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Development Of Robot-Based Cognitive And Motor Assessment Tools For Stroke And Hiv Neurorehabilitation

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Abstract

Stroke and HIV are leading causes of disability worldwide. HIV is an independent risk factor for stroke, resulting in an emerging population dealing with both but without guidelines on how to manage the co-presentation of these conditions. There is a need for solutions to combat functional decline that results from the cognitive and motor dysfunction associated with these conditions. Rehabilitation robotics has been explored as a solution to provide therapy in the stroke population, but its application to people living with HIV has not yet been examined. Additionally, current technology-based approaches generally tend to treat cognitive and motor impairments in isolation. As such, a major barrier to the clinical utility of these approaches is that improvements on robotic rehabilitation tasks do not transfer to activities of daily living. In this thesis, I combine rehabilitation robotics, cognitive neuroscience, and bioengineering principles to design robot-based assessment tasks capable of measuring both cognitive and motor impairment. I use clinical assessment and robotic tools to first explore the impact of cognitive impairment on motor performance in the chronic stroke population. The results from this investigation demonstrate that motor performance on a robotic task is sensitive to cognitive impairment due to stroke. I then tested additional assessment tasks against standard clinical assessments of cognitive and motor function relevant in both HIV and stroke. These results showed the ability of robot-based metrics to capture differences in performance between varying levels of impairment among people living with HIV. After demonstrating the concurrent validity of this approach in the U.S., I implemented this approach in Botswana. The preliminary results demonstrated that robotic assessment was feasible in this context and that some of our models had good predictive value. This work expands the application of rehabilitation robotics to new populations, including people living with HIV, those with cognitive impairments, and people residing in LMICs. My hope is that the work presented in this thesis will lead to future efforts that can overcome the barriers to better health by enabling the development of more effective and accessible rehabilitation technologies.

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Kevin Doan-Khang Bui

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DEVELOPMENT OF ROBOT-BASED COGNITIVE AND MOTOR ASSESSMENT TOOLS FOR STROKE AND HIV NEUROREHABILITATION

Dedicated to Henry, Linh, and Peter

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ABSTRACT

DEVELOPMENT OF ROBOT-BASED COGNITIVE AND MOTOR ASSESSMENT TOOLS FOR STROKE AND HIV NEUROREHABILITATION

Kevin Doan-Khang Bui

Michelle J. Johnson

Stroke and HIV are leading causes of disability worldwide. HIV is an independent risk factor for stroke, resulting in an emerging population dealing with both but without guidelines on how to manage the co-presentation of these conditions. There is a need for solutions to combat functional decline that results from the cognitive and motor dysfunction associated with these conditions. Rehabilitation robotics has been explored as a solution to provide therapy in the stroke population, but its application to people living with HIV has not yet been examined. Additionally, current technology-based approaches generally tend to treat cognitive and motor impairments in isolation. As such, a major barrier to the clinical utility of these approaches is that improvements on robotic rehabilitation tasks do not transfer to activities of daily living. In this thesis, I combine rehabilitation robotics, cognitive neuroscience, and bioengineering principles to design robot-based assessment tasks capable of measuring both cognitive and motor impairment. I use clinical assessment and robotic tools to first explore the impact of cognitive impairment on motor performance in the chronic stroke population. The results from this investigation demonstrate that motor performance on a robotic task is sensitive to cognitive impairment due to stroke. I then tested additional assessment tasks against standard clinical assessments of cognitive and motor function relevant in both HIV and stroke. These results showed the ability of robot-based metrics to capture differences in performance between varying levels of impairment among people living with HIV. After demonstrating the concurrent validity of this approach in the U.S., I implemented this approach in Botswana. The preliminary results demonstrated that robotic assessment was feasible in this context and that some of our models had good predictive

value. This work expands the application of rehabilitation robotics to new populations, including people living with HIV, those with cognitive impairments, and people residing in LMICs. My hope is that the work presented in this thesis will lead to future efforts that can overcome the barriers to better health by enabling the development of more effective and accessible rehabilitation technologies.

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CHAPTER 1 : INTRODUCTION

1.1 Stroke

Stroke is a leading cause of serious long-term disability in the United States and worldwide. There are 7 million people living with stroke in the United States and 795,000 incidents of stroke each year (Virani et al., 2020). The combined direct and indirect costs of stroke is 45.5 billion U.S. dollars (Virani et al., 2020). Globally, the prevalence of stroke is estimated to be 104.2 million people, with 70% residing in low- and middle-income countries (Krishnamurthi et al., 2013; Virani et al., 2020). Functional, motor, and cognitive decline impact the ability to live independently and are common outcomes after stroke. An estimated 25%–74% of stroke survivors are somewhat dependent or fully dependent on others for help with activities of daily living, which include eating, bathing, getting dressed, toileting, mobility, and continence (Anderson et al., 1995; Kalra and Langhorne, 2007).

A barrier to improving long-term functional outcomes is how financial resources are allocated. An estimated 70% of stroke care costs in the first year are for in-patient acute care, leading to significant health disparities compared to later phases of stroke care (Miller et al., 2010). The availability of fewer resources dedicated to the rehabilitation process misses the opportunity to capitalize on the neuroplasticity potential that has been shown to occur even in later stages of stroke (Kleim and Jones, 2008). Given this, there is a pressing need for more cost-effective and accessible neurorehabilitation strategies to address the long-term outcomes after stroke.

1.2 Rehabilitation and Rehabilitation Engineering

Rehabilitation refers to a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment. Neurorehabilitation focuses specifically on rehabilitation after nervous system injury. In the context of stroke, rehabilitation services are provided by a team of rehabilitation profes-

sionals and clinicians. These teams often consist of physical medicine and rehabilitation physicians, neuropsychologists, physical and occupational therapists, speech and language pathologists, and rehabilitation nurses (Miller et al., 2010). However, in low- and middle-income countries, there is a lack of skilled rehabilitation professionals available, with many of these countries having less than ten skilled rehabilitation professionals per one million residents (Gupta et al., 2011). This number ranges from 1000-4000 skilled rehabilitation professionals per one million residents in high-income countries, but there are still regions within these countries, particularly in rural areas, where individuals experience difficulties accessing rehabilitation services (Gupta et al., 2011).

The use of technology to address the gap in rehabilitation services and to augment the capacity of existing rehabilitation professionals to provide care has led to the emergence of the field of rehabilitation engineering. For example, robotic devices have been developed to provide therapy while reducing the burden on a therapist. These systems have been shown to be as effective as high-intensity physical therapy (Lum et al., 2002). However, a key challenge in developing more effective robotic rehabilitation strategies is the lack of transfer of improvements on robotic tasks to activities of daily living. Additionally, the application of rehabilitation robotics remains limited to a few distinct populations, despite a growing population of people who could benefit from rehabilitation.

1.3 HIV

There are 1.2 million people living with human immunodeficiency virus (PLWH) in the U.S. and nearly 37 million PLWH worldwide (Murray et al., 2014). As PLWH age due to the success of antiretroviral therapy, the challenges have shifted to managing the chronic effects of living with HIV. These include HIV-associated comorbidities and complications such as neurologic damage, cardiovascular complications, premature aging, and frailty. This area has become a high priority research area given the long-term impacts of the issues that arise(Goodenow, 2017). The need for rehabilitation strategies in the care of PLWH is

becoming an increasing focus, but there is still a paucity of solutions available to address the range impairments related to HIV(O'Brien et al., 2014). PLWH experience a range of physical, cognitive, and mental health-related challenges that detrimentally impact their ability to perform instrumental activities of daily living that span employment, managing finances, and medication management.

1.4 Significance

The specific problem this thesis aims to address is the lack of transfer of improvements on robotic rehabilitation tasks to activities of daily living, which are critical to regaining or maintaining independence. The effects of cognitive and motor impairments on everyday function resulting from either stroke or HIV warrants rehabilitation, and this is a need that will continue to increase as the general population ages. Developing relevant strategies to address this need will advance the development of effective neurorehabilitation strategies that address functional decline in both stroke and HIV populations. It will equip clinicians with the awareness, knowledge, and tools needed to manage the complexities resulting from two neurological diseases. Additionally, it will provide new quantitative methods to study neurocognitive impairment, expanding the types of populations that can benefit from a rehabilitation robotics-based approach.

1.5 Organization of Thesis

The goal of this thesis is to develop robot-based tools and methods that allow for the assessment of cognitive and motor impairment in populations that experience neurological injury, namely stroke and HIV. Developing these assessments will allow for the development of future neurorehabilitation strategies that can better translate into improvements on activities of daily living. The following questions guide the work in this thesis:

1. How can robot-assisted rehabilitation systems be designed to measure both cognitive and motor impairment? I review the mechanisms of neurological injury in both HIV

and stroke and the underlying principles used to guide the design of the assessment tasks used in this thesis.

2. How does cognitive impairment impact motor performance? I examine the sensitivity of robot-based metrics to cognitive impairment in a chronic stroke population.

3. What clinical characteristics of HIV-related impairment can be measured with a robot-based approach? I demonstrate the concurrent validity between robot-based assessment tasks and standard clinical assessments used in the HIV population.

4. How do impairments in cognitive and motor function relate to performance on a robot-based cognitive-motor assessment task? I examine the utility of kinematic and non-kinematic measures in identifying differences in performance between groups with varying levels of impairment.

5. Is a robot-based approach feasible in a limited-resource setting? I take the methods developed in the lab and implement them to assess the ability to study PLWH in Botswana.

This thesis consists of six chapters. Chapter 2 provides background on the mechanisms of neurological impairment in stroke and HIV. It explains the key considerations that influenced the design of the robot-based assessments used extensively throughout this thesis.

Chapter 3 presents a study examining how cognitive impairments influence performance on a robot-based motor assessment task. It highlights the relationship between visuospatial and executive function impairments and upper-limb motor performance.

Chapter 4 presents a study demonstrating the concurrent validity of robot-based metrics with existing clinical measures of cognitive and motor function in people living with HIV. This study supports the utility of rehabilitation robotics to study impairment in the HIV population.

Chapter 5 presents a study exploring kinematic and non-kinematic measures derived from a

cognitive-motor robot assessment task. It demonstrates that various metrics from this task are sensitive to differences in performance between groups with varying levels of cognitive and motor function.

Chapter 6 presents preliminary results examining the feasibility of a robotics-based approach to studying HIV and stroke in Botswana.

Chapter 7 discusses the contributions of this work and potential future directions that could be pursued.

CHAPTER 2 : ROBOT-BASED TOOLS TO ASSESS COGNITIVE AND MOTOR IMPAIRMENT ACROSS STROKE AND HIV

2.1 Contribution

This chapter is adapted from a review paper published in the Journal of Neuroengineering and Rehabilitation with Dr. Michelle J. Johnson (Bui and Johnson, 2018). It provides a review of the mechanisms behind neural injury due to HIV and stroke, the neurorehabilitation challenges resulting from these conditions, and discusses rehabilitation engineering approaches to address these challenges.

2.2 Abstract

There is increasing evidence that HIV is an independent risk factor for stroke, resulting in an emerging population of people living with both HIV and stroke all over the world. However, neurorehabilitation strategies for the HIV-stroke population are distinctly lacking, which poses an enormous global health challenge. In order to address this gap, a better understanding of the HIV-stroke population is needed, as well as potential approaches to design effective neurorehabilitation strategies for this population. This review goes into the mechanisms, manifestations, and treatment options of neurological injury in stroke and HIV, the additional challenges posed by the HIV-stroke population, and rehabilitation engineering approaches for both high and low resource areas. The aim of this review is to connect the underlying neurological properties in both HIV and stroke to rehabilitation engineering. It reviews what is currently known about the association between HIV and stroke and gaps in current treatment strategies for the HIV-stroke population. We highlight relevant current areas of research that can help advance neurorehabilitation strategies specifically for the HIV-stroke population. We then explore how robot-assisted rehabilitation combined with community-based rehabilitation could be used as a potential approach to meet the challenges posed by the HIV-stroke population. We include some of our own work exploring

a community-based robotic rehabilitation exercise system. The most relevant strategies will be ones that not only take into account the individual status of the patient but also the cultural and economic considerations of their respective environment.

2.3 Background

Stroke is a leading cause of death and disability in high income countries while both stroke and human immunodeficiency virus (HIV) are leading causes of death and disability in lower income countries (Murray et al., 2014; Mozaffarian et al., 2016). There is increasing evidence that HIV is an independent risk factor for stroke, resulting in an emerging population of people living with both HIV and stroke all over the world in both high and low resource areas (Tipping et al., 2007; Ovbiagele and Nath, 2011; Benjamin et al., 2012; Chow et al., 2012; Heikinheimo et al., 2012; Singer et al., 2013; Okeke et al., 2016). Little research has been conducted on this population, particularly from a neurorehabilitation standpoint. It is important to consider the HIV-stroke population from this viewpoint because both are chronic diseases associated with lasting neurological injury and require extensive amounts of monitoring, assessment, and treatment. While dealing with one is difficult enough, the added burden on the patient, their family, and health care providers from both diseases is a global health challenge that must be addressed.

Studies to date looking into the relationship between HIV and stroke have taken an epidemiological or pathophysiological approach, both confirming and trying to understand the cause for increased stroke rates in the HIV population (Mochan et al., 2005; Ortiz et al., 2007; Tipping et al., 2007; Ovbiagele and Nath, 2011; Benjamin et al., 2012; Chow et al., 2012; Okeke et al., 2016; Heikinheimo et al., 2012; Singer et al., 2013). However, very little is being done to address the physical, cognitive, social, and other problems that the HIV-stroke population currently faces. There is a need to develop relevant evidence-driven neurorehabilitation strategies for the HIV-stroke population to address the gaps in care and improve outcomes related to quality of life. There is evidence that the presence of HIV can

negatively impact outcomes after stroke on activities of daily living Augustyn et al. (2020). This is an issue that is globally relevant given the rapidly aging HIV population in high income countries (HICs) and the increasing stroke rates in low and middle income countries (LMICs), where HIV is more prevalent (Feigin et al., 2009). Developing these solutions can also lead to advancements that may benefit stroke, HIV, and older adult populations.

As outlined by the National Institutes of Health, improving prevention or treatment of HIV-associated comorbidities and complications has become a high priority area in HIV/AIDS-related research (Goodenow, 2017). Additionally, in the context of LMICs, the World Health Organization (WHO) has said that addressing the disability issue "is a development priority because of the higher prevalence of disability in lower-income countries and because disability and poverty reinforce and perpetuate one another" (WHO, 2015b). This review approaches the HIV-stroke population from a neurorehabilitation viewpoint — a viewpoint that is currently lacking for this population. Neurorehabilitation refers to the concept of intentionally affecting recovery in the nervous system through targeted rehabilitation exercises that span the physical, cognitive, psychological, social, and cultural domains. To successfully develop neurorehabilitation strategies for the HIV-stroke population, a thorough understanding of multiple areas is needed, ranging from the molecular to the behavioral to the engineering. This includes the mechanisms, manifestations, and treatment options of neurologic injury in stroke and HIV, the additional challenges posed by the HIV-stroke population, and rehabilitation engineering approaches for both high and low resource areas.

This review also goes into strategies for developing robot-based neurorehabilitation strategies. Robot-assisted technologies have shown to be a promising approach in rehabilitation with the emergence of the rehabilitation robotics field. We explore how robot-assisted rehabilitation could be used as a potential approach to designing neurorehabilitation strategies for the HIV-stroke population. We highlight relevant areas of research in the field of rehabilitation robotics that can help advance research on the HIV-stroke population such as robot-based biomarkers of motor impairment, motor learning, cognitive assessment and

rehabilitation, and affordable rehabilitation robotics. Other rehabilitation techniques, such as community-based rehabilitation, also have utility in designing new neurorehabilitation strategies. We detail a system we have built that combines both robotic and community-based rehabilitation — the Rehabilitation Community-Assisted Robot Exercise System (Rehab CARES) Gym — and is specifically designed to be deployed in LMICs that can be used as a way to provide neurorehabilitation to the HIV-stroke population.

The aim of this review is to connect the underlying neurologic properties in both HIV and stroke to rehabilitation engineering. By doing so, we hope to highlight both the gaps in research in order to spur the development of novel neurorehabilitation approaches for the HIV-stroke population and the opportunities to expand the scope of the rehabilitation robotics field.

2.4 Neurologic Injury in Stroke

Stroke affects 800,000 people in the United States each year, costing roughly 34 billion U.S. dollars in health care services, medications, and lost productivity (Mozaffarian et al., 2016). It is the fifth leading cause of death and a leading cause of disability (Mozaffarian et al., 2016). In LMICs, stroke rates have increased by 100 percent from 2002-2012 (Feigin et al., 2009). The heterogeneous nature of stroke poses a challenge in developing effective solutions that are applicable to the spectrum of stroke outcomes. Many of the advancements in the field have not yet made it to LMICs. As such, making these solutions accessible in a global context poses an additional unmet need.

Stroke is a neurologic disease resulting from either a blockage in a blood vessel supplying the brain or a rupture of a blood vessel in the brain, termed an ischemic or a hemorrhagic stroke, respectively. Standard stroke risk factors include high blood pressure, high cholesterol, diabetes mellitus, sedentary lifestyle, and smoking (Ovbiagele et al., 2013). Because these factors are addressable, stroke is seen as a preventable disease. Depending on factors such as the size and location of the brain lesion resulting from the stroke, varying degrees of cognitive

and motor impairment can result in difficulties performing activities of daily living and significantly reduce the quality of life for the stroke patient. These life-altering impairments can manifest as physical impairment — such as hemiparesis, muscle weakness, and spasticity — or cognitive impairment — such as vision problems, memory loss, aphasia, and other issues.

2.4.1 Functional Brain Changes After Stroke

Functional changes in the brain have been extensively studied in various magnetic resonance imaging (MRI) studies, and provide a glimpse into the changes that happen in the brain on a systems level. Functional changes refer to how regions of the brain activate differently after a stroke in a resting state or during the performance of a task. Functional MRI (fMRI) studies have demonstrated that the brain can respond in several different ways following stroke. Ward showed that in stroke patients who had intact primary motor cortices, more complete recovery was achieved when brain activation patterns mirrored that of healthy controls, while those with poorer recovery recruited additional motor-related regions in the brain (Ward et al., 2003b). A negative correlation was shown between outcome and task-related activation in regions associated with motor movement (Ward et al., 2003b). Bilateral and contralesional recruitment can occur involving the contralesional (the side of the brain not affected by the lesion) and ipsilesional (the side of the brain with the stroke lesion) parts of the supplementary motor area, cingulate motor areas, premotor cortex, posterior parietal cortex, and cerebellum (Ward et al., 2003b). Non-motor brain regions can be involved in motor recovery as well (Ward et al., 2003b,a). Other longitudinal fMRI studies have shown similar results as Ward, with a consistent pattern of initial contralesional recruitment, with recovery dependent on how much activity is restored to the ipsilesional side (Tombari et al., 2004; Calautti and Baron, 2003; Kim et al., 2006).

2.4.2 Structural Brain Changes After Stroke

Structural changes have been examined using diffusion tensor imaging, which visualizes the structural integrity of white matter tracts in the brain by measuring the diffusion of water across these tracts (Basser and Pierpaoli, 2011). Damage to the white matter results in reduced anisotropic diffusion, and this can be quantified in values such as fractional anisotropy (FA) and mean diffusivity (Basser and Pierpaoli, 2011). Warach used diffusion-weighted imaging to measure changes in apparent diffusion coefficients (ADCs), showing that these values decreased after stroke and slowly returned toward normal values in the chronic phase of stroke, allowing for acute lesions adjacent to chronic infarcts to be readily distinguished (Warach et al., 1995). Others have shown that the infarct regions in the ipsilateral descending corticospinal tract of stroke patients resulted in lower FA values (Werring et al., 2000).

2.4.3 Stroke Treatment

Acute Phase

The acute phase of stroke refers to the first month after stroke onset. There are limited treatment options at the time of stroke onset. An ischemic stroke can be treated with tissue plasminogen activator (TPA) — a protein that dissolves blood clots — if it is administered within four and a half hours of stroke onset (Saver et al., 2013). The clot can also be mechanically removed. These treatments can reduce the long term effects but do not guarantee full recovery given the short time window for success. Full recovery is associated with a return to pre-stroke neurologic and functional conditions. On the neurologic side, recovery involves reversal of diaschisis, neurogenesis and repair, and alteration of existing pathways (Wieloch and Nikolich, 2006; Pekna et al., 2012). Functional recovery is closely intertwined with neurologic recovery, as changes in physical or cognitive ability are reflective of changes in brain function.

2.4.4 Spontaneous vs Use-Dependent Recovery

Sub-Acute Phase

Despite the limited window for administering TPA, recovery can still occur after stroke. Recovery can generally be broken in two separate categories — spontaneous and use-dependent recovery. Spontaneous recovery is the period of time shortly following a stroke when the brain naturally compensates for lost function by forming new neurons or recruiting other parts of the brain to execute a damaged function and is thus in a state of increased neuroplasticity (Cramer, 2008). Neurogenesis can occur in the affected brain region following a stroke, and the more neurogenesis there is, the more function is recovered (Jin et al., 2006). However, the specific mechanisms of neurogenesis or how to increase the output remains an open question.

The time between the first month and sixth month after stroke onset is referred to as the sub-acute phase. The majority of regained function occurs in the first three months following a stroke and spontaneous recovery plateaus after six months (Bonita and Beaglehole, 1988). The ability of a patient to naturally recover function is dependent on the severity and location of the stroke — mild and moderate stroke patients more so than severe stroke patients have much greater chances of recovering or improving function (Bonita and Beaglehole, 1988).

Chronic Phase

Use-dependent recovery can serve two purposes. It aims to help the patient regain additional function more quickly than spontaneous recovery alone and can also promote recovery in the chronic phase of stroke, which is beyond six months after stroke onset. Use-dependent therapy promotes additional neuroplasticity to improve recovery through repetition (Arya et al., 2011; Michaelsen et al., 2006; Richards et al., 2008). Intensive use-dependent therapy during the acute phase of stroke leverages the period of spontaneous neuroplasticity to maximize recovery outcomes. Inducing additional recovery in the chronic phase — beyond

six months after the onset of stroke — is a key focus in rehabilitation, as 55-75 percent of stroke patients experience lasting upper limb impairment (Lai et al., 2002).

2.4.5 Rehabilitation Strategies

Understanding the functional and structural changes that result from a stroke and how these progress over the course of recovery is important in order to design neurorehabilitation strategies that can drive brain reorganization and functional recovery in a targeted manner. Conventional treatment after a stroke involves a combination of physical, cognitive, occupational, and speech therapy, among other forms of support. These therapies require dedicated rehabilitation professionals, and data show that the burden of stroke management will continue to increase (Feigin et al., 2014). Combined with current trends reflecting a shortage of physical therapists in the U.S. workforce, quality and access to care will be significantly impacted (Zimbelman et al., 2010). This pressure is already felt in LMICs (WHO, 2015b). Even some regions in HICs, particularly rural areas, are experiencing the effects of a shortage on rehabilitation professionals and services (Leira et al., 2008).

The need for innovative stroke rehabilitation strategies is a global need. As a result, a lot of research has gone into developing more effective rehabilitation strategies that can augment the abilities of therapists and bring rehabilitation services to more patients. Going hand in hand with the need for innovative stroke rehabilitation strategies is the need for reliable, quantitative ways to assess and measure progress. Clinical assessments are useful for providing insight on the overall status of the patient, but the distinction between different groups is often very coarse (i.e. severe vs. moderate vs. low impairment or dementia vs. no dementia). Current assessments include motor function tests such as the Fugl-Meyer Test, Wolf Motor Function Test, Nine-hole Pegboard Test, Grooved Pegboard Test, Box and Blocks Test, Timed Up and Go Test, Ten Meter Walk, and Modified Ashworth Scale; cognitive tests such as the Montreal Cognitive Assessment, Trail Making Tests, and Mini-Mental State Examination; and overall neurologic examinations such as the National Institutes of Health Stroke Scale, the Barthel Index, Functional Independence Measure, and

the Modified Rankin Scale (Fugl-Meyer et al., 1975; Wolf et al., 2001; Mathiowetz et al., 1985; Platz et al., 2005; Podsiadlo and Richardson, 1991; Ruff and Parker, 1993; Steffen et al., 2002; Charalambous, 2014; Nasreddine et al., 2005; Tombaugh and McIntyre, 1992; Adams et al., 1999; Collin et al., 1988; Heinemann et al., 1993; Sulter et al., 1999). The ideal clinical test would be quick, easy to use, reliable, and responsive to meaningful clinical change, but no test currently meets all the criteria (Harrison et al., 2013).

There are multiple limitations to current clinical tests. They often require a trained professional and take time to administer. In addition, the set of clinical tests that are administered can vary by the resources and time available. Even when the same test is administered, results can vary depending on who is administering the test, thus limiting the ability to identify milder changes. As such, even though there are established assessments and rehabilitation strategies, there is a lot of room for improving these areas with innovative approaches.

2.5 Neurologic Injury in HIV

Each year, 40,000 new people are diagnosed with HIV, and 1.2 million people live with HIV in the U.S. (Centers for Disease Control and Prevention,, 2015). There are 36.7 million people living with HIV worldwide, with the majority living in LMICs (Murray et al., 2014). HIV is an incurable disease that attacks the body's T cells, which if left untreated, leads to acquired immune deficiency syndrome (AIDS) and opportunistic diseases infecting the body. With the advent of antiretroviral therapy (ART), HIV has changed from a life-threatening to a chronic disease, resulting in a rapidly aging HIV population. By 2020, half of the HIV population in the U.S. will be over 50 years old (Brooks et al., 2012). ART has been a life-changing development, but there remain problems that have yet to be addressed. These include the prevalence of neurocognitive disorders, impairments, activity limitations, and disability.

2.5.1 HIV-Associated Neurocognitive Disorders

HIV-associated neurocognitive disorders (HAND) are a set of neurologic disorders of varying severity that affect cognitive, motor, and behavioral domains (Clifford and Ances, 2013). The categories of HAND, as defined by the Frascati criteria, include asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), and HIV-associated dementia (HAD) (Antinori et al., 2007). ART has decreased the incidence of HAD, while the incidence and prevalence of milder forms of HAND remains high at about 40 percent of the HIV population (Heaton et al., 2014; Lindl et al., 2010). HAND can impact the quality of life of a patient by contributing to HIV-associated disability and interfering with their ability to independently perform activities of daily living, such as adhering to medication, leading to more serious downstream problems (Hanass-Hancock et al., 2015; Clifford and Ances, 2013). When the Frascati criteria was established, minor cognitive-motor disorder was encompassed into MND and motor-related assessments were minimized for the most part. However, HAND can also impact physical domains as well, leading to neuropathy, slowed movement, ataxia, impaired gait, and diminished fine motor skills (Pullen et al., 2014).

The gold standard for diagnosing HAND is by an extensive neuropsychological battery that assesses a patient's information processing, learning and memory, executive function, verbal fluency, working memory, and motor domains (Antinori et al., 2007). This requires a trained professional and is a time-consuming process. In settings where an in-depth assessment cannot be administered, brief screening tests are desired (Antinori et al., 2007). The most commonly used screening test is the International HIV Dementia Scale (IHDS) (Sacktor et al., 2005). Other screening tests include the HIV Dementia Scale (HDS) and Montreal Cognitive Assessment (MoCA), but neither performs well in distinguishing the milder forms of HAND (Janssen et al., 2015). Motor impairment is not extensively tested in these assessments, but may have utility in diagnosing neurocognitive disorders when normative data is not available (Robinson-Papp et al., 2008).

2.5.2 Pathophysiology of HIV-Associated Neurocognitive Disorders

The prevalence of HAND likely remains high because current ART regimens are not successfully penetrating the central nervous system (Heaton et al., 2014). The most widely accepted model states that HIV invades the brain via a "Trojan Horse" method in which infected monocytes cross the blood-brain barrier and differentiate into macrophages (Liu et al., 2002; Albright et al., 2003). This then leads to neurodegeneration and the symptoms seen in HAND. The neurodegeneration is caused from chronic neuroinflammation resulting from a combination of cytokine and chemokine effects, excitotoxicity, or oxidative stress (Lindl et al., 2010). This in turn leads to synaptic disruption and impaired neurogenesis. While these issues may be addressed by developing different drug therapies that are better able to cross the blood-brain barrier and target the mechanisms of neurodegeneration, other approaches should be considered to manage the symptoms. There is also emerging research suggesting that ART itself could have neurotoxic effects on the brain, leading to the production of compounds similar to those seen in Alzheimer's disease (Lindl et al., 2010).

2.5.3 Functional Brain Changes After HIV Infection

Much like stroke, the effects of HIV on the central nervous system have been observed using MRI methods. The changes in the brain due to HIV are visible even before HAND can be clinically diagnosed (Ernst et al., 2002). Fronto-striatal circuits have been shown to be altered by HIV, with the left inferior frontal gyrus and left caudate being the most commonly affected regions (Ernst et al., 2002; Du Plessis et al., 2014; Melrose et al., 2008; Ipser et al., 2015). Studies have shown that HIV also impacts complex information processing and selective attention, establishing a connection between the affected fronto-striatal circuits and observable behavior (Ipser et al., 2015). Melrose demonstrated that functional changes in the prefrontal cortex and basal ganglia, which are associated with working memory, occur before structural changes (Melrose et al., 2008; McNab and Klingberg, 2008). Neurologic changes can result in minor cognitive or motor disorders and progress to more severe dementia if the HIV is left untreated (McArthur et al., 2005). Other neurologic effects of HIV

include increased activation in the lateral prefrontal cortex and delayed motor learning in HIV-infected children (Ernst et al., 2002; Von Giesen et al., 2003).

2.5.4 Structural Brain Changes After HIV Infection

Structurally, HIV results in cortical thinning in primary sensorimotor, premotor, and visual areas, with prefrontal and parietal tissue loss showing a correlation with slowing of psychomotor speed (Thompson et al., 2005). Volume loss in the striatal, hippocampal, and white matter areas has been shown to begin in the asymptomatic stages of HAND (Stout et al., 1998). Studies have shown that people with HIV had significant reductions in brain volumetrics in the amygdala, caudate, corpus callosum, and putamen despite ART treatment (Ances et al., 2012; Becker et al., 2011). These findings were independent of aging, which can also increase the vulnerability of the brain. Changes in brain structure have been shown to occur within a year of HIV infection (Ragin et al., 2012). Another study showed that gray matter decreases in the anterior cingulate and temporal cortices along with white matter reduction in the midbrain region were associated with cognitive decline, while motor dysfunction was associated with basal ganglia gray matter atrophy (Küper et al., 2011). These structural changes and the prevalence of HAND demonstrate that while HIV can be well controlled by ART, there are still detrimental effects of HIV that have yet to be addressed.

2.5.5 Rehabilitation Strategies for the HIV Population

In a Canada-based study, upwards of 80 percent of Canadians living with HIV reported dealing with an impairment, activity limitation, or social participation restriction (Rusch et al., 2004). Another study in South Africa on over 1,000 people living with HIV showed that more than a third experience the onset of disability (Hanass-Hancock et al., 2015). HIV can accelerate the aging process and lead to frailty and physical impairment earlier on in life (Desquilbet et al., 2007). Thus, rehabilitation strategies must address both the cognitive and physical impairments resulting from HIV.

Physical impairments resulting from HIV include chronic pain, joint stiffness, and muscle weakness (Pullen et al., 2014). However, the number of HIV patients receiving physical therapy is much lower than the number who report dealing with physical limitations (Kinirons and Do, 2015). In addition, the fluctuating, episodic nature of HIV can pose additional complications in the day-to-day performance of the patient (Worthington et al., 2005). Episodic disability is defined as periods of good health interrupted by potentially debilitating periods of disability, which can lead to fluctuations in performance on both short and long timescales over the course of living with HIV and can impact activities of daily living or the ability to hold a job, making occupational therapy useful for the HIV population (O'Brien et al., 2009). These periods of disability can manifest either from HIV or the treatment itself.

