a mediator in the relationship between explicit processes and retention. Further, age and cognition may both impact this relationship in complex ways; thus, future work examining the impact of cognition and age on this relationship would provide a more comprehensive understanding of the relationship between learning mechanisms and retention.

Unlike the relationship with retention, we did not find a significant relationship between the amount of explicit, strategic processes and performance during the task in either stroke survivors or age-matched healthy adults. In other words, individuals performed similarly <u>despite</u> the underlying learning processes. For example, two individuals may perform with the same amount of error, yet the processes used to accomplish the task may be very different (e.g., high OR low contribution of explicit processes). This suggests that the strategic processes were flexibly combined with the ongoing implicit processes to successfully learn. This is consistent with upper extremity work which has found that strategic processes are highly flexible and can be

adjusted over time to accomplish the task at hand (Bond and Taylor 2015; Taylor and Ivry 2011; Taylor et al. 2014).

The discrepancy in the relationship between the amount of explicit processes and performance and retention is important to note because it suggests that underlying learning mechanisms have a greater implication for retention than for performance during visually-guided locomotor learning. Additionally, the analysis examining the relationship between performance and retention illustrates the importance of understanding the underlying learning mechanisms, since performance was not significantly related to immediate or 24-hour retention. Since rehabilitation aims to improve long-term behavior, this work supports the need for mechanistic motor learning research to further understand how different learning processes impact retention of a newly learned locomotor task. This line of research will allow for the design of more effective rehabilitation interventions that impact long-term behavior.

3.7.2 *Contributions of implicit and explicit, strategic processes.*

When quantifying the contribution of implicit and explicit, strategic processes during this task, we found that both implicit and explicit processes contributed to the acquisition of the new walking pattern. This was expected given that we have previously found that the behavioral change observed during DVF is contributed to by both implicit and explicit, strategic processes in young, healthy subjects (French et al. 2018; Wood et al. 2020). Other work has also shown that implicit and explicit, strategic processes can occur in parallel during locomotion in stroke survivors (Cherry-Allen et al. 2018) and healthy adults (Long et al. 2016; Malone and Bastian 2010; Roemmich et al. 2016); however, this past work had utilized dual task paradigms using a split belt treadmill paradigm and visual feedback. In contrast, our

results provide evidence that multiple learning processes can occur *within a single locomotor task*, as commonly occurs in everyday life, in individuals after stroke and age-matched healthy adults.

Interestingly, we found that there was no difference between the amount of explicit, strategic processes in stroke survivors and age-matched healthy adults, although there is significant variability in both stroke survivors and age-matched healthy adults. We hypothesized that explicit, strategic processes would be reduced in stroke survivors due to the high cognitive demands of this type of learning (Taylor and Ivry 2014) and the prevalence of cognitive impairments after stroke (Barker-Collo and Feigin 2006; Hochstenbach et al. 1998; Hochstenbach et al. 2003). However, cognition also declines with age; thus, it is likely that subjects in the age-matched healthy adult group had normal age-related cognitive changes that impacted the use of explicit, strategic processes. Therefore, both of our groups may have had some level of cognitive changes, either due to age, stroke, or both, that impacted the use of explicit, strategic processes and that may explain the significant variability observed in both groups. Several studies have examined the impact of cognitive capacity with upper extremity motor learning and found that cognitive capacity relates to motor learning in older (Anguera et al. 2011; Bo et al. 2009; Trewartha et al. 2014) and younger adults (Anguera et al. 2010; Christou et al. 2016; Lingo VanGilder et al. 2018). Few of these studies have examined explicit, strategic processes specifically. Christou et al (2016), however, examined the relationship between cognitive capacity and specific learning processes during an upper extremity visuomotor rotation task. Their work found that individuals with poorer visuospatial working memory used more implicit processes than individuals with higher visuospatial working memory (Christou et al. 2016).

Thus, an individual's cognitive capacity may influence what type of learning they use during specific tasks. Future work examining the role of cognition on the use of specific learning processes during this and other locomotor learning tasks would provide additional insight into the underlying mechanisms of locomotor learning and help deliver targeted motor learning based interventions to older adults and individuals post stroke.

As we hypothesized, there was no difference in the amount of implicit processes used between groups, suggesting that implicit processes used in this task were intact in stroke survivors. Based on recent work from our lab, use-dependent plasticity is likely the primary contributor to the implicit process within this task despite the presence of a sensory prediction error due to the distortion of the visual feedback (Wood et al. 2020). Use-dependent plasticity is dependent on neural pathways that include the primary motor cortex (Classen et al. 1998; Mawase et al. 2017) and, therefore, could be impaired in individuals with cortical lesions. Additionally, it has been suggested that age impacts use-dependent plasticity (Berghuis et al. 2016; Berghuis et al. 2017; Rogasch et al. 2009; Sawaki et al. 2003; Tecchio et al. 2008). If age does impact use-dependent plasticity, the magnitude of the implicit processes in both groups may be affected. As a result, further examination of the contribution of different learning processes in young healthy adults would provide a better understanding of the underlying implicit mechanisms occurring within this task.

Lastly, while not a direct question of this study, the amount of variability in the contribution of each learning process for both groups is notable. As detailed above, on average both groups used the same amounts of implicit and explicit, strategic

processes; however, some individuals used explicit processes exclusively, while others used implicit processes exclusively. This is particularly interesting given that we intentionally made the task as explicit as possible through the instructions provided. This suggests that there are factors other than the design of the task that impact how learning processes are used during a single task. Given the relationship between the amount of explicit processes and retention, especially in stroke survivors, it is critical to understand sources of this inter-subject variability in order to deliver targeted rehabilitation interventions that will be effective for each specific patient. As described above, age and cognitive capacity appear to be factors that may help explain this variability. Thus, work examining how these factors are related to the type of learning used is crucial for applying this work to rehabilitation practice. For example, identifying individuals who are likely to use one type of learning over another would provide rehabilitation professionals with insight into how well an individual may retain the locomotor pattern being trained. This would also allow rehabilitation professionals to select interventions that cater to the learning processes that specific patients are prone to use.

3.7.3 *Limitations and future directions.*

Although this work provides valuable insight into the underlying learning processes occurring during a locomotor learning task with visual feedback, it is not without limitations. First, we calculated the contributions of implicit and explicit processes through a subtraction; thus, we are assuming that only implicit and explicit processes are contributing to the behavioral change that occurs over the course of Acquisition1 and 2. Although this assumption has been made previously (McDougle et al. 2015; Morehead et al. 2015; Taylor et al. 2014), it is important to note that it is

an assumption. The explicit portion of this calculation likely represents strategic aiming as well as the use of online visual feedback, while the implicit portion of this calculation cannot distinguish between different forms of implicit processes. As a result, future work to distinguish the unique role of each of these specific implicit and explicit mechanisms would be valuable. In addition, we did not test whether subjects were able to accurately step to a target by taking a longer step at baseline and so it is possible that some of the subjects were quite good at this task at the start, requiring limited learning. This, however, has not been found to be the case in a study using a similar paradigm in young, healthy subjects (Wood et al. 2020). Another limitation is that we used absolute value when examining performance and retention. While this was necessary to accurately understand the group data (i.e., prevent group averages from being close to zero due to some individuals with positive values while other have negative values), it does not reflect the presence of over and under shooters in our data. Lastly, we only examined this paradigm over two days with one day of training. Previous work has found that repeated practice can make behaviors learned through explicit, strategic processes more automatic and less cognitively demanding (Haith and Krakauer 2018; Huberdeau et al. 2019); thus, the relationships we found between explicit, strategic processes and retention may be different if multiple practice session occur.

3.7.4 *Conclusions.*

This work provides evidence that the underlying learning processes were related to retention of a newly learned walking pattern even though performance was not. This relationship was particularly strong in individuals after stroke, potentially due to cognitive changes that often accompany stroke. Additionally, the results

highlight the significant inter-subject variability in the type of learning processes used during the same task. Together this understanding of locomotor learning processes will allow for the development of rehabilitation interventions that optimize retention of the learned task and that are tailored to the specific individual being treated; however, future work is needed to understand how factors, such as cognition and age, and repetitive practice impact the use of implicit and explicit processes and how that impacts the retention of newly learned walking patterns.

3.8 Acknowledgements.

The authors would like to thank the participants of this study as well as the undergraduate research assistants for their assistance with data processing and analysis.

3.9 Funding.

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by the National Institutes of Health [grant numbers 1R01-HD-078330-01A, S10RR028114-01, and F31NS111806] and The Foundation for Physical Therapy Research [2016 Florence P. Kendell Doctoral Scholarship, 2018-2019 Promotion for Doctoral Studies (PODS) Level I Award, and 2019-2020 Promotion for Doctoral Studies (PODS) Level II Award].

3.10 Disclosures.

The authors have no conflicts of interest to disclose.

3.11 Supplemental Analysis.

In addition to the analysis presented above, we also examined the relationship between the contribution of explicit learning and retention using a measure of retention that accounted for the impact of the removal of visual feedback during the retention test ***and*** the amount that was learned. This metric is called Percent Forgotten (%Forgot) and was calculated as follows:

$$\%Forgot = \frac{|\overline{RSL}_{Imm} - \overline{RSL}_{24}|}{\overline{SL}_{LA}} \; x \; 100.$$

In this metric, the numerator represents the change from Day 1 to Day 2 as the absolute value of the difference between $\overline{RSL}_{Imm}$, the average SL_{ML} during Immediate Retention, and $\overline{RSL}_{24}$, the average SL_{ML} during 24-hour Retention. The denominator then was $\overline{SL}_{LA}$ was the average SL_{ML} during Late Acquisition (i.e., the last 30 strides of Acquistion2); therefore, this metric expresses what was forgotten relative to how much was learned at the end of Acquisition. Similar to the analysis described in the Methods section above, we performed a correlation between the amount of explicit learning and %Forgot in individuals after stroke and healthy adults.

Upon completing this analysis, we found a moderate relationship between EXP and %Forgot in individuals with stroke (r=0.44, p=0.05; Figure S3.1a); however, the relationship in healthy adults was not significant (r=-0.09, p=0.71; Figure S3.1b). These results are consistent with the results presented in the primary document, suggesting that stroke survivors who used more explicit learning processes did not retain as well; however, this was not the case in age-matched healthy adults.

Chapter 4

FLUID COGNITIVE ABILITIES ARE IMPORTANT FOR LEARNING AND RETAINING A NEW EXPLICITLY-LEARNED WALKING PATTERN IN INDIVIDUALS AFTER STROKE

4.1 Preface.

In this chapter, the terminology regarding behavior while the visual feedback is present is slightly different than the terminology used in previous chapters. Here we describe this behavior as "learning," while in other chapters this is referred to as "performance." This has the potential to cause confusion. Thus, to improve the clarity of this chapter, I wish to address this possible source of confusion. We have used the word "learning" to describe a change in behavior that occurs when visual feedback is present. This terminology is that same as that used during the visuomotor rotation task when visual feedback is present. While this is not an incorrect description of the behavior occurring, some in the motor learning field argue that learning can only be assessed via a retention or transfer test. In this view, what we describe as "learning" in this chapter should be referred to as acquisition or performance. In other chapters we have done just that and referred to behavior when the visual feedback is present as performance. Because this manuscript was in review at the time this document was prepared, we have not changed the language of this chapter to be consistent with other chapters. Thus, rather than describing behavior while visual feedback is present as performance we will refer to in as learning throughout this chapter. It is important to

note that despite the differing terminology from pervious chapters, we are in fact using the same metric, Percent Error.

4.2 Abstract.

Background: There is significant variability in post-stroke locomotor learning that is poorly understood and impacts individual responses to rehabilitation interventions. Cognitive abilities relate to upper extremity motor learning in neurologically intact adults, but have not been studied in post-stroke locomotor learning.

Objective: To understand the relationship between locomotor learning and retention and cognition after stroke.

Methods: Participants with chronic (>6 months) stroke participated in three testing sessions. During the first session, participants walked on a treadmill and learned a new walking pattern through visual feedback about their step length. During the second session, participants walked on a treadmill and 24-hour retention was assessed. Physical and cognitive tests, including the Fugl-Meyer-Lower Extremity (FM-LE), Fluid Cognition Composite Score (FCCS) from the NIH Toolbox -Cognition Battery®, and Spatial Addition from the Wechsler Memory Scale-IV®, were completed in the third session. Two sequential regression models were completed: one with learning and one with retention as the dependent variables. Age, physical impairment (i.e., FM-LE), and cognitive measures (i.e., FCCS and Spatial Addition) were the independent variables.

Results: Forty-nine and thirty-four participants were included in the learning and retention models, respectively. After accounting for age and FM-LE, cognitive measures explained a significant portion of variability in learning (ΔR^2=0.17, p=0.008;

overall model R^2=0.31, p=0.002) and retention (ΔR^2=0.17, p=0.023; overall model R^2=0.44, p=0.002).

Conclusions: Cognitive abilities appear to be an important factor for understanding locomotor learning and retention after stroke. This has significant implications for incorporating locomotor learning principles into the development of personalized rehabilitation interventions after stroke.

4.3 Introduction.

Improving one's walking ability after stroke is a common goal of patients and rehabilitation professionals.(Bohannon et al. 1988) As a result, significant time and money are spent on improving walking during stroke rehabilitation. Despite this, only 50% of individuals regain the ability to walk independently after their stroke (Jorgensen et al. 1995). This is in part due to highly variable responses to interventions across individuals (Bowden et al. 2013; Dobkin et al. 2014). Since motor learning is the foundation of most rehabilitation interventions, differences in how well individuals learn likely contributes to these varied responses. Thus, understanding sources of individual variability during locomotor learning can improve the field's understanding of varied responses to rehabilitation interventions and ultimately lead to the delivery of personalized rehabilitation interventions to improve walking after stroke. However, individual differences during locomotor learning have been largely ignored. The few studies that have sought to understand variability in locomotor learning after stroke have focused on a limited number of factors, specifically demographic information and sensorimotor impairment (Reisman et al. 2013; Tyrell et al. 2014). These factors are unable to explain a significant portion of the observed variability in locomotor

learning. Thus, it remains unclear what factors predict how well an individual will be able to learn and retain a new walking pattern after stroke.