The call for rehabilitation strategies specific to the HIV population has been a relatively recent development by developed countries, but it is a need that is magnified in LMICs. Stroke neurorehabilitation strategies have received far greater focus while there is a paucity of neurorehabilitation successes in HIV populations, who are in dire need of such strategies. Rehabilitation in HIV consists of activities and services that address these restrictions while taking into account the distinct physiological, emotional, and societal features of HIV (Worthington et al., 2005). Within the framework of rehabilitation for people living with HIV, ensuring a wide selection of traditional and specialized professionals (i.e. physical and occupational therapists), services (i.e. AIDS service organizations and alternative therapists), and support (i.e. community workers, legal counselors, social support groups) is a key focus (Worthington et al., 2005). Despite the existence of a rehabilitation framework, people living with HIV still struggle to gain access to the rehabilitation services they need, often from a lack of awareness on both the patient and care provider side (O'Brien et al., 2014). A challenge in HIV and rehabilitation is the increasing presence of comorbidities — such as diabetes, Hepatitus C, cardiovascular disease, renal disease, and frailty — that can complicate already existing disabilities (Desquilbet et al., 2007; Schouten et al., 2014).

A first step in addressing the need is increasing awareness among health care professionals to facilitate access to rehabilitation services for people with HIV, as few rehabilitation professionals knowingly work with someone living with HIV (Worthington et al., 2005). This indicates a gap in service and a need for HIV-specific training and guidance. Another necessary step is a concerted effort to assess the effectiveness of rehabilitation services (O'Brien et al., 2010). A method for developing clinical practice guidelines in HIV rehabilitation has been proposed by O'Brien and colleagues, focused on understanding the diversity of people living with HIV, taking a client-centered and holistic approach, and maximizing access to rehabilitation services (O'Brien et al., 2010). These guidelines or a similar approach can inform HIV rehabilitation practices that are evidence-based, practical, and accessible. To achieve this, it has been suggested that research in HIV rehabilitation should focus on access to rehabilitation and models of rehabilitation service provision such as early screening and assessment for disability to identify the need for rehabilitation, understanding the transition throughout the HIV continuum of care, and tailoring service delivery to increase the accessibility of rehabilitation to different populations (O'Brien et al., 2010).

2.6 Stroke in the HIV Population

The life expectancy of someone living with HIV in the United States has increased from under 40 years in 1996 to 73.1 years in 2011 (Marcus et al., 2016). While it is still below the general population's life expectancy of 78.8 years, the increased lifespan naturally exposes the HIV population to conventional stroke risk factors (Murphy et al., 2017). This means that the presentation of both HIV and stroke in a patient can sometimes be coincidental.

However, there is a body of research using epidemiological and pathophysiological methods establishing an association between HIV and stroke (Benjamin et al., 2012; Ovbiagele and Nath, 2011; Chow et al., 2012; Okeke et al., 2016; Tipping et al., 2007; Heikinheimo et al., 2012; Singer et al., 2013; Mochan et al., 2005; Ortiz et al., 2007). Several possible explanations for why HIV causes an increased risk of stroke have been hypothesized. These

include opportunistic infection, HIV-associated vasculopathy, cardioembolism, chronic inflammation, and the neurotoxicity of ART itself (Benjamin et al., 2012). A study on the Veterans Aging Cohort, consisting of 76,835 male veterans, showed that HIV infection is associated with an increased ischemic stroke risk among HIV-infected compared with demographically and behaviorally similar uninfected male veterans (Sico et al., 2015). In 2012, Chow reported that stroke rates were higher in the HIV population — particularly in young patients and women — independent of typical stroke risk factors compared to the general population in a Boston healthcare system (Chow et al., 2012). From 1997-2006, there was a 60 percent increase in stroke rates in the U.S. HIV population despite stroke rates in the general population decreased by seven percent (Ovbiagele and Nath, 2011). Combined with increasing stroke rates in LMICs where HIV is more prevalent, the HIV-stroke population is one that is emerging in both HICs and LMICs (Feigin et al., 2009).

In the U.S., the mean age of patients with HIV at the time of their first stroke was 48.4 years old as of 2006, up from 42.9 years of age in 1997 since the introduction of ART (Ovbiagele and Nath, 2011). This is considerably lower than the average age of stroke onset of the general population, which is 70.7 years of age (Mozaffarian et al., 2016). In a recent study in a U.S. HIV population, the incidence of cerebrovascular event — defined as ischemic stroke, hemmoraghic stroke, and transient ischemic attack — was 3.87 per 1000 years lived (Vinikoor et al., 2013). Another study found the incidence of just ischemic stroke to be 1.25 per 1000 years lived (Marcus et al., 2014). Compared to the HIV-stroke population in the U.S., the HIV-stroke population in areas such as Sub-Saharan Africa is considerably younger. Two studies in South Africa and Malawi showed that the mean age of stroke in HIV patients was 33.4 and 39.8 years old, respectively (Tipping et al., 2007; Heikinheimo et al., 2012). Besides the lower age of stroke in HIV patients compared to the U.S., it is also important to note that these particular HIV-stroke patients did not present with typical risk factors of stroke. The HIV prevalence in these countries is 11 and 12 percent of the total population, compared to under 0.5 percent in the U.S. (Tipping et al., 2007; Heikinheimo et al., 2012). In some reported cases in LMICs, stroke was the presenting factor that led to

HIV diagnosis (Tipping et al., 2007).

2.6.1 Treatment Strategies

Current treatment strategies for people with both HIV and stroke often do not account for the presence of both diseases. For example, the HIV status of someone who has suffered a stroke is usually not a factor when administering treatment or therapy. In other cases, stroke can be the initial manifestation of HIV (Tipping et al., 2007; Manwani et al., 2016). In addition, emergency rooms are often not equipped for real-time HIV testing (Singer et al., 2013). The effects of drug interactions on the patient remain unknown and thus warrant further investigation. Efforts toward reducing the neurotoxicity of ART, making the central nervous system more permeable to ART to limit chronic neuroinflammation, and finding a cure to HIV are long-term, high-priority goals that will help the treatment and management of the HIV-stroke population (Goodenow, 2017). However, these do not benefit the current population living with the challenges of both conditions, and there is a distinct lack of rehabilitation strategies specific to the HIV-stroke population. This is an important need because ignoring the episodic nature and associated comorbidities of HIV during stroke recovery could affect outcomes in ways that are not seen in the stroke population (O'Brien et al., 2009). For example, stroke survivors with HIV demonstrated a decline in activities of daily living performance one month after discharge while the stroke group without HIV continuing to improve (Augustyn et al., 2020). While HIV alone may present with deficits that necessitate rehabilitation, the occurrence of both HIV and stroke is different from other comorbidities that may show up in either HIV or stroke alone because both result in neurological damage. Thus, this necessitates a treatment approach that has not yet been implemented that accounts for both HIV and stroke.

2.6.2 Challenges

There are various challenges that should be considered when coming up with rehabilitation and treatment strategies for the HIV-stroke population. The presence of HIV prior to stroke

can alter the approach to managing a person with both HIV and stroke. These challenges — while not necessarily exclusive to the HIV-stroke population but are certainly magnified — include joint cognitive and motor deficits, lack of uniform clinical assessments, unknown changes in the brain, psychosocial issues, and accessibility to services.

2.6.3 Joint Cognitive and Motor Deficits

The presentation of motor and cognitive deficits could be much more varied in the HIV-stroke population. Factors such as the severity of HAND compounded with the stroke lesion location and size means that the presentation of deficits spanning both motor and cognitive domains could require additional management strategies compared to the HIV population or stroke population alone. For example, compared to a patient with just stroke, someone with HAND who suffered a stroke confined to the primary motor cortex would have the neurocognitive deficits associated with HAND on top of the motor impairment from the stroke. The increased variability across the spectrum of combined cognitive and motor impairments could introduce added complexity in both assessment and treatment of the patient. More research needs to be done to shed light on this area as cognitive impairment can be an important factor in choosing the most effective motor recovery intervention(Cirstea et al., 2006). The connection between cognitive and motor function can be seen in HIV, where studies have shown that cognitive function can improve from aerobic or strength resistance activity (O'Brien et al., 2016). Thus, understanding how the presence of impairment impacts the interactions between cognitive and motor domains is a challenge that must be addressed in order to develop effective neurorehabilitation strategies.

2.6.4 Lack of Uniform Clinical Assessments

HIV and stroke have their own sets of clinical tests to assess motor, cognitive, and other domains. One of the few studies looking at both the HIV and stroke populations establishes a measure of fatigue across the HIV, stroke, and cancer (Butt et al., 2013). The lack of uniform clinical tests makes it more difficult to assess the HIV-stroke population, and there

are no established ways to account for the presence of the other disease during assessment. For example, a pen-and-paper cognitive test during a neuropsychological assessment for HAND would be difficult for someone who suffered a stroke resulting in hemiparesis of their dominant hand. This could also apply to a stroke patient without HIV presenting with neurocognitive deficits. In addition, the results could be misrepresentative even if the patient were able to complete the task with their non-dominant hand. Certain tests require data from a large healthy population in order to normalize the scores, which could vary by country and could be affected by cultural factors, such as the Trail Making Tests (Tombaugh, 2004). On top of this, a number of other coinfections and comorbidities such as diabetes, bone and muscle dysfunction, and age-related frailty can impact the management of the patient and the ability to perform assessments.

2.6.5 Unknown Structural and Functional Changes in the Brain

It is unknown how the presence of HIV and stroke jointly affects the functional and structural properties of the brain. As discussed earlier, both diseases independently result in neurologic changes (Ward et al., 2003b,a; Tombari et al., 2004; Calautti and Baron, 2003; Kim et al., 2006; Basser and Pierpaoli, 2011; Warach et al., 1995; Werring et al., 2000; Ernst et al., 2002; Du Plessis et al., 2014; Melrose et al., 2008; Ipser et al., 2015; McNab and Klingberg, 2008; McArthur et al., 2005; Von Giesen et al., 2003; Thompson et al., 2005; Stout et al., 1998; Ances et al., 2012; Becker et al., 2011; Ragin et al., 2012; Küper et al., 2011). To date, comorbidities that may have an effect on neurologic properties have often been criteria for exclusion in imaging studies, thus imaging data on the HIV-stroke population is lacking. However, the presence of HIV could be priming the brain prior to the onset of stroke and could have various implications that are still unknown. Given the advances in imaging technologies and analytical methods, there is the opportunity for useful knowledge regarding the combined neurologic effects of HIV and stroke to emerge that can drive the development of neurorehabilitation strategies.

2.6.6 Psychosocial Issues

Psychosocial issues resulting from both stroke and HIV can pose a challenge in effectively reaching those who would benefit from a targeted rehabilitation strategy (O'Brien et al., 2014; Bogart et al., 2000; Williams et al., 2004). Because of the stigma associated with HIV in various countries, seeking care or revealing one's HIV status can be a daunting prospect (Maman et al., 2009). The psychological effects of living with both HIV and stroke should be taken into account and may require additional considerations when designing treatment regimens.

2.6.7 Accessibility

There is a lack of health care professionals who are familiar with the needs of both the HIV and stroke populations and the available resources. This challenge is magnified in LMICs, where an increasing double burden exists of malnutrition and infectious diseases with new problems such as chronic conditions (WHO, 2015b). These resource challenges can also be seen in some areas in HICs, particularly rural areas where it is harder to access the necessary care (Leira et al., 2008). In both these areas, the supply chain for rehabilitation services may not be effective or adequate in reaching a lot of people.

2.7 Designing Robot-Assisted Neurorehabilitation Strategies for HIV and Stroke

The ideal solution to the challenges posed by the HIV-stroke population would be one that is applicable across the combined spectrum of cognitive, motor, and social impairments. On top of that, it should be scalable and accessible to the HIV-stroke populations not only in the U.S. and other high resource areas but also in lower resource areas around the world. While no such solution currently exists, there are potential approaches that can be leveraged.

As highlighted earlier, one of the biggest challenges with the HIV-stroke population is the increased prevalence of joint cognitive and motor deficits. While this challenge is magnified in the HIV-stroke population, this is not a challenge that is unique to this population, as many neurologic diseases can result in some combination of cognitive and motor deficits. Advanced assistive and rehabilitation technologies, namely robot-based methods, provide an approach to assess impairment and provide rehabilitation that can address many of the challenges faced with the HIV-stroke population (Bejarano et al., 2016). Rehabilitation robotics has demonstrated the ability to be at least as effective as high-intensity physical therapy (Lum et al., 2002; Husemann et al., 2007). The upside that they provide over conventional therapy is the ability to provide consistent treatment over longer periods of time. Patients with all levels of impairment can be treated based on the adaptive nature of the robots. These technologies can reduce the load on rehabilitation professionals and augment their ability to provide care to patients. Another benefit of these technologies is the added capability to collect vast amounts of data, track progress, and provide feedback to the patient and caregiver. This opens the door for other technological advances, such as those made in mobile health, machine learning, and telemedicine, to be incorporated into the rehabilitation engineering space and improve the quality of care.

2.7.1 Potential Robot-Based Areas of Focus

While there are many areas that rehabilitation robotics span, we will briefly highlight a few that are relevant to designing neurorehabilitation strategies and considerations for applying these to people living with both HIV and stroke. These areas include robot-based biomarkers of motor impairment, motor learning, cognitive assessment and rehabilitation, and affordable rehabilitation robots. We discuss various open questions and potential research directions in each of these areas as they relate to the HIV-stroke population.

Robot-Based Biomarkers of Motor Impairment

The ability to quantify kinematic and dynamic measures of motor impairment is a key feature of robot-based systems, allowing for both higher resolution and reliability compared to clinical tests. There has been a lot of research into different metrics that are reflective of motor impairment (Lum et al., 2002; Bosecker et al., 2010; Krebs et al., 2014). The development of these metrics allows for assessment to be administered in a quicker manner and for progress to be tracked throughout the course of rehabilitation. Another benefit of robot-based biomarkers is the ability to potentially reduce the sample size needed to test a rehabilitation strategy, allowing for more efficient experiments (Krebs et al., 2014). In areas where trained rehabilitation professionals are in short supply or assessments are not feasible, having a robot assist in assessment and treatment can increase accessibility to quality treatment as well as reveal new information about areas that have been typically difficult places to gather data. Robot-based biomarkers of motor impairment have shown to be effective as it relates to stroke and has the potential to be useful for the HIV and HIV-stroke populations as well. However, the episodic nature of HIV causes patients to have variability as it relates to task performance, and how the episodic nature might affect motor recovery before and after stroke is an open question that could potentially be addressed by robot-based biomarkers.

Motor Learning

Recovery of motor function is often seen as an extension of the motor learning process, consisting of motor adaptation, skill acquisition, and decision making (Shadmehr and Wise, 2005). Motor learning principles have been used to develop more effective rehabilitation strategies such as impairment-oriented training, constrained-induced movement therapy, electromyogram-triggered neuromuscular stimulation, robot-based therapy, and virtual-reality based rehabilitation (Krakauer, 2006). Other strategies based on motor learning have also been explored, such as errorless learning or error augmentation (Connor et al., 2002; Wei et al., 2005). A typical motor learning experiment involving a robot consists of

holding the end of a planar robotic arm and making reaching movements while the robot produces a perturbation force unknown to the subject that alters their trajectory (Shadmehr et al., 1994). A challenge to applying motor learning principles to robot-based rehabilitation is ensuring that actual learning rather than just motor adaptation is occurring (Huang and Krakauer, 2009).

Implicit and explicit learning are the two main methods of achieving motor outcomes. Explicit motor learning is defined as "learning which generates verbal knowledge of movement performance, involves cognitive stages within the learning process and depends on the involvement of working memory" while implicit learning "progresses with no or minimal increase in verbal knowledge of movement performance and without awareness" (Kleynen et al., 2014). This implies that implicit learning involves the development of inherent habitual responses while explicit learning involves systematic processing of each step of the task (Kleynen et al., 2014). Implicit and explicit learning have been studied in controlled laboratory environments, without a clear consensus of the value of one versus the other or which method is more effective in rehabilitation (Green and Flowers, 2003; Orrell et al., 2006; Steenbergen et al., 2010; van Tilborg et al., 2011; Verneau et al., 2014). Some literature suggests that explicit feedback can interfere with the motor learning process in patients recovering from stroke and that implicit learning strategies may be more effective for patients with more cognitive deficits (Krebs et al., 2009; Boyd and Winstein, 2004; Patton et al., 2006).

The combination of robotics and models of motor learning has resulted in the emergence of the computational neurorehabilitation field (Reinkensmeyer et al., 2016). While there are many challenges associated with the field and dealing with an impaired population, grounding strategies in motor learning principles can lead to beneficial outcomes in the HIV-stroke population. Given the wide range of cognitive and motor impairments, identifying the best motor learning strategies under different conditions remains an open research question but, if addressed, can personalize and optimize recovery for this population.

Cognitive Assessment and Rehabilitation

Based on people who acquire brain injury including stroke, there is a need to expand the diversity of populations who can benefit from robot-based rehabilitation. A recent review of 120 rehabilitation robots show that a majority of the treatment strategies are force-based or vision-based (virtual reality) systems using explicit motor learning strategies, and only a few robot therapy systems use implicit motor learning strategies such as error-augmentation control strategy (Patton et al., 2006; Maciejasz et al., 2014). Research has shown that there is an association between cognition — particularly executive function and memory — and motor recovery, thus necessitating a focus on the cognitive aspects as well during rehabilitation (Mullick et al., 2015). Non-robot based strategies combining cognitive strategy and task-specific training demonstrated transfer of improvements to untrained activities and better performance compared to regular occupational therapy in stroke patients (McEwen et al., 2015). Cirstea and colleagues showed that successful motor intervention involving knowledge of performance feedback rather than knowledge of results led to motor and clinical improvements that were related to better memory, mental flexibility, and planning abilities (Cirstea et al., 2006).

However, robot-based strategies have the potential to be applied to the cognitive space. Bourke used a robotic hit-and-avoid task to test rapid selection and generation of motor responses which involve cognitive and motor processes (Bourke et al., 2016). Additionally, robot-based measures have been shown to correlate with clinical measures in TBI patients (Logan et al., 2017). Assessing cognitive performance can allow for novel rehabilitation applications, such as closed-loop control of cognitive load during a robot-assisted gait training task (Koenig et al., 2011). A better understanding of the cognitive aspects of impairment and how they affect motor recovery is important for designing rehabilitation strategies for the HIV-stroke population going forward, given the increased likelihood of joint cognitive and motor impairments. While neuropsychological and screening tests often separate the assessment of motor and cognitive domains, robot-based strategies are an opportunity to

provide assessment and rehabilitation of tasks that involve both motor and cognitive domains.

Toward Affordable Rehabilitation Robotics

The rapid development in the field of robot-assisted technologies in rehabilitation has opened the door for affordable solutions to take hold, making care more accessible (Valles et al., 2016). Despite this, these technologies are not yet widely available even in HICs and thus may limit accessibility to such solutions and thus may limit implementation and accessibility to such solutions in LMICs. Similarly, current rehabilitation robotics systems, while potentially cost-effective in the long run, require an initial amount of capital that may not be feasible for lower resource areas. The WHO guidelines state that cost-effective therapy solutions are those that cost less than three times the national gross domestic product for each respective country (Marseille et al., 2015). An example of this can be seen when Bustamante-Valles and colleagues were able to set up a robot-assisted rehabilitation gym in Mexico to supply care in an affordable and effective manner that allowed therapists to see more patients (Valles et al., 2016). As the majority of people living with disabilities reside in LMICs, a more concerted effort to design cost-effective robot-based solutions for rehabilitation will increase the utility and application of such devices in LMICs, expanding the reach and scope of the rehabilitation robotics field.

2.7.2 Potential Non Robot-Based Areas of Focus

While rehabilitation robotics is a potential approach to designing neurorehabilitation strategies for the HIV-stroke population, it is not the only solution available. There has been development in other forms of rehabilitation that have focused on LMICs. These strategies can more readily address psychosocial and accessibility issues than the rehabilitation robotics field can in its current state. Two strategies in particular — community-based rehabilitation and home-based rehabilitation — have been particular areas of focus.

Community-Based Rehabilitation

In order to improve the quality of life for people with disabilities in LMICs and address some of the barriers, the WHO introduced the concept of community-based rehabilitation (CBR), which consists of programs that "are designed to meet the basic needs of people with disabilities, reduce poverty, and enable access to health, education, livelihood, and social opportunities" (WHO, 2015a). According to the WHO's global disability action plan for 2014-2021, barriers that prevent access to rehabilitation, assistive technologies, and services for the disabled population in LMICs include high costs, insufficient number of trained professionals, absence of facilities and equipment, ineffective service models, and lack of integration and decentralization of services (WHO, 2015b). However, CBR programs have shown initial success in LMICs in increasing independence, self-esteem, and income (WHO, 2010).

In the context of HIV management, a study conducted in the United Kingdom and Canada demonstrated that community-based exercise programs are safe and can improve the quality of life of people living with HIV (Li et al., 2017). Benefits of community-based rehabilitation include increased social support, enhanced engagement in social activities, and reduced isolation and stigma associated with HIV (Li et al., 2017). A recent review of 24 studies showed that performing aerobic and resistive exercise is safe and can lead to improvements in cardio-respiratory fitness, strength, body composition and quality of life for adults with HIV (O'Brien et al., 2016). CBR has also been tested in the stroke population and shown to be safe and effective (Stuart et al., 2009; Salbach et al., 2014). The initial CBR research in both HIV and stroke populations indicate that CBR has the potential to be applied in the HIV-stroke population. Other forms of community-based rehabilitation need to be tested beyond exercise-based programs, such as incorporating telemedicine, as well as the effectiveness of implementing these strategies in lower resource areas. The additional challenges posed by the HIV-stroke population and how those might change the approach of CBR strategies also needs to be further researched.

Home-Based Rehabilitation

A component of CBR is home-based rehabilitation (HBR). HBR has been shown to be effective in HICs for chronic disease management and has the potential to be extended to LMICs (Cobbing et al., 2016). A recent randomized controlled study in South Africa showed that a 16-week home-based rehabilitation program for people living with HIV carried out by community healthcare workers showed similar benefits to the standard of care (Cobbing et al., 2017). HBR relies more on the patients themselves to drive rehabilitation, but this method can reduce costs by being based outside of institutions. Patients can still be observed by professionals either with follow ups or on home visits.

In the context of HIV-stroke care, CBR and HBR would allow patients to receive treatment in a more comfortable setting while avoiding some of the challenges presented with seeking institution-based treatment, such as high costs and traveling long distances. HBRs can be more easily implemented than CBRs, which require coordination across many different moving parts. However, some of the potential challenges of HBRs include generating support among policy makers, training sufficient workers, ensuring patient adherence, and translating the same successes seen in HICs to LMICs (Cobbing et al., 2016). The lack of monitoring also makes assessing the true effects of HBRs a difficult task. A major challenge is the compatibility of HBR with other rehabilitation strategies that require equipment that people may not be able to afford. Further research into effective CBR and HBR strategies is needed, but they are a potential approach for designing rehabilitation strategies for the HIV-stroke population that can increase the accessibility to treatment.

2.8 A Potential Approach for HIV and Stroke Neurorehabilitation

2.8.1 Combining Robot-Assisted and Community-Based Rehabilitation Techniques

While both robot-assisted and community-based rehabilitation strategies address some of the challenges, neither of these approaches is suited perfectly for the HIV-stroke population. With robot-assisted rehabilitation, the social factors, such as the stigma associated with HIV, are not necessarily taken into account. In addition, given that rehabilitation robotics is mostly targeted at motor recovery but the HIV-stroke population will also present with varying degrees of cognitive deficits, the cognitive load of a task and its impact on task performance must also be taken into account. With CBR, there remains the challenge of reducing poverty, scaling up solutions, and promoting evidence-based practices. Mechanisms to track data and integrate services are also missing. In other words, there is still a need in LMICs for a solution rooted in accessibility, affordability, and analytics.

Combining the two approaches, however, could be a way to develop an effective, innovative form of neurorehabilitation. The strengths of each fill in the holes of the other. CBR provides a way to address the social aspects that are not met with rehabilitation robotics alone. The potential for scalable, affordable treatment and the ability to record data using robot-assisted rehabilitation would be a way to provide the quantitative analysis needed to promote the best evidence-based practices.

Current commercial rehabilitation robotic systems could be adapted to incorporate CBR-based methods(Díaz et al., 2011; Maciejasz et al., 2014). For example, the In Motion system (Bionik Labs) for upper limb rehabilitation and the variety of lower limb rehabilitation systems from Hocoma Inc. can be used in ways that promote increased health, livelihood, and social opportunities for the HIV-stroke population. The drawbacks of current commercial solutions are the high cost and scalability of these systems to LMICs. Thus, more innova-

tion in this space is needed to be able to meet the functional, social, and emotional needs of the population.

2.8.2 The Rehab CARES Gym

Our lab has designed a system called the Rehabilitation Community-Assisted Robot Exercise System (Rehab CARES) Gym, that is meant to provide robot-assisted rehabilitation in a community-based setting with the intention of deploying it in various LMICs through partnerships with local universities and health systems. We envision this system being based in primary care, tertiary care, or community centers. The current system is a compact robotic gym that provides affordable, game-based rehabilitation for the upper and lower limbs, based on concepts first tested in Mexico (Johnson et al., 2017; Valles et al., 2016). Unlike existing rehabilitation systems that are bulky, expensive, and serve a single patient at a time, our setup enables one rehabilitation professional to treat multiple patients at a time in a more efficient manner (Valles et al., 2016). It promotes a community-based approach by creating a fun and social therapy environment where patients can interact with each other, increasing their motivation to exercise and receive treatment. The unique aspects of this system include its modularity and adaptation of rehabilitation technologies that can be implemented in low-resource settings(Johnson et al., 2017).

The system consists of various stations that serve different purposes and can be configured in a number of different ways. One scenario could be a mix of both passive and active stations. The passive stations consist of off-the-shelf rehabilitation equipment that provide patients with minor to moderate disability the capacity to improve functionality, with the ability to manually adjust the resistance. While these do not provide assistance, we have equipped them with sensors and motors to interface with games to adaptively adjust the resistance based on performance. The active station of the gym consists of a low-cost, single-degree-of-freedom adaptive haptic robot for upper limb rehabilitation called the Haptic TheraDrive (Theriault et al., 2014). This robot adjusts the amount of assistance based on the user's performance in order to provide haptic feedback, allowing for people with severe

impairments to interact with the system as well. Parallel bars and a sensorized walking platform for lower limb gait assessment and training are also part of the system. Together, the separate stations provide caregivers the ability to oversee multiple patients at once and provide patients access to consolidate different forms of rehabilitation in a single location. In the cases of cognitive impairment, we envision the tasks adapting the difficulty or cognitive load to the patient in a way that maintains a caregiver's ability to oversee multiple patients at once, although what this would exactly look like is an open question. This way, the system may be adapting the robotic assistance in addition to the task itself to suit the patient's motor and cognitive impairments. Each station is designed to collect assessment and performance data, which can be used to monitor progress and offer recommendations for a more personalized approach to rehabilitation. While the current configuration has three passive stations, one active station, and one gait station, the overall design of the system is modular in nature, meaning that the parts and combinations can be adjusted to meet the needs and resources of different areas. All of these stations would be integrated to allow for cooperative or competitive multiplayer games or for data to be collected for the same patient across different stations.

The Rehab CARES Gym's data collection capabilities allow for experiments on robot-based biomarkers of motor and cognitive impairment as well as exploration of motor learning to be conducted. More research should focus on the best ways to measure motor and cognitive deficits with the system. One approach we have tried is assessing unilateral upper limb kinematics in both the impaired and less impaired limb sides using a variety of tasks that engage both motor and cognitive domains. Our hypothesis is that metrics exploring the relationship between the impaired and less impaired side could potentially be used to assess both cognitive and motor deficits across the stroke, HIV, and HIV-stroke populations (Bui et al., 2017). This approach is supported by other recent work in stroke subjects (Bourke et al., 2016). Other avenues to explore include designing additional robot-based tasks that can jointly quantify a wider variety of cognitive and motor domains. Eventually, our goal is that these solutions can be implemented together in one system able to provide an

opportunity to treat a variety of cognitive and motor impairments regardless of the cause, from subtle deficits due to HAND to severe upper limb impairment due to stroke while addressing the social component of dealing with either or both HIV and stroke.

The possible limitations and challenges of this solution vary depending on the context in which it is being implemented. In HICs, a challenge would be convincing high resource areas that have sufficient access to rehabilitation services to adopt such technologies. Therapists' preference for interacting directly with their patients can slow the acceptance of robot-based solutions even if it provides similar benefits. Additionally, rehabilitation robot technologies are still considered experimental by many health insurance companies and are thus not reimbursed. In LMICs, additional social and cultural considerations may come into play, on top of other challenges such as powering the system, mobility of the system, and training to operate the system. Cost and resource constraints may also reduce some of the functionality of the system, making cost effectiveness analyses important (Valles et al., 2016).

2.9 Conclusion

Developing relevant neurorehabilitation strategies is a critical component in the care and treatment of people living with the effects of both HIV and stroke. The long term physical, cognitive, and social effects of both conditions necessitate extensive monitoring, assessment, and treatment. The most relevant strategies will be ones that not only take into account the complex interactions occurring in the patient but also the cultural and economic considerations of their respective environment.

While there are many challenges posed by the HIV-stroke population, addressing them can benefit additional populations beyond just the HIV-stroke population to advance research in a variety of fields. It will require coordination between experts in various fields such as stroke, HIV, rehabilitation engineering, global health, and health care, among other areas. With a more concerted effort toward designing affordable rehabilitation robotics solutions and drawing on other rehabilitation strategies such as community-based rehabilitation, there

is an opportunity to expand multiple fields in new and exciting directions.

2.10 Funding

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2.11 Acknowledgements

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CHAPTER 3 : THE INFLUENCE OF COGNITIVE IMPAIRMENT ON ROBOT-BASED UPPER-LIMB MOTOR ASSESSMENT IN CHRONIC STROKE

3.1 Contribution

This chapter is adapted from a journal paper that was submitted and is currently under review to Neurorehabilitation and Neural Repair with Breanna Lyn, Matthew Roland, Carol Wamsley, Rochelle Mendonca, and Michelle J. Johnson.

3.2 Abstract

Chronic upper extremity motor deficits are present in up to 65% of stroke survivors, and cognitive impairment is prevalent in 46-61% of stroke survivors even 10 years after their stroke. Robot-assisted therapy programs tend to focus on motor recovery and do not include stroke patients with cognitive impairment. This study aims to investigate performance on the individual cognitive domains evaluated in the MoCA and their relation to upper-limb motor performance on a robotic system. Participants were recruited from the stroke population with a wide range of cognitive and motor levels to complete a trajectory tracking task using the Haptic TheraDrive rehabilitation robot system. Motor performance was evaluated against standard clinical cognitive and motor assessments. Our hypothesis is that the cognitive domains involved in the visuomotor tracking task are significant predictors of performance on the robot-based task and that impairment in these domains results in worse motor performance on the task compared to subjects with no cognitive impairment. Our results confirmed the hypothesis that visuospatial and executive function have a significant impact on motor performance, with differences emerging between different functional groups on the various robot-based metrics. We also show that the kinematic metrics from this task differentiate cognitive-motor functional groups differently. This study demonstrates that performance on a motor-based robotic assessment task also involves a significant visuospa-

tial and executive function component and highlights the need to account for cognitive impairment in the assessment of motor performance.

3.3 Introduction

Motor and cognitive impairments are common occurrences after stroke. These can impact the ability to perform activities of daily living (ADLs) and to live independently. Long-term upper extremity motor deficits persist in up to 65% of stroke survivors(Mayo et al., 2002), while cognitive impairment is prevalent in 46-61% of stroke survivors even 10 years after their stroke (Delavaran et al., 2017)

Robotic therapy systems have emerged as an approach to address the motor impairments that result from stroke. Previous robot-assisted therapy studies have demonstrated improvements in motor capacity with similar efficacy to conventional, high-intensity therapy(Lum et al., 2002; Fasoli and Adans-Dester, 2019). However, these studies largely ignore the presence of cognitive impairments. A recent systematic review showed that 10 out of 66 clinical trials involving robotic therapy systems included participants with impaired cognition, and only five of those used cognitive measures as outcomes(Everard et al., 2020). The presence of cognitive impairment has been shown to negatively influence motor outcomes after upper limb therapy, including robotic therapy(Leem et al., 2019).