Although cognition has been found to relate to motor outcomes after stroke (Barker-Collo and Feigin 2006; Buchman et al. 2011; Hayes et al. 2016; Rasmussen et al. 2019; Robertson et al. 1997), it has been unexplored related to locomotor learning after stroke. In neurologically intact adults, however, lower cognitive abilities have been found to relate to poorer motor learning and retention of upper extremity tasks (Anguera et al. 2010; 2011; Bo et al. 2009; Bo and Seidler 2009; Christou et al. 2016; Holland et al. 2019; Lingo VanGilder et al. 2018; Schaefer and Duff 2017; Unsworth and Engle 2005). Specifically, visuospatial working memory, or one's ability to temporarily store visual and/or spatial information for manipulation (Kent 2016), has drawn significant attention in past work. In upper extremity sequence learning (Bo et al. 2009; Bo and Seidler 2009; Unsworth and Engle 2005) and visuomotor rotation tasks (Anguera et al. 2010; 2011; Christou et al. 2016; Holland et al. 2019), neurologically intact adults with lower visuospatial working memory scores have been found to learn and retain new motor patterns worse than individuals with higher visuospatial working memory scores. However, visuospatial working memory is highly related to other domains of cognition, specifically attention and executive functions (Harvey 2019; Kent 2016; Unsworth and Engle 2005). Additionally, other work has found that nonverbal reasoning (Unsworth and Engle 2005), processing speed (Bock and Girgenrath 2006), decision-making (Bock and Girgenrath 2006), delayed memory (Schaefer and Duff 2017), and visuospatial construction ability (Lingo VanGilder et al. 2018; Lingo VanGilder et al. 2019) are related to upper extremity motor learning. Thus, it is unclear if the relationship between motor learning

and cognition is specific to visuospatial working memory. All of the domains of cognition that have been found to relate to motor learning can broadly be classified as fluid cognitive abilities, which is a global cognitive measure reflecting one's abilities to problem solving and learn new things in the absence of prior experience (Wasserman and Wasserman 2017). Thus, it is possible that global fluid cognition rather than visuospatial working memory specifically is related to motor learning.

The work described above has all been conducted in upper extremity tasks. Therefore, despite the high prevalence of cognitive impairments after stroke (Barker-Collo and Feigin 2006), it is unclear if cognition is related to locomotor learning similarly. Because of the unique demands of locomotion (i.e., high levels of postural control and bilateral coordination), it is possible that cognition does not have the same relationship with locomotor learning as it does with motor learning involving upper extremity tasks. However, there is evidence that underlying learning processes that occur in the upper extremity and during locomotion are likely the same. For example, sensorimotor adaptation occurs during upper extremity tasks (Brudner et al. 2016; Mazzoni and Krakauer 2006; McDougle et al. 2015; Morehead et al. 2017) and locomotion (Bastian 2008; Morton and Bastian 2006). Similarly, explicit, strategic learning processes have been observed in both upper extremity tasks (McDougle et al. 2015; Morehead et al. 2015; Taylor and Ivry 2011; Taylor et al. 2010) and locomotion (French et al. 2018; Roemmich et al. 2016). Thus, despite the unique demands of walking, the relationship between cognition and locomotor learning may exist due to similar underlying learning processes. Importantly, cognition is believed to relate to explicit motor learning processes in the upper extremity. This is highlighted by the work of Christou et al. (2016), which found that a visuospatial working memory task

was specifically related to the explicit, strategic component of visuomotor adaptation (Christou et al. 2016). The involvement of the dorsolateral prefrontal cortex in both visuospatial working memory and explicit, strategic learning is the hypothesized mechanism of this relationship (Anguera et al. 2010; 2011; Taylor and Ivry 2014). Therefore, it is possible that cognition has the same relationship with locomotor learning when the underlying learning processes are explicit and strategic in nature; however, this is unknown.

Thus, the purpose of this work was to understand the relationship between cognition (i.e., visuospatial working memory and fluid cognitive abilities) and *explicit* locomotor learning and retention after stroke. To do this, we used a visually-guided walking paradigm that primarily results in explicit, strategic learning (French et al. 2018; Wood et al. 2020) to assess locomotor learning abilities after stroke. Additionally, we used a standardized measure of visuospatial working memory and of fluid cognitive abilities to measure cognition. We hypothesized that cognition, specifically visuospatial working memory *and* a composite measure of fluid cognition, would explain a significant portion of variability in learning and retention of a new, strategically-learned walking pattern after accounting for age and physical impairment.

4.4 Methods.

4.4.1 *Participants.*

Community-dwelling stroke survivors were recruited from local physical therapy and physician practices, support groups, and through advertisements. To be included, participants had to meet the following criteria: 1) 18-85 years old, 2) MRI

evidence of a single unilateral chronic (>6 months) stroke, 3) able to walk 10 meters without physical assistance, 4) resting heart rate within 40 to 100 beats per minute, and 5) resting blood pressure within 90/60 and 185/100 mmHg. Participants were excluded if they met the following criteria: 1) MRI evidence of a cerebellar stroke, 2) neurologic conditions other than stroke, 3) changes in vision following their stroke via self-report, 4) neglect via clinical observation, or 5) inability to communicate with investigators via questions 1b and c of the NIH Stroke Scale, 6) history of coronary artery bypass graft or myocardial infarction in the past 3 months, 7) unexplained dizziness in the last 6 months, or 8) pain that limited walking. Participants signed an informed consent approved by the Human Subjects Review Board at the University of Delaware.

4.4.2 *Experimental Protocol.*

Participants completed a three-day protocol that included two days of treadmill walking and one day of physical and cognitive testing. The two sessions of treadmill walking where performed 24 hours (± 2 hours) apart, while the third session consisting of clinical and cognitive tests was performed one to seven days after the second treadmill walking session (Figure 4.1a). Cognitive tests were administered on a separate day to minimize the potential impact of activity before the cognitive assessments. The range of time between Day2 and Day3 (one to seven days) was to ensure that participants were able to complete the three day protocol. On average, subjects completed the cognitive and physical tests 2.4 ± 2.1 days after Day2.

4.4.2.1 *Locomotor Learning Paradigm.*

During the first 2 days of the study, participants walked on a dual-belt treadmill instrumented with dual 6 degrees of freedom force plates (Bertec Corporation, Columbus, OH) while collecting motion capture data from six markers located on bilateral heels, lateral malleoli, and fifth metatarsal heads. Kinematic data were collected at 100 Hz using an eight-camera Vicon Motion Capture system (Vicon MX, Los Angeles, CA) and kinetic data were collected at 1000 Hz. While walking on the treadmill, participants walked at a comfortable, self-selected walking speed with a safety harness and a light grip on the handrail in front of the treadmill. Throughout the treadmill walking, a 20-inch computer monitor was positioned in front of the treadmill.

On Day1, participants completed 5 phases: Baseline, Orientation, Acquisition1, Acquisition2, and Immediate Retention. Day2 consisted of 24-hour Retention (Figure 4.1a). During Baseline, Immediate Retention, and 24-hour Retention, no visual feedback was displayed on the monitor (Figure 4.1b). During Orientation, Acquisition1, and Acquisition2, real-time visual feedback was displayed on the monitor using The Motion Monitor Toolbox (Innovative Sports Training Inc., Chicago, IL; Figure 4.1c).

During Baseline, subjects were instructed to walk normally. During this time, average step length was calculated for each leg. The leg that naturally took the shorter step was identified and will be referred to as the Manipulated Leg (ML). The other leg will be referred to as the Non-Manipulated Leg (NML). The calculated step lengths were used to create the visual feedback display that participants watched during Orientation, Acquisition1, and Acquisition2.

During Orientation, Acquisition1, and Acquisition2, a bar graph was displayed on the monitor. This graph displayed real-time information about the participants step length and has been described previously (French et al. 2018; Wood et al. 2020). Briefly, there were two bars and two horizontal lines representing the participants step length during the Baseline phase on the display. Prior to Orientation, participants were verbally informed about the display. The Orientation phase was 2 minutes long and consisted of 3 separate walking bouts with accurate visual feedback (Figure 4.1d). First, participants were instructed to *"walk normally and watch the display."* Next, they were instructed to *"take the longest possible step"* with their. Finally, participants were again asked to *"walk normally and watch the display"* for 1 minute. This phase ensured that participants understood the display and were physically able to increase their step length enough to complete the learning task.

During Acquistion1 and 2, the same bar graph was displayed; however, there were also numbers positioned above each bar that increased when the bar hit the target line. During these phases, the visual feedback was distorted so that the bar that represented the ML looked as if they were taking a shorter step than they actually were (Figure 4.1d). Specifically, the bar of the ML was shortened by 15% of the baseline step length of the ML; with the goal of increasing the step length by 15%. When subjects increased their step length enough to get within ±2% the horizontal target line, the numbers above the bar increased. Participants were instructed to get these numbers "*as high as possible by getting the bars to hit the target line.*" Additionally, participants were told that the bars would be inaccurate. This was done to maximize

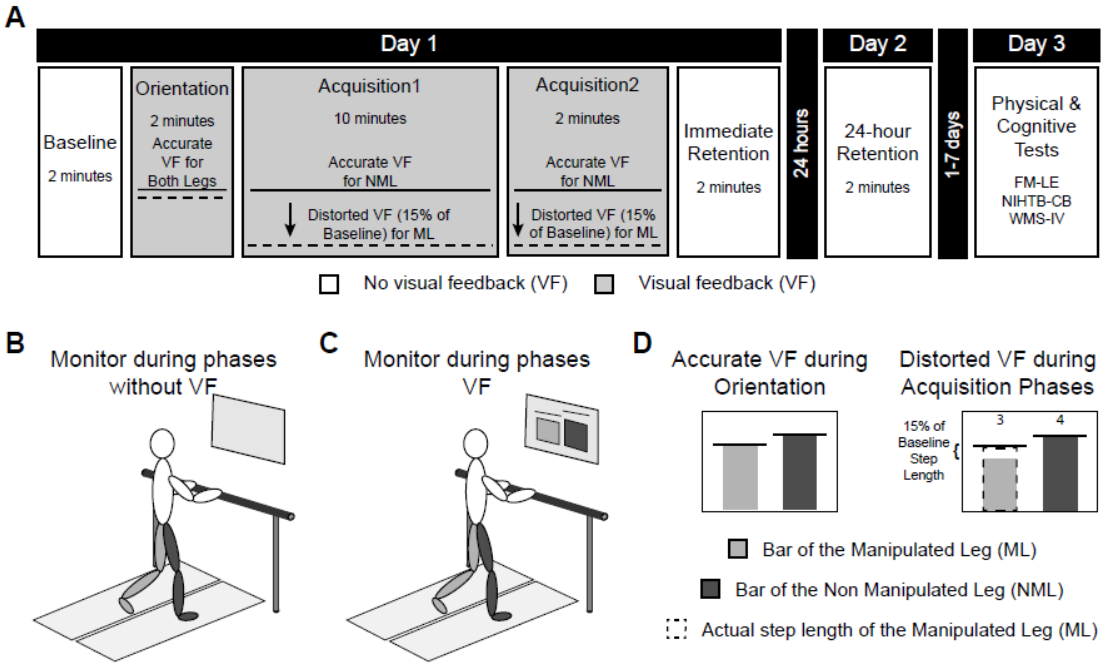

Figure 4.1: Experimental protocol and set up. Participants after stroke completed a three day protocol that included two days of treadmill walking and one day of clinical and cognitive testing (a). During Baseline, Immediate Retention, and 24-hour Retention, no visual feedback was provided (b), while during Orientation and Acquisition1 and 2 a bar graph was displayed on the computer monitor in front of the treadmill (c). During Orientation the feedback was accurate, but during Acquisiton1 and 2, the visual feedback of one of the bars was distorted to make it look as if though that leg was taking a shorter step than they actually were (d). This resulted in participants learning to a new walking pattern where they took a longer than usual step with one leg. During Immediate Retention and 24-hour Retention, participants were instructed to walk with the pattern they had learned during the acquisition phases. The final day included the lower extremity portion of the Fugl-Meyer (FM-LE), the NIH Toolbox Cognitive Battery (NIHTB-CB), and the Wechsler Memory Scale-IV (WMS-IV).

the amount of explicit learning processes occurring since past work suggests that detailed instructions during this paradigm facilitates explicit learning (French et al. 2018).

Lastly, during Immediate Retention on Day1 and 24-hour Retention on Day2, no visual feedback was provided and subjects were instructed to *"walk how you were walking while you watched the display."* These instructions were provided during the retention phases, because tasks learned via explicit, strategic learning are recalled when prompted by a verbal or visual cue (French et al. 2018; Morehead et al. 2015).

4.4.2.2 *Physical and Cognitive Testing.*

On Day3, participants completed a series of physical and cognitive tests. The assessor was not aware of the results from the locomotor learning task prior to administering these tests. First, the lower extremity portion of the Fugl-Meyer (FM-LE) was performed (Fugl-Meyer et al. 1975). This reflects physical impairment after stroke, where high scores indicate less physical impairment. This measure has been found to be reliable and valid in individuals post stroke (Sullivan et al. 2011). Next, participants completed five subtests from the Cognitive Battery of the NIH Toolbox® for Assessment of Neurological and Behavioral Function (NIHTB-CB) in the NIH Toolbox iPad App (version 1.19.2160) (Gershon et al. 2013; Weintraub et al. 2013). The five subtests that were administered were 1) Flanker Inhibitory Control and Attention Test, which measures attention, executive functions of cognitive control, and inhibition, 2) Dimensional Change Card Sort Test, which measures executive functions (an executive function), 3) List Sorting Working Memory Test, which measures working memory, 4) Pattern Comparison Processing Speed Test, which measures processing speed, and 5) Picture Sequence Memory Test, which measures

episodic memory (Akshoomoff et al. 2013; Heaton et al. 2014; Mungas et al. 2014; Tulsky et al. 2017). These subtests combine to create a Fluid Cognition Composite Score (FCCS) (Heaton et al. 2014). This composite score is reported as a Standard Score, where 100 is average and the standard deviation is 15. The NIHTB-CB and FCCS have good evidence for reliability and validity in individuals with stroke (Carlozzi et al. 2017a; Carlozzi et al. 2017b; Tulsky et al. 2017). Lastly, the Spatial Addition subtest from the Wechsler Memory Scale®-IV (WMS-IV) was administered. The WMS-IV is commonly used to assess memory (Drozdick et al. 2011) and has strong evidence for validity in both neurologically intact adults (Holdnack et al. 2011; Miller et al. 2013) and those with acquired cognitive disorders (Carlozzi et al. 2013). The Spatial Addition subtest was specifically selected as it is one of the two measures of the WMS-IV that measures visuospatial working memory (Holdnack et al. 2011; Kent 2013). For both of these cognitive measures, a higher score indicates higher cognitive function.

4.4.3 *Behavioral Data Analysis.*

Analysis of behavioral data was performed with a custom-written Matlab code (MathWorks, Natick, MA). Step length of the ML was used to calculate measures of learning and retention. Step length of the ML was defined as the sagittal distance between heel markers when heel strike occurred, which was identified as the first time point when the force exceeded 20 N. Participants were asked to take their longest possible step during Orientation to ensured that participants were physically able to increase their step length by at least 15% of their step length during Baseline. Individuals who were physically unable to increase their ML step length sufficiently were excluded from the analysis.

Percent Error of the ML (PE) was our measure of learning and represents the relative amount of error during learning as a percent of the subjects' baseline step length; reflecting how accurately participants learned the new walking pattern. It was calculated as:

$$PE_{ML_n} = \frac{|ASL_n - TL|}{\overline{SL}_B} \; x \; 100.$$

The numerator was the absolute value of the difference between the step length of step *n* during the Acquisition phases (ASL_n), and the distance of the targeted step length (i.e., 15% longer than the step length of the ML at Baseline; TL). $\overline{SL}_B$ was the average step length during Baseline for the participant. The relative percent was chosen since the amount of distortion was based on subjects' baseline step length. For this metric a smaller value indicates better learning.

To quantify retention, we calculated the Percent Forgotten (%Forgot) as follows:

$$\%Forgot = \frac{|\overline{RSL}_{Imm} - \overline{RSL}_{24}|}{\overline{ASL}_{30}} \; x \; 100.$$

The numerator was the absolute value of the difference between $\overline{RSL}_{Imm}$, the average step length of the ML during Immediate Retention, and $\overline{RSL}_{24}$, the average step length of the ML during 24-hour Retention. $\overline{ASL}_{30}$ was the average step length of the ML during the last 30 strides of Acquistion2. Thus, this metric expresses how much was forgotten between Day1 and 2 as a percentage of what was learned. For this metric a smaller value indicates better retention.

4.4.4 *Statistical Analysis.*

All statistical analyses were performed in SPSS v26 (IBM, Chicago, IL) with an alpha of 0.05. Prior to completing our primary analyses, we confirmed that participants learned and retained the new walking pattern. To confirm that learning occurred, we compared the average step length of the ML during Baseline and with the average step length during the last 30 strides of Acquisition2 using a paired t-test. Similarly, we confirmed that retention occurred by comparing the average step length of the ML during 24-hour Retention and during the last 30 strides of Acquisition2.

For our primary analysis, two sequential regression models tested the relationship between the primary outcomes of learning and retention with cognition, after accounting for covariates. One model examined the relationship between learning and cognition with the average PE over the last 30 strides of Acquisition2 as the dependent variable, while the other examined the relationship between retention and cognition with %Forget as the dependent variable. Both models included four predictors that were entered in three sequential blocks. The first block consisted of one predictor: age. Similarly, the second block consisted of a single predictor: FM-LE. Finally, block three included the cognitive measures (i.e., FCCS and Spatial Addition). The scores included in the model from these cognitive assessments were not age-corrected as age was included in the first block. All assumptions for regression were tested, including normality, homoscedasticity, and no multicollinearity. Multicollinearity was assessed with the variance inflation factors (VIF), values greater than 10 would indicate a concern for multicollinearity. All VIF values were less than 2 for both regressions; thus, the analysis was conducted as detailed above. Additionally, a correlation matrix of all predictors are presented in the Supplemental Table S1. Normality was initially violated for both models. One outlier was identified (defined

as a residual beyond 3 standard deviations from the mean) in each model and were therefore removed, resulting in the assumptions being satisfied. Sensitivity analyses revealed that the results were consistent whether the outlier was included or not; since the excluded results met all assumptions they are presented here. Here we present the R^2 and change in R^2 (ΔR^2) for the model as each block is added. The p-value associated with the whole model indicates if the model with all entered predictors is significant, while the p-value associated with the ΔR^2 reflects whether the addition of the new block of predictors significantly improves the model. Lastly, we will present the standardized coefficients for both of the complete models (i.e., the learning and retention regression for all 3 blocks of predictors).

4.5 Results.

Thirty five individuals after stroke were enrolled in the study; however, fifteen additional participants who were enrolled in a separate study completed the same protocol on Day1 and the same physical and cognitive tests on Day3 (i.e., these subjects completed a different protocol on Day2). Thus, these additional fifteen individuals were included in the regression model for learning, bringing the total sample for the learning model to fifty. However, one outlier was identified, resulting in forty-nine participants (64.9 ± 9.9 yo; 23F) being included in the final analysis of learning. After removal of an outlier from the retention analysis, thirty-four individuals (63.7 ± 10.0 yo; 14F) were included in the retention regression.

When instructed to take the longest step possible during Orientation, all subjects increased the step length of the ML by more than 15% of their baseline step length (28.3 ± 14.0%); thus, no participants were excluded from the analysis due to inability to physically complete the task. Additional demographic, clinical, and

behavioral information of those included in the learning and retention analyses are presented in Table 1.

Table 4.1: Demographic, Clinical, and Behavioral Characteristics of Participants.

	Participants in Learning Analysis (n=49)	**Participants in Retention Analysis (n=34)**	**p value**
Demographic Information			
Age (yr; mean ± SD)	64.9 ± 9.9	63.7 ± 10.0	0.58
Sex	23F; 26M	14 F; 19M	0.68
Level of education (yr; mean ± SD)	14.4 ± 2.3	14.1 ± 2.3	0.67
TSS (mo; mean ± SD)	49.6 ± 29.3	48.9 ± 26.5	0.92
Side of Lesion	20 L; 29 R	12 L; 22 R	0.49
Clinical Information			
FM-LE (mean ± SD)	26.0 ± 5.9	25.9 ± 5.8	0.90
FCCS (mean ± SD)	84.8 ± 8.2	83.6 ± 8.5	0.53
Spatial Addition (mean ± SD)	10.2 ± 4.3	9.9 ± 4.9	0.81
Behavioral Information			
Manipulated leg	26 P; 23 NP	19 P; 15 NP	0.88
PE (%; mean ± SD)	6.4 ± 3.2		
%Forgot (%; mean ± SD)		4.4 ± 3.4	

Abbreviations: TSS- Time since stroke; FM-LE-Fugl-Meyer: Lower Extremity; FCCS-Fluid Cognition Composite Score; P- Paretic; NP- Not paretic; PE- Percent Error; %Forgot- Percent Forgotten

To summarize, scores on the cognitive tests indicate that our sample had below average cognitive abilities. This is specifically illustrated by scores on the FCCS, which is reported as a standard score (i.e., 100 is average and 15 is the standard deviation of the population). In our sample, 22 out of 49 individuals were more than 1 standard deviation below average on the FCCS (i.e., less than 85). This was expected given the prevalence of cognitive deficits following stroke. Additionally, on average

our sample included individuals who had mild physical impairment as measured by the FM-LE (26.0 ± 5.9). Lastly, the characteristics of those in the learning and retention analysis were not significantly different ($p>0.05$).

As a whole, participants after stroke learned a new walking pattern that was significantly different from their walking pattern at Baseline ($t(48)=-13.8$, $p<0.001$; Figure 4.2a). Similarly, as a group, participants after stroke retained a walking pattern

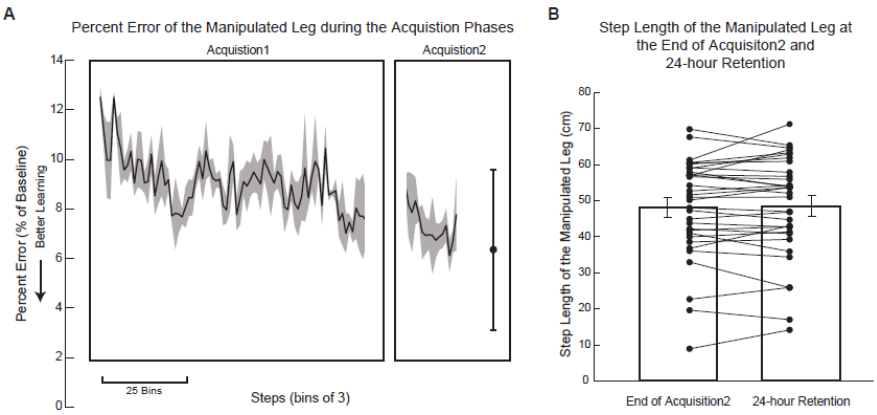

Figure 4.2: Learning and retention. A) Percent Error decreased throughout Acquisition1 and 2 (n=49), suggesting that they learned a new pattern over the course of these walking bouts. Solid line represents the group average Percent Error in bins of 3 steps, while the shaded region is the standard error of the mean. Data in both Acquistion1 and 2 are truncated to the participant with the fewest number of steps. The final point represents the average Percent Error during the last 30 steps of Acquistion2 with error bars indicating the standard deviation. B) Mean step length of the manipulated leg during the end of Acquistion2 and during 24-hour Retention was not significantly different (n=34), suggesting that the learned walking pattern was retained. Error bars represent standard error of the mean and individual points represent each participant.

that was not significantly different than the pattern that was learned (t(33)=-0.3, p=0.78; Figure 4.2b).This suggests that the group learned and retained the new walking pattern; however, as we have previously observed in neurologically intact adults (French et al. 2018; Wood et al. 2020), there was substantial inter-subject variability in learning and retention that was explored in our primary analyses.

When examining learning, the first block, age, was not a significant predictor of PE (R^2=0.03, p=0.24). The second block, FM-LE, was significant after accounting for age (ΔR^2=0.11, p=0.02). Lastly, the third block containing FCCS and Spatial Addition was a significant predictor of learning above and beyond age and physical impairment (ΔR^2=0.17, p=0.008). These results are presented in Table 2. The final model with all four predictors explained a significant portion of variability in learning (R^2=0.31, p=0.002). As indicated by their standardized coefficients, FM-LE (β= -

Table 4.2: Results of the sequential regression examining the relationship between locomotor learning/retention and cognition. Percent Error was the dependent variable in the model assessing the relationship between learning and cognition, while Percent Forgotten was the dependent variable in the model assessing the relationship between retention and cognition.

	Block	Predictor	R^2	Model *p*	ΔR^2	ΔR^2 *p*
Learning						
	1	Age	0.03	0.24		
	2	FM-LE	0.14	0.04	0.11	0.02
	3	FCCS, Spatial Addition	0.31	0.002	0.17	0.008
Retention						
	1	Age	0.05	0.20		
	2	FM-LE	0.27	0.008	0.22	0.005
	3	FCCS, Spatial Addition	0.44	0.002	0.17	0.02

0.34, p=0.01) and FCCS (β= - 0.39, p=0.008) were the only significant predictors of learning (Table 3). As indicated by the standardized coefficients, these results suggest that less physical impairment and higher fluid cognition were associated with better learning. For completeness, this analysis was also performed with the 34 individuals who were included in the retention analysis detailed below. The results of this analysis mirror the results when 49 subjects were included. Specifically, the addition of the cognitive assessments resulted in a significant increase in R^2 (ΔR^2=0.16, p=0.04). Also FCCS, but not Spatial Addition, was a significant predictor in the final model (β= - 0.41, p=0.02 and β= - 0.02, p=0.89, respectively).

Table 4.3: Standardized coefficients for all variables in the final model examining the relationship between 1) learning and cognition and 2) retention and cognition.

	Predictor	**Standardized Coefficient**	***p* value**
Learning			
	Age	0.04	0.16
	FM-LE	-0.34	0.01
	FCCS	-0.39	0.008
	Spatial Addition	-0.06	0.69
Retention			
	Age	0.06	0.67
	FM-LE	-0.51	0.001
	FCCS	-0.37	0.02
	Spatial Addition	-0.12	0.47

When examining retention, we found a similar pattern, where the first block, age, was not significant predictor of %Forgot (R^2=0.05, p=0.20). Physical impairment (i.e., FM-LE) in the second block was significant (ΔR^2=0.22, p=0.005). Lastly, the

addition of the third block with FCCS and Spatial Addition was a significant predictor of retention above and beyond age and physical impairment (ΔR^2=0.17, p=0.023). These results are presented in Table 2. The final model with all four predictors explained a significant portion of variability in learning (R^2=0.44, p=0.002). As indicated by the standardized coefficients (Table 3), FM-LE (β= - 0.51, p=0.001) and FCCS (β= - 0.38, p=0.02) were the only significant predictors. Again these standardized coefficients indicate that less physical impairment and better fluid cognition were associated with better retention.

As an exploratory analysis, we examined which subtest of the FCCS was most related to learning and retention. Due to the exploratory nature of this analysis alpha was set to 0.1. This analysis showed that Flanker Inhibitory Control and Attention Test (ρ=-0.49, p<0.001), Dimensional Change Card Sort Test (ρ=-0.30, p=0.04), and Pattern Comparison Processing Speed Test (ρ=-0.27, p=0.06) were related to learning. Additionally, Flanker Inhibitory Control and Attention Test was related to retention (ρ=-0.32, p=0.07). Complete results are presented in the Supplemental Table S2.

4.6 Discussion.

The purpose of this work was to examine the relationship between locomotor learning/retention and cognition. We found that cognition explained a significant portion of variability in locomotor learning and retention *above and beyond* that explained by age and physical impairment. As evident by the coefficients, fluid cognition but not visuospatial working memory was a significant predictor of locomotor learning and retention. Specifically, individuals after stroke who had lower fluid cognitive abilities did not learn or retain the new walking pattern as well as individuals who had higher fluid cognitive abilities. This is in contrast to past work

which has found that visuospatial working memory is the relevant domain of cognition (Anguera et al. 2010; 2011; Bo et al. 2009; Bo and Seidler 2009; Christou et al. 2016; Holland et al. 2019; Unsworth and Engle 2005). While previous work has shown that cognitive abilities are related to motor function (Barker-Collo and Feigin 2006; Buchman et al. 2011; Hayes et al. 2016; Rasmussen et al. 2019; Robertson et al. 1997), this is the first study to demonstrate the impact of fluid cognitive abilities on *locomotor learning* after stroke. The implications of these findings are discussed below.

4.6.1 *The Role of Cognition in Locomotor Learning.*

Our finding that cognition is a significant predictor of locomotor learning and retention is consistent with previous upper extremity work in neurologically intact adults (Anguera et al. 2010; 2011; Bo et al. 2009; Bo and Seidler 2009; Christou et al. 2016; Holland et al. 2019; Lingo VanGilder et al. 2018; Lingo VanGilder et al. 2019; Schaefer and Duff 2017; Unsworth and Engle 2005). In the current work, we used a visually-guided walking task that is largely explicit (French et al. 2018; Wood et al. 2020). Thus, this work suggests that during a task that is largely explicit, some individuals after stroke will be able to learn and retain well, while others will not. The most common techniques used in gait rehabilitation are those that rely on explicit, strategic learning techniques, such as verbal and visual cues (Durham et al. 2009; Urquhart and Skidmore 2014). However, based on our results, using explicit learning techniques clinically would be effective for individuals with higher fluid cognitive abilities.