Exploring cognitive function through rehabilitation robotics remains an emerging area and there is a need to develop tools to study how cognitive deficits impact motor performance and outcomes. Aprile et al. demonstrated improvements in episodic memory, calculation, and visual attention in a pilot study of 51 stroke subjects going through a combined cognitive training and upper limb robotic therapy regimen(Aprile et al., 2020). Another pilot study explored the use of an active learning protocol as a cognitive training tool during upper limb robotic therapy, demonstrating that this approach was well-tolerated and resulted in significant gains in upper extremity function(Fasoli and Adans-Dester, 2019). Other works have demonstrated moderate relationships between overall cognition scores using the

Montreal Cognitive Assessment (MoCA) and robot-based metrics in stroke and traumatic brain injury populations (Bourke et al., 2016; Logan et al., 2018).

A major barrier to widespread clinical adoption of rehabilitation robotics is the lack of evidence that motor capacity improvements transfer to untrained tasks or ADLs (Fasoli and Adans-Dester, 2019). One potential explanation for this barrier is that the presence of cognitive impairments could be preventing this transfer. Thus, there is a subset of stroke patients presenting with both cognitive and motor impairments for which existing rehabilitation robotic strategies are not currently effective. There is a need to better understand the interactions between specific cognitive and motor impairments to develop more effective neurorehabilitation strategies to improve patient outcomes.

Cognitive-motor interactions have been explored in the cognitive neuroscience field, where studies have demonstrated relationships such as that of secondary motor network supporting working memory tasks. Studies have shown that people with lower working memory capacity recruit motor networks more actively and at lower thresholds of cognitive difficulty than people with higher working memory capacity.10 A common clinical method of screening for cognitive impairment is the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA has been validated to identify the likelihood of mild to moderate cognitive impairment across various domains – visuospatial ability, executive function, naming, attention, language, abstraction, delayed recall, and orientation – in the elderly, stroke, traumatic brain injury, and other populations. A recent study by VanGilder demonstrated a relationship between the visuospatial and executive function section of the MoCA to motor skill transfer (VanGilder et al., 2019). To date, there has not been a study examining performance on the individual domains evaluated in the MoCA and their relation to motor performance on a robotic system in the chronic stroke population.

This study aims to explore this cognitive-motor interaction in the context of a visuomotor trajectory tracking assessment task. Individuals recruited from the stroke population with a wide range of cognitive and motor levels completed a classic trajectory tracking task

using the Haptic TheraDrive rehabilitation robot system (Theriault et al., 2014; Johnson et al., 2017). Performance on this task was evaluated against clinical cognitive and motor assessment scores. Our hypothesis is that the cognitive domains involved in the visuomotor tracking task – namely visuospatial ability, executive function, and attention domains – are significant predictors of performance on the robot-based task. We also hypothesize that mild to moderate impairment in these domains results in worse motor performance on the task compared to individuals with no cognitive impairment.

3.4 Methods

3.4.1 Subject population

Individuals were eligible for the study if they were older than 18 years of age and were at least three months past their stroke. Individuals were excluded if they were unable to sit upright for more than 2 hours at a time, had received a Botox injection within the past three months, experienced severe spasticity in the upper-limb, or experienced greater than mild pain. This protocol was approved by the Internal Review Board of the University of Pennsylvania (Protocol numbers 819787 and 823511). A total of 31 individuals – 16 males and 15 females – participated across the two studies. 17 were from Protocol 819787 and 14 were from Protocol 823511. The average age of the combined patient population was 57.06 years old. After written informed consent was obtained in-person, a clinical evaluation was performed, followed by the robot assessment portion. Table 1 includes descriptive statistics of the demographics and clinical assessments.

3.4.2 Clinical evaluation

Montreal Cognitive Assessment (MoCA)

The MoCA is a cognitive screening tool to detect impairment in various cognitive domains – visuospatial and executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation – and reflects the degree of cognitive impairment in an

individual (Nasreddine et al., 2005). A score above 25 out of 30 generally indicates normal cognitive function, while a score below 19 indicates a high likelihood of severe cognitive impairment. Both the total score and individual domain subscores were recorded. The subscores were determined by summing the points of the individual tasks for each domain section according to the manufacturer's guidelines (Nasreddine et al., 2005).

Box and Blocks (BBT)

The BBT is a test of gross motor function measuring how many blocks subjects are able to transfer across a partition in one minute, with a higher number of transferred blocks indicating better motor function(Mathiowetz et al., 1985). Scores were normalized by age, gender, and limb. It is typically used to measure reach and grasp function in the stroke population.

Upper Extremity Fugl Meyer (UE-FM)

The UE-FM is a scored index that assesses upper limb motor control in stroke patients (Fugl-Meyer et al., 1975). The maximum score for upper limb is 66. A cutoff score of 48 and below was used to determine the presence of moderate motor impairment (Woytowicz et al., 2017).

Grip Strength

Grip strength was measured with a Jamar (Chicago, IL) digital hand dynamometer. Three trials were taken with each hand, with the average being recorded and standard deviation calculated.

3.4.3 Rehabilitation Robot System

The rehabilitation robot used in this study, the Haptic TheraDrive, is a one degree-of-freedom robot for upper limb stroke rehabilitation (Fig. 6) (Johnson et al., 2017). The user operates the TheraDrive by manipulating a vertically-mounted crank handle equipped

Table 1: Subject Demographics and Clinical Scores

Demographic Info or Clinical Score	Mean ± Standard Deviation
Age (years old)	57.06±9.50
Gender (Male/Female)	16M/15F
Impaired Arm (RH/LH)	17RH/14LH
Upper Extremity Fugl-Meyer (66 max)	48.10±19.26
Box and Blocks – Dominant (blocks)	47.26±10.02
Box and Blocks – Non-Dominant (blocks)	26.73±19.99
Grip Strength – Dominant (kg)	28.11±8.34
Grip Strength – Non-Dominant (kg)	16.33±12.13
Montreal Cognitive Assessment (30 max)	22.73±3.89
MoCA – Visuospatial/Executive Function (5 max)	3.84±0.85
MoCA – Attention (6 max)	4.48±1.66
MoCA – Naming (3 max)	2.74±0.51
MoCA – Language (max 3)	1.55±1.16
MoCA – Abstraction (max 2)	1.13±0.66
MoCA – Delayed Recall (max 5)	2.97±1.62
MoCA – Orientation (max 6)	5.77±0.50

with force sensors and an optical encoder. For assessment purposes, it is run in a gravity-compensation mode, which uses force sensors as an input to a proportional-integral-derivative (PID) controller to calculate the necessary response by the motor to give the sensation that there is no resistance or assistance while the user manipulates the handle. A flow chart of the system is provided in Appendix A.1.

3.4.4 Trajectory tracking assessment

After clinical assessment, participants then completed a tracking task on a rehabilitation robot. The robot used in this study, the Haptic TheraDrive (Fig. 1, is a one degree-of-freedom robot for upper limb stroke rehabilitation (Theriault et al., 2014). The user operates the TheraDrive by manipulating a vertically mounted crank handle equipped with force sensors and an optical encoder. For assessment purposes, it is run in a gravity-compensation mode, which uses force sensors as an input signal to a proportional-integral-derivative controller to calculate the necessary response by the motor to give the sensation that there is no resistance or assistance while the user manipulates the handle.

The trajectory tracking task is designed to assess upper limb motor performance. A single trial consists of the user moving the crank arm forward and backward to follow a sinusoidal path that vertically scrolls at a fixed speed. There were slight differences in how the tasks were administered between the two protocols, but the equation to generate the trajectory and robotic system were identical. In Protocol 819787, subjects performed three trials that lasted 90 seconds each (270 seconds total). In Protocol 823511, subjects performed 15 trials that lasted 15 seconds each (225 seconds total). To standardize the analysis, the last 45 seconds from the last trial were omitted from those who completed the task with Protocol 819787 such that 225 seconds of trial data matched that in Protocol 823511. A set of kinematic measures were then extracted.

The outcome measures from the trajectory tracking task included performance error, the distance traversed, and mean velocity. Performance error was calculated as the root mean square error of the position relative to the displayed trajectory and normalized by the root mean square error assuming zero movement. A lower performance error indicates better tracking performance.

The distance traversed was as the total angular distance that the subject traversed and normalized by the expected angular distance of the displayed trajectory path. A normalized value closer to 1 reflects that the actual distance traversed matched the expected distance. A lower value could reflect moderate motor impairment, while a higher value could reflect inefficient movement. A recent review showed multiple studies that demonstrate a relationship between kinematic measures like those used in this study and clinical motor assessments such as the Fugl-Meyer Assessment, Motor Status Score, Modified Ashworth Scale, and Motor Power (Do Tran et al., 2018).

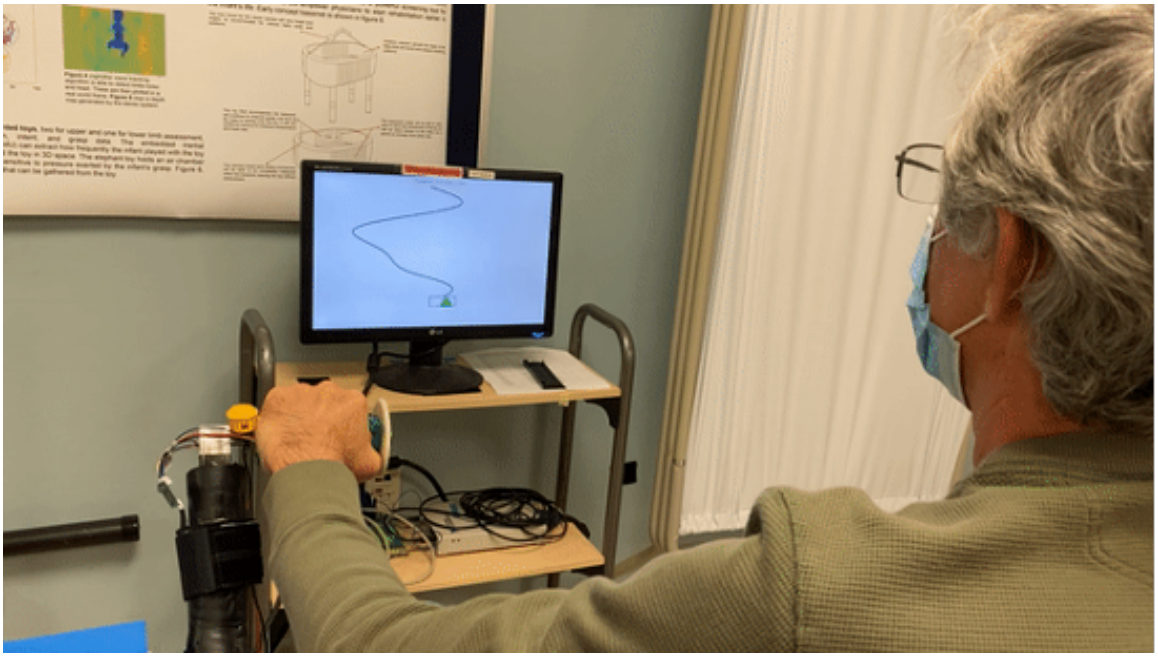

Figure 1: An individual performing the trajectory tracking task on the Haptic TheraDrive, a one-degree-of-freedom robot system used in this study.

3.4.5 Data analysis

Multiple linear regression

To investigate the relationship between clinical scores and robot-based metrics, a forward stepwise multiple linear regression approach was used to identify the clinical scores that were significant predictors of performance on the trajectory tracking task. This consisted of individually testing each clinical score and subsequently adding it to the model only if it was a statistically significant individual predictor ($p < 0.05$) and also increased the adjusted coefficient of determination (adj R^2) compared to the model without that term. The adjusted R^2 is reported to allow for comparison of performance between models with different numbers of terms.

Given the sample size of the subject population, the linear regression model was limited to a maximum of three terms. A sample size analysis determined that the linear regression models were powered to detect a minimum R^2 of 0.22 with one predictor, 0.25 with two

predictors, and 0.29 with three predictors (n = 31, power = 0.80, alpha = 0.05). Small, medium, and large effect sizes were defined as an R^2 value of 0.01, 0.25, and 0.50, respectively. All analysis was conducted in Matlab 2019A.

Cognitive-motor subgroup analysis

All study participants were categorized by their cognitive and motor status based on clinical score cutoffs. To categorize subjects by motor status, a UE-FM score above 48 was classified as low motor impairment, while a score at or below 48 with moderate motor impairment. Because the MoCA-Visuospatial/Executive Function subscore emerged from the linear regression analysis as the only cognitive metric to be a significant predictor across all robot-based metrics, that score was used to categorize subjects by cognitive status, with a cutoff of 3.5 and below out of 5 categorized as moderate visuospatial and/or executive function impairment. Subjects were then categorized into one of four cognitive-motor functional subgroups based on the possible combinations of cognitive and motor status. There were 15 subjects in the low cognitive and low motor impairment group, 7 subjects in the low cognitive and moderate motor impairment group, 5 subjects in the moderate cognitive and low motor impairment group, and 5 subjects in the moderate cognitive and moderate motor impairment group.

For each robot-based metric, a one-way analysis of variance (ANOVA) was conducted with the cognitive-motor functional group as the factor. To correct for all pairwise comparisons between the four functional groups, a Tukey-Kramer honest significance difference test was applied to identify significant differences between groups. An alpha level of 0.05 was used to establish statistical significance on the Tukey-Kramer test.

3.5 Results

3.5.1 Representative Examples and Functional Group Breakdown

Figure 2 shows the average trajectory across the trials of a representative subject from each of the four functional groups. The example low motor and low cognitive impairment subject (blue trace) is a 58-year-old with a UE-FM score of 66 and a MoCA-Visuospatial/Executive Function subscore of 4. The average trace tracks well with the desired trajectory, represented by the dotted line. The example moderate motor and low cognitive impairment subject (red trace) is a 53-year-old with a UE-FM score of 42 and a MoCA-Visuospatial/Executive Function subscore of 4. Qualitatively, while the individual is able to perform the task, they are not able to navigate the full range of motion and display a large variance across trials as demonstrated by the shaded region. The example low motor and moderate cognitive impairment subject (yellow trace) is a 43-year-old with a UE-FM score of 66 and a MoCA-Visuospatial/Executive Function subscore of 2. Their performance falls between that of the example low motor and low cognitive impairment subject and the moderate motor and low cognitive impairment subject. The variance across the trials is also low. The example moderate motor and moderate cognitive impairment subject (purple trace) is a 58-year-old with a UE-FM score of 25 and a MoCA-Visuospatial/Executive Function subscore of 2. Their performance indicates an inability to follow the trajectory after the first part. Figure 3 shows the distribution of subjects by their functional groups as determined by the cognitive and motor cutoff scores.

3.5.2 Identifying Relationships Between Clinical Scores and Trajectory Tracking Performance

Figure 4 shows the multiple linear regression models for each of the robot-based metrics using the clinical cognitive and motor scores as predictors.

A combination of non-dominant BBT and MoCA Visuospatial/Executive Function sub-

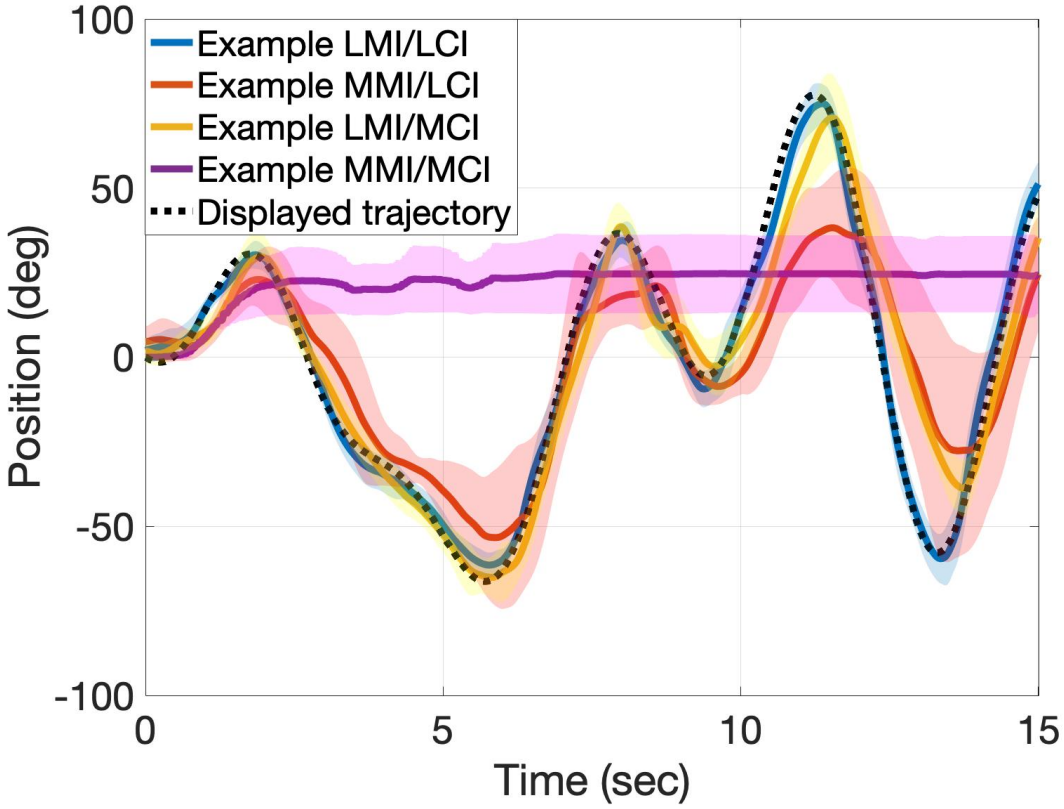

Figure 2: Mean trajectories for representative subjects from each functional group recreated from raw position data (degrees) collected from the robot. The shaded region represents the standard deviation across all trials for a particular subject. The displayed trajectory is shown as a black dotted line. (LMI = low motor impairment; LCI = low cognitive impairment; MMI = moderate motor impairment; MCI = moderate cognitive impairment)

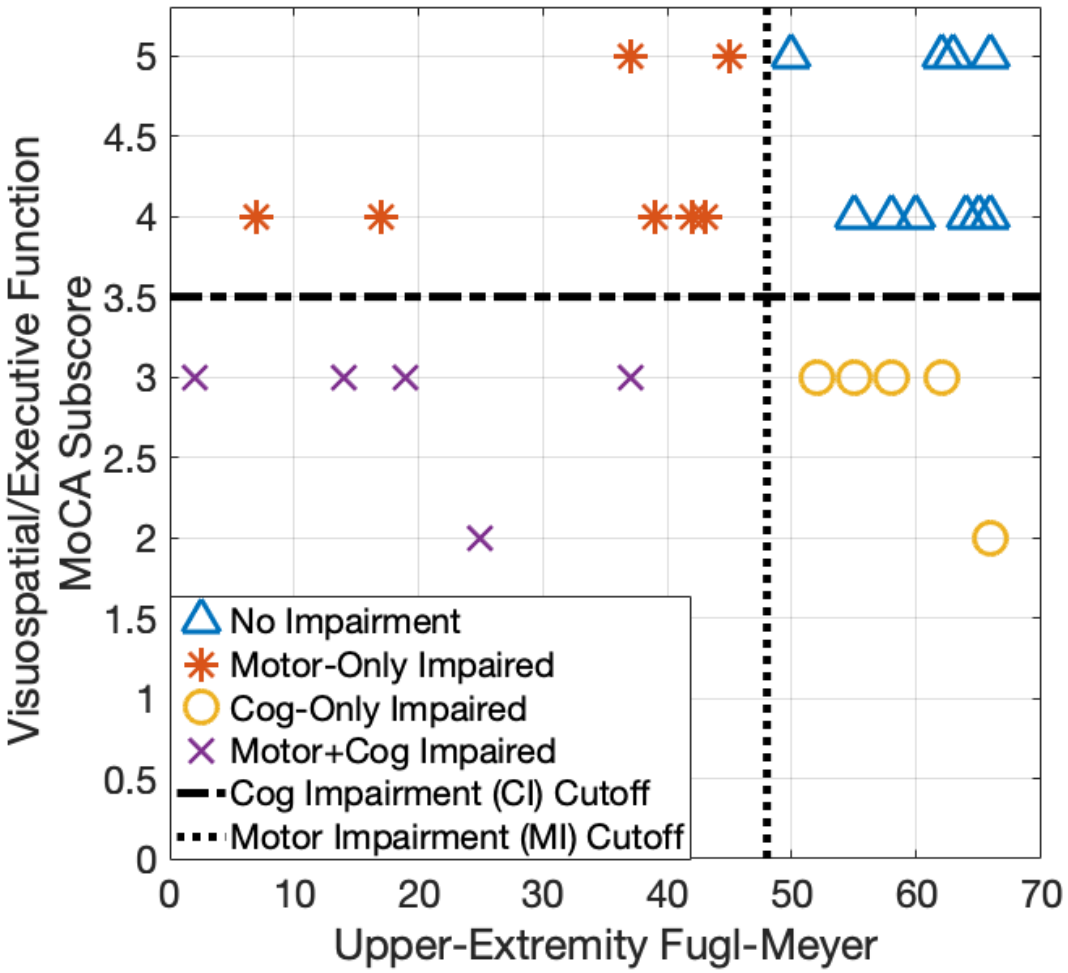

Figure 3: Distribution of subjects by cognitive and motor function, using a score of 3.5 for the MoCA-Visuospatial/Executive Function cutoff and 48 as the UE-FM cutoff. (LMI = low motor impairment; LCI = low cognitive impairment; MMI = moderate motor impairment; MCI = moderate cognitive impairment)

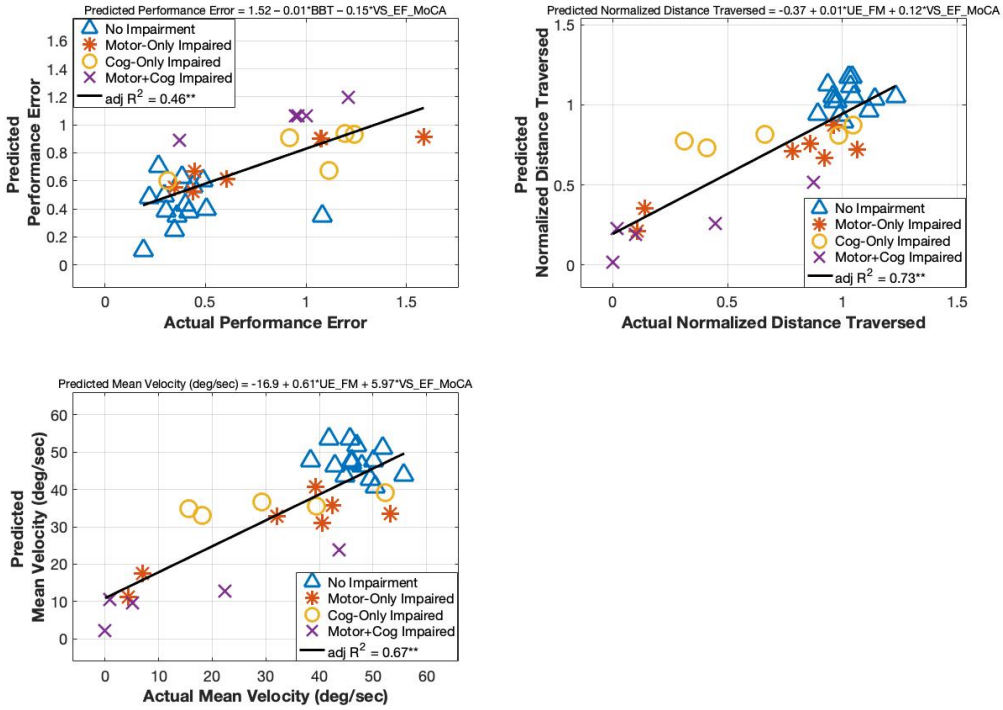

Figure 4: Predicted robot-based scores plotted against actual robot-based scores for performance error (top left, normalized distance traversed (top right), and mean velocity (bottom left). Cognitive-motor functional groups are also identified by different colors and shapes. The multiple linear regression equation is included at the top of each plot. (** = $p < 0.001$; LMI = low motor impairment; LCI = low cognitive impairment; MMI = moderate motor impairment; MCI = moderate cognitive impairment)

scores accounted for 46% of the variance observed in trajectory tracking performance error scores (adj $R^2 = 0.46$, $p = 6.64*10^{-5}$). This model performed better than the model with non-dominant BBT as the only predictor (adj $R^2 = 0.37$). A combination of UE-FM and MoCA Visuospatial/Executive Function subscores accounted for 73% of the variance observed in normalized distance scores (adj $R^2 = 0.73$, $p = 3.84\text{x}10^{-9}$). This model performed better than the model with UE-FM as the only predictor (adj $R^2 = 0.66$). A combination of UE-FM and MoCA Visuospatial/Executive Function accounted for 68% of the variance observed in trajectory tracking mean velocity (adj $R^2 = 0.67$, $p = 6.48*10^{-8}$). This model performed better than the model with UE-FM as the only predictor (adj $R^2 = 0.60$).

3.5.3 Differences Between Cognitive-Motor Functional Groups

Figure 5 shows the performance across the different robot-based metrics according to the cognitive-motor functional groups. There was a statistically significant effect of functional group on trajectory tracking performance error. The low cognitive and low motor impairment group had significantly lower performance error scores compared to the low motor and moderate cognitive impairment group (0.42±0.23 vs 0.96±0.38, $p = 0.02$) and the moderate motor and moderate cognitive impairment group (0.42±0.23 vs 0.90±0.31, $p = 0.04$).

There was a statistically significant effect of functional group on trajectory tracking normalized distance. The low cognitive and low motor impairment group had higher normalized distance scores compared to the low cognitive and moderate motor impairment group (1.03±0.09 vs 0.69±0.40, $p = 0.05$) and moderate cognitive and moderate motor impairment group (1.03±0.09 vs 0.29±0.37, $p = 0.0001$).

There was a statistically significant effect of functional group on trajectory tracking mean velocity. The low cognitive and low motor impairment group had higher mean velocity scores compared to the moderate cognitive and moderate motor impairment group (46.99±4.29 deg/s vs 14.41±18.70 deg/s, $p = 0.0002$).

The moderate motor impairment and low cognitive group was indistinguishable from the low motor impairment and moderate cognitive group for performance error (0.80±0.46 vs 0.96±0.38, $p = 0.83$) , normalized distance traversed (0.69±0.40 vs 0.68±0.33, $p = 0.99$) and mean velocity (31.28±18.61 deg/s vs 30.93±15.25 deg/s, $p = 0.99$).

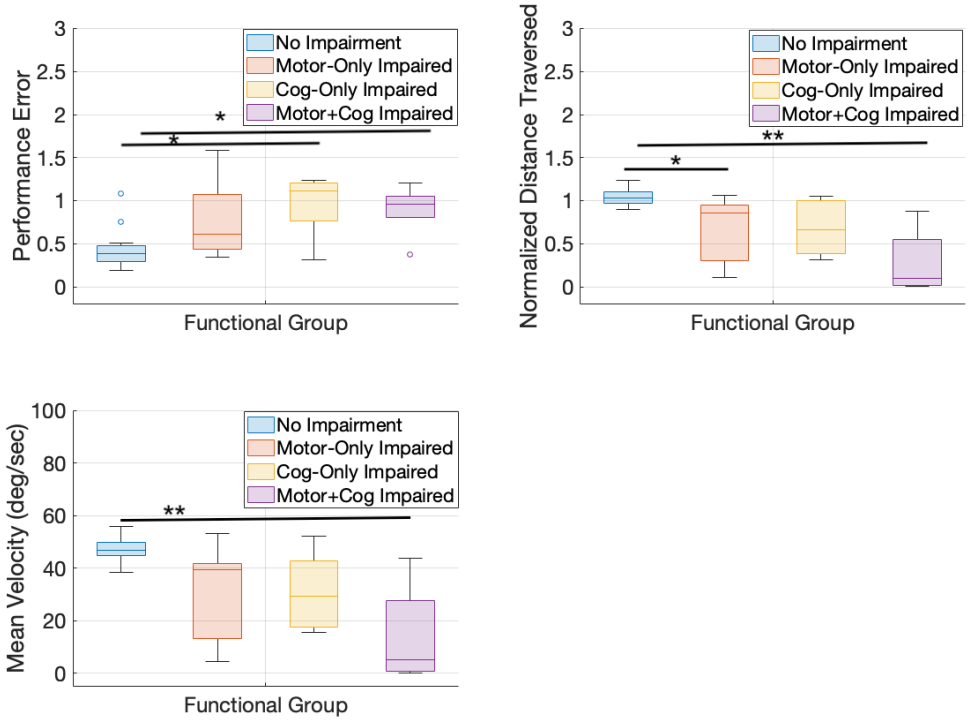

Figure 5: Box and whisker plots showing performance by cognitive-motor functional group on trajectory tracking metrics. The central red line is the median, the edges of the box are the 25th and 75th percentiles, and the whiskers extend to the most extreme non-outlier data points. Outliers are plotted individually as a red cross. (*: $p < 0.05$; **: $p < 0.001$)

3.6 Discussion

3.6.1 Visuospatial and executive function significantly influence motor performance.

This study aimed to explore how cognitive impairments in specific domains affect performance across different groups of cognitive and motor function. We found that executive function and visuospatial ability significantly contributed to performance on the trajectory tracking task. While clinical measures of motor function still strongly predicted performance, we found that the visuospatial-executive function subscore on the MoCA was an independent predictor of motor performance for all three robot-based metrics. The linear regression models for normalized distance traversed and mean velocity demonstrated strong relationships between clinical scores and the robot-based measures, while the model for performance error demonstrated a moderate relationship. All multiple linear regression models exceeded the effect size for which the study was powered. These results support our hypothesis that visuospatial and executive function play a role in the performance of the trajectory tracking task that cannot be overlooked. Our results did not support the role of attention, but other robotic assessment experiments suggest that attention can play a large role in performance (Bourke et al., 2016). Our results also support the findings from VanGilder and colleagues that demonstrated the visuospatial-executive function subscore on the MoCA was related to motor skill training (VanGilder et al., 2019). Their best performing multiple linear regression model had an adjusted R^2 of 0.16, while the values in our study had a range of 0.46-0.72. However, this can partially be explained by the different populations evaluated in the two studies (healthy aging vs. chronic stroke), with a wider range of impairments evaluated in this study. Given the evidence in this study that visuospatial and executive function has a significant influence on motor performance, this suggests the importance of actively measuring these and other relevant cognitive domains in the context of developing robot-assisted neurorehabilitation strategies.

3.6.2 Some kinematic metrics may be more sensitive to cognitive performance than others.

Another key observation from this study is that some kinematic metrics used in robot-based assessments may be more sensitive to cognitive performance than others. This study demonstrated that kinematic metrics from the trajectory tracking task were sensitive to differences between the various cognitive-motor functional groups. Taken together, the results demonstrate that the presence of mild-to-moderate cognitive impairment can influence the interpretation of results. However, one thing to note is that the robot-based metrics did not perform the same in differentiating between the cognitive-motor functional groups. Compared to the low cognitive and low motor impairment group, the moderate cognitive and low motor impairment group performed worse on performance error, while the low cognitive and moderate motor impairment group performed worse on the normalized distance traversed metric. This result suggests different kinematic metrics may be more sensitive to cognitive impairment, while others may be more sensitive to motor impairment.