From this work, however, we do not know if this relationship holds when the task is practiced for a longer period of time. It is possible that individuals with lower

cognitive abilities would do as well as those with higher cognitive abilities if they were provided more practice; thus, future work to examine the effect of increased practice on this relationship would facilitate the delivery of effective rehabilitation of walking for individuals after stroke. Additionally, this work does not speak to the relationship between implicit learning processes and cognition during locomotion. Past work in the upper extremity has found that the relationship between cognition and motor learning is unique to explicit, strategic learning rather than implicit forms of learning (Anguera et al. 2010; 2011; Christou et al. 2016), but this has not been tested during locomotion. Future work examining the relationship between cognition and different learning processes during locomotion is needed to direct the development of customized rehabilitation interventions that are rooted in an understanding of motor learning for individuals after stroke.

4.6.2 *Impact of the Learning Task.*

Visuospatial working memory was not found to be a significant predictor of learning or retention in the current work. This is inconsistent with what has been found in past work, which has largely suggested the visuospatial working memory is the specific domain of cognition related to upper extremity motor learning (Anguera et al. 2010; 2011; Bo et al. 2009; Bo and Seidler 2009; Christou et al. 2016; Holland et al. 2019; Unsworth and Engle 2005). One possible reason for this discrepancy is that locomotion is different than upper extremity tasks and, therefore, may relate to different cognitive processes. For example, past work has found that the dorsolateral prefrontal cortex, the region of the brain thought to explain the relationship between visuospatial working memory and upper extremity motor learning (Anguera et al. 2010; 2011), is not highly active during steady-state walking (Miyai et al. 2001).

Therefore, it is possible that we did not observe a significant relationship between locomotor learning and visuospatial working memory because different brain areas are active during walking compared to upper extremity tasks. Conversely, locomotion requires greater postural control and balance than seated upper extremity tasks that have been used in past work, resulting in a large role of the cerebellum during locomotion (Morton and Bastian 2004a), Past work indicates that the cerebellum is also involved in a variety of fluid cognitive functions, including problem-solving, executive functions, and visuospatial working memory (Koziol et al. 2014; Schmahmann 2019). Thus, the involvement of the cerebellum in walking may explain why fluid cognitive abilities were related to locomotor learning in this work. Future work using Functional near Infrared Spectroscopy (fNIRS) or EEG may be helpful to further characterize the relationship between locomotor learning and cognition.

Similarly, the region of the brain specifically active during the *learning* task (as opposed to walking itself) may have influenced the relationship we observed between locomotor learning and visuospatial working memory. Past work from our lab has found that there are both explicit and implicit learning processes occurring during the visually guided walking task (French et al. 2018; Wood et al. 2020). Based on the size of the aftereffects and the ability of individuals to use the learned walking pattern when cued, explicit learning processes appear to contribute the most to the learned walking pattern (French et al. 2018; Wood et al. 2020). Similarly, visuomotor rotation involves multiple learning processes and has been used in past work to examine the relationship with visuospatial working memory and motor learning. Past work has suggested that the relationship between upper extremity motor learning and visuospatial working memory is specific to the explicit, strategic learning processes

due to overlapping brain activation in the dorsolateral prefrontal cortex (Anguera et al. 2010; 2011). Additionally, there is evidence that sequence motor learning involves the dorsolateral prefrontal cortex, which may explain the significant relationship between visuospatial working memory and motor sequence learning (Bo et al. 2009; Bo and Seidler 2009; Unsworth and Engle 2005). However, unlike the visuomotor rotation task and sequence learning, it is unclear what regions of the brain are active during the visually-guided learning task used in the current work. Because it is primarily an explicit, visually-guided task it is possible that the dorsolateral prefrontal cortex is also active; however, we did not assess this. Therefore, it is possible that different regions of the brain are involved in this learning task, thus, explaining the discrepancy between our results and past results. Additional work with fNIRS and other techniques to provide insight into the active regions of the brain is warranted to help understand this relationship.

4.6.3 *Impact of Cognitive Assessment Methods.*

Another important factor to consider when interpreting our results is how cognition was measured. This work and past work have used a variety of different tasks and assessments to measure visuospatial working memory. Because visuospatial working memory is highly related to other cognitive functions (Harvey 2019; Kent 2016), it is possible that the measures of visuospatial working memory used in this work and past work reflect visuospatial working memory differently and may capture aspects of other domains of cognition. Further exacerbating this issue is the limited used of standardized measures when assessing visuospatial working memory in past work. Instead of standardized cognitive assessments, much of the previous work has used tasks that are thought to represent the complex construct of visuospatial working

memory (Anguera et al. 2010; 2011; Bo et al. 2009; Bo and Seidler 2009; Holland et al. 2019). As highlighted in a recent review by Lingo vanGilder et al (2020), the use of tasks that are not standardized and not validated hinder our ability to compare and replicate research findings; thus, despite limitations to current standardized cognitive assessments that are beyond the scope of this work, future work using standardized cognitive assessments with good construct validity is needed (Lingo VanGilder et al. 2020). Lastly, because cognitive domains are latent constructs (i.e., they cannot be measured directly) it is likely that more than one assessment is needed to most accurately measure specific cognitive domains. The use of multiple assessments that purport to measure the same cognitive domain would likely reflect that specific domain more accurately. However, in this work and much of the previous work, visuospatial working memory and other cognitive domains have been quantified with only one assessment. Future work should utilize multiple assessments as indicators of specific domains of cognition to more fully understand the relationship between motor learning and specific cognitive domains.

4.6.4 *Fluid Cognition is a Broad Construct.*

In the current work, fluid cognition was measured as a composite score of five subtests. As discussed above, these five subtests assess a range of fluid cognitive abilities including attention, executive function, working memory, processing speed, and episodic memory (Akshoomoff et al. 2013; Heaton et al. 2014; Tulsky et al. 2017). Thus, it is possible that locomotor learning is related to one specific domain reflected by the FCCS or that locomotor learning is related to fluid abilities broadly. Based on our exploratory analysis, it seems that attention, cognitive control, and inhibition, as measured by Flanker Inhibitory Control and Attention Test, may be

particularly important for understanding variability in locomotor learning and retention. This finding is particularly interesting given the strong relationship between attention and visuospatial working memory. It is possible that these two domains of cognition are so tightly linked that distinguishing between these domains has not been successful in past work. However, it is important to note that like other domains of cognition, attention is a complex construct that is likely better measured using multiple cognitive assessments. Therefore, the findings of this exploratory analysis should be interpreted cautiously. Instead, we suggest that this finding indicates the importance of further examining the relationship between various cognitive domains, including attention, and locomotor learning. To more thoroughly understand the relationship between locomotor learning and cognition, future work should carefully select multiple cognitive tests to measure specific cognitive domains and then use techniques, such as factor analyses, to reflect cognitive domains.

4.6.5 *Limitations.*

The work adds important information to the body of literature on cognition and locomotor learning, however, it is not without limitations. First, we did not include all factors that may explain variability in learning and retaining a new walking pattern. For example, patient information, such as time since stroke and level of education, and genetic information, such as brain-derived neurotrophic factor genotype, may be important predictors of locomotor learning and should be explored in future work. Additionally, the cognitive tests were administered after the motor testing; therefore, it is possible that completion of the motor testing influenced performance on the cognitive testing. Although this is unlikely due to the duration between motor testing and cognitive testing (2.4 ± 2.1 days), it is a possibility. Next, we manipulated the leg

that took a shorter step for every participant. As a result, some participants were required to change their step length on the paretic leg, while others were required to change their step length on the non-paretic leg. While this is similar to what is done in clinical practice, it is possible that this impacted the relationship between FM-LE and learning/retention, thereby impacting our results. Lastly, while we included a fairly broad sample in this work (i.e., we did not have inclusion criteria related to gait speed or cognition), we did exclude individuals who had evidence of neglect or reported vision changes after their stroke. These individuals were excluded to ensure that all participants could see the visually display; however, it does limit the generalizability of our findings to stroke survivors who have these conditions.

4.7 Conclusions.

This work is the first to examine the relationship between cognition and locomotor learning after stroke. Based on our results, fluid cognition relates to the ability of individuals after stroke to learn and remember a new walking pattern that was learned through an explicit, strategic learning paradigm. This provides a foundation for developing our understanding of the complex relationship between locomotor learning and cognition. Coupled with future work, this work will facilitate the development and prescription of interventions that capitalize on the learning processes each individual can successfully accomplish in order to provide more effective and efficient rehabilitation interventions to improve gait after stroke.

4.8 Acknowledgements.

The authors would like to thank the participants of this study and the undergraduate research assistants who aided with data collection, processing, and analysis.

4.9 Declaration of Conflict of Interest.

The authors declare that there are no conflict of interests.

4.10 Funding.

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institutes of Health [2R01HD078330-05A1, S10RR028114-01, and F31NS111806]; and The Foundation for Physical Therapy Research [2016 Florence P Kendall Scholarship, 2018 Promotion of Doctoral Studies (PODS) Level I Award, and 2019 Promotion of Doctoral Studies (PODS) Level II Award].

4.11 Supplemental Materials.

Table 4.4: Correlations between predictors.

	Age	FM-LE	FCCS	Spatial Addition
Age	1			
FM-LE	0.03	1		
FCCS	-0.007	-0.02	1	
Spatial Addition	-0.21	0.09	0.41*	1

Abbreviations: FM-LE-Fugl-Meyer: Lower Extremity; FCCS- Fluid Cognition Composite Score
* indicates p=0.003

Table 4.5: Exploratory analysis between learning (i.e., Percent Error) and retention (i.e., Percent Forgotten) and the subtests of the NIH Toolbox - Cognitive Battery used to calculate the Fluid Cognition Composite Score.

	Percent Error	**Percent Forgotten**
Flanker Inhibitory Control and Attention Test	-0.49 **	-0.32 ¥
Dimensional Card Sorting Test	-0.30 *	-0.22
List Sorting Working Memory Test	-0.15	-0.21
Pattern Comparison Processing Speed Test	-0.27 ¥	-0.25
Picture Sequence Memory Test	0.06	-0.21

**indicates $p<0.001$; * indicates $p<0.05$; ¥ indicates $p<0.1$

Chapter 5

THE EFFECT OF EXERCISE PRIMING ON RETENTION OF A NEW WALKING PATTERN LEARNED THROUGH AN EXPLICIT, VISUALLY-GUIDED LOCOMOTOR LEANRING TASK

5.1 Abstract.

Background: The coupling of an acute bout of exercise with a motor learning task (i.e., exercise priming) has been found to improve retention of upper extremity tasks in healthy adults (Dal Maso et al. 2018; Ferrer-Uris et al. 2017; Lundbye-Jensen et al. 2017; Mang et al. 2014; Mang et al. 2016; Neva et al. 2019; Perini et al. 2016; Roig et al. 2012; Singh et al. 2016; Skriver et al. 2014) and individuals after stroke (Nepveu et al. 2017); thus, exercise priming may improve the effectiveness of rehabilitation interventions after stroke. Unfortunately, exercise priming does not appear to improve retention of split belt treadmill learning (i.e., sensorimotor adaptation) after stroke (Charalambous et al. 2018). One potential reason for this discrepancy is that the tasks used in the upper extremity literature that demonstrate a beneficial effect of exercise priming are more similar to explicit, strategic learning than to sensorimotor adaptation. Thus, it is possible that exercise priming can improve retention of a new walking pattern if it is learned through explicit, strategic locomotor learning (Charalambous et al. 2018; Charalambous et al. 2019; Roig and de Las Heras 2018). However, the effect of exercise priming on explicit strategic learning during locomotion has not been examined. Thus, the purpose of this work was to examine the impact of exercise

priming on locomotor learning in stroke survivors using an explicit, strategic learning paradigm.

Methods: Participants with chronic stroke (>6 months) participated in two sessions of treadmill walking. Participants were randomized into two groups: Control (CON) and Exercise (EXE). All participants completed Baseline, Acquisition1, Catch Trial, Acquisiton2, and Immediate Retention treadmill walking phases on Day 1 and 24-hour Retention on Day 2. During the acquisition phases, participants learned a new walking pattern through distorted visual feedback paradigm, which is a primarily explicit, strategic learning task (French et al. 2018; Wood et al. 2020). Specifically, the distorted visual feedback taught participants to increase the step length of the leg with which they usually take a shorter step. At the end of Day 1, participants in CON rested for five minutes and participants in EXE exercised for five minutes at a high intensity. After confirming that the new walking pattern was learned similarly between groups on Day 1, we examined the effect of exercise priming on retention by compared step length during the End of Acquisition2, Immediate Retention, and 24-hour Retention between groups using a 2 x 3 ANOVA. If exercise priming improved retention, we expected to observe a significant interaction between group and time.

Results: The results of the 2 x 3 ANOVA showed that there was no significant main effect of group ($F(1, 28)=0.4$, $p=0.52$) or time ($F(1.4, 40.5)=1.8$, $p=0.19$) and no significant interaction ($F(1.4, 40.5)=0.8$, $p=0.44$).

Conclusion: Our results suggest that exercise priming did not improve retention of the new, explicitly-learned walking pattern in individuals after stroke; however, there are several limitations to this work. As a result, we are unable to conclude that exercise priming is not beneficial to explicit, strategic learning during locomotion. Future work

to address these limitations is needed to further understand the potential benefits of exercise priming on locomotor learning after stroke.

5.2 Introduction.

Following stroke, walking ability is significantly limited (Mayo et al. 1999; Michael et al. 2005); thus, improving walking is a primary goal of individuals who have had a stroke (Bohannon et al. 1988). As a result, significant time is spent improving walking during rehabilitation. Improving walking is dependent on neuroplastic changes that occur during rehabilitation tasks. Therefore, interventions that facilitate neuroplasticity may result in more effective interventions to improve walking after stroke. Exercise, including acute bouts of high intensity exercise, is one intervention that has been suggested to be effective for promoting neuroplasticity after stroke (Mang et al. 2013; Roig and de Las Heras 2018). As a result, the potential benefits of coupling acute bouts of high intensity exercise with motor learning tasks (i.e., exercise priming) has been examined in both neurologically intact adults (Dal Maso et al. 2018; Ferrer-Uris et al. 2017; Helm et al. 2017; Roig et al. 2012; Snow et al. 2016; Statton et al. 2015; Thomas et al. 2016a) and neurologic populations (Charalambous et al. 2018; Nepveu et al. 2017).

Most of the work examining the role of exercise priming has been conducted in neurologically intact adults during a variety of upper extremity tasks. As a whole, this work has found that exercise priming improves motor learning, specifically retention (Angulo-Barroso et al. 2019; Dal Maso et al. 2018; Ferrer-Uris et al. 2017; Lundbye-Jensen et al. 2017; Mang et al. 2014; Mang et al. 2016; Neva et al. 2019; Perini et al. 2016; Roig et al. 2012; Singh et al. 2016; Skriver et al. 2014). Based on this work, it is believed that exercise of any kind (Lundbye-Jensen et al. 2017; Thomas et al. 2017)

that is performed at high intensity (Thomas et al. 2016b) after the learning task (i.e., during memory consolidation) (Roig et al. 2012; Thomas et al. 2016a) is most effective for improving retention. While the underlying mechanism is unclear, it has been proposed that exercise causes the increased release of neurotrophic factors and catecholamines, which lengthens the duration of long-term potentiation during consolidation, thus, allowing for improved memory formation, or retention (Moriarty et al. 2019; Ostadan et al. 2016; Roig et al. 2016; Skriver et al. 2014). As a result, it has been proposed that exercise priming may be a useful tool to promote neuroplasticity during rehabilitation of individuals with neurologic conditions, such as stroke (Roig and de Las Heras 2018; Roig et al. 2012; Snow et al. 2016; Thomas et al. 2016b). Nepveu et al (2017) was the first to examine the effect of exercise on retention after stroke. They found a beneficial effect of exercise priming on retention of an upper extremity time on target task in individuals after stroke (Nepveu et al. 2017). This work supported the notion that exercise priming could be used to improve motor learning in individuals with stroke.

Given the strength of evidence in the upper extremity and the importance of walking in post stroke rehabilitation, we previously examined the impact of exercise priming on locomotor learning after stroke (Charalambous et al. 2018). Contrary to findings in the upper extremity work, we found that a single bout of high intensity exercise performed after the locomotor learning task did not improve retention of a newly learned walking pattern (Charalambous et al. 2018). There are several potential reason for these differing results, including differences in the *form* of motor learning occurring during the learning task. Specifically, our previous work examined the impact of exercise priming on learning through a split belt treadmill paradigm

(Charalambous et al. 2018). Learning during the split belt treadmill paradigm is dominated by implicit, sensorimotor adaptation, which is reliant on cerebellar processes (Bastian 2008; Doya 2000; Morton and Bastian 2006; Taylor and Ivry 2014). The learning tasks that have been primarily examined in the upper extremity (e.g., visuomotor rotation tasks, tracing tasks) are quite different than split belt treadmill walking and typically include visual information and online feedback. As a result, the tasks used in the upper extremity work generally reflect strategic learning, which is explicit and more reliant on pre-frontal processes, rather than to sensorimotor adaptation (Slachevsky et al. 2001; Slachevsky et al. 2003; Taylor and Ivry 2014).

Given that exercise has been found to affect the prefrontal cortex (Basso et al. 2015; Loprinzi and Kane 2015; Nanda et al. 2013) ***and*** strategic learning is primarily a prefrontal process (Slachevsky et al. 2001; Slachevsky et al. 2003; Taylor and Ivry 2014), it is possible that exercise priming positively impacts explicit, strategic learning, but not implicit, sensorimotor adaptation (Charalambous et al. 2018; Roig and de Las Heras 2018). If this is the case, exercise priming may be a viable option to improve retention of a new walking pattern if it is learned through an explicit, strategic learning paradigm. Therefore, the purpose of this work is to examine the impact of exercise priming on locomotor learning in stroke survivors using a paradigm that relies primarily on explicit, strategic learning. We hypothesize that exercise priming will improve 24 hour retention of a walking pattern that is learned through an explicit, strategic locomotor learning paradigm in individuals after stroke. To test this, participants completed a 2-day walking paradigm using distorted visual feedback. We first confirmed that all participants learned the task similarly and then compared 24 hour retention between those who performed exercise priming and those who did not.

If exercise priming positively impacts explicit locomotor learning, clinicians would have a relatively simple method to improve post-stroke learning during walking.

5.3 Methods.

5.3.1 *Participants.*

Chronic (>6 months) stroke survivors were recruited from the community through support groups, physical therapy practice, and advertisements. To be included in the study, participants had to meet the following inclusion criteria: 1) MRI evidence of a single stroke, 2) age 18-85, 3) able to walk 10 meters without physical assistance, 4) rest heart rate between 40 and 100 beats per minute, and 5) resting blood pressure between 90/60 and 185/100 mmHg. Participants were excluded if they met any of the following criteria: 1) MRI evidence of a cerebellar stroke, 2) neurologic conditions other than stroke, 3) visual changes post stroke, 4) neglect, 5) inability to communicate with of understand investigators, 6) history of coronary artery bypass graft or myocardial infarction within 3 months, 7) unexplained dizziness in the last 6 months, or 8) pain that limited walking. All participants signed an informed consent approved by the Human Subjects Review Board at the University of Delaware prior to participation.

5.3.2 *Experimental Design.*

Participants participated in a two day, treadmill walking paradigm that included learning a new walking pattern and testing retention of that walking pattern (Figure 5.1a). All treadmill walking was performed at a comfortable, self-selected walking speed on a dual-belt instrumental treadmill (Bertec Corporation, Columbus, OH). While walking on the treadmill, participants wore a ceiling mounted safety

harness, which did not support any body weight. Additionally, a computer monitor was positioned in front of the treadmill (Figure 5.1b).

Day 1 consisted of six treadmill walking phases: Baseline, Orientation, Acquisition1, Catch Trial, Acquisition2, and Immediate Retention. Day 2 consisted of a single walking phase: 24-hour Retention (Figure 5.1a). Prior to starting Day 1, participants were randomized into one of two groups, control (CON) or primed (EXE), which determined whether they rested or exercised after Immediate Retention on Day 1 (see Exercise Priming Protocol below).

During the 2 minute Baseline phase, participants walked at a comfortable pace on the treadmill while the average step length for each leg was determined. Based on this calculation, we identified which leg took a shorter step. This leg will be called the Manipulated Leg (ML). This information was used to create a visual feedback display during Orientation, Acquisition1, and Acquistion2 on Day 1.

During Orientation, Acquisition1, and Acquistion2, a bar graph was displayed on the monitor that was positioned in front of the treadmill. This bar graph was created using The Motion Monitor Toolbox (Innovated Sports Training, Chicago, IL) and displayed real-time information regarding the participant's step length similar to work previously done in our lab (French et al. 2018; Wood et al. 2020). The bar graph had 2 bars, one for each leg, which increased in height during the swing phase and then held its position until the next swing phase was initiated (Figure 5.1c). There were also two horizontal lines across the screen that represented the step length of each leg that was calculated during Baseline. During the 3 minute Orientation phase, participants first walked normally so they could see how the display worked and then were asked to take the *"longest possible step"* with their ML. This allowed us to confirm that

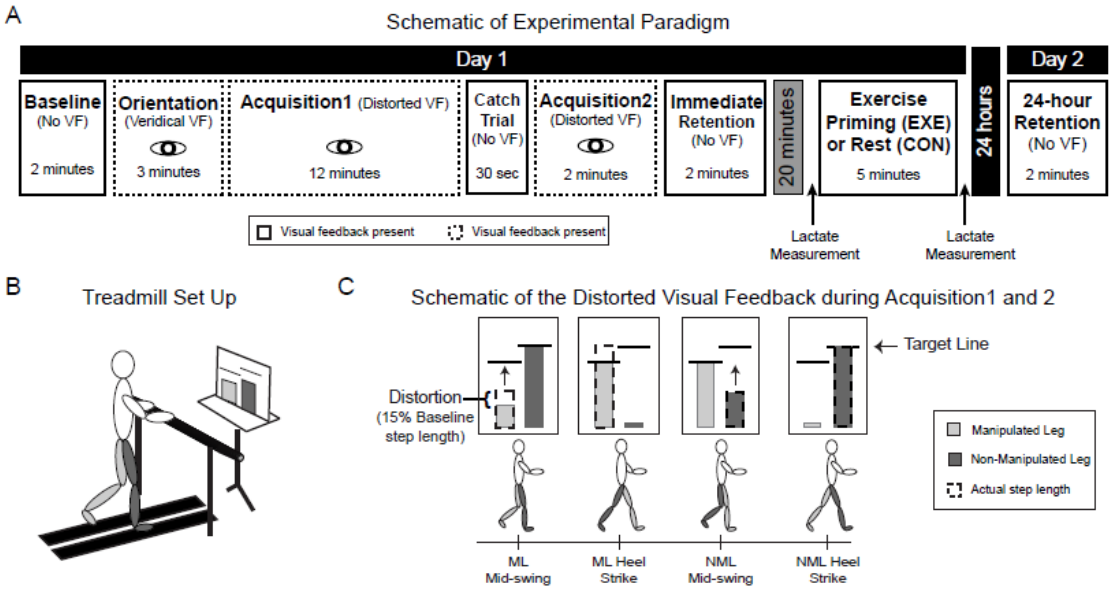

Figure 5.1: Experimental Set Up. A) Subjects participated in a two day study with treadmill walking. On Day 1, participants completed 6 treadmill walking phases: Baseline, Orientation, Acquisition1, Catch Trial, Acquistion2, and Immediate Retention. Walking phases outlined with solid lines indicate phases with no visual feedback, while dotted lines indicate phases during which visual feedback was displayed. During Acquisitoin1 and 2, participants learned to walk with a new walking pattern through a visually guided walking task. Twenty minutes after completing these six bouts of treadmill walking, participants either exercised (EXE) or rested (CON) for 5 minutes. Before and after exercising/resting blood lactate measures were obtained. On Day 2, participants completed one phase, 24-hour Retention, during which participants were instructed to recreate the walking pattern they learned on Day 1. B) Throughout the two day protocol a computer monitor was positioned in front of the treadmill. This monitor was black during the phases when no visual feedback and displayed a bar graph during phases with the visual feedback. C) During Orientation, Acquisition1, and Acquistion2, a bar graph and target line, based on the participant's baseline step length, was displayed on the computer monitor. Each bar provided real-time visual feedback regarding step length. The bars increased in height until heel strike occurred at which point the bar held that position until the next swing phase was initiated. During Acquisition1 and 2, distortion equal to 15% of the subject's baseline step length was added to one of the bars on the display (dashed lines). This resulted in participants needing to take a longer step with that leg in order to get the bar to hit the target line.

participants were physically able to increase the step length enough to complete the learning task. In other words, this phase allowed us to remove biomechanical impairments as a potential confounder to learning the new walking pattern.

During Acquisition1 and 2, we used distorted visual feedback (DVF), similar to what we have previously described (French et al. 2018; Wood et al. 2020), to teach participants a new walking pattern. In this paradigm, the bar representing the ML was distorted by 15% of their baseline step length on that leg (Figure 5.1c). Specifically, the bar looked as if participants were taking a shorter step than they actually were; thus, for the bar representing the ML to hit the target line, participants had to take a 15% longer step on the ML. The bar representing the other leg was accurate during Acquisition1 and 2. The same instruction based on a script were given to all participants. During these instructions, participants were explicitly informed of the distortion and asked to walk so that both bars hit the horizontal target lines. Additionally, all participants were told with which leg they would need to lengthen their step length in order to successfully complete the task. It is important to note that in previous work, we have found that this paradigm primarily results in explicit, strategic learning (French et al. 2018). Additionally, the instructions were intentionally designed to make the task as explicit as possible, given that we are interested in the effect of exercise priming on the retention during an explicit, strategic learning task.

Between Acquisition1 and 2, participants completed the Catch Trial. During this phase, no visual feedback was provided and participants were instructed to "walk normally." Similarly, during Immediate Retention on Day 1 and 24-hour Retention on Day 2, participants did not see any visual feedback; however, during these retention phases, subjects were asked to recreate the walking pattern that they used during

Acquisition1 and 2. Immediate Retention was performed to control for the potential effect of the change in context (i.e., the removal of the visual feedback), while 24-hour Retention on Day 2 was the time point used to assess the impact of exercise priming.

5.3.3 *Exercise Protocol.*

Twenty (± 5) minutes after Acquistion2 on Day 1, participants in the EXE group completed a 5-minute bout of exercise in the EXE group, while the CON group rested in sitting for 5 minutes (Figure 5.1a). The EXE group exercised at high intensity for 5 minutes on a total body ergometer, similar to previously described methods (Charalambous et al. 2018; Charalambous et al. 2019; Charalambous et al. 2017). Due to the prevalence of beta blocker medication use in individuals after stroke and their impact on the response of heart rate to exercise (Medicine 2016), we used two methods to quantify intensity: heart rate and the rate of perceived exertion (RPE) scale (Borg 1982). The target heart rate zone for individuals in the EXE who were not on beta blockers was 70-85% of their age-predicted heart rate maximum (HR_{max}=220-age), while the target RPE zone was 13-15 on the 6-20 RPE scale for those on beta blockers. Heart rate was monitored in real-time and documented every 15 seconds (Polar Electro Inc., Lake Success, NY). RPE was monitored and documented every 30 seconds. Lastly, exercise intensity was quantified by blood lactate levels as done in previous work (Charalambous et al. 2018; Charalambous et al. 2019; Helm et al. 2017; Skriver et al. 2014; Thomas et al. 2016a; Thomas et al. 2016b). Blood lactate levels were collected using a finger-stick automated portable Lactate Plus analyzer and test strips (Noval Medical, Waltham, MA) two minutes before the exercise/rest bout and immediately after the exercise/rest bout. To ensure that changes in lactate in the EXE

group exceeded the error of the analyzer, blood lactate was collected in the CON group as well.

5.3.4 *Data and Statistical Analysis.*

We collected motion capture data from six markers placed on bilateral heels, lateral malleoli, and fifth metatarsal heads. Kinematic data were collected at 100 Hz using an eight-camera Vicon Motion Capture system (Vicon MX, Los Angeles, CA) and kinetic data were collected at 1000 Hz. Following the identification of gait events using kinetic information (with a threshold of 20 N), we used a custom written Matlab script (MathWorks, Natick, MA) to calculate step length of the ML, which was defined as the distance between the heel markers when heel strike occurred on the ML, and metrics of learning and retention. Step length of the ML, rather than a measure of step symmetry index, was used to quantify locomotor learning for two reasons. First, the visual feedback was only distorted on one leg, resulting in participants learning to walk with a new step length on only one leg; thus, step length of that leg (i.e., the ML) most accurately reflects what participants were learning. Secondly, in Aim 1 of this work, we examined step symmetry index and found that the results were unchanged whether examining step length of the ML or step symmetry index; thus, we have only included analyses using step length of the ML.