While there are a variety of kinematic metrics that can be used to assess upper-limb performance during robot-assisted rehabilitation (Do Tran et al., 2018), the impact of cognitive impairment on these metrics is not fully known. Going forward, more work needs to be done to determine how other kinematic metrics relate to specific cognitive and motor impairments. The knowledge of how impairment in various cognitive domains influences motor performance will allow for better treatment of people living with stroke and other neurological injuries that result in motor and cognitive impairments. This will require expanding the current cognitive evaluation tools beyond those that are traditionally used (i.e. the MoCA, Mini-Mental State Exam, etc.) to more targeted evaluations of cognitive function, such as those that assess more specific cognitive domains, such as information processing, working memory, and executive function. Examples of such tests include the Color Trails, Digit Symbol – Coding, Spatial Span, and Stroop tests (D'Elia et al., 1996; Wechsler, 1981; Golden and Freshwater, 1978; Bui et al., 2021).

3.6.3 Limitations of existing robotic assessments

Given its significant involvement, the presence of cognitive impairment can confound results on a task that has traditionally been used to assess motor function in robot-assisted neurorehabilitation. This was shown across all robot-based metrics, as the group with moderate motor and low cognitive impairment was indistinguishable from the group with low motor impairment and moderate cognitive impairment. The difficulty in separating cognitive influence during motor performance highlights the need for new approaches to robotic assessments. Possible approaches include assessing both limbs to remove the impaired limb as a confounding factor or developing tasks that more specifically target working memory, attention, or executive function. Our group has developed such an approach, expanding the robot-assisted technologies to the assessment of cognitive and motor impairments in the HIV and HIV-stroke populations(Bui et al., 2021). Consideration should be given as to how to measure these domains in isolation as well as when motor demands are jointly present. Addressing these barriers will allow for broader populations to benefit from robotic therapy systems.

Expansion of robot-assisted neurorehabilitation to stroke survivors with motor impairments and mild to moderate cognitive impairments is possible if we consider what aspect of motor and cognitive domain is being trained. Failure to account for cognitive impairment, which can mask motor ability, may mean the failure to see transfer of any improvements in motor performance to everyday ADLs that have both cognitive and physical demands.

3.6.4 Study limitations

Given the small sample size, we may not be able to fully generalize these results. While we had adequate distribution across the various variables, the results could have been biased from an uneven distribution across the different cognitive-motor functional groups. Another limitation was the grouping of the visuospatial and executive function domains on the MoCA, which did not allow for examination of each individual domain's contribution to

motor performance. The study would also benefit from other clinical cognitive metrics, as the MoCA is a screening tool that does not extensively evaluate individual cognitive domains. Despite these limitations, these results lay the groundwork for future studies to further explore the role of cognitive function on motor performance.

3.7 Conclusion

In this study in a chronic stroke population with a range of cognitive and motor impairment levels, we demonstrate that performance on a motor-based robotic assessment task also involves a significant visuospatial and executive function component. We also show that the kinematic metrics from these tasks differentiate performance by cognitive-motor functional group in different ways, indicating that some metrics may be more sensitive to cognitive impairment while others more sensitive to motor impairment. These findings warrant further exploration of the role impairments in visuospatial and executive function – as well as other cognitive domains beyond these – have on motor performance.

3.8 Acknowledgements

This work was made possible through core services and support from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (T32NS091006); the University of Pennsylvania's Center for AIDS Research (P30AI 045008); and the University of Pennsylvania's Departments of Bioengineering and Physical Medicine and Rehabilitation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CHAPTER 4 : ROBOT-BASED ASSESSMENT OF HIV-RELATED MOTOR AND COGNITIVE IMPAIRMENT

4.1 Contribution

This chapter is adapted from a journal paper published in Transactions on Neural Systems and Rehabilitation Engineering with Carol A. Wamsley, Frances S. Shofer, Dennis L. Kolson, and Michelle J. Johnson (Bui et al., 2021).

4.2 Abstract

There is a pressing need for strategies to slow or treat the progression of functional decline in people living with HIV. This paper explores a novel rehabilitation robotics approach to measuring cognitive and motor impairment in adults living with HIV, including a subset with stroke. We conducted a cross-sectional study with 21 subjects exhibiting varying levels of cognitive and motor impairment. We tested three robot-based tasks – trajectory tracking, N-back, and spatial span – to assess if metrics derived from these tasks were sensitive to differences in subjects with varying levels of executive function and upper limb motor impairments. We also examined how well these metrics could estimate clinical cognitive and motor scores. The results showed that the average sequence length on the robot-based spatial span task was the most sensitive to differences between various cognitive and motor impairment levels. We observed strong correlations between robot-based measures and clinical cognitive and motor assessments relevant to the HIV population, such as the Color Trails 1 (rho=0.83), Color Trails 2 (rho=0.71), Digit Symbol – Coding (rho=0.81), Montreal Cognitive Assessment – Executive Function subscore (rho=0.70), and Box and Block Test (rho=0.74). Importantly, our results highlight that gross motor impairment may be overlooked in the assessment of HIV-related disability. This study shows that rehabilitation robotics can be expanded to new populations beyond stroke, namely to people living with HIV and those with cognitive impairments.

4.3 Introduction

Today, there are nearly 37 million persons living with human immunodeficiency virus (PLWH) worldwide (UNAIDS, 2014). As PLWH age due to the success of antiretroviral therapy (ART), the challenges have shifted to managing the chronic effects of living with HIV. Many of these challenges can be attributed to neurological complications caused by HIV-associated neurocognitive disorders (HAND), accelerated aging, drug abuse, and HIV-related comorbidities (Gill and Kolson, 2014). Together, the broad range of impairments experienced by PLWH has been shown to impact instrumental activities of daily living (IADLs), such as medication management, telephone communication, cooking, and financial management (Heaton et al., 2004). In one study, upwards of 80% of PLWH reported dealing with at least one impairment, activity limitation or disability, or social participation restriction (Rusch et al., 2004). These deficits are often tied to impairments in executive function, memory, and visuospatial domains (Heaton et al., 2011). PLWH also experience motor impairments in gait, coordination, upper limb fine motor skills, and strength, with 69% of PLWH in one study demonstrating at least one motor impairment (Pullen et al., 2014; Wilson et al., 2013; Lawler et al., 2011; Robinson-Papp et al., 2019). As such, there is a pressing need for effective neurorehabilitation strategies to slow or treat the progression of functional decline in PLWH.

The gold standard for diagnosing neurocognitive impairment has been established by the Frascati criteria, an extensive neuropsychological battery that classifies HAND subtypes as asymptomatic neurocognitive impairment, mild neurocognitive disorder, or HIV-associated dementia (Antinori et al., 2007). However, the assessments used to diagnose HAND often test domains in isolation, which is not reflective of the dual involvement of cognitive and motor demands in most IADL tasks. Differences between HIV and non-HIV populations are also seen in more nuanced tasks. Kronemer et al. demonstrated that even when there was no motor impairment detected on clinical assessments, PLWH demonstrated upper limb motor impairment while multitasking compared to a non-HIV control group that did

not relate to HAND stage (Kronemer et al., 2017). Assessments of multitasking have been shown to be more reflective of IADL performance in PLWH compared to standard clinical assessments (Scott et al., 2011). These results demonstrate that current clinical assessments and biomarkers of HIV do not necessarily correspond well to more subtle impairments in cognition and motor performance (Kronemer et al., 2017).

HIV-associated non-communicable diseases, such as cerebrovascular disease (CVD), are a secondary effect of HIV infection that can further exacerbate existing cognitive and motor impairments. HIV is an independent risk factor for CVD such as stroke (Chow et al., 2012). With an incidence rate of 3.87 per 1000 years lived, CVDs occur at an average age of 48 years in the HIV population (Chow et al., 2012). These numbers are 1.5 times higher and 22 years younger than the general U.S. population (Vinikoor et al., 2013). Augustyn et al. recently showed that stroke survivors with HIV experienced a decline in ADL functions one month after discharge compared to stroke survivors without HIV who continued to show improvement, highlighting how HIV can impact stroke recovery (Augustyn et al., 2020).

Efforts to develop neurorehabilitation strategies have been made in the stroke population, but there is a paucity of established solutions for PLWH despite evidence that rehabilitation can positively address HIV-related challenges in physical, social, and psychological well-being (Weber et al., 2013; deBoer et al., 2019). The rehabilitation robotics field provides a potential solution to address these challenges (Bui and Johnson, 2018). Robot-assisted stroke therapy has been shown to be as effective as high-intensity physical therapy for chronic stroke patients (Lo et al., 2010). Additionally, robotic systems allow for a variety of kinematic metrics to be observed that relate to clinical measures of motor impairment (Do Tran et al., 2018; Bourke et al., 2016; Logan et al., 2018; Bosecker et al., 2010; Krebs et al., 2014).

While the primary focus to date has been on motor impairment, recent studies have started to look at robot-based measures of cognitive impairment in stroke and traumatic brain injury populations (Bourke et al., 2016; Logan et al., 2018). Both of these studies have demon-

strated a relationship between robot-based metrics and overall cognitive scores. However, given that cognition is broadly defined, more work needs to be done to establish robot-based metrics relating to specific domains.

The strengths of a rehabilitation robotics-based approach include the ability to standardize assessments with a greater range of objective measures, collect a vast amount of data, and develop personalized neurorehabilitation strategies based on the patient's presenting characteristics. Our prior work has also shown the feasibility of deploying cost-effective rehabilitation robotics systems in lower-resource contexts (Johnson et al., 2017). Cost-effective rehabilitation robotics systems can bridge healthcare gaps in countries with low-to-middle income economies that are dealing with large populations of patients with impairments and a shortage of rehabilitation professionals. This approach has the potential to positively impact PLWH by building upon the body of work that has been done in the stroke population.

This preliminary cross-sectional study aims to establish objective, robot-based measures of executive function and upper limb motor impairment in PLWH – including a subset with stroke – and assess the strength of the relationship between these robot-based and clinical assessment scores. This study tests three hypotheses to demonstrate the utility of a robotic approach in assessing impairments in PLWH. Given the heterogeneous nature of impairments in this population, the first part of this study tests the hypothesis that robot-based metrics can differentiate subjects with and without moderate executive function or upper-limb motor impairments (H1). The second hypothesis measures the relationship between robot-based metrics and clinical assessments used in PLWH by testing whether robot-based metrics are good predictors of clinical cognitive assessment scores (H2) as well as clinical motor assessment scores (H3). This work lays the foundation for the development of novel neurorehabilitation strategies for PLWH.

4.4 Methods

4.4.1 Subject Population and Procedure

Individuals over the age of 18 years old were recruited from the community through flyers posted at local HIV clinics and organizations. Inclusion criteria for the HIV group consisted of documented HIV status that was ART-treated and virally-suppressed, the ability to ambulate, the ability to comprehend study procedures, and the ability to provide written informed consent. Individuals with neuropathy (i.e. distal symmetric polyneuropathy) were excluded.

Subjects were included in the HIV-stroke subgroup if they met the inclusion criteria for the HIV group and were at least three months removed from a stroke event. HIV-stroke subjects with severe aphasia, visual neglect, or basal ganglia stroke were excluded. Subjects were excluded if they were more than mildly depressed as assessed by the Beck's Depression Inventory – Fast Screen (score ≥ 4) (Beck et al., 2000). Subjects were compensated for time and travel. This protocol was approved by the Internal Review Board of the University of Pennsylvania (Protocol no. 823511).

Subjects underwent a preliminary phone screen to screen for study eligibility. They were then sent a copy of the informed consent to review prior to coming in for their scheduled in-person appointment. After written informed consent was obtained in-person, cognitive and motor assessments were performed. Participants then completed three robot-based tasks in a randomized order with the dominant and non-dominant upper-extremity limb.

4.4.2 Cognitive Assessments

The cognitive assessments consisted of the Color Trails, Digit Symbol–Coding (WAIS-III ®), Montreal Cognitive Assessment (MoCA), and International HIV Dementia Scale (IHDS) (D'Elia et al., 1996; Wechsler, 1981; Nasreddine et al., 2005; Sacktor et al., 2005). These tests have all been administered in PLWH previously to measure neurocognitive im-

pairment (Maj et al., 1993; Sacktor et al., 2005; Ettenhofer et al., 2009; Lawler et al., 2011; Fazeli et al., 2017). These tests were chosen to reflect the cognitive domains commonly affected by HIV.

Color Trails

The Color Trails is a set of two cognitive pencil and paper tests based on the Trail Making Test but does not require knowledge of the alphabet, thus reducing potential bias (D'Elia et al., 1996). Color Trails 1 tests for sustained visual attention and simple sequencing, while Color Trails 2 assesses frontal systems such as selective attention, mental flexibility, visual spatial skills, and motor speed. Performance was measured by the time to complete the task, with a higher time indicating worse performance. These scores were normalized by age, gender, and education (D'Elia et al., 1996).

Digit Symbol – Coding (WAIS-III ®)

The Digit Symbol–Coding (WAIS-III ®) test is another neuropsychological test assessing processing speed (Wechsler, 1981). Subjects use a number-symbol key to copy symbols under a sequence of numbers. Performance was measured by the number of symbols coded in the span of two minutes, with a higher number of symbols copied in the time span representing better performance. Scores were normalized by age, gender, and education.

Montreal Cognitive Assessment (MoCA)

The MoCA is a screening tool to detect impairment in a number of cognitive domains – visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation – and reflects the degree of cognitive impairment in a subject (Nasreddine et al., 2005). A score above 25 out of 30 generally indicates normal cognitive function, while a score below 19 indicates likely moderate cognitive impairment.

An executive function subscore (MoCA-EF) was calculated to serve as a proxy in place of a more extensive neuropsychological assessment of executive function, based on work by

Lam et al. demonstrating good convergent validity between this subscore and standardized neuropsychological tests of executive function (Lam et al., 2013). This subscore, scored out of five points, was calculated from summing the scores from the backward digit span, trail making, word similarities, and 'F'-word list generation tasks (Lam et al., 2013). Lam et al. demonstrated that a cutoff score of 4 had a sensitivity of 0.79 to executive function impairment (Lam et al., 2013).

International HIV Dementia Scale (IHDS)

The IHDS is a screening test for cognitive impairment designed to screen for HAND, with a score below 10 out of 12 indicating potential cognitive impairment (Sacktor et al., 2005). It was developed as a culturally appropriate adaptation of the HIV Dementia Scale. However, the IHDS has not been validated in the stroke population.

4.4.3 Motor Assessments

The motor assessments tested gross motor function, fine motor function, and strength. They consisted of the Box and Blocks Test (BBT), Grooved Pegboard (GP), and grip strength.

Box and Blocks (BBT)

The BBT is a test of gross motor function measuring how many blocks subjects are able to transfer across a partition in one minute, with a higher number of transferred blocks indicating better motor function (Mathiowetz et al., 1985). Scores were normalized by age, gender, and limb. It is typically used to measure reach and grasp function in the stroke population.

Grooved Pegboard (GP)

GP is a common motor assessment in PLWH. It tests fine motor function and dexterity, measuring the amount of time a subject takes to insert all of the grooved pegs into matched holes on a board. Performance was measured by the time to complete the task with longer

Figure 6: The Haptic Theradrive, a one degree-of-freedom rehabilitation robot system used in this study. Image used with permission from (Bui et al., 2017).

times indicating worse fine motor function (Ruff and Parker, 1993). GP data for subjects unable to complete the task were not included in the analysis (one subject).

Grip Strength

Grip strength is measured with a dynamometer. Three trials were taken with each hand, with the average and standard deviation being recorded. Accelerated grip strength decline has been shown in a study of HIV-infected men, which may contribute to decreased life expectancy and lower quality of life with aging (Schrack et al., 2016).

4.4.4 Robot Assessment

Rehabilitation Robot System

The rehabilitation robot used in this study, the Haptic TheraDrive, is a one degree-of-freedom robot for upper limb stroke rehabilitation (Fig. 6) (Johnson et al., 2017). The user operates the TheraDrive by manipulating a vertically-mounted crank handle equipped with force sensors and an optical encoder. For assessment purposes, it is run in a gravity-compensation mode, which uses force sensors as an input to a proportional-integral-derivative (PID) controller to calculate the necessary response by the motor to give the sensation that there is no resistance or assistance while the user manipulates the handle.

Trajectory Tracking Motor Task

The trajectory tracking task is designed to assess upper limb motor performance. A single trial consists of the user moving the crank arm forward and backward to follow a vertically scrolling sinusoidal path for 15 seconds. This task is repeated 15 times after one training trial. The outcome measures include performance error, movement smoothness, and the normalized distance traversed. Performance error was calculated as the root mean square error (RMSE) of the position relative to the displayed trajectory and normalized by the RMSE assuming no movement. A lower performance error indicates better tracking performance. Spectral arc length was used as the measure of smoothness, which has the benefit of being less sensitive to noise compared to other measures of smoothness (Balasubramanian et al., 2015). More negative values of smoothness indicate less smooth movements. Normalized distance traversed was calculated from dividing the total angular distance that the subject traversed by the expected angular distance of the displayed trajectory path. A value closer to 1 reflects that the actual distance traversed matched the expected distance. A lower value could reflect moderate motor impairment, while a higher value could reflect inefficient movement.

N-Back Cognitive Task

The N-back test is commonly used in the cognitive neuroscience field as a test of working memory and working memory capacity (Owen et al., 2005). In this version, the subject is presented with a sequence of numerical digits (1-4) with three different conditions. For the 0-back condition, the easiest condition, the subject indicates when the current stimulus shown on the screen is the number '2.' For the more cognitively-involved 1-back and 2-back conditions, the subject indicates when the current stimulus matches the stimulus shown one stimulus or two stimuli prior, respectively. The subject indicates a match by pressing a button on the TheraDrive. The number then flashes green or red for a correct or incorrect response, respectively. Each subject performed the task with each limb, cycling through the 0-back, 1-back, and 2-back conditions four times for a total of 12 trials, all with different numerical sequences. The first set of trials is used as a training set and not included in the analysis. Ten responses are recorded per trial. Each subject was shown the same set of 12 sequences, with each sequence having a minimum of three button press responses. N-back performance was measured as the total number of correct responses divided by the total number of responses across the trials, resulting in a score ranging from 0 to 1, with a score closer to 1 representing better performance.

Spatial Span Cognitive-Motor Task

The Spatial Span is a test of visuospatial working memory based on the Corsi block-tapping task used in neuropsychological assessments (Kessels et al., 2000). While computerized versions of the Spatial Span exist (Brunetti et al., 2014), this version incorporates an added motor component to concurrently test for arm coordination, visuospatial ability, and working memory. A 3-by-3 grid of tiles is displayed to the user on a computer screen, and a sequence of tiles is shown one tile at a time. The user must operate the TheraDrive to select the tiles in the order shown. If the user successfully repeats the sequence by selecting the correct tiles in order, the next displayed sequence increases in length by one to make the task more difficult. If the user is unsuccessful, the sequence decreases in length by one.

The metrics of interest for the task include the normalized distance traversed, movement smoothness, mean sequence length across all the trials, and performance. Normalized distance traversed and movement smoothness were calculated the same way as in the trajectory tracking task. Mean sequence length is the average number of tiles displayed to the user per trial and reflects the capacity of the subject. Spatial span performance was measured as the total number correct tile matches divided by the total number of tiles shown across the trials. Thus, spatial span performance is a score ranging from 0 to 1, with 1 representing perfect performance.

4.4.5 Data Processing

A one-sample Kolmogorov-Smirnov test for normal distribution was run on the raw continuous demographic, clinical, and robot metrics. Given that the data were not normally distributed, non-parametric Wilcoxon rank-sum tests were conducted to test for differences between HIV and HIV-stroke groups. To adjust for multiple comparisons, separate Bonferroni corrections were applied for the clinical (adjusted p=0.004) and robot-based (adjusted p=0.006) scores.

All robot metrics were Z-score normalized by the entire subject population in this study, resulting in a distribution with a mean of zero and standard deviation of one. This was done to ensure metrics were evenly weighted in the regression analysis.

4.4.6 Functional Subgroup Comparisons

To investigate the first hypothesis that robot-based metrics can differentiate between subjects with and without moderate executive function impairments or upper-limb motor impairment, all study subjects were categorized by their motor and cognitive status based on clinical score cutoffs. The subject population demonstrated motor impairment on both the BBT and GP based on healthy population norms, but BBT was chosen to avoid excluding individual subjects who did not complete the GP. To categorize subjects by motor status, raw BBT scores were normalized by published gender, age, and limb side norms and

converted into a Z-score. A BBT Z-score of -2 and below was used to indicate moderate motor impairment. To categorize subjects by cognitive status, a MoCA-EF score of 3.5 and below was used as a cutoff for likely moderate executive function impairment (Lam et al., 2013). Subjects were then categorized into one of four functional subgroups based on the possible combinations of motor and cognitive status. Because this was done for both dominant and non-dominant limb motor status, subjects could be classified into two different functional subgroup classifications based on differing motor performance between dominant and non-dominant limbs.

For each robot-based metric, a two-way analysis of variance (ANOVA) was conducted where the factors were functional group and limb performance side. To adjust for all pairwise comparisons between functional groups, a Tukey-Kramer honest significance test was applied if the ANOVA was significant. An alpha level of 0.05 was used to establish the significance on all statistical tests.

4.4.7 Multiple Linear Regression

To investigate whether the robot-based metrics were significant predictors of clinical assessment scores, a multiple linear regression approach was used. Bosecker et al. previously used a backward multiple linear approach to identify a set of robot-based metrics reflective of various stroke outcome measures (Bosecker et al., 2010). Rather than start with all of the robot-based metrics and remove terms, a forward stepwise approach was implemented here. This consisted of individually testing each robot-based metric and subsequently adding it to the model only if it was a statistically significant predictor individually. Given the sample size of the subject population, the model was limited to two terms. In order to adjust for the number of predictors used in the model and to compare performance between models with different numbers of predictors, the adjusted R^2 is reported. A power analysis revealed that the linear regression models were powered to detect a minimum R^2 of 0.40 with one predictor and 0.43 with two predictors (n=21, power=0.80, alpha=0.05). A small, medium, and large effect size were defined as an R^2 value of 0.01, 0.25, and 0.50, respectively. The

non-parametric Spearman's rho was also calculated to measure the correlation between predicted and actual clinical scores. All analysis was conducted in Matlab 2019A.

4.5 Results

4.5.1 Subject Population Breakdown

The descriptive statistics for demographic and clinical information for the subject groups (HIV, HIV-stroke, and combined) are presented in Table 2. Twenty-one subjects in total – thirteen male and eight female – participated in the study. Six subjects had a history of stroke. The average age of the HIV and HIV-stroke groups were 56.2±5.4 years old and 54.2±8.1 years old, respectively, while the average age of the entire subject population was 55.5±6.3 years old. Fifteen subjects had 12 or more years of education. Fourteen subjects had MoCA-EF scores below 3.5 and sixteen subjects displayed moderate motor impairment in at least one limb based on BBT scores. There were no statistically significant differences – even at the unadjusted alpha level of 0.05 – between HIV and HIV-stroke groups or between limbs on the clinical motor assessments.

4.5.2 Robot-Based Performance for Example Subjects

Performance data from two sample subjects (Subjects 12 and 18) on the trajectory tracking and spatial span tasks are presented, highlighting the wide variety of impairments seen in the subject population (Fig. 7). Subject 12 is a 56-year-old male HIV subject with moderate cognitive and moderate motor impairment, scoring a 13 on the MoCA and more than two standard deviations below Box and Block population norms on both the dominant and non-dominant limb. Subject 18 is a 49-year-old male HIV-stroke subject with low cognitive and low motor impairment, scoring a 25 on the MoCA and less than two standard deviations below BBT populations norms on both the dominant and non-dominant limb. Qualitatively, Subject 12 demonstrates poorer performance compared to Subject 18 (Fig. 7; left). This can be seen in comparing the average trajectory of each subject to the desired trajectory

Table 2: Subject Demographics and Clinical Scores

Characteristics	HIV-only mean±standard deviation (n=15)	HIV-stroke group mean±standard deviation (n=6)	Subject population mean±standard deviation (n=21)
Age (years old)	56.2 ± 5.4	54.2±8.1	55.5 ±6.3
Gender (Male/Female)	10M/5F	3M/3F	13M/8F
$\geq$ 12 years edu (count)	10	5	15
Color Trails 1 (seconds)	50.27±21.74	41.83±13.48	47.86±20.10
Color Trails 2 (seconds)	125.53±67.30	105.50±22.60	119.81±58.85
Digit Symbol–Coding Score	45.07±12.48	49.67±6.16	46.38±11.24
MoCA (out of 30)	21.47±4.43	23.83 ±2.19	22.14±4.06
MoCA-EF (score out of 5)	2.87±1.31	2.83±0.69	2.86±1.17
IHDS (out of 12)	7.47±2.60	8.00±2.75	7.62±2.66
Dominant BBT (blocks)	54.20±9.73	52.75±11.57	53.79±10.01
Non-Dominant BBT (blocks)	54.40±9.54	47.83±18.62	52.52±12.63
Dominant GP (seconds)	91.60±26.36	102.92±40.55	94.83±30.41
Non-Dominant GP (seconds)	111.53±49.49	160.33±84.63	125.48±63.36
Dominant Grip Strength (kg)	29.56±12.15	30.93±3.22	29.95±10.31
Non-Dominant Grip Strength (kg)	28.08±13.60	22.13±10.97	26.38±12.93

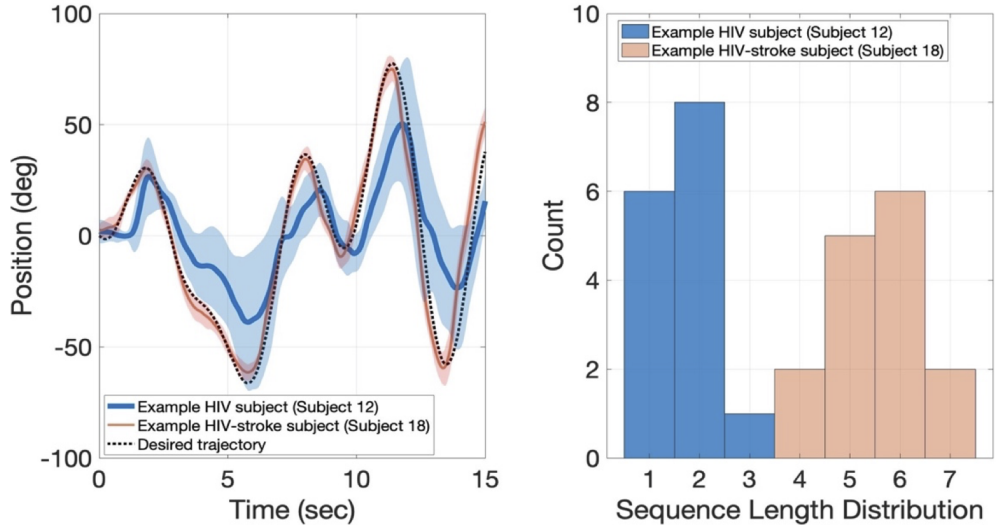

Figure 7: Left: The mean trajectory from the trajectory tracking task is shown for an example HIV (blue) and HIV-stroke (pink) subject. The expected trajectory is shown as a black dotted line. The shaded region represents the standard deviation across all the trials. Right: Histograms showing the distribution of sequence lengths on the spatial span task for the same HIV and HIV-stroke subject.

and the larger variance across the trials as seen in the shaded regions. On the robotic spatial span task, the histogram of sequence lengths across the trials shows a distinct difference between the two subjects (Fig. 7; right).

4.5.3 Raw Robot Performance Metrics

Table 3 shows the mean and standard deviations for the raw robot-based metrics across the HIV-only group, HIV-stroke group, and the entire subject population. The scores for both the dominant and non-dominant limb are reported. There were no statistically significant differences – even at the unadjusted alpha level of 0.05 – in any robot metrics between dominant and non-dominant limbs or between HIV and HIV-stroke groups. However, some qualitative differences are notable. For example, while trajectory tracking performance was similar on both limbs in the HIV-only group, it was noticeably different for the HIV-stroke group, reflecting the presence of motor impairments in the non-dominant limb likely caused by stroke. The spatial span mean sequence length in each group was lower than the reported

Table 3: Group Robot Performance Results by Dominant (D) and Non-Dominant (ND) Limbs (Mean ± Standard Deviation)

Robot Metrics	HIV-only	HIV-Stroke	Subject population
N-back performance	D: 0.86±0.08 ND: 0.87±0.07	0.85±0.07 0.84±0.03	0.86±0.07 0.86±0.06
Trajectory tracking performance	0.34 ±0.15 0.34±0.14	0.44±0.23 0.54±0.37	0.37±0.18 0.39±0.24
Trajectory tracking normalized distance traversed	1.01±0.11 1.04±0.10	1.06±0.07 0.96±0.29	1.02±0.10 1.02±0.17
Trajectory tracking smoothness	-9.19±1.16 -9.56±1.23	-10.26±1.06 -10.41±2.46	-9.50±1.21 -9.80±1.65
Spatial span mean sequence length	2.83±0.97 3.22±0.99	2.97±0.88 3.02±1.32	2.87±0.93 3.16±1.06
Spatial span performance	0.62±0.13 0.69±0.09	0.67±0.06 0.59±0.20	0.63±0.12 0.66±0.13
Spatial span normalized distance traversed	1.57±0.56 1.61±0.35	1.58 ±0.26 1.50±0.29	1.57±0.48 1.59±0.33
Spatial span smoothness	-2.18±0.41 -2.35±0.51	-2.36±0.42 -2.59±0.97	-2.23±0.41 -2.42±0.65

average span of 4.8 in a study that developed a computer-based version of the Corsi block-tapping task (Brunetti et al., 2014). Given that moderate cognitive impairment may mask motor performance, the study subjects were further stratified by their cognitive and motor function.

4.5.4 Stratification by Functional Subgroups (Hypothesis 1)

Figure 8 shows the distribution of the subject population by their functional groups using MoCA-EF subscores and BBT Z-scores to separate subjects by cognitive and motor function, respectively. The number of subjects in each of the four functional groups were the same when using dominant versus non-dominant BBT Z-scores. There were two subjects in the low cognitive and low motor impairment group, five subjects in the low cognitive and

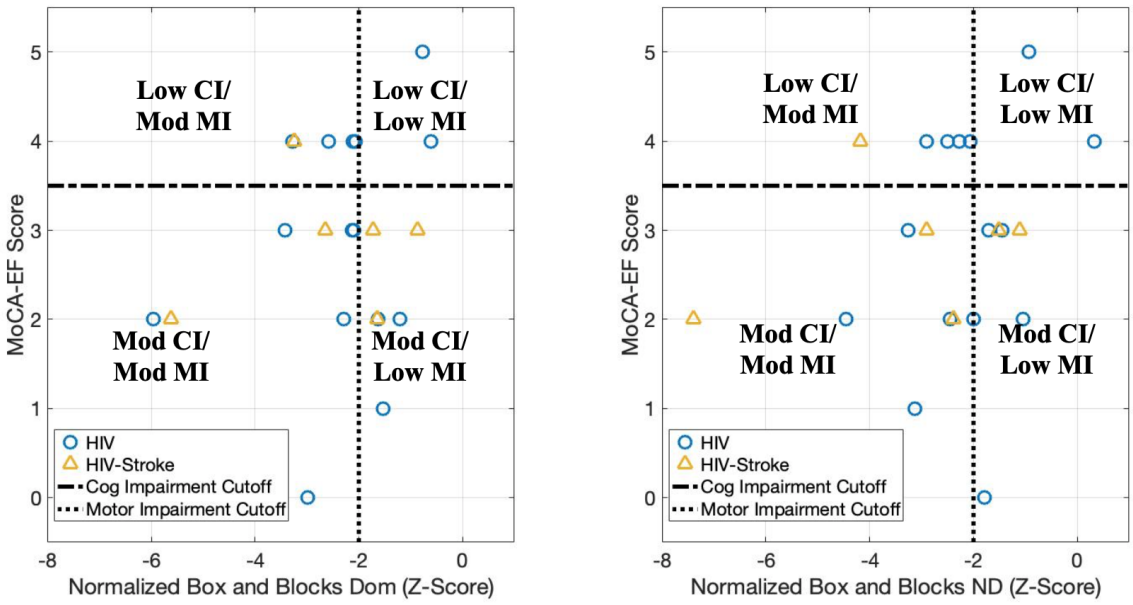

Figure 8: Distribution of subjects by cognitive and motor function, using a score of 3.5 for the MoCA-EF cutoff and -2 as the BBT Z-score cutoff. The left figure is the distribution using the dominant limb BBT scores, while the right is from non-dominant limb BBT scores. (CI=cognitive impairment; MI=motor impairment; mod=moderate)

moderate motor impairment group, six subjects in the moderate cognitive and low motor impairment group, and eight subjects in the moderate cognitive and moderate motor impairment group. Five HIV subjects and one stroke subject had different functional group classifications based on their dominant and non-dominant motor scores.