Statistical analyses were performed in SPSS v25 (IBM, Chicago, IL) as detailed below. By convention, alpha was set at 0.05. Assumptions for all analyses were checked. Specifically, Shapiro-Wilks and Levene's test were used to assess normality and homogeneity. If any assumption was violated, non-parametric tests were used as detailed in the results section. If sphericity was violated during the proposed ANOVAs, a Greenhouse-Geisser correction was used.

5.3.4.1 *Behavioral Metrics and Analysis.*

Prior to our primary analysis, we confirmed that there was no difference in performance on Day 1 between the EXE and CON groups. In particular we assessed two things: 1) the change in step length during Day 1 walking phases and 2) the accuracy of performance during the acquisition phases. To examine the change in step length during Day 1 walking phases between groups, we compared Baseline-corrected Step Length of the ML (BC-SL) at specific time points. BC-SL reflects step length of ML while accounting for Baseline differences in step length and was calculated by subtracting the average step length of the ML during the Baseline walking phase from each step. The average BC-SL during Baseline, the first 10 steps of Acquisition1, the last 30 steps of Acquisition2, and Immediate Retention were compared between groups using a 4 x 2 repeated-measures ANOVA. We expected a significant effect of time, but no effect of group as the bout of exercise occurred at the end of Day 1. Additionally, we performed preplanned pairwise comparisons using a Bonferroni correction. These comparisons were of BC-SL during 1) Baseline and at the end of Acquisition2, 2) the end of Acquistion2 and Immediate Retention, and 3) Baseline and Immediate Retention. We expected a significant difference in BC-SL between 1) Baseline and at the end of Acquisition2 and 2) Baseline and Immediate Retention, indicating that a new walking pattern was learned and retained, respectively. We also expected no significant difference between the end of Acquistion2 and Immediate Retention, indicating that the learned pattern was not impacted when the visual feedback was removed.

Next, we compared accuracy during the acquisition phases using Percent Error (PE) during Acquisition1 and 2. PE was calculated as follows:

$$PE_{ML_n} = \frac{|ASL_n - SL_{Target}|}{\overline{SL_{BL}}} \; x \; 100,$$

where ASL_n is the step length of the ML on step *n* during the acquisition phases and SL_{Target} is the step length of the ML that would result from hitting the target line on every step (i.e., the target step length which was 15% longer that the step length of the ML during Baseline). With this metric, a lower value indicated better performance. PE_{MLn} was averaged across the first 10 steps of Acquisition1 and the last 30 steps of Acquisition2 to reflect performance at the beginning and end of acquisition, respectively. It is important to note that absolute value was used in this metric to ensure accurate comparisons between groups. Without the absolute value, the average of each group would be close to zero due to the positive and negative signs cancelling each other out; thus, absolute value was needed to obtain the most accurate depiction of the data. The average PE at the beginning and end of the acquisition phases was compared between groups using 2 x 2 repeated-measures ANOVA. Again we did not expect an effect of group as the exercise priming bout occurred after these time points.

To address our primary question of the impact of exercise priming on retention of a newly learned walking pattern, we used three measures of retention. First, we compared the average BC-SL at the end of Acquisition2 (i.e., the last 30 steps), Immediate Retention, and 24-hour Retention between groups using a 3 x 2 repeated-measures ANOVA with time and group as factors. Next, we calculated the Amount Forgotten as the absolute difference between the average SL during Immediate Retention and during 24-hour Retention. We compared the Amount Forgotten between groups with an independent t-test. Lastly, we calculated the amount forgotten as a percentage of what was learned (Percent Forgotten). This was done by dividing the

Amount Forgotten by the average step length during the last 30 steps of Acquisition2. Percent Forgotten was compared between groups with an independent t-test. Again, it is important to note that we were interested in group differences; thus, absolute value was needed to calculate these metrics to prevent averages of zero.

5.3.4.2 *Exercise Variables.*

To describe the exercise priming bout, we used three metrics that have been described previously (Charalambous et al. 2018; Charalambous et al. 2019; Charalambous et al. 2017). First, we quantified the total time spent in the target zone (i.e., 70-85% HR or 13-15 RPE based on presence/absence of beta blockers). Next, we quantified the intensity of the exercise bout with the Average Intensity as follows:

$$AI = \frac{\overline{HR_{TZ}}}{HR_{Max}}\ x\ 100 \quad \text{or} \quad AI = \frac{\overline{RPE_{TZ}}}{RPE_{Max}}\ x\ 100.$$

In these equations, $\overline{HR_{TZ}}$ and $\overline{RPE_{TZ}}$ is the average heart rate or RPE, respectively, while exercising in the target zone and HR_{Max} and RPE_{Max} is the age predicted maximum heart rate or the maximum RPE (i.e., 20), respectively. Lastly, we calculated the change in blood lactate concentration from pre to post exercise (ΔLactate). We expected EXE to have a higher time spent in the target zone, a higher Average Intensity, and a greater ΔLactate. All three of these metric were compared between groups using independent t-tests.

5.3.5 *Exploratory Analyses.*

Based on the results of the first two aims of this work, we performed several additional exploratory analyses to better understand the impact of exercise priming of locomotor learning. First, we set out to examine if exercise priming impacted *explicit, strategic locomotor learning* due to work suggesting that exercise priming may be

most beneficial for explicit, strategic learning (Charalambous et al. 2018; Charalambous et al. 2019; Roig and de Las Heras 2018). Based on the results of the additional analyses of the data in Aim 1 (Chapter 3), it appears that although the task was structured as explicitly as possible with visual feedback and verbal cues, significant inter-subject variability in the contribution of implicit and explicit learning processes remained. Therefore, it is possible that the benefits of exercise priming would be observed if we looked at individuals who used more explicit learning processes than implicit processes during acquisition. Thus, as an exploratory analysis, we compared retention between groups when including only individuals for whom explicit learning processes constituted more than 50% of the total learning. To identify this subset of participants, we followed the same approach as was presented in the follow up work to Aim 1 (Chapter 3) to determine the amount of implicit and explicit learning processes. Our approach was adapted from methods used during visuomotor rotation tasks to measure contributions of specific forms of learning (McDougle et al. 2015; Morehead et al. 2015; Taylor et al. 2014). Briefly, in visuomotor rotation tasks, participants report the specific location to which they were aiming prior to the reach to represent the amount of explicit, strategic learning and then the difference between that reported aim and the observed behavior reflects the implicit learning processes. Since locomotion is a continuous task, a similar reporting method to quantify the explicit, strategic learning process is not practical. However, catch trials are commonly used during locomotion to quantify implicit learning processes (French et al. 2018; Long et al. 2016; Reisman et al. 2009; Sombric et al. 2017). Thus, rather than first measure the explicit, strategic learning as done in visuomotor rotation tasks, we estimated the implicit learning processes and then calculated the amount of explicit,

strategic learning. To do this, we first determined Total Learning as the difference between step length of the ML at the end of Acquistion2 and Baseline (Figure 5.2). Then we calculated the percent explicit, strategic learning (%EXP) as the difference between the average step length of the ML during the end of Acquisition2 (i.e., last 30 steps) and during the Catch Trial divided by Total Learning (Figure 5.2). In this calculation, the step length of the ML during Catch Trial represents the amount of implicit learning. As noted in Chapter 3, there are limitations to this approach. For example, it assumes that individuals follow the instructions to walk normally during the Catch Trial and does not specifically account for the potential impact of online

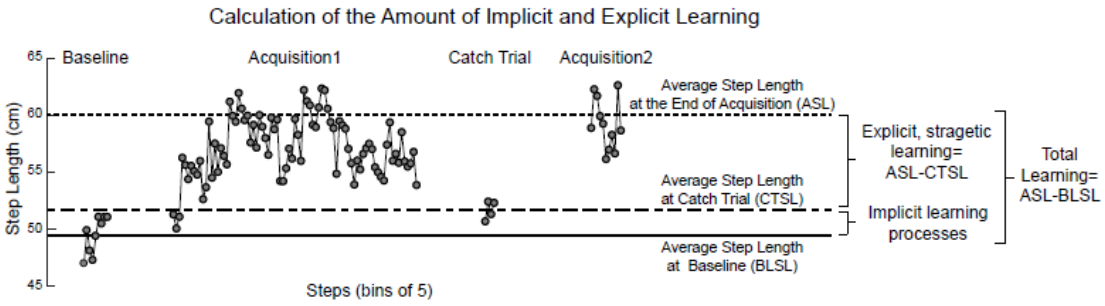

Figure 5.2: Calculation of the Contribution of Implicit and Explicit Learning Processes. To identify individuals who used more than 50% explicit learning processes, we first calculated Total Learning. Total Learning was calculated as the difference between the average step length at the end of acquisition (i.e., the last 30 steps; ASL) and the average step length at baseline (BLSL). Then we estimated the amount of explicit learning, as the difference between ASL and the average step length at Catch Trial (CTSL). We then determined the percent of explicit learning relative to the total amount of learning. Individuals for whom explicit learning processes contributed at least 50% towards Total Learning were included in this exploratory analysis.

feedback. However, currently this is the best approach to understanding the contribution of implicit and explicit learning processes during the same walking task. Thus, after calculating %EXP, we compared the Amount Forgotten and Percent Forgotten in the subset of participants in the CON and EXE groups who had %EXP greater than or equal to 50% using a Mann Whitney U. A non-parametric test was used, because the sample size was rather small after identifying those with more than 50% explicit learning.

In a second exploratory analysis we examined if exercise priming had an effect on a subset of individuals based on cognitive capacity. In Aim 2 (Chapter 4), we found that individuals who had higher fluid cognitive abilities, or a higher ability to problem solving and learn new things in the absence of prior knowledge or experience (Horn 1968; Wasserman and Wasserman 2017), retained the learned walking pattern better. Thus, it is possible that exercise priming may improve retention of a new walking pattern when examining a subset of individuals who are likely to have poorer retention. Therefore, in an exploratory analysis we examined if exercise priming improved retention of the new walking pattern in individuals with below average fluid cognitive abilities. The Fluid Cognition Composite Score (FCCS) from the Cognitive Battery of the NIH Toolbox® for Assessment of Neurological and Behavioral Function (NIHTB-CB) (Gershon et al. 2013; Weintraub et al. 2013) was used to determine if participants' cognition was below average. Briefly, the composite score is created from five subtests of the NIHTB-CB and assess a range of fluid cognitive abilities including attention, executive function, working memory, processing speed, and episodic memory (Akshoomoff et al. 2013; Heaton et al. 2014; Tulsky et al. 2017). The results from these subtests are combined to create the FCCS (Heaton et al. 2014),

which has good evidence for reliability and validity in individuals with stroke (Carlozzi et al. 2017a; Carlozzi et al. 2017b; Tulsky et al. 2017). The FCCS is reported as a Standard Score, where 100 is average and lower scores indicate lower fluid cognitive abilities; thus, only participants with a FCCS score less than 100 were included in this exploratory analysis. To make this determination we used age-corrected FCCS scores, since age was not included elsewhere in the analysis. The assessment of cognition was administered on a third day and is not displayed in Figure 5.1 since it was not involved in our primary analysis. After identifying the subset of participants with below average FCCS, we compared Amount Forgotten and Percent Forgotten between the CON and EXE groups using a Mann Whitney U. Again, a non-parametric test was used because the sample size was rather small.

5.4 Results.

5.4.1 *Participants.*

Fifteen chronic stroke survivors were allocated to the CON (n= 15, 64.5 ± 9.4, 4F) and 15 to the EXE group (n=15, 68.0 ± 7.2, 7F). There were no significant differences between groups on demographic information (e.g., age and gender) or clinical characteristics (e.g., self-selected walking speed and Fugl-Meyer Lower Extremity). Additionally, there were no differences between groups in treadmill speed during the task or in step length of the ML when asked to take the longest possible step during Orientation (Table 5.1). Complete details about demographic and clinical characteristics as well as task information are presented in Table 5.1.

Table 5.1: Participant demographic, clinical, and behavioral information. Independent t-test were used for group comparisons of continuous variables. Chi-squared tests were used to compare categorical variables between groups.

	CON (n=15)	TBE (n=15)	p-value
Demographic Information			
Age (yrs; mean ± SD)	64.5 ± 9.4	68.0 ± 7.2	0.26
Gender	4F; 11M	7F; 8M	0.27
Time Since Stroke (mo; mean ± SD)	54.1 ± 29.2	54.2 ± 35.5	0.99
Side of Lesion	2L; 13R	7L; 8R	0.05
Clinical Characteristics			
FMLE (mean ± SD)	25.7 ± 4.7	24.9 ± 7.0	0.72
SSWS (m/s; mean ± SD)	0.96 ± 0.23	0.85 ± 0.25	0.22
Task Information			
Treadmill speed (m/s; mean ± SD)	0.70 ± 0.1	0.67 ± 0.2	0.58
Manipulated Leg	5 P; 10 NP	6 P; 9 NP	0.70
Orientation Step Length (%BL; mean ± SD)	26.6 ± 12.2	26.2 ± 12.6	0.93

Abbreviations: FMLE: Fugl-Meyer Lower Extremity; SSWS: Self-selected walking speed; %BL: Percent Baseline step length

5.4.2 *Primary Analyses.*

Prior to our primary analysis, we confirmed that there was no difference in change in step length between groups by comparing BC-SL. A 4 x 2 repeated measures ANOVA of BC-SL at Baseline, beginning of Acquisition1, end of Acquisition2, and Immediate Retention found no effect of group ($F(1, 63.3)=.22$, $p=0.64$) and no group by time interaction ($F(2.3,63.3)=0.28$, $p=0.78$); however, there was a significant effect of time ($F(2.26,63.3)=40.6$, $p<0.001$; Figure 5.3a). Importantly, this suggests that the groups did not change their step length differently when walking with the visual feedback and were not affected differently by the

removal of the visual feedback during Immediate Retention. The preplanned comparisons showed that the walking pattern at the end of Acquistion2 was significantly different than Baseline ($t(29)=-12.0$, $p<0.001$), but not different than Immediate Retention ($t(29)=-1.2$, $p=0.25$), indicating that participants learned and retained a new walking pattern (Figure 5.3a). Additionally, BC-SL during Immediate Retention was significantly different than Baseline ($t(29)=-9.0$,$p <0.001$), indicating that the retained walking pattern was not only not significantly different than the pattern used at the end of Acquistion2, but was significantly different than the Baseline walking pattern (Figure 5.3a). Next, we examined PE to evaluate accuracy between groups. As shown in Figure 5.3b, PE decreased over the duration of the acquisition phases. Due to non-normality, a 2 x 2 repeated measures ANOVA was not performed to compare PE at the beginning of Acquisition1 and at the end of Acquisition2. Instead, we compared PE at these time points between groups using Mann Whitney U tests. This showed no significant difference between groups at the beginning of Acquisition1 ($Z=-1.26$, $p=0.21$) or at the end of Acquisition2 ($Z=-0.06$, $p=0.95$), providing additional evidence that the EXE and CON groups performed similarly during the acquisition phases (Figure 5.3c). Together, these analyses indicate that there was no difference between groups prior to the bout of exercise at the end of Day 1.

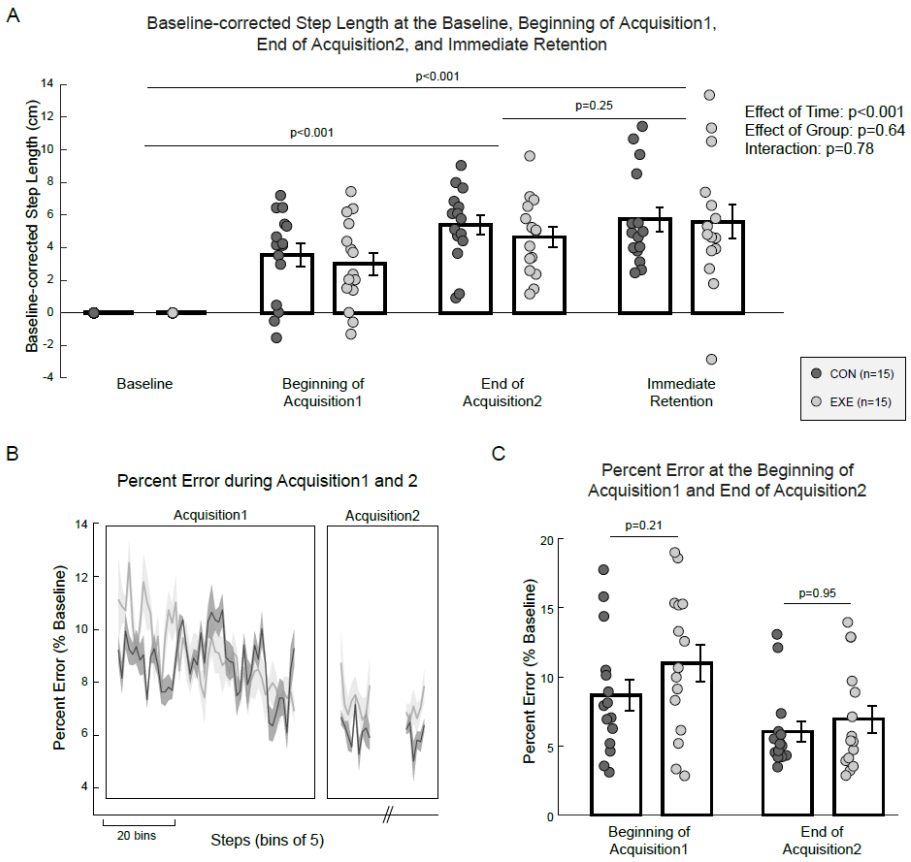

Figure 5.3: Performance in the CON and EXE groups. A) Baseline-corrected step length for the CON (dark grey) and EXE (light grey) groups at Baseline, the beginning of Acquistion1, the end of Acquisition2, and Immediate Retention. A 4 x 2 ANOVA showed no effect of group (p=0.64) and no group by time interaction (p=0.78). B) Percent error in bins of 5 steps during the Acquisition1 and 2. Data are truncated to the individual with the shortest steps and then the last 30 steps of Acquisition2 (in bins of 5) is shown for all subjects. The solid lines indicate the group average, while the shaded region indicates the standard error of the mean. C) Percent error for the CON and EXE groups at the beginning of Acquisition1 and end of Acquisition2. Mann Whitney U tests showed no difference between groups at the beginning of Acquistion1 (p=0.21) or at the end of Acquistion2 (p=0.95). In A and C, the individual dots represent each subjects and error bars represent standard error of the mean.

Additionally before performing our primary analysis, we confirmed that individuals in the EXE group were successfully primed. To do this, we compared time spent in the target zone, Average Intensity, and ΔLactate between groups with independent t-tests. On average, individuals in the EXE group spent 4.0 ± 0.8 minutes in the target zone during which the average intensity was 77.4 ± 6.3% of maximum (Table 5.2). As expected, the CON group did not reach the target zone during the 5 minute rest session. Independent t-tests found significant differences between groups on total time in target zone ($t(28)=18.6$, $p<0.001$) and average intensity ($t(28)=47.3$, $p<0.001$) (Table 5.2). Additionally, the EXE had a 4.0 ± 2.6 mmol/L increase in lactate, which was significantly greater than the change in lactate in the CON group ($t(28)=3.6$, $p=0.001$)) (Table 5.2).

Table 5.2: Exercise related measures. Independent t tests were used to compare our three metrics of exercise between groups.

	CON (n=15)	**TBE (n=15)**	**p-value**
Time in Target Zone (min; mean ± SD)	0 ± 0	4.0 ± 0.8	<0.001
Average Intensity (% max intensity; mean ± SD)	0 ± 0	77.4 ± 6.3	<0.001
ΔLactate (mmol/L)	-0.74 ± 2.4	4.0 ± 2.6	<0.001

Having confirmed that the behavior on Day 1 was not different between groups and that the EXE group exercised at a high intensity, we examined retention to determine the effect of exercise priming on an explicit, strategically learned walking pattern. First, a 3 x 2 repeated measures ANOVA of BC-SL at the end of Acquisition2, Immediate Retention, and 24-hour Retention found no significant main

effect of group (F(1, 40.5)=0.4, p=0.52) or time (F(1.4, 40.5)=1.8, p=0.19) and no significant interaction (F(1.4, 40.5)=0.8, p=0.44) (Figure 5.4a). Due to non-normality we compared Amount Forgotten and Percent Forgotten between groups using a Mann Whitney U test. This comparison showed no significant difference in Amount Forgotten (Z=-0.06, p=0.95; Figure 5.4b or Percent Forgotten (Z=-0.6, p=0.57; Figure 5.4c) between groups.

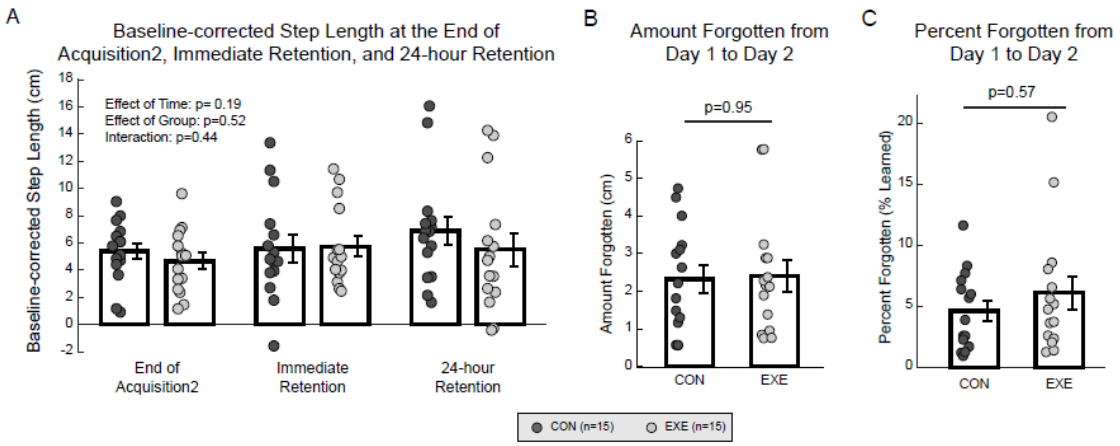

Figure 5.4: Retention between the CON and EXE groups. A) Baseline-corrected step length for the CON (dark grey) and EXE (light grey) groups at the end of Acquisition2, Immediate Retention, and 24-hour Retention. A 3 x 2 ANOVA found no effect of group (p=0.52) and no interaction (p=0.44), suggesting that retention was not different between groups. B) A Mann Whitney U test found no difference between groups in Amount Forgotten (p=0.95). C) Similarly, a Mann Whitney U test found no difference between groups in the Percent Forgotten (p=0.57). In all panels, individual dots represent each subject and error bars represent standard error of the mean.

5.4.3 *Exploratory Analyses.*

To gain a further understanding of the impact of exercise priming on retention of a new walking pattern, we examined if retention was different between specific

subsets of participants in the CON and EXE group. First, eight individuals in the CON group and seven in the EXE were identified as learning the new walking pattern through greater than 50% explicit processes. When comparing the Amount Forgotten between groups in this subset of participants with a Mann Whitney U test, we found that there was no significant difference between groups (Z=-0.6, p=0.56; Figure 5.5a). Similarly, there was no significant difference in Percent Forgotten between groups (Z=-0.1, p=0.91; Figure 5.5b).

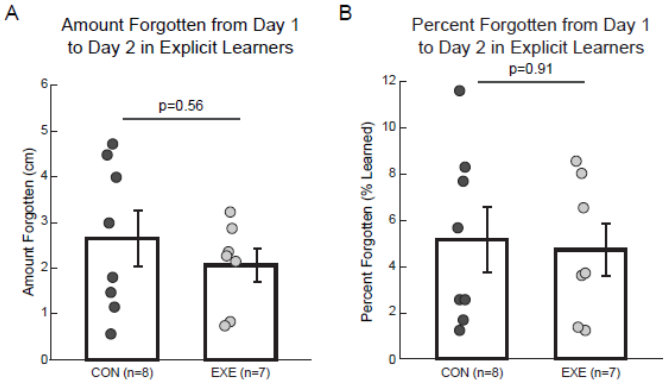

Figure 5.5: Retention in Explicit Learners. In the subset of individuals who used more than 50% explicit learning, independent t-tests found no difference in Amount Forgotten (A; p=0.56) or Percent Forgotten (B; p=0.91) between groups. Individual dots represent each subject and error bars represent standard error of the mean.

Next, we identified eleven individuals in the CON group and nine in the EXE who had below average FCCS given their age. When comparing the Amount Forgotten between groups with a Mann Whitney U test, we found that there was no significant difference between groups when using this subset of participants (Z=-1.2,

p=0.21; Figure 5.6a). Similarly, there was no significant difference between groups when comparing Percent Forgotten (Z=-0.8, p=0.45; Figure 5.6b).

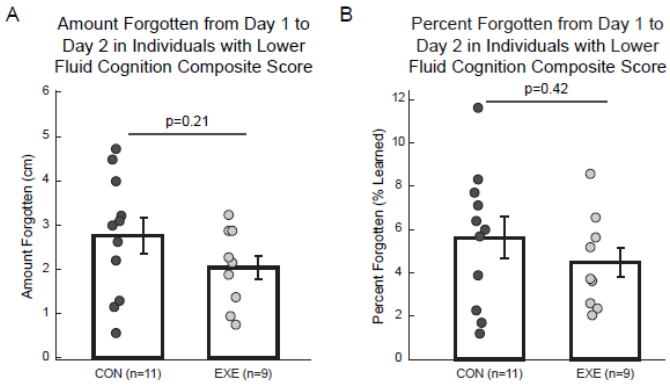

Figure 5.6: Retention in Individuals with Below Average Fluid Cognition. In the subset of individuals with below average Fluid Cognition Composite Score, independent t-tests found no difference in Amount Forgotten (A; p=0.21) or Percent Forgotten (B; p=0.42) between groups. Individual dots represent each subject and error bars represent standard error of the mean.

5.5 Discussion.

The purpose of this aim was to examine the impact of exercise priming on the retention of a new walking pattern learned through an explicit paradigm in individuals after stroke. In contrast to our hypothesis, we found that an acute bout of high intensity exercise after learning (i.e., during the consolidation phase) did not improve retention of the new walking pattern in individuals after stroke. While these results agree with previous work examining the effect of exercise priming on locomotor learning in healthy adults (Charalambous et al. 2019; Helm et al. 2017) and individuals after stroke (Charalambous et al. 2018), but are contrary to earlier findings using simple upper extremity tasks in healthy adults (Mang et al. 2014; Perini et al. 2016; Roig et

al. 2012; Skriver et al. 2014; Thomas et al. 2016a; Thomas et al. 2017; Thomas et al. 2016b) and individuals after stroke (Nepveu et al. 2017). There are several potential explanations for this discrepancy that will be discussed in detail below.

5.5.1 *Task Demands.*

One potential reason for the discrepant results observed here is that the demands of locomotion compared to other tasks previously used to examine the impact of exercise priming are very different. The previous work that found a positive effect of exercise priming has used upper extremity tasks performed in a seated position (Angulo-Barroso et al. 2019; Dal Maso et al. 2018; Lundbye-Jensen et al. 2017; Mang et al. 2014; Mang et al. 2016; Nepveu et al. 2017; Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a; Thomas et al. 2017; Thomas et al. 2016b). These tasks do not require postural control or bilateral coordination and often require isometric or single joint movement. This is drastically different than the high levels of postural control, interlimb coordination, and multijoint control that is required for locomotion. These demands of locomotion may alter the effect of exercise priming. Supporting this notion is a series of recent work suggesting that exercise priming does not have a beneficial effect on walking (Charalambous et al. 2018; Charalambous et al. 2019; Helm et al. 2017), other non-walking, whole body tasks (Loras et al. 2020; Wanner et al. 2020), or multijoint coordination of the upper extremities (Baird et al. 2018). The neural pathways involved in tasks that have these more complex demands, such as walking, may explain the lack of effect of exercise on locomotor learning. For example, exercise has been suggested to affect the prefrontal cortex (Basso et al. 2015; Loprinzi and Kane 2015; Nanda et al. 2013); however, the need to control one's posture increases the involvement of the cerebellum (Taubert et al. 2010). Therefore,

the need to maintain postural control during locomotion and other whole body tasks may interfere with the positive effects of exercise priming that have been observed in seated upper extremity tasks. Additionally, upper extremity activities, such as picking up a cup or writing your name, require more accuracy than is typically required during walking. Therefore, the control of the lower extremity may inherently be different than the upper extremity and may also explain the differing findings. As a result, future work examining the effect of exercise priming on a lower extremity task that does not require postural control (i.e., a seated tracing task completed with the lower extremity) may help the field further understand when exercise priming may be beneficial.