There was a statistically significant main effect of functional group on N-back performance ($F(3,34) = 6.64$, $p = 0.001$). There was no main effect of limb side or interaction effect. Subjects with low cognitive and low motor impairments performed better on the N-back task compared to subjects with moderate cognitive and moderate motor impairments (0.96 ± 0.01 vs. 0.83 ± 0.05, $p = 0.001$) and subjects with moderate cognitive and low motor impairments (0.96 ± 0.01 vs. 0.85 ± 0.06, $p = 0.01$). Fig. 9 (top) shows the N-back performance scores for each of the functional subgroups.

There was a statistically significant main effect of functional group on trajectory tracking performance error ($F(3,34) = 7.78$, $p = 0.0004$). There was no main effect of limb side or

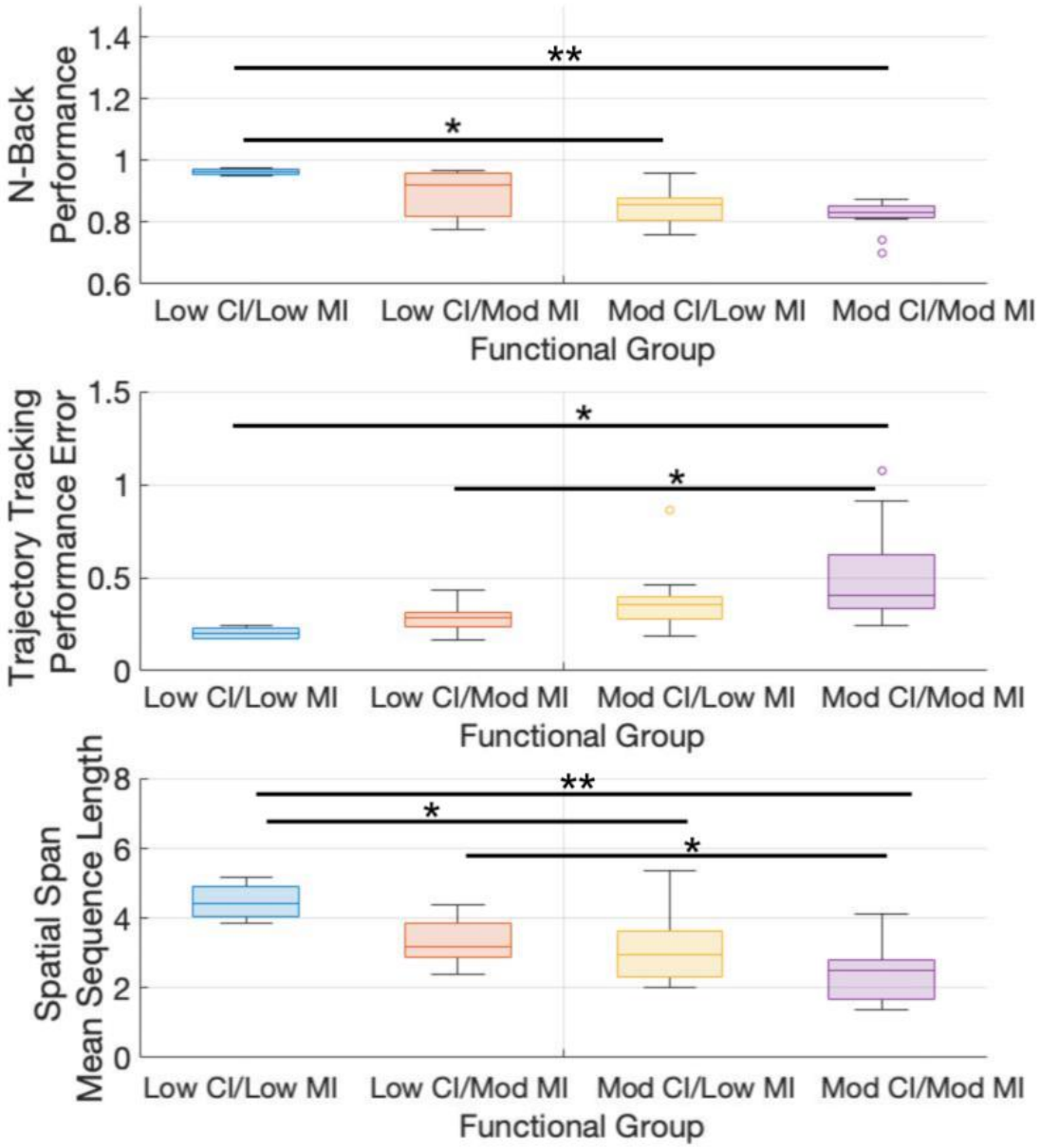

Figure 9: Box plots for each of the functional subgroups on N-back performance (top), trajectory tracking performance error (middle), and spatial span mean sequence length (bottom). CI=cognitive impairment; MI=motor impairment (*: $p < 0.05$, **: $p < 0.005$ after correcting for multiple comparisons)

interaction effect. Subjects with moderate cognitive and moderate motor impairment had significantly higher performance error scores compared to subjects with low cognitive and moderate motor impairment (0.50± 0.25 vs. 0.28±0.08, $p = 0.04$) and subjects with low cognitive and low motor impairment (0.50± 0.25 vs. 0.20±0.04, $p = 0.04$). Fig. 9 (middle) shows the trajectory tracking performance for each of the functional groups.

There was a statistically significant main effect of functional group on spatial span mean sequence length ($F(3, 34) = 8.23$, $p = 0.0004$). There was no main effect of limb side or interaction effect. Subjects with low cognitive and low motor impairment had longer average sequence lengths compared to subjects with moderate cognitive and moderate motor impairments (4.48±0.56 vs. 2.39±0.74, $p = 0.0004$) and subjects with moderate cognitive and low motor impairments (4.48±0.56 vs. 3.12±1.00, $p = 0.04$). Subjects with low cognitive and moderate motor impairment also had longer average sequence lengths compared to subjects with moderate cognitive and moderate motor impairment (3.31±0.70 vs. 2.39±0.74, $p = 0.04$). Fig. 9 (bottom) shows the spatial span mean sequence length for each of the functional subgroups.

There was a statistically significant main effect of functional group on spatial span performance, but there were no significant differences between any of the functional subgroups after correcting for multiple comparisons.

There were no statistically significant main or interaction effects for trajectory tracking normalized distance traversed, trajectory tracking smoothness, spatial span normalized distance traversed, or spatial span smoothness scores.

4.5.5 Estimating Clinical Cognitive Scores (Hypothesis 2)

Dominant Limb Predictors

Fig. 10 shows the multiple linear regression models for each of the clinical cognitive assessments using dominant limb robot-based metrics as the predictors.

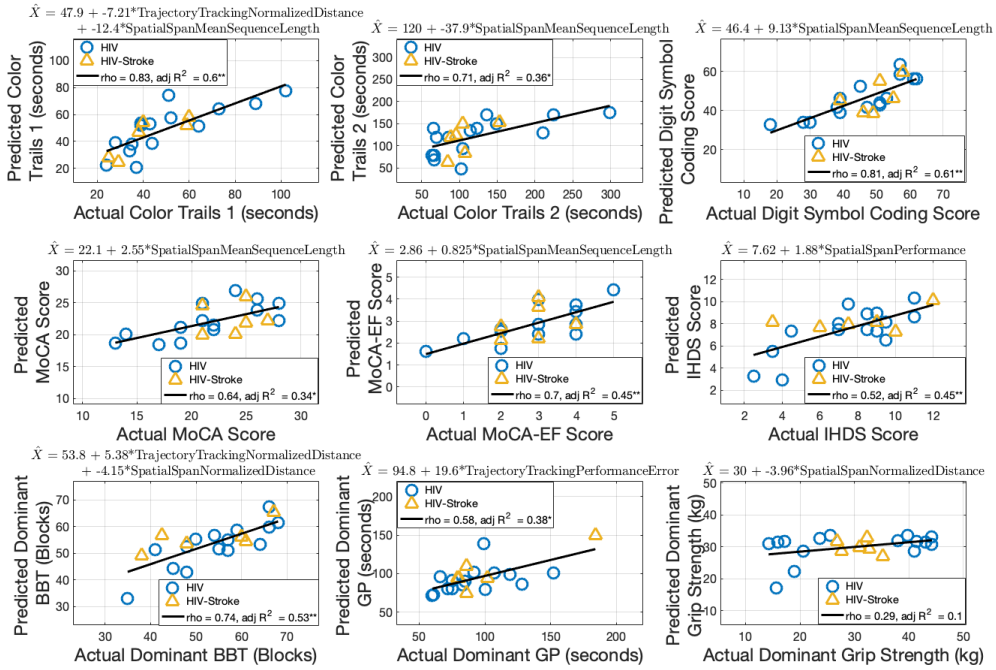

Figure 10: Multiple linear regression for clinical assessments using dominant limb robot-based metrics. The robot-based predictors for each model are included in the equation at the top of each subplot. Spearman's rho and adjusted R^2 are shown. (*: $p < 0.05$, **: $p < 0.001$)

Color Trails 1 was predicted by a combination of trajectory tracking normalized distance traversed and spatial span mean sequence length ($p = 0.03$ and 0.001, respectively). The robot-based predictors accounted for 60% of the variance in the model, and the predicted scores strongly correlated with actual Color Trails 1 scores (rho = 0.83, $p = 3.33\times10^{-6}$; adjusted $R^2 = 0.60$, $p = 1.13\times10^{-4}$).

Color Trails 2 was predicted by spatial span mean sequence length ($p = 0.002$). The robot-based predictor accounted for 36% of the variance in the model, and the predicted scores strongly correlated with actual Color Trails 2 scores (rho = 0.71, $p = 3.34\times10^{-4}$; adjusted $R^2 = 0.36$, $p = 0.002$).

Digit Symbol Coding was predicted by spatial span mean sequence length (p=1.83×10^{-5}). The robot-based predictor accounted for 61% of the variance in the model, and the predicted scores strongly correlated with actual Digit Symbol Coding scores (rho=0.81, $p =$

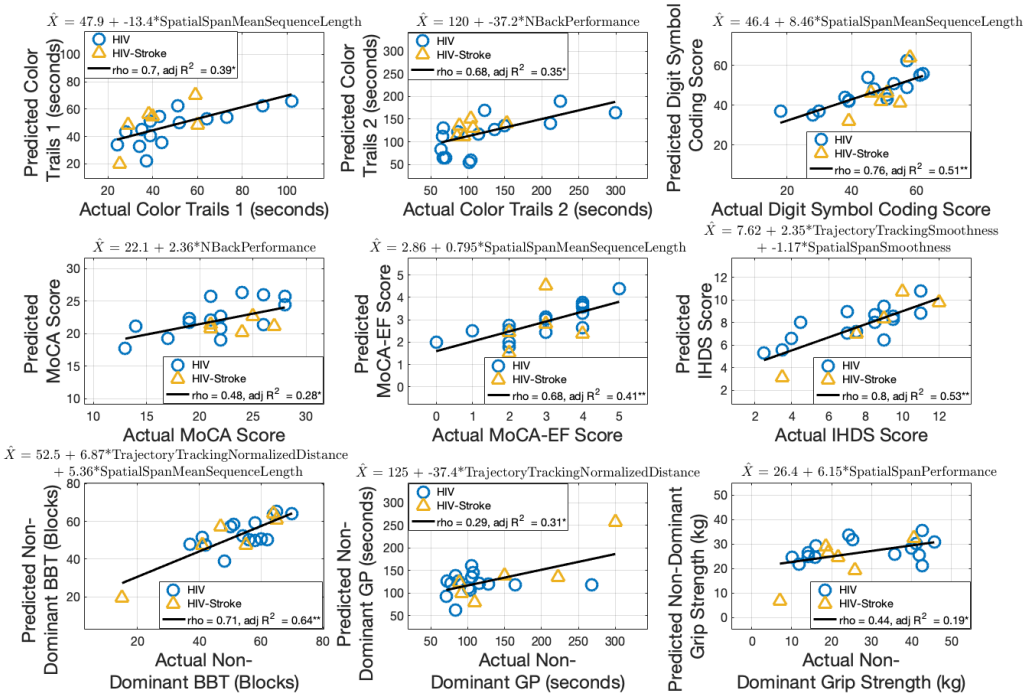

Figure 11: Multiple linear regression for clinical assessments using non-dominant limb robot-based metrics. The robot-based predictors for each model are included in the equation at the top of each subplot. Spearman's rho and adjusted R^2 are shown. (*: $p < 0.05$, **: $p < 0.001$)

7.06×10^{-6}; adjusted $R^2 = 0.61$, $p = 1.83\times 10^{-5}$).

MoCA was predicted by spatial span mean sequence length ($p = 0.003$). The robot-based predictor accounted for 34% of the variance in the model, and the predicted scores moderately correlated with actual MoCA scores (rho=0.64, $p = 0.002$; adjusted $R^2 = 0.34$, $p = 0.003$).

MoCA-EF was predicted by spatial span mean sequence length ($p = 5.30\times10^{-4}$). The robot-based predictor accounted for 45% of the variance in the model, and the predicted scores strongly correlated with actual MoCA-EF scores (rho=0.70, $p = 4.07\times10^{-4}$; adjusted $R^2 = 0.45$, $p = 5.30\times10^{-4}$).

IHDS was predicted by spatial span performance ($p = 5.31\times10^{-4}$). The robot-based predictor accounted for 45% of the variance in the model, and the predicted scores moderately correlated with actual IHDS scores (rho=0.52, $p = 0.02$; adjusted $R^2 = 0.45$, $p = 5.30\times10^{-4}$).

Non-Dominant Limb Predictors

Fig. 11 shows the linear regression models for each of the clinical cognitive assessments using non-dominant limb robot-based metrics as the predictors.

Color Trails 1 was predicted by spatial span mean sequence length ($p = 0.001$). The robot-based predictor accounted for 39% of the variance in the model, and the predicted scores strongly correlated with actual Color Trails 1 scores (rho=0.70, $p = 3.73\times10^{-4}$; adjusted $R^2 = 0.39$, $p = 0.001$).

Color Trails 2 was predicted by N-back performance ($p = 0.003$). The robot-based predictor accounted for 35% of the variance in the model, and the predicted scores moderately correlated with actual Color Trails 2 scores (rho=0.68, $p = 7.79\times10^{-4}$; adjusted $R^2 = 0.35$, $p = 0.003$).

Digit Symbol Coding was predicted by spatial span mean sequence length ($p=1.51\times10^{-4}$).

The robot-based predictor accounted for 51% of the variance in the model, and the predicted scores strongly correlated with actual Digit Symbol Coding scores (rho=0.76, $p = 6.38\times10^{-5}$; adjusted $R^2 = 0.51$, $p = 1.51\times10^{-4}$).

MoCA was predicted by N-back performance ($p = 0.007$). The robot-based predictor accounted for 28% of the variance in the model, and the predicted scores weakly correlated with actual MoCA scores (rho=0.48, $p = 4.07\times10^{-4}$; adjusted $R^2 = 0.28$, $p = 0.007$).

MoCA-EF was predicted by spatial span mean sequence length (p=0.001). The robot-based predictor accounted for 41% of the variance in the model, and the predicted scores moderately correlated with actual MoCA-EF scores (rho=0.68, $p = 7.00\times10^{-4}$; adjusted $R^2 = 0.41$, $p = 0.001$).

IHDS was predicted by a combination of trajectory tracking smoothness and spatial span smoothness (p=9.76×10^{-5} and 0.02, respectively). The robot-based predictors accounted for 53% of the variance in the model, and the predicted scores strongly correlated with actual IHDS scores (rho=0.80, $p = 1.46\times10^{-5}$; adjusted $R^2 = 0.53$, $p = 4.12\times10^{-4}$).

4.5.6 Estimating Clinical Motor Scores (Hypothesis 3)

Dominant Limb Predictors

Fig. 10 shows the linear regression models for each of the clinical motor assessments using dominant limb robot-based metrics as the predictors.

Dominant limb BBT was predicted by a combination of trajectory tracking normalized distance traversed and spatial span normalized distance traversed ($p = 0.003$ and 0.02, respectively). The robot-based predictors accounted for 53% of the variance in the model, and the predicted scores strongly correlated with actual BBT scores (rho=0.74, $p = 1.46\times10^{-4}$; adjusted $R^2 = 0.53$, $p = 4.72\times10^{-4}$).

Dominant limb GP was predicted by trajectory tracking performance ($p = 0.002$). The robot-based predictor accounted for 38% of the variance in the model, and the predicted

scores moderately correlated with actual GP scores (rho=0.58, $p = 0.006$; adjusted $R^2 = 0.38$, $p = 0.002$).

Dominant limb grip strength was predicted by spatial span normalized distance traversed, but it was neither a significant predictor nor correlated to actual grip strength scores (rho=0.29, $p = 0.20$; adjusted $R^2 = 0.10$, $p = 0.09$).

Non-Dominant Limb Predictors

Fig. 11 shows the linear regression models for each of the clinical motor assessments using non-dominant limb robot-based metrics as the predictors.

Non-dominant limb BBT was predicted by a combination of trajectory tracking normalized distance traversed and spatial span mean sequence length (p=0.002 and 0.01, respectively). The robot-based predictors accounted for 64% of the variance in the model, and the predicted scores strongly correlated with actual BBT scores (rho=0.71, $p = 3.41\times10^{-4}$; adjusted $R^2 = 0.64$, $p = 4.44\times10^{-5}$).

Non-dominant limb GP was predicted by trajectory tracking normalized distance traversed (p =0.005). The robot-based predictor accounted for 31% of the variance in the model while the predicted scores were not significantly correlated with actual GP scores (rho=0.29, $p = 0.21$; adjusted $R^2 = 0.31$, $p = 0.005$).

Non-dominant limb grip strength was predicted by spatial span performance ($p = 0.03$). The robot-based predictor accounted for 19% of the variance in the model, and the predicted scores weakly correlated with actual grip strength scores (rho=0.44, $p = 0.04$; adjusted $R^2 = 0.19$, $p = 0.03$).

4.6 Discussion

Gross motor impairments are prevalent in PLWH

This study aimed to use a robot-based approach to explore objective measures of cognitive and motor impairment in HIV and HIV-stroke populations. The HIV and HIV-stroke groups displayed no significant differences in clinical or robot-based scores. Subjects in both the HIV and HIV-stroke groups demonstrated mild to moderate impairment in executive function, information processing, and upper limb fine and gross motor domains relative to published population normal performance values in uninfected populations. These results are consistent with previous research demonstrating impairments in these domains in PLWH (Antinori et al., 2007; Pullen et al., 2014; Fellows et al., 2014).

We found it notable that the HIV-only group demonstrated not only fine motor impairment as previously reported in the literature(Wilson et al., 2013; Kronemer et al., 2017; Lawler et al., 2011; Robinson-Papp et al., 2019), but also gross upper limb motor impairment. Gross motor impairment has generally been considered a pre-ART era manifestation of HIV infection, and studies since then have focused on the fine motor deficits that result from HIV (Wilson et al., 2013). Moderate bilateral gross motor impairment, as measured by the BBT and adjusted to healthy population norms, was present in 7 of 15 subjects in the HIV group. The prevalence of moderate bilateral fine motor impairment in the HIV-only subjects in this study (5 out of 15), as measured by the GP, is higher than what was reported in Wilson et al. (2 out of 12) in a group of PLWH with a similar average age of 57.9 years old (Wilson et al., 2013). These results suggest that gross upper limb motor impairments may be an overlooked effect of chronic HIV and that the BBT can be used to identify these impairments as an alternative to the GP. This approach could be useful when examining patients with both HIV and stroke in particular, when motor impairments may be more prevalent (Elicer et al., 2018).

Robot-based metrics capture differences in functional subgroups

A wide range of impairments was observed in the subject population and there was no clear separation between the HIV and HIV-stroke groups on either the clinical assessments or robot-based metrics. As such, subjects were classified into one of four functional groups by their cognitive and motor performance. The results provide evidence in support of the study's first hypothesis that robot-based metrics can differentiate subjects with and without moderate executive function or upper-limb motor impairments.

Subjects with moderate executive function impairment, regardless of motor status, performed worse on the N-back compared to subjects with low cognitive and low motor impairment. These results suggest the robot-based N-back can be used to isolate executive function deficits. This is consistent with previous findings that the paper-based N-back test, although specifically a test for working memory, engages executive function domains impacted by HIV (Cohen et al., 2018).

Subjects with moderate executive function and moderate gross motor impairments performed worse on the robot-based trajectory tracking task compared to subjects with low cognitive impairment, regardless of motor status. This suggests that there might be a cognitive component to the trajectory tracking task that exacerbates performance error in the presence of executive function impairments.

Similarly to the robot-based N-back, subjects with moderate executive function impairment, regardless of motor status, had shorter sequences on the robot-based spatial span task compared to subjects with low cognitive and low motor impairment. Additionally, subjects with low cognitive and moderate motor impairment performed better than subjects with moderate cognitive and moderate motor impairment. These results suggest that a robot-based spatial span task can be used to detect executive function impairment, even in the presence of moderate motor impairment.

Together, these robot-based metrics provide a set of measures that are able distinguish

between certain functional groups. Going forward, these represent a potential set of objective metrics that can be used to track longitudinal performance that relate to functional status in PLWH, stroke, and other conditions presenting with both motor and cognitive impairments.

Robot-based metrics relate to HIV-related clinical assessments

To our knowledge, we are the first group to explore objective robot-based measures of both motor and cognitive impairments in PLWH. This study is a first step in developing more targeted neurorehabilitation strategies for PLWH exhibiting both motor and cognitive decline. The results support the study's second hypothesis and show that both individual and linear combinations of robot-based metrics can successfully estimate clinical cognitive scores. The regression models for Color Trails 1, Digit Symbol–Coding, MoCA–EF and IHDS (adjusted R^2=0.41–0.60) — excluding the non-dominant limb model for Color Trails 1 – performed the best, exceeding the effect size for which the study was powered. The robot-based measures also demonstrated statistically significant relationships with Color Trails 2 and MoCA.

This is one of the first studies to establish objective robot-based measures that relate to Digit Symbol–Coding, MoCA-EF subscores, or IHDS. Given that the Digit Symbol–Coding, MoCA-EF, and IHDS look at more specific cognitive domains related to executive function, this suggests the potential of robot-based metrics to identify more specific impairments going forward that are relevant to PLWH. Notably, the robot-based metrics that best predicted these clinical scores were consistent with the robot-based metrics that showed differences between functional groups.

Two other studies that examine the relationship between robotic metrics and MoCA scores in stroke and traumatic brain injury populations reported correlation coefficients ranging between 0.49 and 0.65 that are similar to the values observed in this study (rho=0.48–0.64) (Bourke et al., 2016; Logan et al., 2018).

The results provide evidence that robot-based metrics can successfully estimate clinical motor scores in PLWH. The dominant and non-dominant limb models for BBT scores (adjusted R^2=0.53 and 0.64, respectively) performed the best, exceeding the effect size for which the study was powered and demonstrating strong correlations between predicted and actual scores. Using a multiple linear regression with eight robotic predictors derived from three tasks, Bosecker et al. demonstrated correlation coefficients between estimated and actual scores for the Fugl-Meyer, Motor Status Score, Motor Power Scale, and Modified Ashworth Scale of 0.42–0.80 on training models (Bosecker et al., 2010). While the clinical motor metrics differed from those used in this study, these values were similar for the dominant and non-dominant BBT and GP models (rho=0.31–0.74, respectively) with fewer predictors.

While computerized versions of the spatial span exist (Brunetti et al., 2014), the robotic aspect implemented in this study allows for kinematic measures to be observed that are reflective of motor function. This enables more detailed study of the interactions between cognitive and motor domains. The utility of this task can be seen by the high prevalence of metrics from this task demonstrating strong relationships with both cognitive and motor clinical scores.

Relevance to HAND assessment, neurorehabilitation, global health, and robotics

Taken together, these results show the potential clinical utility of a robotics-based approach to assess motor and cognitive function in PLWH. Due to the involved nature of performing a complete HAND assessment, other alternatives have been explored to capture HIV-related neurocognitive impairments. For example, Fogel et al. used a stepwise multiple linear regression approach to predict a global deficit score (GDS) from a set of 24 metrics extracted from basic medical history in an older HIV population with an average age of 61.1±4.6 years, which was similar to the average of the HIV-only population in this study (56.2±5.4 years old) (Fogel et al., 2015). The GDS was calculated from a set of neuropsychologi-

cal tests encompassing working memory and memory, motor, information processing, and learning domains that overlapped with some of the assessments in this study – specifically the GP, Trail Making A (equivalent to the Color Trails 1), and Digit Symbol–Coding. The ultimate three-term model from the Fogel et al. study had a R^2 of 0.29, which is weaker compared to the R^2 values for the Color Trails 1,Digit Symbol–Coding, and GP models in this study (R^2=0.31–0.60) (Fogel et al., 2015). In Botswana, a lower-resource setting, a six-part neurocognitive battery, which also utilizes many of the same assessments as this study, was used to identify impairments in cognitive-motor areas in PLWH (Lawler et al., 2011).

From a clinical rehabilitation perspective, increasing access to effective rehabilitation interventions and enhancing outcome measurement have been identified as research priorities in HIV, disability, and rehabilitation (O'Brien et al., 2014). There is a need to develop interventions addressing the rapid aging and frailty associated with HIV to reduce disparities in health outcomes that can compound in the presence of other comorbidities or complications. No gold standard exists to capture the relationship between cognitive impairment and physical frailty as it relates to HIV (Piggott et al., 2016). While a limited number of studies have shown that physical exercise can induce improvements in physical, cognitive, and emotional wellbeing in both HIV and non-HIV populations, there is a need for further work to understand what impact exercise – including robot-based exercise – might have on the aging immune system in PLWH. A benefit to the objective quantification used in this study is the ability to track changes during the course of rehabilitation with specific metrics. This approach can be practical within a neurorehabilitation context because the metrics are reflective of clinically-relevant tests and can be administered in a less time-intensive way.

From a global health perspective, this technology-based approach provides a possible scalable strategy that is sensitive to subtle signs of functional decline. With more affordable rehabilitation robot systems becoming increasingly available, this approach has the potential to meet a huge rehabilitation need in lower resource settings where the capacity to supply

additional rehabilitation professionals is lacking but the prevalence of non-communicable diseases necessitating rehabilitation is increasing (Johnson et al., 2017). This would be valuable particularly when medical history may be lacking or harder to assess. This preliminary work lays the groundwork for identifying specific impairments and developing HIV-specific neurorehabilitation strategies to address the various cognitive and motor impairments associated with aging with HIV. Our group is currently exploring this in Botswana.

From a robotics perspective, this study expands the application of rehabilitation robotics beyond stroke to PLWH and those living with cognitive impairments. Given that neurocognitive impairment is associated with instrumental ADL function (Johs et al., 2017), assessments and treatments should reflect the integration of both motor and cognitive domains that are often assessed in isolation. Like other robotic studies, large effect sizes were observed in this study, which can significantly reduce the sample size needed for clinical trials going forward (Krebs et al., 2014). This study also shows that clinical measures can be estimated from both limbs, which can be helpful in avoiding confounding factors, such as the presence of unilateral motor impairment that could result from stroke. Although these results do not provide enough information to generalize to other neurological conditions, this approach allows for future studies on other neurological conditions because it is rooted in standard clinical assessments used in other populations beyond HIV and stroke.

Study Limitations

Given the small sample size, lack of control group (either non-HIV healthy control or non-HIV stroke group), and predominance of Black persons within the HIV group, we may not be able to fully generalize these results. Although, the sample population is small, we were able to see significant differences and the population was reflective of the aging HIV population in the U.S. While we observed strong correlations between robot-based measures and clinical cognitive and motor assessments relevant to the HIV population, correlation studies are susceptible to the distribution of the data across the span of the predictor variables. While we had adequate distribution across many variables, we were

not able to get an even distribution across functional groups, which could have biased the analysis. Despite these limitations, further studies with a larger sample size and a longitudinal evaluation of this approach is warranted.

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CHAPTER 5 : ANALYSIS OF KINEMATIC AND NON-KINEMATIC MEASURES ON A COGNITIVE-MOTOR ROBOTIC ASSESSMENT TASK

5.1 Contribution

This chapter extends on work done in the previous chapter to assess the utility of different metrics derived from a robot-based cognitive-motor task.

5.2 Abstract

Motor dysfunction is often overlooked but continues to persist in the HIV population. There is a lack of tools to characterize motor deficits in people living with HIV. In this study, we examine the utility of kinematic measures derived from a cognitive-motor task performed on a robot to determine if these metrics are sensitive to differences in motor function. We examined a set of kinematic and non-kinematic metrics that have been used in the stroke rehabilitation field and how they vary by the individual's motor and cognitive status, the difficulty of task, and the limb side used to perform the task. Our results showed that non-kinematic metrics were more sensitive to differences between functional groups, while normalized speed was the only kinematic metric sensitive to functional group differences. These results have implications on the design of assessment strategies for people living with HIV going forward.

5.3 Introduction

In the United States, over half of people living with HIV (PLWH) are over the age of 50 (Gant et al., 2020). While antiretroviral therapy has significantly increased the lifespan of PLWH, this has resulted in a rapidly aging population managing a variety of HIV-associated comorbidities, coinfections, and complications for which comprehensive solutions are needed

(Pahwa et al., 2021).

HIV-associated neurocognitive disorders (HAND) continue to persist in the HIV population, with the majority of cases consisting of the milder phenotypes —asymptomatic neurocognitive impairment and mild neurocognitive disorder — rather than the severe cases of HIV-associated dementia that were more prevalent before the introduction of antiretroviral therapy. While a big focus has been on the cognitive domains impacted by HIV, multiple recent studies have demonstrated the persistence of motor dysfunction in PLWH (Elicer et al., 2018; Tierney et al., 2019; Robinson-Papp et al., 2019). In a study by Tierney et al., older adults with HIV demonstrated extrapyramidal motor signs that were associated with dependence on activities of daily living and decreased quality of life (Tierney et al., 2019). Motor dysfunction was observed in 69% of participants in another study, with gait abnormality, impaired coordination, and strength as the most commonly reported Robinson-Papp et al. (2019). A different study demonstrated that motor function declined over time in PLWH (Elicer et al., 2018). In more extreme cases of motor impairment, HIV has been shown to be an independent risk factor for stroke and impacts recovery after stroke, resulting in worse performance on activities of daily living one month after discharge compared to stroke survivors without HIV (Augustyn et al., 2020).

Current approaches to assessing HIV-related impairment often examine individual domains in isolation (Schouten et al., 2014). However, it has been shown that HAND scores and biomarkers of HIV do not predict cognitive or motor performance consistently (Anderson et al., 2016). The current methods to assess HAND as outlined by the Frascati criteria do not include extensive examination of motor function (Antinori et al., 2007). The HIV Motor Scale is a validated tool that captures motor abnormalities and is associated with cognitive impairment (Robinson-Papp et al., 2008). While these motor assessments can be used in routine neurologic examination, they may lack the sensitivity to detect early signs of motor decline. Kronemer et al. demonstrated that PLWH who performed normally on clinical assessments of motor and cognitive function failed to maintain performance on a multitask

that engaged cognitive and motor domains simultaneously (Kronemer et al., 2017).

A direct consequence of the lack of tools to characterize motor deficits in PLWH is the paucity of rehabilitation strategies to address these challenges. Despite calls and frameworks for including rehabilitation into the long-term care of PLWH, there still remains a gap in implementing and educating clinicians and patients (O'Brien et al., 2010, 2014; O'Brien et al., 2014). Our current work aims to address this gap by applying rehabilitation engineering approaches to characterize motor deficits in PLWH.

One advantage of using a robotic system in rehabilitation is the ability to analyze motor performance through kinematic data recorded by the robot. These measures provide an objective and repeatable way to assess performance and identify more subtle signs of abnormal function. For example, point-to-point motions that require an individual to navigate from one location to another in a discrete movement demonstrate predictable speed profiles that follow a bell curve (Flash and Hogan, 1985). Different kinematic metrics have been explored in rehabilitation robotics, with a large focus on measuring motor performance in the stroke population (Do Tran et al., 2018). Examples of such metrics include mean and peak velocity, acceleration, and various methods of measuring movement smoothness. These measures have been shown to be good markers of motor recovery in stroke and relate to clinical measures of motor function (Bosecker et al., 2010; Balasubramanian et al., 2012).

To date, very little work has been done to characterize the kinematics of upper limb movement in PLWH. In this study, we examine both kinematic and non-kinematic measures across varying levels of cognitive and motor function that are present in PLWH. In previous work, we demonstrated a novel application of a cognitive-motor task performed on a rehabilitation robot system to detect differences between PLWH with varying levels of cognitive and motor function (Bui et al., 2021). While that work identified overall performance metrics that detected differences from a cognitive standpoint and strongly related to clinical assessments of cognitive function, it did not fully explore the utility of different metrics derived from the task. Our hypothesis is that kinematic measures from the task are sensitive

to differences between motor and cognitive impairment. Additionally, we anticipate this relationship to be dependent on the complexity of the task.

5.4 Methods

The study population, procedure, clinical assessment, and robotic assessment are described in a previous paper (Bui et al., 2021). A summary of those methods is provided here.

5.4.1 Study Population and Procedure

Individuals over the age of 18 years old were recruited from the community through flyers posted at local HIV clinics and organizations. Inclusion criteria for the HIV group consisted of documented HIV status that was ART-treated and virally-suppressed, the ability to ambulate, the ability to comprehend study procedures, and the ability to provide written informed consent. Individuals with neuropathy (i.e. distal symmetric polyneuropathy) were excluded. This protocol was approved by the Internal Review Board of the University of Pennsylvania (Protocol no. 823511). After informed consent was obtained, individuals then completed a clinical assessment and robotic assessment.

Twenty-one individuals in total – thirteen male and eight female – participated in the study. Six subjects had a history of stroke. The average age of the HIV and HIV-stroke groups were 56.2±5.4 years old and 54.2±8.1 years old, respectively, while the average age of the entire subject population was 55.5±6.3 years old. Fifteen subjects had 12 or more years of education.

5.4.2 Clinical Assessment

A set of cognitive and motor assessments was administered to each individual. The cognitive assessments consisted of the Color Trails, Digit Symbol–Coding (WAIS-III ®), Montreal Cognitive Assessment (MoCA), and International HIV Dementia Scale (IHDS) (D'Elia et al., 1996; Wechsler, 1981; Nasreddine et al., 2005; Sacktor et al., 2005). These tests have

all been administered in PLWH previously to measure neurocognitive impairment (Maj et al., 1993; Sacktor et al., 2005; Ettenhofer et al., 2009; Lawler et al., 2011; Fazeli et al., 2017). These tests were chosen to reflect the cognitive domains commonly affected by HIV.

An executive function subscore (MoCA-EF) was calculated to serve as a proxy in place of a more extensive neuropsychological assessment of executive function, based on work by Lam et al. demonstrating good convergent validity between this subscore and standardized neuropsychological tests of executive function (Lam et al., 2013). This subscore, scored out of five points, was calculated from summing the scores from the backward digit span, trail making, word similarities, and 'F'-word list generation tasks (Lam et al., 2013). Lam et al. demonstrated that a cutoff score of 4 had a sensitivity of 0.79 to executive function impairment (Lam et al., 2013).

The motor assessments tested gross motor function, fine motor function, and strength. They consisted of the Box and Blocks Test (BBT), Grooved Pegboard (GP), and grip strength. Scores were normalized by age, gender, and limb. There were no statistically significant differences – even at the unadjusted alpha level of 0.05 – between HIV and HIV-stroke groups or between limbs on the clinical assessments.

5.4.3 Robot Assessment

Rehabilitation Robot System

The rehabilitation robot used in this study, the Haptic TheraDrive, is a one degree-of-freedom robot for upper limb stroke rehabilitation (Johnson et al., 2017). The user operates the TheraDrive by manipulating a vertically-mounted crank handle equipped with force sensors and an optical encoder. For assessment purposes, it is run in a gravity-compensation mode, which uses force sensors as an input to a proportional-integral-derivative (PID) controller to calculate the necessary response by the motor to give the sensation that there is no resistance or assistance while the user manipulates the handle.

Spatial Span Cognitive-Motor Task

The Spatial Span is a test of visuospatial working memory based on the Corsi block-tapping task used in neuropsychological assessments (Kessels et al., 2000). While computerized versions of the Spatial Span exist (Brunetti et al., 2014), this version incorporates an added motor component to concurrently test for arm coordination, visuospatial ability, and working memory. A 3-by-3 grid of tiles is displayed to the user on a computer screen, and a sequence of tiles is shown one tile at a time. Each tile corresponds to a 20-degree angular range of motion on the TheraDrive. The user must operate the TheraDrive to select the tiles in the order shown. If the user successfully repeats the sequence by selecting the correct tiles in order, the next displayed sequence increases in length by one to make the task more difficult. If the user is unsuccessful, the sequence decreases in length by one. Each individual completed 15 trials with each limb. The sequence length of each trial was recorded as a non-kinematic measure of performance.

Completing the sequence can be represented as a series of point-to-point movements ranging from 20-180 degrees of angular motion. The kinematic measures of interest include normalized distance traversed, average speed, and movement smoothness. Normalized distance traversed was calculated by dividing the total angular distance traveled by the expected distance over one trial.

Three different measures of smoothness were examined in this task. The first was to measure the average number of peaks in the speed profile for each point-to-point submovement in one trial, with a higher number indicating less smooth movement. This metric has been shown to translate to activities of daily living among older adults (Gulde and Hermsdörfer, 2017). The second measure of smoothness was spectral arc length, which was also calculated for each point-to-point submovement in one trial and averaged to provide one measure per trial (Balasubramanian et al., 2015). This measure has the benefit of being less sensitive to changes in signal-to-noise ratio compared to other measures of smoothness and accounts for varying speeds of performance (Balasubramanian et al., 2015). The last measure of

smoothness was normalized speed, which was calculated by dividing the average speed by the peak speed within one trial(Rohrer et al., 2002). For all smoothness metrics, a value closer to zero represents smoother movement.

Each trial was then categorized by the task difficulty and limb side. To examine the effects of task difficulty, each sequence length was assigned one of three task difficulty levels. The easy difficulty consisted of sequence lengths of one and two. The medium difficulty consisted of sequence lengths of three and four. The hard difficulty consisted of sequence lengths of five and six. Multiple trials completed at the same difficulty and limb were averaged. Given the adaptive nature of the task, some individuals did not perform all levels of difficulty.

5.4.4 Statistical Analysis

For the sequence length metrics, a two-sample non-parametric Kolmogorov-Smirnoff test was used to test if the distributions between two functional groups were significantly different from each other. To correct for multiple comparisons, the original alpha value was divided by the number of comparisons performed (adjusted alpha = 0.008). To examine for differences across trials, a repeated measures ANOVA was run on the sequence lengths with the functional group as a between-subjects factor and trial number as a within-subjects factor.

A multi-way ANOVA was performed on each metric with functional group, limb, and difficulty as the factors. To adjust for all pairwise comparisons between functional groups, a Tukey-Kramer honest significance test was applied if the ANOVA was significant. Group means and standard error are reported unless specified otherwise. An alpha level of 0.05 was used to establish the significance on all statistical tests. Analysis was done in Matlab.

5.5 Results

5.5.1 Sample Individual Performance Data

Performance data from one sample individual from each functional group are shown in Fig. 12. The top plot shows the position trace of the four individuals, while the bottom plot shows the filtered speed profile. Each individual correctly performed the same sequence with their non-dominant limb. The no impairment example (blue trace) is a 58-year-old male with a non-dominant BBT Z-score of 0.33 and a MoCA-EF score of 4 out of 5. The motor-only example (red trace) is a 50-year-old male with a non-dominant BBT Z-score of -2.07 and a MoCA-EF score of 4 out of 5. The cognitive-only impaired example (yellow trace) is a 62-year-old male with a non-dominant BBT Z-score of 0.07 and a MoCA-EF score of 2 out of 5. The motor-and-cognitive impaired example (purple trace) is a 64-year-old male with a non-dominant BBT Z-score of -2.90 and a MoCA-EF score of 3 out of 5.The no impairment individual (blue trace) demonstrated the a higher peak velocity and smoother movement compared to the other individuals. This can be seen in the fewer number of peaks in the speed plot.

5.5.2 Non-Kinematic Results

The relative probability distribution of sequence lengths across all trials by functional group can be seen in Fig. 13. A two-sample non-parametric Kolmogorov-Smirnoff test showed that the distribution for the no impairment group was significantly different compared to each of the other groups ($p < 0.0001$ for all). Additionally, the group with both motor and cognitive impairment had significantly different distributions compared to the motor-only impairment group ($p < 0.0001$) as well as the cognitive-only impairment group ($p = 0.0001$).

There was a main effect of functional group ($F(3,38) = 7.66$, $p = 0.0004$) on sequence length as well as an interaction effect of trial number and functional group ($F(3,38) = 8.91$, $p = 0.0001$). The difference in performance between functional groups can also be seen across

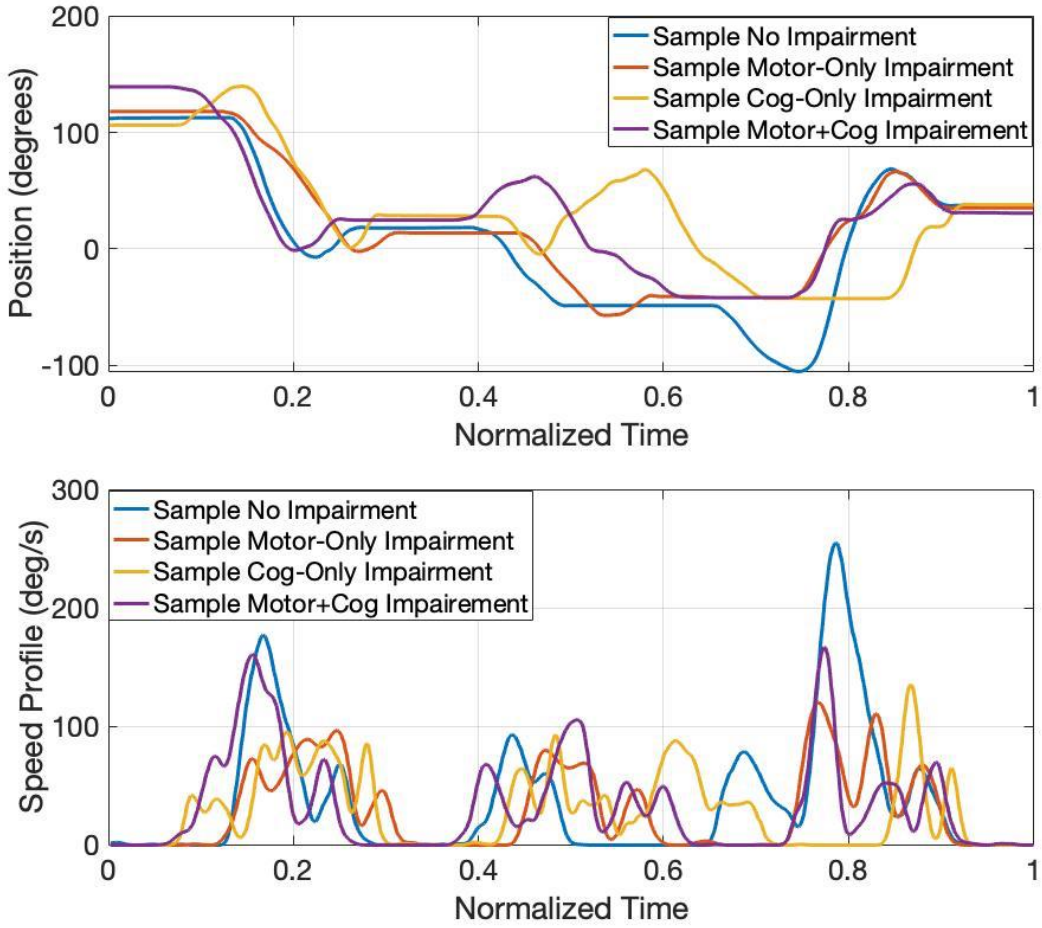

Figure 12: Top: Sample position data for a trial on the spatial span task. Bottom: Speed profiles of the example trial.

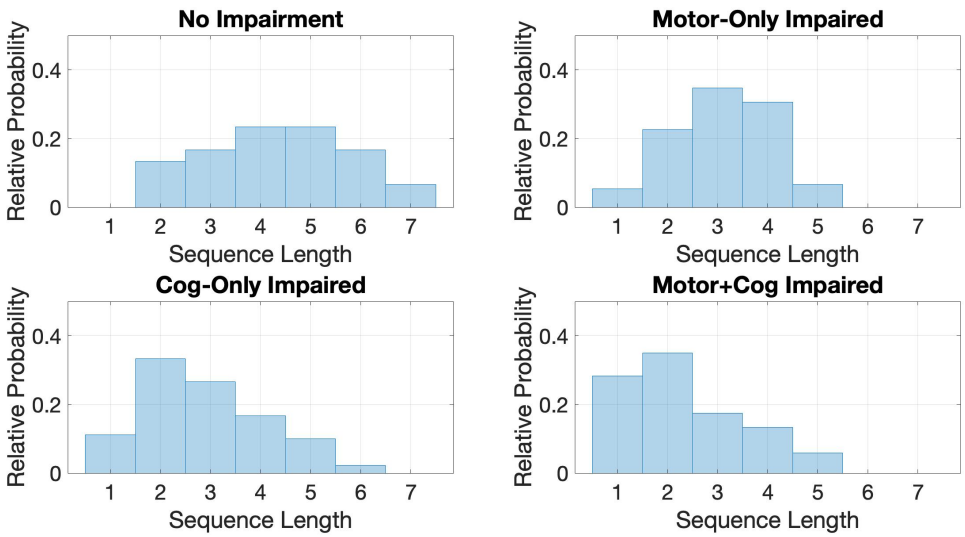

Figure 13: Relative probability distribution of each functional group's sequence length distribution. The no impairment group and the group with both motor and cognitive impairments were significantly different from each of the other groups. Top left: no impairment group. Top right: motor-only impaired group. Bottom left: cognitive-only impaired group. Bottom right: motor- and cognitive-impaired group.

trials, as shown in Fig. 14.

5.5.3 Kinematic Results

There was a main effect of limb side ($F(1, 81) = 4.03$, $p = 0.04$) on average speed, with the non-dominant limb demonstrating higher speeds compared to the dominant limb (22.06 ± 0.84 deg/s vs. 20.26 ± 0.58 deg/s, $p = 0.04$). These results are shown in Fig. 15.

There was a main effect of functional group ($F(3,81) = 3.63$, $p = 0.02$) and task difficulty ($F(2, 81) = 4.41$, $p = 0.02$) on normalized speed. The motor-only impaired group had higher speed metric values — indicating less smooth movement — compared to the cognitive-only impaired group (0.20 ± 0.007 vs. 0.17 ± 0.006, $p = 0.02$) as well as the motor-cognitive impaired group (0.20 ± 0.007 vs. 0.17 ± 0.006, $p = 0.04$). The easy difficulty had a higher normalized speed compared to the hard difficulty (0.19 ± 0.006 vs. 0.16 ± 0.005, $p = 0.01$). The results are shown in Fig. 16.

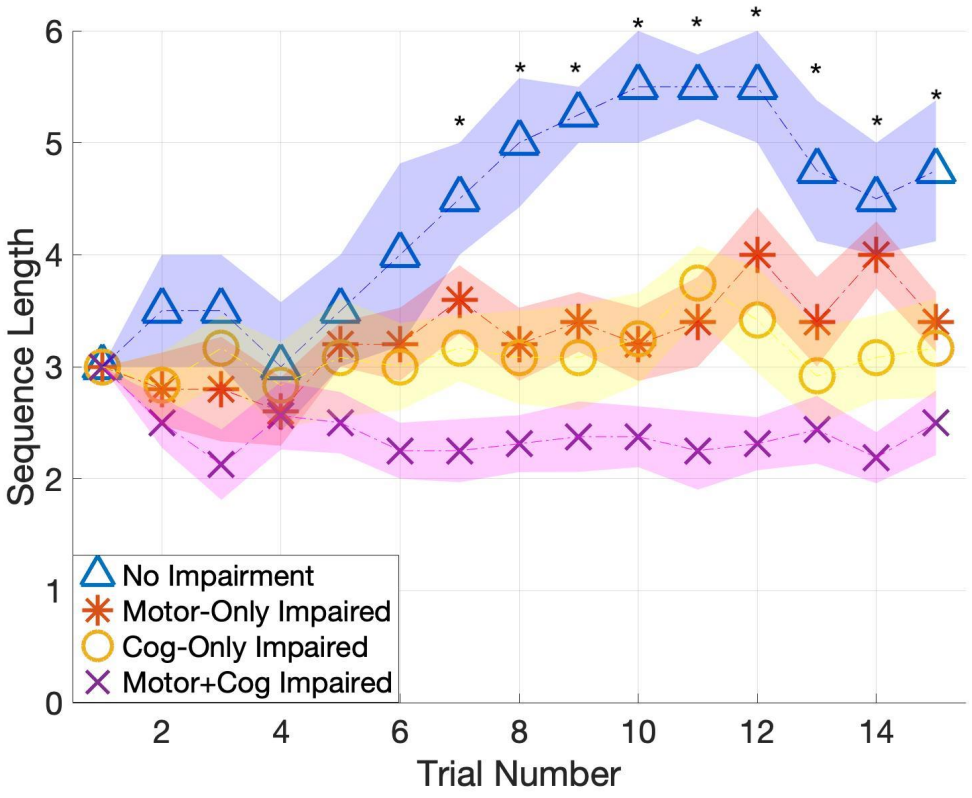

Figure 14: Sequence length by functional group over trials. Shaded regions represent the standard error for the functional group at a particular trial number. Asterisk denotes that a significant difference between two or more functional groups was detected at that trial number. (*: $p < 0.05$)

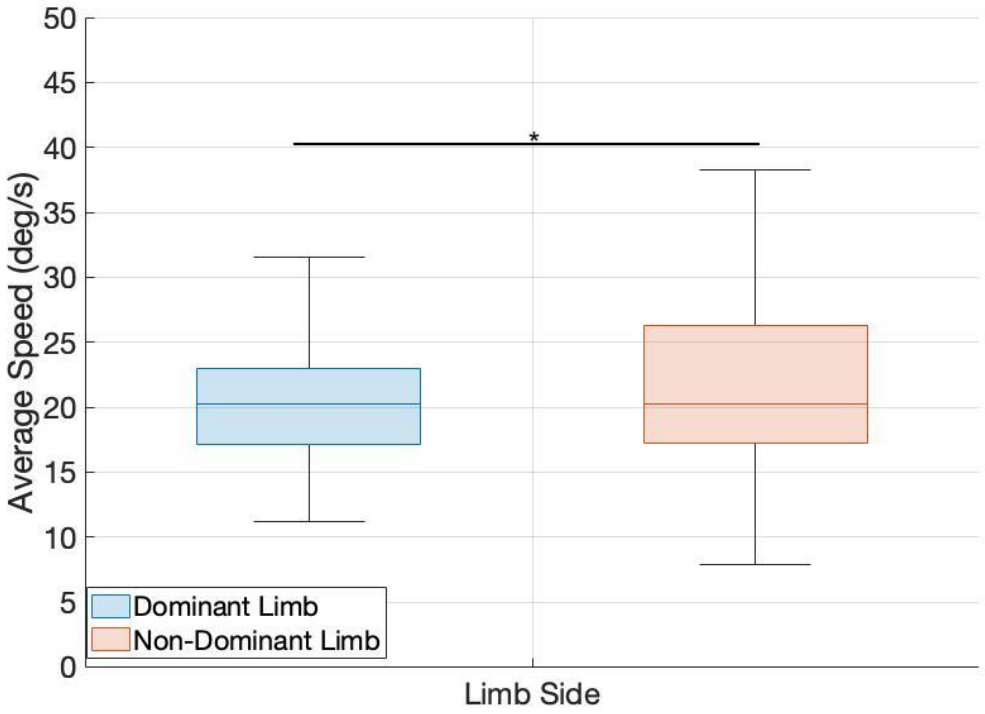

Figure 15: Mean speed by limb performance. (*: $p < 0.05$)

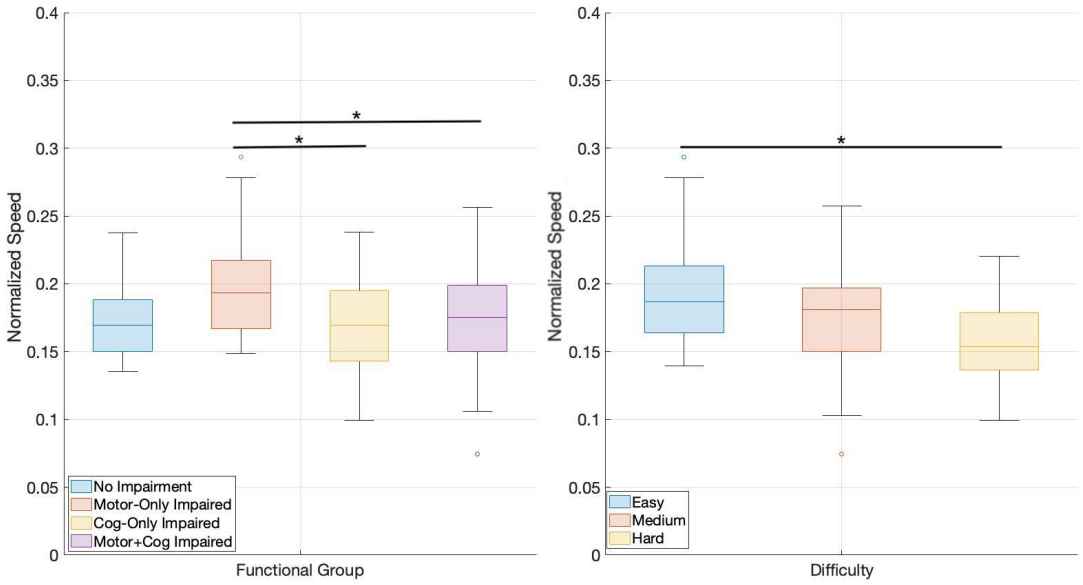

Figure 16: Left: Normalized speed by functional group. Right: Normalized speed by difficulty. (*: $p < 0.05$)

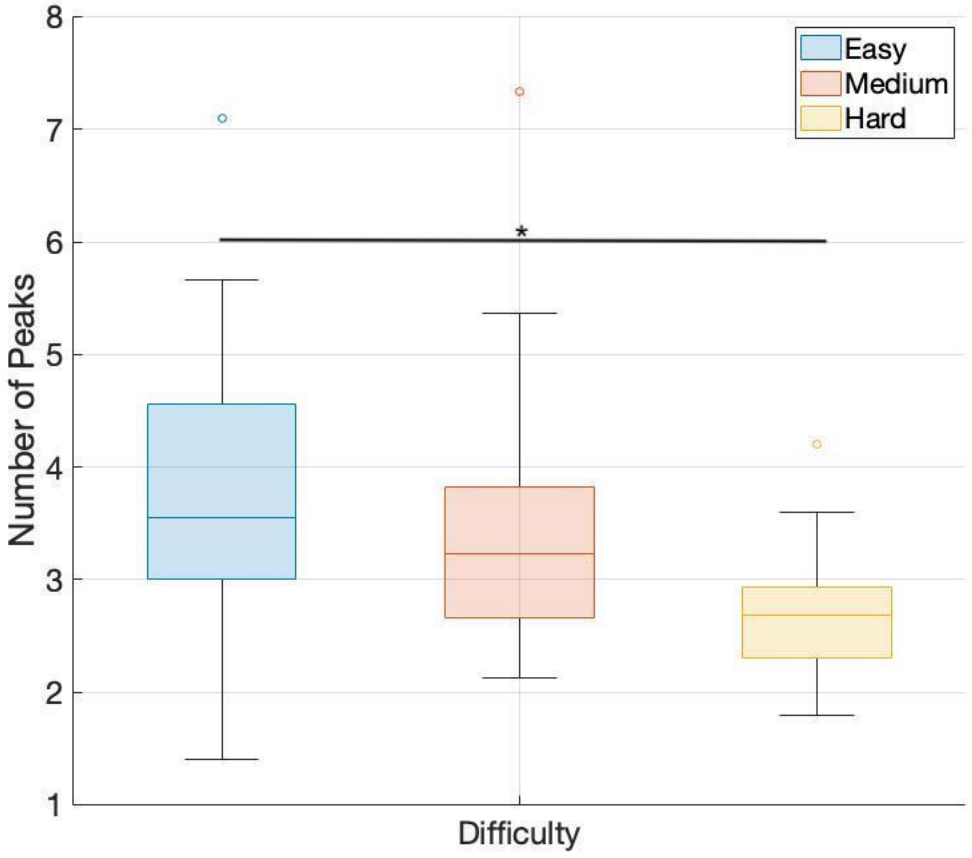

Figure 17: Left: Number of peaks by difficulty. (*: $p < 0.05$)

There was a main effect of difficulty ($F(2,81) = 3.75$, $p = 0.03$) on the number of speed peaks per submovement, with the easy difficulty tasks demonstrating a higher number of peaks per trial compared to the hard difficulty (3.77 ± 0.18 peaks vs. 2.69 ± 0.09 peaks, $p = 0.03$). The results are shown in Fig. 17.

There were no main or interaction effects for normalized distance traversed or spectral arc length.

5.6 Discussion

Non-Kinematic Measures are More Sensitive than Kinematic Measures

This study aimed to examine the utility of kinematic metrics from a cognitive-motor task as a motor performance measure in PLWH. Non-kinematic metrics based on sequence length demonstrated that functional groups performed differently on the spatial span task. Additionally, the difference between functional groups could also be seen over the course of the task (Fig. 14). The no impairment group showed a steady increase of sequence length over the trials, which went down slightly toward the end, which suggests a possible fatigue effect. The motor-only and cognitive-only impaired groups performed similarly to each other. The motor-cognitive impaired group generally ended up below the starting sequence length and performed the worst of the four groups.

However, the normalized speed metric was the only kinematic metric sensitive to differences between functional groups out of the five different kinematic metrics examined in this study. Additionally, there were main effects of difficulty and limb side that emerged on some of the kinematic metrics. This indicates that the task difficulties may have some inherent differences that need to be controlled for in order to allow for comparisons across difficulty. Additionally, there is a possible learning effect, given that the non-dominant limb demonstrated higher average speeds compared to the dominant limb, which was tested first in all individuals. The biggest drawback was the lack of sufficient data in each task condition to be able to compare performance as a function of task difficulty.

Given these results, non-kinematic metrics showed more sensitivity to differences in functional group performance on the spatial span task, while more work needs to be done to uncover the utility of kinematic metrics. Other work has shown that progressive training can enhance motor learning and neuroplasticity (Christiansen et al., 2020). Thus, the adaptive nature of the spatial span task used here might be better suited as a training strategy rather than an assessment strategy.

Study Limitations

Given the small sample size and lack of control group (either non-HIV healthy control or non-HIV stroke group), we may not be able to fully generalize these results. Additionally, the lack of sufficient data across the different task conditions limited the analysis that could be conducted. In future studies, this can be addressed by ensuring a minimum number of trials done at each task difficulty, rather than adapting the difficulty in a dynamic fashion.

Implications for Cognitive-Motor Assessment in PLWH

Given the complex interactions between cognitive and motor function and how these are impacted not only by HIV but also by other factors such as aging, there is a need for tools and methods to carefully characterize these interactions. Doing this will allow for a better understanding of the progression of functional decline and potential opportunities to develop more effective strategies to slow or stop this decline. The results from this study provide useful considerations going forward.

Novel methods of assessing impairment in PLWH, such as the cognitive-motor multitasking assessment use by Kronemer et al. (Kronemer et al., 2017), have the ability to detect more subtle signs of impairment in PLWH. One aspect of the spatial span task that has not yet been explored to date is if there are differences in kinematics based on whether the individual performed the trial correctly or incorrectly. The relationship of metrics derived from this task to activities of daily living also needs to be explored further.

Another consideration that emerged from this study is how to evaluate the clinical utility of novel metrics. The kinematic metrics were drawn from those used in the stroke literature, but different metrics may be more relevant to the HIV population. Metrics can be evaluated on a holistic level or consist of repeated measures.

Lastly, the accessibility of these assessments should be considered. A challenge with current strategies to assessing cognitive and motor function in PLWH is the training required and

lack of adequate resources to administer them, particularly in low- and middle-income countries. Thus, technology-based assessments provide a standardized way to administer these tasks, but additional factors such as the cultural context and technical support need to be accounted for.

5.7 Conclusion

In this study, we examine the kinematic and non-kinematic metrics derived from a motor-cognitive assessment task performed on a robotic system by people living with HIV. Non-kinematic metrics were sensitive to differences in performance by functional group, highlighting an advantage of the adaptive nature of the task. However, kinematic measures were not as sensitive, which could have been impacted by the design of the task. These results provide useful considerations going forward in developing tools to study motor and cognitive impairment in PLWH.

5.8 Acknowledgements

This work was made possible through core services and support from the National Institute Of Neurological Disorders and Stroke of the National Institutes of Health (T32NS091006); the University of Pennsylvania's Center for AIDS Research (P30AI 045008); and the University of Pennsylvania's Departments of Bioengineering and Physical Medicine and Rehabilitation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CHAPTER 6 : FEASIBILITY OF REHABILITATION ROBOTIC SOLUTIONS IN BOTSWANA

6.1 Contribution

Parts of this chapter are adapted from a book chapter published with Michelle Johnson and Narges Rahimi in the Handbook of Global Health (Johnson et al., 2021). This study uses the robot-based assessment methods developed in previous chapters and implements them in a new setting to study HIV-related impairments in Botswana.

6.2 Abstract

Although the majority of disability is experienced in low- and middle-income countries, there is a lack of research in these settings demonstrating the feasibility and efficacy of technology-based solutions. In this ongoing study, we test the feasibility of implementing an upper limb rehabilitation robot system in Botswana, a country in sub-Saharan Africa with the fourth highest prevalence of HIV in the world and limited rehabilitation resources. We compare the results to previously collected data in the U.S. HIV population. Our preliminary findings show that despite the Botswana cohort being younger, they experience higher rates of cognitive impairment, while the U.S. population experienced higher rates of motor impairment. These findings were reflected in the robot-based metrics as well. Additionally, we demonstrate a relationship between the robot-based and clinical assessments in the Botswana population. Our approach provides a potentially more affordable and efficient way to further study PLWH in limited resource settings and to meet the global shortage of rehabilitation professionals.

6.3 Introduction

According to the World Health Organization, 74% of the total number of years lived with a disability is linked to conditions which could benefit from rehabilitation (Organization et al.,

2017). However, not everyone is receiving the rehabilitation they need. In Southern Africa, only 26-55% of people who need rehabilitation actually receive it (Bickenbach, 2011). As the global population continues to age and the prevalence of chronic conditions increases, the global need for rehabilitation will continue to rise.

Rehabilitation refers to a set of measures that assist individuals who experience disability to achieve optimal functioning within their environments (Bickenbach, 2011). Disability leads to poorer health outcomes, lower education achievements, and less economic participation, which results in a cycle of disability and poverty (Bickenbach, 2011). Despite evidence that rehabilitation is highly effective in improving clinical outcomes and quality of life, people residing in low- and middle-income countries (LMICs) face specific barriers to accessing rehabilitation.