5.5.2 *Exercise Priming Protocol.*

Another potential reason for the differing results is the exercise priming paradigm itself. In the current work, the acute bout of high intensity exercise was five minutes in duration. Although these five minutes were at high intensity and generated an increase in lactate, our exercise paradigm is shorter than the paradigms used in previous work. Specifically, much of the previous work have used exercise priming protocols that are at least 15 minutes long and include short intervals of high intensity exercise within the 15 minute period (Dal Maso et al. 2018; Lundbye-Jensen et al. 2017; Nepveu et al. 2017; Perini et al. 2016; Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a; Thomas et al. 2017; Thomas et al. 2016b). As a result, it is possible that our priming protocol was not of sufficient duration to initiate the increase in neurotrophic factors and catecholamines hypothesized to cause improved retention after exercise (Moriarty et al. 2019; Ostadan et al. 2016; Roig et al. 2016; Skriver et al. 2014). Although Angulo-Barroso et al (2019) recently demonstrated that five minutes of exercise was as effective as 13 minutes of exercise at improving retention during an

upper extremity visuomotor rotation task in young, healthy adults, the effect of exercise duration has not been thoroughly examined. Thus, future work to determine if a longer bout of exercise improves retention of a new walking pattern is needed. Further, systematic examination of the optimal duration of exercise to improve retention is critical to the implementation of exercise priming in rehabilitation.

5.5.3 *Form of Learning.*

Previous work examining the impact of exercise priming on locomotor learning has demonstrated no benefit (Charalambous et al. 2018; Charalambous et al. 2019; Helm et al. 2017). The three previous studies used the split belt treadmill to examine the potential benefit of exercise priming. The split belt treadmill paradigm is well studied and is traditionally believed to result in sensorimotor adaptation (Bastian 2008; Morton and Bastian 2006). Previous work that has found positive benefits of exercise priming, however, has used learning tasks that are more similar to skill learning or strategic learning (Mang et al. 2014; Nepveu et al. 2017; Roig et al. 2012; Thomas et al. 2016a; Thomas et al. 2017; Thomas et al. 2016b). For example, many of these studies use a tracing task that requires participants to modify their force generation or range of motion to trace a sinusoidal curve as closely as possible. Because of the differences in the form of learning occurring in the split belt treadmill and these tracing tasks, it was suggested that exercise priming may only be effective for explicit, strategic learning tasks (Charalambous et al. 2018; Charalambous et al. 2019; Roig and de Las Heras 2018). Based on our results, however, we did not observe improved retention in a paradigm designed to facilitate learning of a new walking pattern using primarily explicit, strategic processes.

Based on the results of Aim 1, however, it appears that despite this learning task being designed to maximize the amount of explicit, strategic learning there is significant variability in how much explicit process contribute to learning in this paradigm. Thus, it is possible that the benefits of exercise priming would only present in individuals who used mostly explicit processes during learning. Therefore, in our first exploratory analysis we examined retention in those who were identified as learning the new walking pattern through greater than 50% explicit processes. First, we found that only half of the participants (8 in CON and 7 in EXE) used more that 50% explicit, strategic processes during acquisition, confirming that for some individuals this task may not have resulted in primarily explicit learning. Importantly, we did not observe improved retention in the subset of individuals that exercised compared to those who did not, even when explicit learning was the dominate form of learning. It is important to note, however, that this exploratory analysis was conducted in a small sample. Therefore, this may not be the case if a larger group of individuals was included in this analysis. Given the variability in amount of explicit versus implicit learning that occurs with this task, it is possible that this learning paradigm is not the ideal task to answer this research question. Instead, it may be advantageous to utilize a different task that exhibits less variability in the form of learning used to further understand if the form of locomotor learning impacts the effect of exercise priming of retention.

5.5.4 *Inter-subject Variability.*

Lastly, there was significant variability in how well individuals retained the new walking pattern, with some individuals even in the CON group being good retainers (see Figure 5c and d). This suggests that some individuals may be good

retainers regardless of if they undergo exercise priming. In other words, it is likely that a portion of the participants in both the CON and EXE group were going to be good retainers regardless of if they exercised or not. These individuals do not need an intervention to improve retention. Thus, the variability observed makes identifying *for whom* exercise priming may be beneficial critical in order to accurately understand the potential benefit of exercise priming. In order to further understand the potential role of exercise priming on explicit, strategic learning, we conducted an exploratory analysis on a subset of subjects who would be most appropriate for exercise priming. Based on the results of Aim 2 (Chapter 4), we identified individuals with below average FCCS as individuals who were more likely to retain poorly and then compared retention between groups in that subset of participants. Based on these exploratory results, there was no difference in retention between those with lower cognitive capacity in each group; however, the sample size was relatively small in each group. Future work with a larger sample of individuals who have lower cognitive capacity could help determine if exercise priming is beneficial for a specific group of individuals after stroke. Additionally, understanding *for whom* exercise priming may be most effective would improve our ability to assess the benefits of exercise priming on locomotor learning after stroke.

5.5.5 *Conclusions.*

In conclusion, we aimed to examine the effect of exercise priming on the retention of an explicitly-learned walking pattern in individuals after stroke. Our results do not support a positive effect of exercise priming on the retention of a new walking pattern; however, variability in individual performance and in the use of different forms of learning make it challenging to conclude that there is not effect of

exercise priming on explicit, strategic locomotor learning. It is also possible that the lack of effect of exercise priming observed in the current work may be the result of the short duration of exercise priming and postural demands of the task. Thus, additional work is needed to more completely understand the potential benefits of exercise priming on locomotor learning.

5.5.6 *Acknowledgements*

The authors would like to thank the participants of this study and the undergraduate research assistants who aided with data collection, processing, and analysis.

5.5.7 *Funding*

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institutes of Health [2R01HD078330-05A1, S10RR028114-01, and F31NS111806]; and The Foundation for Physical Therapy Research [2016 Florence P Kendall Scholarship, 2018 Promotion of Doctoral Studies (PODS) Level I Award, and 2019 Promotion of Doctoral Studies (PODS) Level II Award].

Chapter 6

CONCLUSION

Overall this work aimed to understand explicit locomotor learning and factors that influence it after stroke. Specifically, this work used a primarily explicit, visually-guided learning paradigm to 1) measure the ability of individuals after stroke to acquire and retain a new walking pattern compared to healthy adults, 2) examine the relationship between cognitive abilities and the acquisition/retention of a newly learned walking pattern, and 3) explore the impact of exercise priming on retention of the new walking pattern. The findings from each aim and importance of this work will be summarized below.

6.1 Aim 1 Findings.

Despite the common use of explicit techniques during rehabilitation after stroke (Durham et al. 2009; Urquhart and Skidmore 2014), explicit, strategic learning has not been examined after stroke. *As such, **Aim 1** sought to examine the ability of stroke survivors to learn a new walking pattern through a primarily explicit, strategic locomotor learning paradigm.* Specifically, we hypothesized that stroke survivors would be able to learn (**H1.1**) and retain (**H1.2**) a new walking pattern through the visually-guided walking task. Our results support **H1.1** by demonstrating a significant change in step length when learning the new pattern that was accompanied by improved performance. Our results also support **H1.2** as evident by no significant change in step length from the end of acquisition to the retention test 24 hours later.

Additionally, we hypothesized that stroke survivors would not learn (**H1.3**) or retain (**H1.4**) the new walking pattern as well as neurologically intact healthy adults. Our results did not support these hypotheses, indicating that stroke survivors and healthy adults are able to learn and retain a new walking pattern similarly. These findings suggest that rehabilitation interventions that utilize explicit strategic learning processes may to useful for improving walking after stroke; however, we found substantial variability across individuals in both the group of stroke survivors and the neurologically intact adults. Therefore, it is more likely that interventions that use explicit learning processes are most appropriate only for a subset of individuals. As a result, future work to understand for whom explicit learning is appropriate is needed (see Aim 2 Findings in section 6.2).

Further, because motor learning tasks rarely result in one pure type of learning, we wondered if stroke survivors and healthy adults used similar types of learning processes during this task and if that explained a portion of the variability observed in learning and retention. Thus, in Chapter 3 we presented an additional analysis that was driven by Aim 1. In this work, we found that there was significant variability in the learning processes used by healthy adults and individuals after stroke. In other words, some individuals used a significant amount of implicit learning processes to change their walking pattern, while others used a significant amount of explicit learning processes to change their walking pattern. This suggests that individuals, both with and without a history of stroke, flexibly combine learning processes to complete the desired task. Additionally, we found that in individuals after stroke who used a larger amount of explicit learning retention was impaired. This highlights the importance of

additional work to advance our understanding of forming habits and increasing the automaticity of new behaviors to improve retention in these individuals.

6.2 Aim 2 Findings.

Past locomotor learning work, including the work in Aim 1, indicate that there is significant individual variability in the ability to learn and retain new walking patterns in individuals after stroke (Charalambous et al. 2018; Reisman et al. 2013; Reisman et al. 2007; Tyrell et al. 2014). However, these individual differences are poorly understood (Reisman et al. 2013; Reisman et al. 2007; Tyrell et al. 2014). Thus, **Aim 2 examined the relationship between cognition and learning/retaining a new walking pattern through a primarily explicit, strategic locomotor learning paradigm in individuals post stroke.** Specifically, we hypothesized that cognitive abilities would explain variability in learning (**H2.1**) and retention (**H2.2**) above and beyond the variability explained by age and physical impairment. Our results support these hypotheses as evident by the significant increase in R^2 values with the addition of cognitive measures to our regression model. Further, we hypothesized that both fluid cognition and visuospatial working memory would be significant predictors of learning (**H2.3**) and retention (**H2.4**). Interestingly, however, we found that fluid cognition but not visuospatial working memory was a significant predictor of both learning and retention. These results suggest that individuals with higher fluid cognitive abilities can learn and retain a new walking pattern through this visually guided walking paradigm better than individuals with lower fluid cognitive abilities. These findings suggest that understanding an individual's cognitive abilities after stroke would be useful in the prescription of rehabilitation interventions. Additional work to understand how to improve explicit learning (see Aim 3 Findings in section

6.3) and to find alternative learning paradigms (i.e., implicit learning tasks) for individuals with lower cognitive abilities is needed to improve the provision of individualized care for individuals after stroke. Additional work to understand why visuospatial working memory was not a significant predictor of learning and retention in locomotion is needed, since this domain of cognition is thought to be particularly important in upper extremity motor learning (Anguera et al. 2010; 2011; Bo et al. 2009; Bo and Seidler 2009; Christou et al. 2016; Holland et al. 2019). Lastly, these findings coupled with the findings presented in Chapter 3 suggest that there may be a complex interaction between the type of motor learning process used within a specific task, cognitive abilities, and the ability of individuals to learn and retain a new walking pattern.

6.3 Aim 3 Findings.

Lastly, exercise priming, or the coupling of a short bout of high intensity exercise with a motor learning task, has been shown to improve retention of upper extremity tasks (Nepveu et al. 2017; Roig et al. 2012; Statton et al. 2015; Thomas et al. 2016a; Thomas et al. 2017) but not locomotor learning on a split belt treadmill (i.e., sensorimotor adaptation) (Charalambous et al. 2018; Charalambous et al. 2019; Helm et al. 2017). Past work has suggested that exercise priming may relate to explicit strategic learning specifically, thus explaining the discrepancies in previous work. Therefore, in **Aim 3 we determined if exercise priming could improve explicit, strategic locomotor learning in stroke survivors.** We hypothesized that exercise priming will improve 24-hour retention of a walking pattern learned through an explicit locomotor learning paradigm in stroke survivors. Our results, however, do not support that hypothesis. There are numerous reasons that we may not have seen a

beneficial effect of exercise priming in this task including individual variability. It is possible that including only individuals who would be poor retainers in future work would provide a clearer understanding of the potential impact of exercise priming. The findings of Aim 2 may prove useful to this. Other reasons for the negative finding of this work include different control processes involved in whole body tasks like walking and differences in our priming protocol; thus, future research should examine these factors as well in order to determine the utility of exercise priming in post-stroke gait rehabilitation.

6.4 Summary.

In summary, this series of work demonstrates that explicit, strategic learning appears to be a viable learning process to improving gait after stroke; however, accounting for relevant factors, such as cognition, is critical to achieving optimal outcomes. Additionally, this work highlights the need for additional work that considers exercise parameters and factors explaining responders and non-responders in order to understand the potential effect of exercise priming on locomotor learning.

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Appendix A

INTERNAL REVIEW BOARD APPROVAL LETTERS

UNIVERSITY OF DELAWARE
RESEARCH OFFICE
210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	November 17, 2017
TO:	Darcy Reisman, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1139080-1] Feedback and cognition during locomotor learning post stroke
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	October 18, 2017
EXPIRATION DATE:	October 17, 2018
REVIEW TYPE:	Full Committee Review

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: October 5, 2018

TO: Darcy Reisman, PhD
FROM: University of Delaware IRB

STUDY TITLE: [1139080-3] Feedback and cognition during locomotor learning post stroke

SUBMISSION TYPE: Continuing Review

ACTION: APPROVED
APPROVAL DATE: October 5, 2018
EXPIRATION DATE: October 17, 2019
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(9)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	September 17, 2019
TO:	Darcy Reisman, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1139080-4] Feedback and cognition during locomotor learning post stroke
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	September 17, 2019
EXPIRATION DATE:	October 17, 2020
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(9)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on October 17, 2020. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	October 15, 2020
TO:	Darcy Reisman, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1139080-6] Feedback and cognition during locomotor learning post stroke
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	October 15, 2020
EXPIRATION DATE:	October 17, 2021
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(9)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.
- In-person research interaction with subjects cannot begin until the UD moratorium in response to the declaration of national emergency related to the COVID-19 pandemic is lifted. Please continue to reference https://research.udel.edu/coronavirus for the most up-to-date recommendations.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on October 17, 2021. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Appendix B

PERMISSIONS

B.1 Permission to use papers published in Journal of Neurophysiology (Chapter 3)

Per the Journal's website (American Physiological Society, 2020): "Authors may reproduce whole published articles in dissertations and post to thesis repositories without charge and without requesting permission. Full citation is required." Thus, the citations for the manuscript presented in Chapter 3 is provided in the preface of that chapter (section 3.1).

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