Barriers to wider use of rehabilitation include inadequate policies and standards, negative attitudes toward disability, problems with service delivery, lack of accessibility, and a lack of data and evidence. Additionally, there is a global lack of rehabilitation professionals to provide rehabilitation services. These professionals include physical and rehabilitation medicine doctors (physiatrists), physiotherapists, occupational therapists, speech and language pathologists, prosthetists, and orthotists. In many LMICs, there are fewer than 10 physiotherapists per 1 million residents, whereas high-income countries often have several times more rehabilitation professionals (Organization et al., 2017). Addressing these barriers to rehabilitation can provide a positive societal impact by building human capacity, improving quality and affordability of services, and achieving the Sustainable Development Goal of ensuring healthy lives and promoting well-being for all (Bickenbach, 2011). Given the lack of rehabilitation professionals, using technology can help address the gap. In the field of rehabilitation, robotic systems have been explored as a possible solution to improve health outcomes and have been shown to be as effective as high-intensity physical therapy. However, the vast majority of solutions are only available in high-income countries, with high costs often associated with limited market penetration of rehabilitation robotic sys-

tems. In addition to the high costs of these systems, other barriers to adoption in LMICs include a lack of training for maintaining these systems, high duty or import taxes, and the lack of studies establishing the feasibility and cost-effectiveness of therapy in relevant settings.

However, there are strategies to address these barriers. One way to reduce costs while increasing capacity within a country is to promote local production of solutions. Improving the economies of scale based on established need can also reduce costs (Bickenbach, 2011). The WHO has provided guidelines on the affordability of cost-effective health solutions, suggesting that interventions that avert one disability-adjusted life year (DALY) for less than three times the average per capita income of a given country are cost-effective, while anything less than the average per capita income would be considered very cost-effective (Hutubessy et al., 2003). DALYs are a metric that capture the impact of a disease on a population on a global, national, or local level (Murray, 1994). Malaysia is an example of a LMIC that has successfully been able to produce a very cost-effective RAT solution with the CR2-Haptic, costing 3,000 USD relative to an average per capita income of roughtly 10,000 US dollars (Khor et al., 2019). Mexico has also explored the use of a robot-therapy gym for stroke rehabilitation, and found it to be more cost-effective and equally as effective compared to conventional therapy (Valles et al., 2016). Thus, there is preliminary evidence that RAT can be implemented in lower-resource areas effectively. While much of this work has been done in stroke, we have demonstrated the utility of rehabilitation robotics to assess cognitive and motor impairment in people living with HIV (Bui et al., 2021).

HIV and stroke represent two of the five top leading causes of death and disability worldwide. Stroke resulted in 116.4 million DALYs, or 42% of all global neurological DALYs in 2016, and over 80% of DALYs occur in LMICs. Meanwhile, global HIV infection caused 47.5 million DALYs in 2019, with an increase in disability outpacing premature death (Wu et al., 2021). More than two-thirds of HIV-related DALYs are experienced in Sub-Saharan countries (Wu et al., 2021). While rehabilitation interventions have been extensively studied in stroke,

there is a lack of such a body of work in PLWH. Given the rapid aging in the HIV population, a "need remains for the development of culturally appropriate and discriminative outcome measures in the field of HIV, disaiblity and rehabilitation... to better determine the impact of neurocognitive impairment on the daily function and lives of people with HIV" (O'Brien et al., 2014).

6.3.1 HIV, Stroke, and Rehabilitation in Botswana

Botswana, as an upper-middle income country in Sub-Saharan Africa, is a prime example of a LMIC facing the previously mentioned barriers to rehabilitation. It has the fourth-highest prevalence of HIV in the world, at 20% of the population of 2 million. Despite its aggressive response to HIV, 37% of PLHIV in Botswana were found to have cognitive impairment even though 97.5% of the participants were on highly active antiretroviral therapy (Lawler et al., 2011).

Unpublished data showed that a third of the roughly 150 patients admitted with stroke to Princess Marina Hospital, the main referral hospital in Botswana's capital city, had HIV over the course of one year. As in Malawi and South Africa, people living with HIV-associated stroke were younger than typical stroke survivors in the USA (Heikinheimo et al., 2012; Mochan et al., 2005; Vinikoor et al., 2013). In a younger HIV-associated stroke cohort, long-term disability is more debilitating, thus compromising ability to work and quality of life (Onwuchekwa et al., 2009). HIV has also been shown to result in worse stroke recovery outcomes compared to stroke survivors without HIV (Augustyn et al., 2020), highlighting the need to take into account the presence of HIV.

In Botswana, hospitals lack the rehabilitation staff to provide assessment of disability and regular follow-up care. For example, Princess Marina Hospital has 530 beds, but no physiatrists, two occupational therapists, and seven physical therapists on staff, making it impossible to meet recommended rehabilitation standards for every patient. It is essential to develop relevant evidence-based neurorehabilitation strategies that can improve perfor-

mance on activities of daily living and increase access to more consistent rehabilitation, despite the limited number of therapists and medical doctors.

In this study, we first compare the clinical assessment data to previously collected data in the U.S. to identify the prevalence of HIV-related impairments. We then assess the ability of robot-based metrics to predict the clinical scores of the Botswana cohort using the previously collected data as the training set. We discuss the feasibility of implementing a rehabilitation robotic system in Botswana to assess cognitive and motor impairment in people living with HIV, stroke, or both.

6.4 Methods

6.4.1 Study Population and Procedure

Individuals over the age of 18 years old were recruited from the Princess Marina Hospital Infectious Disease Care Clinic as well as occupational and physical therapy clinics around Gaborone. Inclusion criteria for the HIV group consisted of documented HIV status that was antiretroviral therapy-treated and virally-suppressed, the ability to ambulate, the ability to comprehend study procedures, and the ability to provide written informed consent. Individuals with neuropathy (i.e. distal symmetric polyneuropathy) were excluded.

Individuals were included in the HIV-stroke subgroup if they met the inclusion criteria for the HIV group and were at least three months removed from a stroke event. Individuals were excluded if they were more than mildly depressed as assessed by the Beck's Depression Inventory and were given the contact of a psychiatric clinic (Beck et al., 2000). Individuals were compensated for time and travel. This protocol was approved by the Internal Review Boards of the University of Pennsylvania, Princess Marina Hospital, and University of Botswana.

Prospective participants underwent a preliminary phone screen to screen for study eligibility. When possible, they were then sent a copy of the informed consent to review prior to coming

in for their scheduled in-person appointment. All consent forms and pre-screening questions were translated into Setswana and administered in English or Setswana. After written informed consent was obtained in-person, cognitive, motor, and medical assessments were performed. Participants then completed three robot-based tasks in a randomized order with the dominant limb first and non-dominant upper-extremity limb second.

So far, 11 PLWH have completed the study, with three also presenting with stroke.

6.4.2 Clinical Assessments

A set of cognitive, motor, and activities of daily living assessments were administered to each study participant in English or Setswana based on their preference. These assessments consisted of those used to study HIV or stroke. A neuropsychologist or trained lab research assistant administered the cognitive assessments, while one of two occupational therapists administered the motor assessments.

Where available, the proportion of individuals with impairment was calculated. For available assessments, cutoff scores for the Botswana-based group were taken from a previous study using the lower 10th percentile of performance from a group of 80 HIV-negative individuals in Gaborone, Botswana (Lawler et al., 2011). For the U.S. population, scores were normalized against U.S.-based population norms and converted to a Z-score, with a cut-off Z-score of 1.65. Values exceeding this cut-off corresponded to the lower 10th percentile relative to the population norms. This approach was taken for the Color Trails, Digit Symbol–Coding, and Grooved Pegboard. For assessments where this was not available, namely the MoCA and IHDS, established cut-off scores were used.

6.4.3 Cognitive Assessments

The cognitive assessments consisted of the Color Trails, Digit Symbol–Coding (DSC), Montreal Cognitive Assessment (MoCA), Animal Fluency Test, and International HIV Dementia Scale (IHDS) (D'Elia et al., 1996; Wechsler, 1981; Nasreddine et al., 2005; Sacktor et al.,

2005). These tests have all been administered in PLWH previously to measure neurocognitive impairment (Maj et al., 1993; Sacktor et al., 2005; Ettenhofer et al., 2009; Lawler et al., 2011; Fazeli et al., 2017). These tests were chosen to reflect the cognitive domains commonly affected by HIV. All except the MoCA have previously been used in the Botswana (Lawler et al., 2011). Cut-off scores for the DSC and Color Trails are taken from a previous study using the lower 10th percentile of performance from a group of 80 HIV-negative individuals in Gaborone, Botswana (Lawler et al., 2011).

Color Trails

The Color Trails is a set of two cognitive pencil and paper tests based on the Trail Making Test but does not require knowledge of the alphabet, thus reducing potential bias (D'Elia et al., 1996). Color Trails 1 tests for sustained visual attention and simple sequencing, while Color Trails 2 assesses frontal systems such as selective attention, mental flexibility, visual spatial skills, and motor speed. Performance was measured by the time to complete the task, with a higher time indicating worse performance. These scores were normalized by age, gender, and education (D'Elia et al., 1996). Cut-off scores of 78.5 and 221.5 seconds for Color Trails 1 and 2, respectively, were used to indicate impairment.

Digit Symbol – Coding (DSC)

The DSC test is another neuropsychological test assessing processing speed (Wechsler, 1981). Subjects use a number-symbol key to copy symbols under a sequence of numbers. Performance was measured by the number of symbols coded in the span of two minutes, with a higher number of symbols copied in the time span representing better performance. Scores were normalized by age, gender, and education. A cut-off score of 32 and below was used to indicate impairment.

Montreal Cognitive Assessment (MoCA)

The MoCA is a screening tool to detect impairment in a number of cognitive domains – visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation – and reflects the degree of cognitive impairment in a subject (Nasreddine et al., 2005). A score above 25 out of 30 generally indicates normal cognitive function, while a score below 19 indicates likely moderate cognitive impairment.

International HIV Dementia Scale (IHDS)

The IHDS is a screening test for cognitive impairment designed to screen for HAND, with a score below 10 out of 12 indicating potential cognitive impairment (Sacktor et al., 2005). It was developed as a culturally appropriate adaptation of the HIV Dementia Scale. However, the IHDS has not been validated in the stroke population.

6.4.4 Motor Assessments

The motor assessments tested gross motor function, fine motor function, and strength. They consisted of the Box and Blocks Test (BBT), Grooved Pegboard (GP), and grip strength. Cut-off scores for the GP are taken from a previous study on neurocognitive impairment in PLWH using the lower 10th percentile of performance from a group of 80 HIV-negative individuals based in Gaborone, Botswana (Lawler et al., 2011).

Box and Blocks (BBT)

The BBT is a test of gross motor function measuring how many blocks subjects are able to transfer across a partition in one minute, with a higher number of transferred blocks indicating better motor function (Mathiowetz et al., 1985). Three trials were performed with the dominant and non-dominant limb and averaged. Scores were normalized by age, gender, and limb. It is typically used to measure reach and grasp function in the stroke population.

Grooved Pegboard (GP)

GP is a common motor assessment in PLWH. It tests fine motor function and dexterity, measuring the amount of time a subject takes to insert all of the grooved pegs into matched holes on a board. Performance was measured by the time to complete the task with longer times indicating worse fine motor function (Ruff and Parker, 1993). GP data for subjects unable to complete the task were not included in the analysis. Three trials were performed with the dominant and non-dominant limb and averaged. A cut-off score of 100 seconds and 108.5 seconds was used for the dominant and non-dominant limb, respectively.

Grip Strength

Grip strength was measured with a dynamometer. Three trials were taken with each hand, with the average and standard deviation being recorded. Accelerated grip strength decline has been shown in a study of HIV-infected men, which may contribute to decreased life expectancy and lower quality of life with aging (Schrack et al., 2016). Three trials were performed with the dominant and non-dominant limb and averaged.

6.4.5 Robot Assessment

Rehabilitation Robot System

The rehabilitation robot used in this study, the Haptic TheraDrive, is a one degree-of-freedom robot for upper limb stroke rehabilitation (Johnson et al., 2017). The user operates the TheraDrive by manipulating a vertically-mounted crank handle equipped with force sensors and an optical encoder. For assessment purposes, it is run in a gravity-compensation mode, which uses force sensors as an input to a proportional-integral-derivative (PID) controller to calculate the necessary response by the motor to give the sensation that there is no resistance or assistance while the user manipulates the handle.

Trajectory Tracking Motor Task

The trajectory tracking task is designed to assess upper limb motor performance. A single trial consists of the user moving the crank arm forward and backward to follow a vertically scrolling sinusoidal path for 15 seconds. This task is repeated 15 times after one training trial. The outcome measures include performance error, mean velocity, movement smoothness, and the normalized distance traversed. Performance error was calculated as the root mean square error (RMSE) of the position relative to the displayed trajectory and normalized by the RMSE assuming no movement. A lower performance error indicates better tracking performance. Spectral arc length was used as the measure of smoothness, which has the benefit of being less sensitive to noise compared to other measures of smoothness (Balasubramanian et al., 2015). More negative values of smoothness indicate less smooth movements. Normalized distance traversed was calculated from dividing the total angular distance that the subject traversed by the expected angular distance of the displayed trajectory path. A value closer to 1 reflects that the actual distance traversed matched the expected distance. A lower value could reflect moderate motor impairment, while a higher value could reflect inefficient movement.

N-Back Cognitive Task

The N-back test is commonly used in the cognitive neuroscience field as a test of working memory and working memory capacity (Owen et al., 2005). In this version, the subject is presented with a sequence of numerical digits (1-4) with three different conditions. For the 0-back condition, the easiest condition, the subject indicates when the current stimulus shown on the screen is the number '2.' For the more cognitively-involved 1-back and 2-back conditions, the subject indicates when the current stimulus matches the stimulus shown one stimulus or two stimuli prior, respectively. The subject indicates a match by pressing a button on the TheraDrive. The number then flashes green or red for a correct or incorrect response, respectively. Each subject performed the task with each limb, cycling through the 0-back, 1-back, and 2-back conditions four times for a total of 12 trials, all with different

numerical sequences. The first set of trials is used as a training set and not included in the analysis. Ten responses are recorded per trial. Each subject was shown the same set of 12 sequences, with each sequence having a minimum of three button press responses. N-back performance was measured as the total number of correct responses divided by the total number of responses across the trials, resulting in a score ranging from 0 to 1, with a score closer to 1 representing better performance.

Spatial Span Cognitive-Motor Task

The Spatial Span is a test of visuospatial working memory based on the Corsi block-tapping task used in neuropsychological assessments (Kessels et al., 2000). While computerized versions of the Spatial Span exist (Brunetti et al., 2014), this version incorporates an added motor component to concurrently test for arm coordination, visuospatial ability, and working memory. A 3-by-3 grid of tiles is displayed to the user on a computer screen, and a sequence of tiles is shown one tile at a time. The user must operate the TheraDrive to select the tiles in the order shown. If the user successfully repeats the sequence by selecting the correct tiles in order, the next displayed sequence increases in length by one to make the task more difficult. If the user is unsuccessful, the sequence decreases in length by one. The metrics of interest for the task include the normalized distance traversed, mean velocity, movement smoothness, mean sequence length across all the trials, and performance. Normalized distance traversed and movement smoothness were calculated the same way as in the trajectory tracking task. Mean sequence length is the average number of tiles displayed to the user per trial and reflects the capacity of the subject. Spatial span performance was measured as the total number correct tile matches divided by the total number of tiles shown across the trials. Thus, spatial span performance is a score ranging from 0 to 1, with 1 representing perfect performance.

6.4.6 Linear Regression Models and Comparisons

Three different linear regression models were evaluated for each clinical metric in this study. Model 1 was trained and evaluated on the U.S. cohort (Bui et al., 2021). Model 2 used the linear equation from Model 1 to predict the clinical scores of the Botswana cohort. Model 3 was trained and evaluated on the Botswana cohort. Model performance was reported as the adjusted coefficient of determination (adj R^2) as well as normalized root mean square error (nRMSE). Adjusted R^2 captures the relative performance of the model, accounts for different numbers of predictors, and represents the percent of variance explained. nRMSE evaluates the absolute performance of the model, with a smaller value indicating better predictive ability. It is normalized by the standard deviation of the population data. A small, medium, and large effect size were defined as an R^2 value of 0.01, 0.25, and 0.50, respectively. All analysis was conducted in Matlab 2021A.

6.4.7 Statistical Analysis

To compare the clinical data from the U.S. and Botswana cohorts, a non-parametric Wilcoxon rank sum test was used on continuous variables. A two sample Chi-square test was used on categorical variables and to compare the rates of impairment. An alpha of 0.05 was used to establish statistical significance on all tests. Because of the small sample size, no corrections were made for multiple comparisons at this time.

6.5 Results

6.5.1 Comparing Clinical Assessment Performance

Table 4 shows the mean and standard deviations for the demographic and clinical assessment metrics in the Botswana group compared to previously collected data in the U.S. The Botswana group was younger in age and performed worse on the Color Trails 1 and DSC but performed better on the IHDS compared to the U.S. group. The Botswana group had a statistically significant higher rate of impairment on the Color Trails 1 and DSC, while

the U.S. group had a higher rate of impairment on the IHDS.

6.5.2 Comparing Robot Assessment Performance

Table 3 shows the mean and standard deviations for the raw robot-based metrics in the Botswana group compared to previously collected data in the U.S. The Botswana group performed worse with at least one limb on overall N-back performance, trajectory tracking performance error, trajectory tracking normalized distance traversed, spatial span mean sequence length, and spatial span performance. Non-dominant limb spatial span mean velocity was lower in the Botswana group compared to the U.S. group. There were no differences on trajectory tracking mean velocity, trajectory tracking smoothness, spatial span normalized distance traversed, or spatial span smoothness.

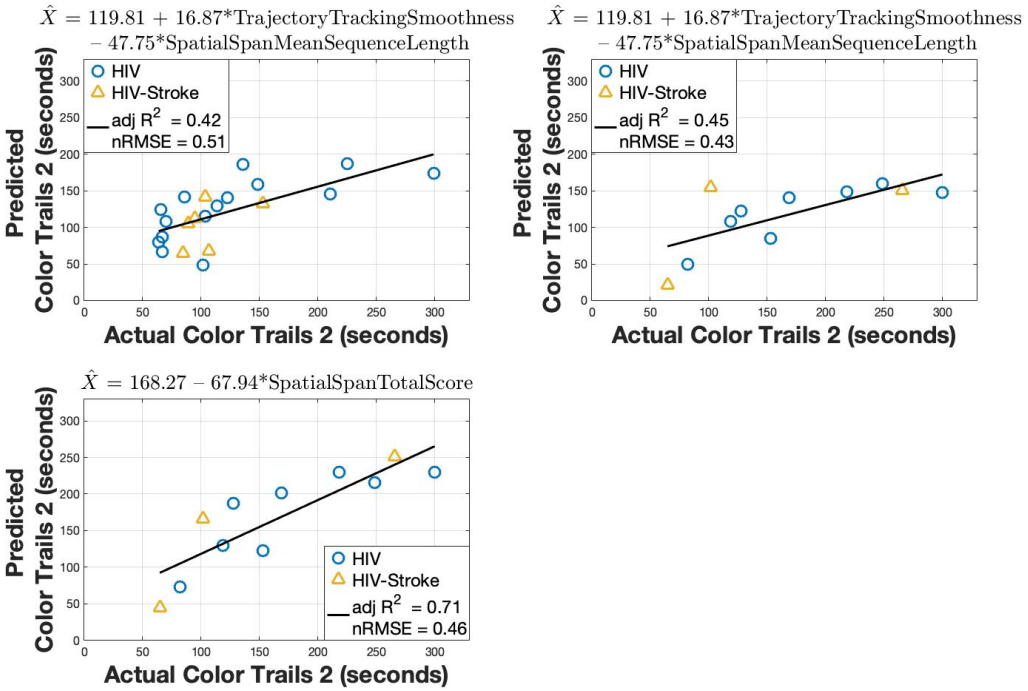

Figure 18: Linear models for Color Trails 2 using dominant limb robot-based measures. Upper left: Trained and evaluated on U.S. cohort. Upper right: Trained on U.S. cohort and evaluated on Botswana cohort. Lower left: Trained and evaluated on Botswana cohort.

Table 4: Subject Demographics and Clinical Scores

Characteristics	U.S. population mean±standard deviation (n=21)	Botswana population mean ± standard deviation (n= 11)	p-value
Age (years old)	55.5 ±6.30	46.91± 5.62	**0.001**
Gender (Male/Female)	13M/8F	3M/8F	0.06
≥ 12 years edu (count)	15	3	0.06
Color Trails 1 (seconds)	47.86±20.10	83.45 ± 42.79	**0.005**
Percent Impaired	19%	55%	**0.04**
Color Trails 2 (seconds)	119.81±58.85	168.27 ± 79.17	0.08
Percent Impaired	19%	27%	0.59
Digit Symbol–Coding Score	46.38±11.24	30.63± 19.18	**0.03**
Percent Impaired	14%	54%	**0.02**
MoCA (out of 30)	22.14±4.06	20.80 ± 4.52	0.37
Percent Impaired	76%	73%	0.83
IHDS (out of 12)	7.62±2.66	10.20 ± 1.11	**0.006**
Percent Impaired	81%	27%	**0.02**
Dominant BBT (blocks)	53.79±10.01	56.48 ± 8.30	0.49
Non-Dominant BBT (blocks)	52.52±12.63	48.12 ± 18.67	0.77
Dominant GP (seconds)	94.83±30.41	92.45 ± 52.15	0.26
Percent Impaired	43%	9%	0.05
Non-Dominant GP (seconds)	125.48±63.36	106.44 ± 62.68	0.15
Percent Impaired	48%	18%	0.10
Dominant Grip Strength (kg)	29.95±10.31	27.26 ± 7.66	0.48
Non-Dominant Grip Strength (kg)	26.38±12.93	24.68± 10.30	0.87

Table 5: Group Robot Performance Results by Dominant (D) and Non-Dominant (ND) Limbs (Mean ± Standard Deviation)

Robot Metrics	U.S. population	Botswana population	p-value
N-back performance	D: 0.86±0.07 ND: 0.86±0.06	0.77±0.12 0.75±0.13	**0.04** **0.003**
Trajectory tracking performance error	0.37±0.18 0.39±0.24	0.77±0.24 0.85±0.20	**0.0002** **0.0002**
Trajectory tracking normalized distance traversed	1.02±0.10 1.02±0.17	0.85±0.09 0.85± 0.22	**0.0002** **0.01**
Trajectory tracking mean velocity	41.77±4.35 41.38±6.81	43.09±4.62 43.20±11.16	0.50 0.55
Trajectory tracking smoothness	-9.50±1.21 -9.80±1.65	-8.49±1.56 -10.08±1.66	0.10 0.69
Spatial span mean sequence length	2.87±0.93 3.16±1.06	2.08±0.64 2.27±0.84	**0.02** **0.01**
Spatial span performance	0.63±0.12 0.66±0.13	0.47±0.16 0.54±0.20	**0.01** 0.06
Spatial span normalized distance traversed	1.57±0.48 1.59±0.33	1.97±0.75 1.77± 0.55	0.16 0.39
Spatial span mean velocity	20.47±4.22 22.37±5.45	17.22±4.17 18.29±2.64	0.10 **0.04**
Spatial span smoothness	-2.23±0.41 -2.42±0.65	-2.42±0.42 -2.21± 0.27	0.18 0.69

Table 6: Model Comparisons - Dominant Limb

Clinical Score	Adjusted R^2 (U.S.)	Normalized RMSE (U.S.)	Adjusted R^2 (Predicted)	Normalized RMSE (Predicted)	Adjusted R^2 (Botswana)	Normalized RMSE (Botswana)
Color Trails 1	0.62	0.49	0.49	0.13	0.67	0.48
Color Trails 2	0.42	0.51	0.53	0.41	0.71	0.46
Digit Symbol–Coding	0.70	0.47	0.11	0.56	0.29	0.51
MoCA	0.40	0.51	0.12	0.25	0.25	0.50
IHDS	0.49	0.51	-0.12	0.25	0.26	0.50
BBT	0.55	0.51	-0.06	0.39	0.25	0.50
GP	0.38	0.51	-0.10	0.10	0.26	0.50
Grip Strength	0.18	0.43	-0.09	0.63	0.001	0.32

Table 7: Model Comparisons - Non-dominant Limb

Clinical Score	Adjusted R^2 (U.S.)	Normalized RMSE (U.S.)	Adjusted R^2 (Predicted)	Normalized RMSE (Predicted)	Adjusted R^2 (Botswana)	Normalized RMSE (Botswana)
Color Trails 1	0.43	0.51	0.32	0.16	0.30	0.51
Color Trails 2	0.35	0.50	-0.09	0.06	0.66	0.49
Digit Symbol–Coding	0.51	0.51	0.74	0.19	0.74	0.45
MoCA	0.37	0.50	0.04	0.49	0.43	0.53
IHDS	0.56	0.51	-0.11	3.8	0.34	0.52
BBT	0.67	0.48	-0.06	3.1	0.21	0.48
GP	0.41	0.51	0.10	3.70	0.31	0.52
Grip Strength	0.41	0.51	-0.08	12	0.05	0.37

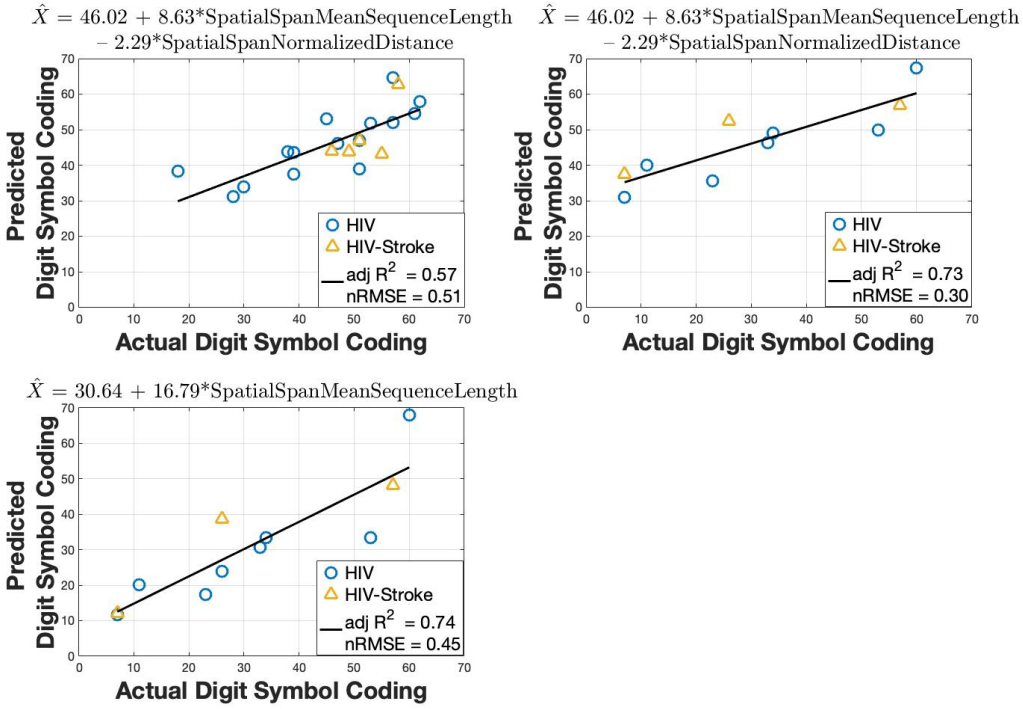

Figure 19: Linear models for Digit Symbol—Coding using non-dominant limb robot-based measures. Upper left: Trained and evaluated on U.S. cohort. Upper right: Trained on U.S. cohort and evaluated on Botswana cohort. Lower left: Trained and evaluated on Botswana cohort.

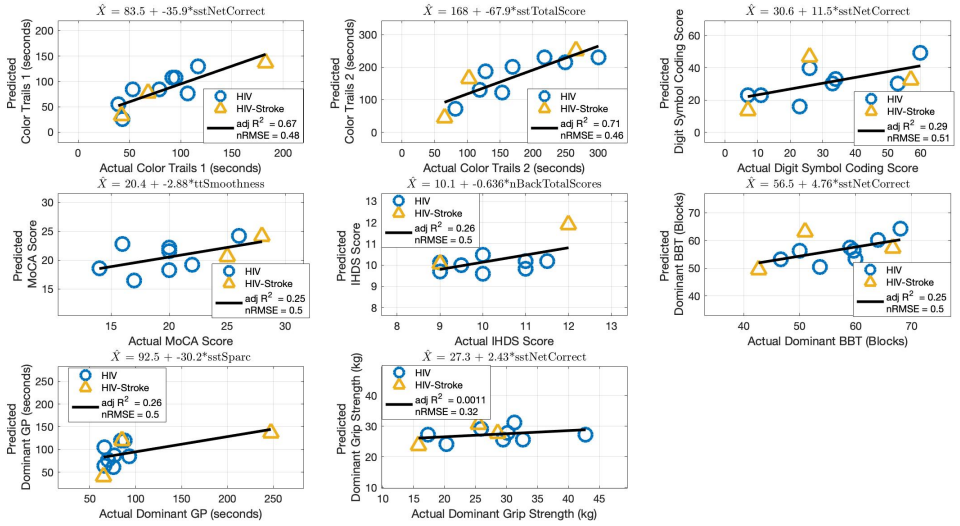

Figure 20: Multiple linear regression for clinical assessments using dominant limb robot-based metrics. The robot-based predictors for each model are included in the equation at the top of each subplot.

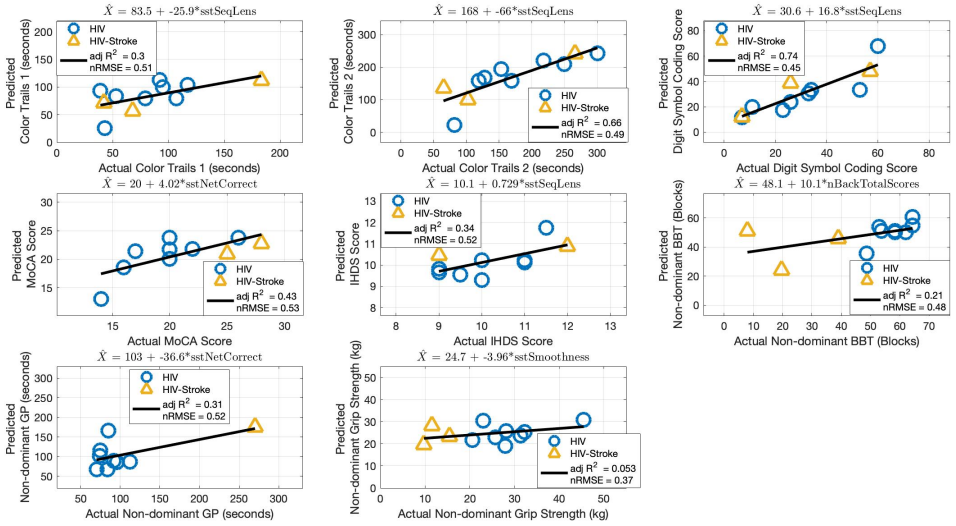

Figure 21: Multiple linear regression for clinical assessments using non-dominant limb robot-based metrics. The robot-based predictors for each model are included in the equation at the top of each subplot.

6.5.3 Linear Model Comparisons

Dominant limb

Table 6 shows the adjusted R^2 and normalized RMSE for each of the three different linear models across the clinical scores using the dominant limb robot-based metrics as predictors. The models trained on the U.S. cohort and used to predict the Botswana cohort demonstrated a large effect size (adj $R^2 > 0.50$) for Color Trails 2 (Fig. 18, upper right). The model used for Color Trails 2 accounted for 53% of the variance in the actual Color Trails 2 scores.

Figure 20 shows the linear regression models for each of the clinical assessments measures using dominant limb robot-based metrics from the Botswana cohort as the predictors. The models trained and evaluated on the Botswana cohort demonstrated a large effect size on Color Trails 1 and Color Trails 2, accounting for 67% and 71% of the variance in the respective models. The three different model performances can be seen for the Color Trails 2 in Fig. 18.

Plots and equations for all clinical scores can be found in Appendix A.2.

Non-dominant limb

Table 7 shows the adjusted R^2 and normalized RMSE for each of the three different linear models across the clinical scores using the non-dominant limb robot-based metrics as predictors. The models trained on the U.S cohort and used to predict the Botswana cohort demonstrated a large effect size for DSC. The model used for DSC accounted for 74% of the variance in actual DSC scores.

Figure 21 shows the linear regression models for each of the clinical assessments using non-dominant limb robot-based metrics as the predictors. The models trained and evaluated on the Botswana cohort demonstrated a large effect size on Color Trails 2 and DSC, accounting for 66% and 74% of the variance in the respective models. The three different model performances can be seen for the DSC in Fig. 19.

Plots and equations for all clinical scores can be found in Appendix A.2.

6.6 Discussion

HIV-related impairments warrant rehabilitation

There was significant overlap in the range of clinical scores among PLWH and PLWH with stroke, with the exception of non-dominant Grooved Pegboard, non-dominant grip strength, and non-dominant Box and Blocks. This is likely due to the stroke-affect limb impacting motor performance. This reinforces the need for rehabilitation strategies to address the cognitive and motor impairments resulting from HIV. It also confirms the presence of both cognitive and motor impairment in PLWH in Botswana, which has previously been demonstrated (Lawler et al., 2011).

In comparing the U.S. and Botswana groups, the Botswana group was younger and tended to have higher frequencies of impairment on the cognitive tests, while the U.S. group tended

to have a higher frequency of motor impairment relative to population norms. This could be due to motor impairments being more common as a result of aging with HIV. However, it demonstrates that cognitive impairment can be present early on in PLWH.

Robot-based assessment is feasible in Botswana

Our preliminary results demonstrate that it is feasible to conduct robot-based assessment in Botswana. Although many of the models trained on the U.S. cohort did not predict the Botswana cohort scores well, the exceptions were Color Trails 2 and Digit Symbol—Coding. However, the small sample size means these are under-powered relationships. As both test for information processing and that the Color Trails was designed to be culturally sensitive, this suggests that information processing assessments translate to different populations.

In comparing the U.S. and Botswana groups, the Botswana group had higher performance error scores on the trajectory tracking task compared to the U.S. group. They also had lower performance on the N-back and mean sequence length on the spatial span task. These metrics mirror the relationship observed in the clinical scores, where the Botswana cohort tended to have worse cognitive scores. Additionally, there were no differences in the kinematic measures, except for non-dominant spatial span mean velocity, which also reflects the lack of differences on the clinical motor assessments.

Relevance to rehabilitation capacity, global health, and robotics

Considering that multiple trained clinicians — one medical doctor, one neuropsychologist, and one occupational therapist — were needed to administer the full clinical battery, the robot-based assessment could provide a potentially more efficient approach to assessment in contexts where trained professionals are not available. In this study, a non-technical research coordinator administered the robot-based assessments in half the time of the clinical assessments. The application of this system for both assessment and rehabilitation across HIV and stroke is a further argument for the increased efficiency of this approach.

Additionally, the total cost of one robot is 1200 USD, while the GDP per capita in Botswana is 8000 USD. More work needs to be done to establish the true cost-effectiveness of this approach. Another benefit of using robotic systems is the increased effect size, which can result in smaller sample sizes being needed thus improve study efficiency (Krebs et al., 2014).

Limitations

Because the study is ongoing, the results and findings are only preliminary. The Botswana cohort is not matched against the U.S. cohort due to the difficulty of recruiting. Additionally, despite choosing clinical assessments that have been previously tested in Botswana, there could be cultural, language, or educational differences that impact the results. Differences in the robotic system used in the U.S. and in Botswana could introduce another variable impacting the results.

Despite the early positive results, there remain challenges in increasing rehabilitation capacity in LMICs. We were only able to recruit in an urban area, but a large proportion of the population resides in rural areas. Overcoming this obstacle remains a challenge. However, incorporating existing strategies, such as community-based rehabilitation, could open opportunities to quantify the impact of community-based rehabilitation in more objective measures, which is something that is currently lacking.

6.6.1 Conclusion

We present preliminary results in this chapter on our work implementing a robot-based assessment in the Botswana context and compare our results to previous results collected in the U.S. Our findings demonstrate differences between the two groups but that HIV-related impairments are present and warrant rehabilitation in Botswana. Our approach provides an affordable and more efficient way to further study PLWH in limited resource settings and to meet the shortage of rehabilitation professionals.

6.7 Acknowledgements

This work was made possible through core services and support from the National Institute Of Neurological Disorders and Stroke of the National Institutes of Health (T32NS091006); the University of Pennsylvania's Center for AIDS Research (P30AI 045008); the Botswana-UPENN Partnership; the Institute of International Education, and the University of Pennsylvania's Departments of Bioengineering and Physical Medicine and Rehabilitation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CHAPTER 7 : CONCLUSION

7.1 Contributions

My work is one of the first efforts to apply rehabilitation robotics, cognitive neuroscience, and bioengineering principles to develop new methods to study HIV-related impairments. I allow for more inclusive studies by developing assessment methods that account for both cognitive and motor impairment. I am able to show that the robot-based assessments relate to clinically relevant measures, and that this approach is feasible in different environments and populations. These efforts lay the groundwork for the continued expansion of rehabilitation robotics to address additional aspects of disability and to develop more effective rehabilitation strategies that improve health outcomes globally.

This thesis is a progression of development, application, and implementation that started in Chapter 2 with a review of the mechanisms, manifestations, and treatment options of neurological injury in stroke and HIV, the additional challenges of managing HIV-associated stroke, and rehabilitation engineering approaches for both high and low resource areas to address the challenges. This laid the foundation to design new cognitive-motor assessments to study stroke and HIV.

In Chapter 3, I demonstrated in a chronic stroke population that a robot-based motor assessment task was sensitive to impairments in visuospatial and executive function. I also showed that performance metrics did not capture the same differences between functional groups. This highlighted the need for robot-based assessment strategies to take into account both motor and cognitive function.

In Chapter 4, I applied these new assessment tasks to measure HIV-related impairments. I showed the concurrent validity between metrics derived from these tasks and clinical assessment measures relevant to HIV. I also showed that PLWH demonstrate a wide range of function on motor and cognitive assessments that could benefit from rehabilitation. The

work in the chapter represents one of the first applications of rehabilitation robotics to quantify HIV-related impairment.

In Chapter 5, I examined in greater detail the performance of PLWH on an adaptive cognitive-motor assessment task, which revealed important considerations in the design of future assessment tasks.

In Chapter 6, I merged the efforts of the previous chapters with efforts to build rehabilitation capacity in limited resource areas by implementing a rehabilitation robot system to study HIV-related impairments in Botswana. This demonstrated the feasibility of a robotics approach in a global context.

In total, I have produced 2 journal publications, 1 book chapter, 6 conference papers, and an additional manuscript that has been submitted for review. The complete list of publications is provided below:

1. Bui KD, Lyn B, Roland M, Wamsley CA, Mendonca R, Johnson MJ. The Impact of Cognitive Impairment on Robot-based Upper Limb Motor Assessment in Chronic Stroke. (In review, submitted to Neurorehabilitation and Neural Repair)

2. Bui KD, Wamsley CA, Shofer FS, Kolson DL, Johnson MJ. Robot-based assessment of HIV-related motor and cognitive impairment for neurorehabilitation. Transactions on Neural Systems and Rehabilitation Engineering. Jan 2021. DOI:10.1109/TNSRE.2021.3056908 (journal publication)

3. Bui KD, Johnson MJ. Objective Robot-Based Measures of Cognitive and Motor Function in Stroke and HIV. International Conference on Biomedical Robotics and Biomechatronics. New York, NY. Nov 2020. (conference paper)

4. Johnson MJ, Bui KD, Rahimi N. Medical and Assistive Robotics in Global Health. Handbook of Global Health. Springer. Dec 2020. `https://doi.org/10.1007/978-3-030-05325-3_76-1` (book chapter)

5. Bui KD, Johnson MJ. Robot-Based Measures of Upper Limb Cognitive-Motor Interference Across the HIV-Stroke Spectrum. International Conference on Rehabilitation Robotics. Toronto, Canada. Jun 2019. (conference paper)

6. Bui KD, Johnson MJ. Designing Robot-Assisted Neurorehabilitation Strategies for People With Both HIV and Stroke. Journal of Neuroengineering and Rehabilitation. Aug 2018. (journal publication)

7. Bui KD, Johnson MJ. Developing Robot-Based Cognitive and Motor Tasks for People Living with Both HIV and Stroke. International Conference on Biomedical Robotics and Biomechatronics. Enschede, Netherlands. Aug 2018. (conference paper)

8. Bui KD, Johnson MJ. Robotic Assessment to Quantify HIV-related Episodic Disability in Stroke. Rehabilitation Engineering and Assistive Technology Society of North America Annual Conference Proceedings. Washington, D.C. Jul 2018. (conference paper)

9. Bui KD, Johnson MJ. Towards Robot-Based Cognitive and Motor Assessment Across the HIV-Stroke Spectrum. International Conference on Engineering and Medicine in Biology Society. IEEE. Honolulu, HI. Jul 2018. (conference paper)

10. Bui KD, Rai R, Johnson MJ. Using Upper Limb Kinematics to Assess Cognitive Deficits in People Living with Both HIV and Stroke. International Conference on Rehabilitation Robotics. London, England. Jul 2017. (conference paper)

7.2 Future Work

This work has many possible future directions, including some that are already in progress. In the immediate future, these robot-based methods will be used to study the interactions between aging with HIV and cognitive and motor performance. A robotics-based approach has the ability to characterize the progression of both motor and cognitive decline in PLWH. A better understanding of this will lead to development of neurorehabilitation strategies for

this population. Another possible direction is to explore the use of robot-based assessments for activities that are relevant to maintaining independence, such as driving.

We continue to evaluate the feasibility of a rehabilitation robotics approach in Botswana. In addition to collecting more assessment data, we will test the impact of robot-based rehabilitation in the chronic stroke population compared to conventional therapy alone. We have tied these research efforts with efforts to build capacity and and increased support for rehabilitation engineering research by partnering with a multidisciplinary team of clinicians, academic institutions, and external organizations. These collaborations are essential to producing much needed evidence that reveal the nature of the rehabilitation landscape in areas in which information is currently limited. This work can continue to lead to alternative approaches to characterizing disability and rehabilitation across additional patient populations around the world.

Additional work is needed to expand assessments to include more cognitive domains. While we focused primarily on executive function, other domains are also essential to maintaining independence, such as information processing, language, and memory. Development in these areas should be validated against clinical measures that specifically assess these domains, rather than relying on screening tests. The intersection of cognitive and motor function is growing area of focus, and relevant assessments are needed to manage the inherent complexities. Possible future areas of exploration with rehabilitation robotics include multitask or dual-task assessments and cognitive-motor interference. This work will shed light on whether cognitive function is an indicator or mediator of overall performance.

By taking into account an individual's performance across various motor and cognitive domains, a personalized rehabilitation approach can be developed. This requires an understanding of which strategies are most beneficial based on given limitations. Currently, individuals are often excluded from both research studies and from receiving rehabilitation because of the presence of moderate to severe cognitive impairment. Strategies and guidelines are needed to make access to rehabilitation more inclusive and accessible.

Given the relevance of the central nervous system to the populations we are studying, it will be critical to test the underlying neural mechanisms, which will involve merging current approaches with neuroimaging methods such as fMRI, MEG, or fNIRS. This will require interdisciplinary teams of clinicians, scientists, and engineers as well as higher-level support for these high-risk, high-reward endeavors.

A.1 TheraDrive Flow Chart

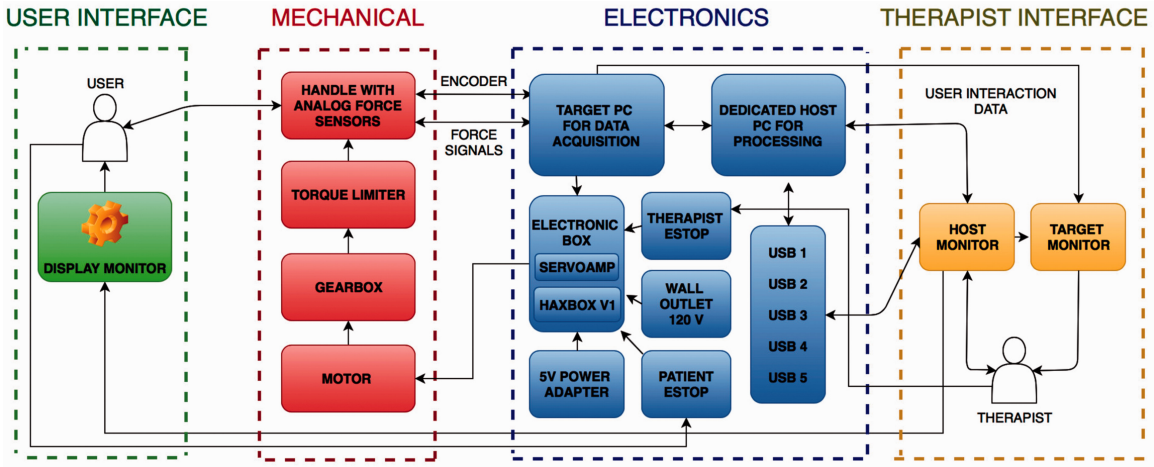

Figure 22: Flow chart for the Haptic Theradrive, a one degree-of-freedom rehabilitation robot system. Image used with permission (Johnson et al., 2017).

A.2 Multiple Linear Regression Models

For all plots, the top left subplot is the best model trained on the U.S. cohort. The top right subplot is the U.S. model applied to predict the Botswana cohort scores. The bottom left subplot is the best-performing Botswana model. The first set contains models trained on the dominant limb, while the second set contains models trained on the non-dominant limb. Adjusted R^2 values, normalized root mean squared error, and the linear equations are included for each model.

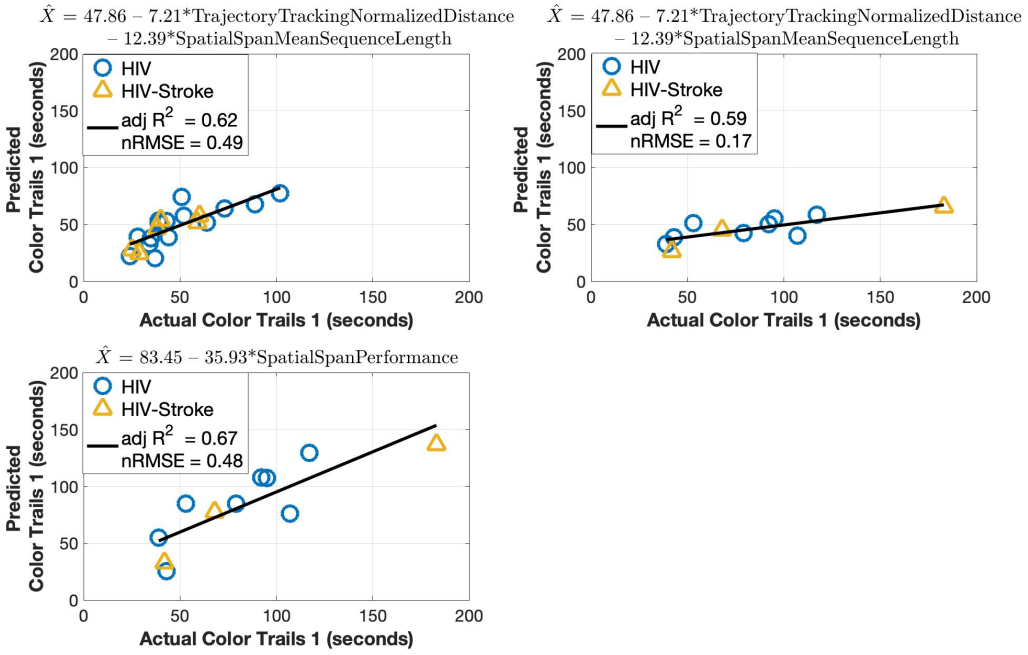

Figure 23: Color Trails 1 Dominant Limb Models

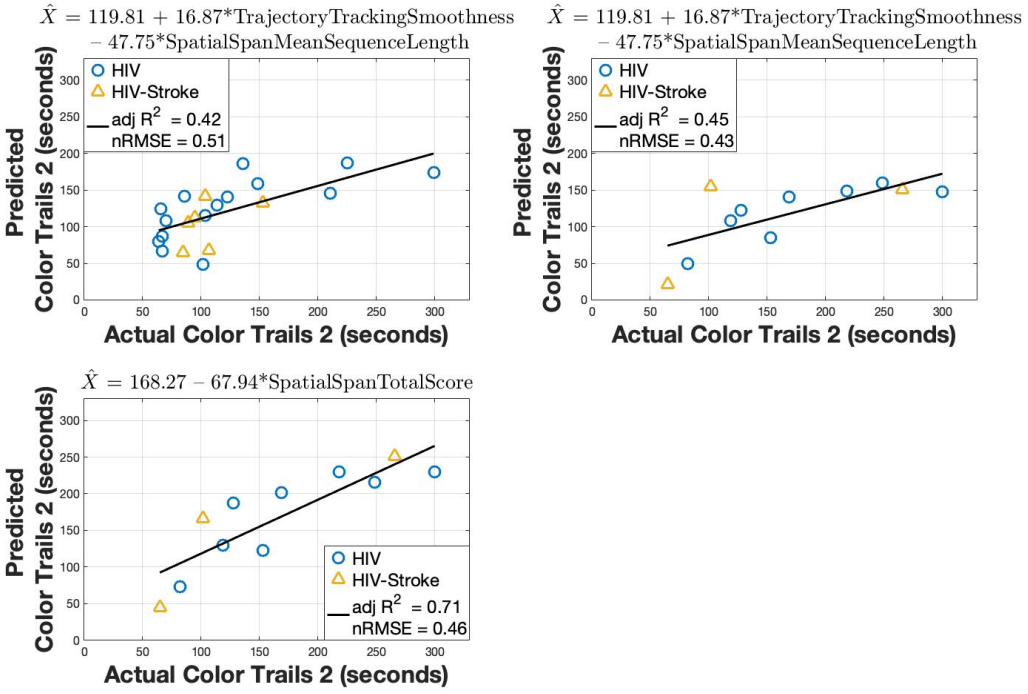

Figure 24: Color Trails 2 Dominant Limb Models

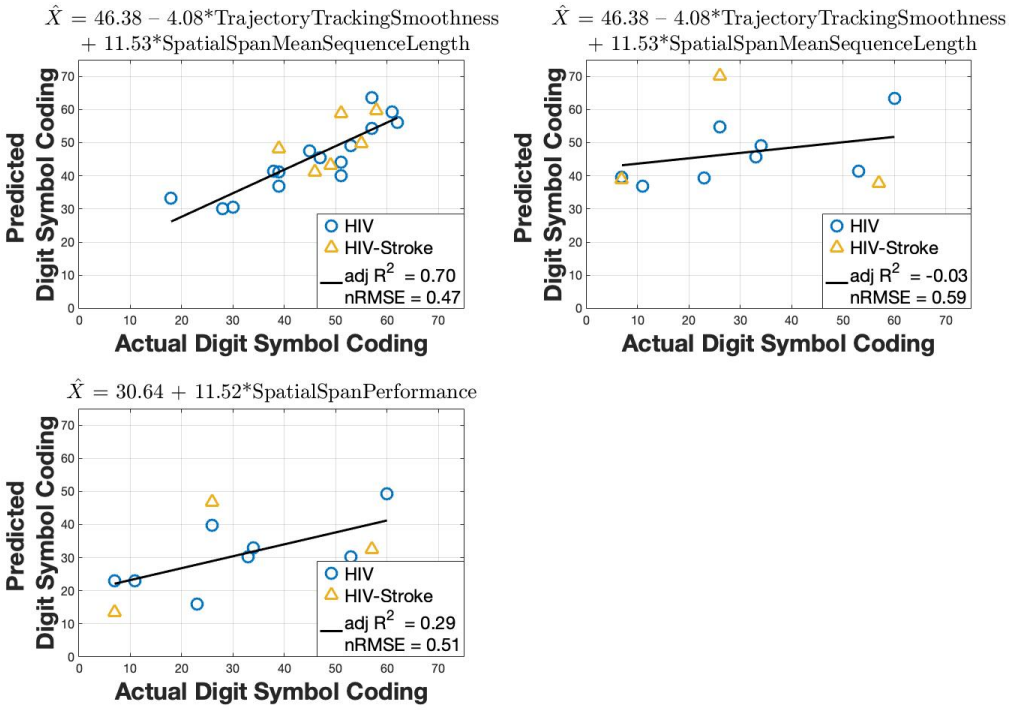

Figure 25: Digit Symbol Coding Dominant Limb Models

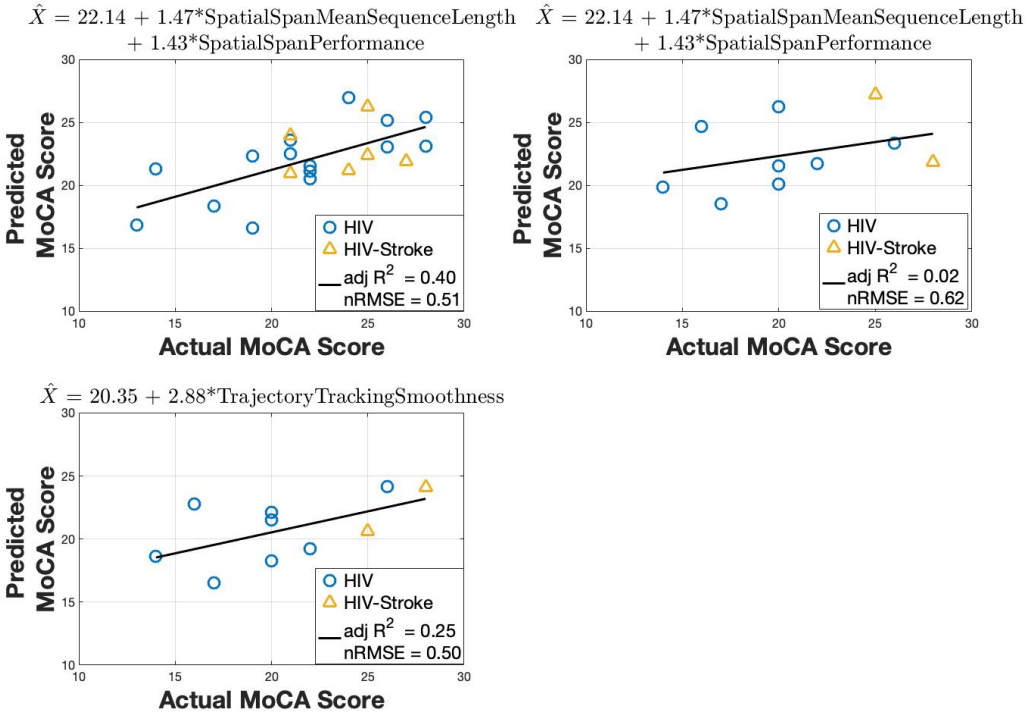

Figure 26: MoCA Dominant Limb Models

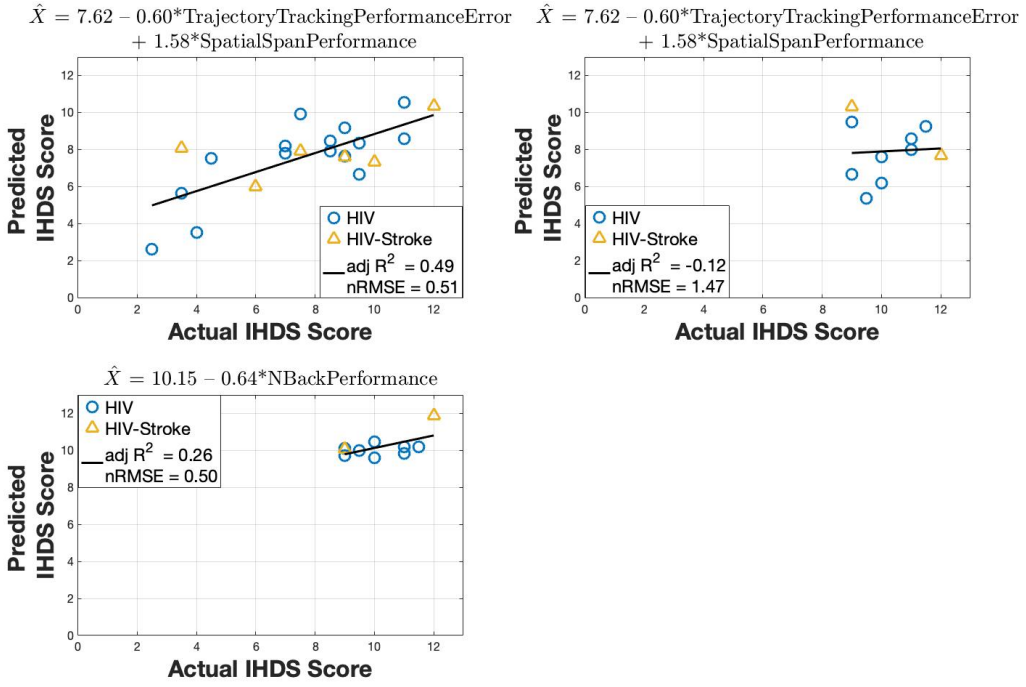

Figure 27: IHDS Dominant Limb Models

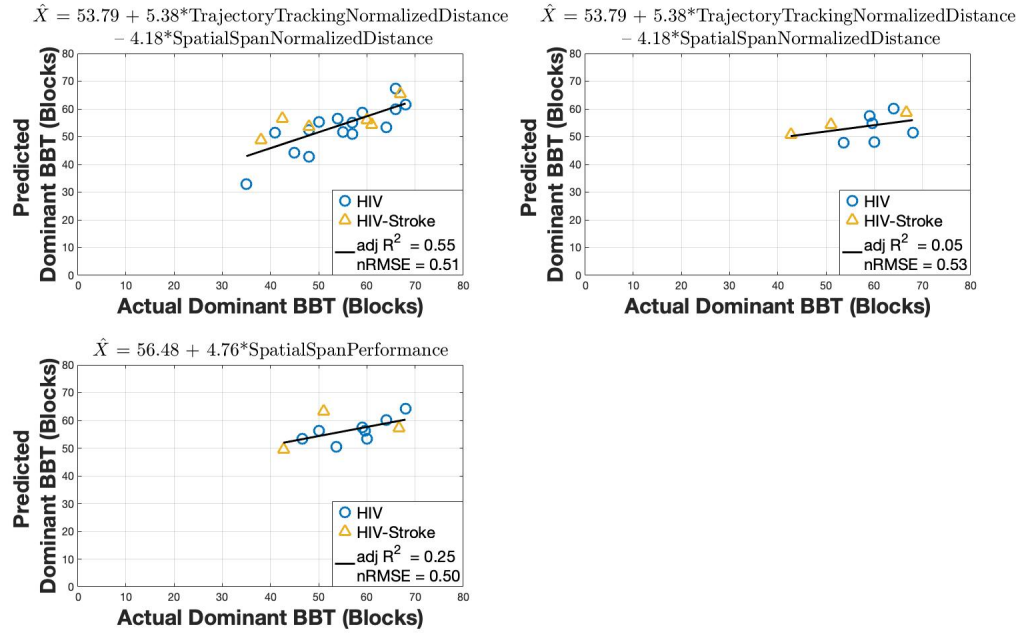

Figure 28: Box and Blocks Dominant Limb Models

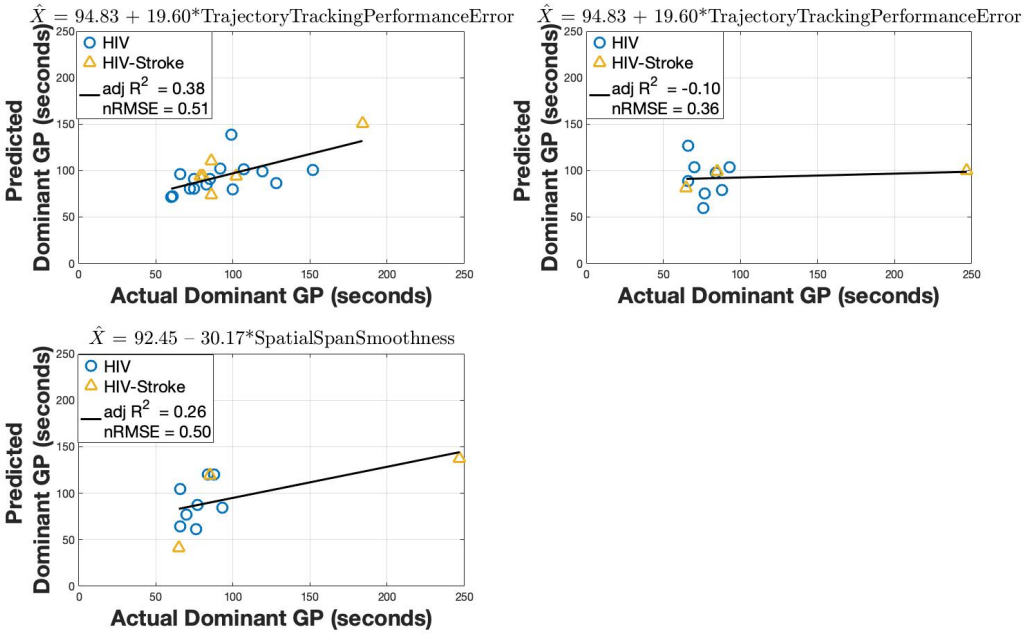

Figure 29: Grooved Pegboard Dominant Limb Models

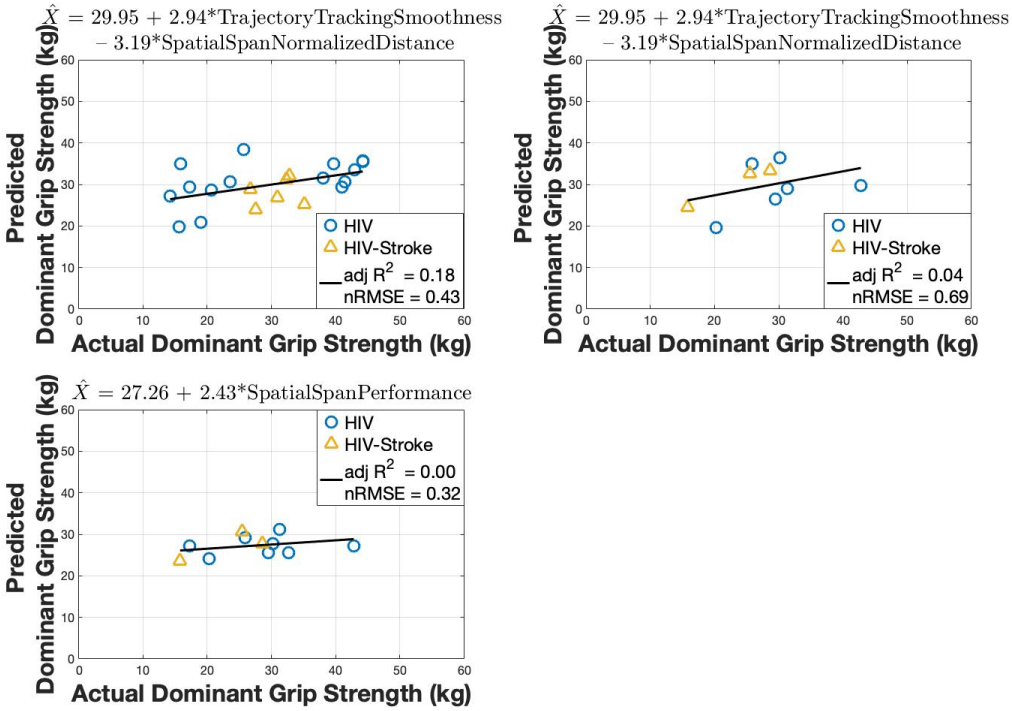

Figure 30: Grip Strength Dominant Limb Models

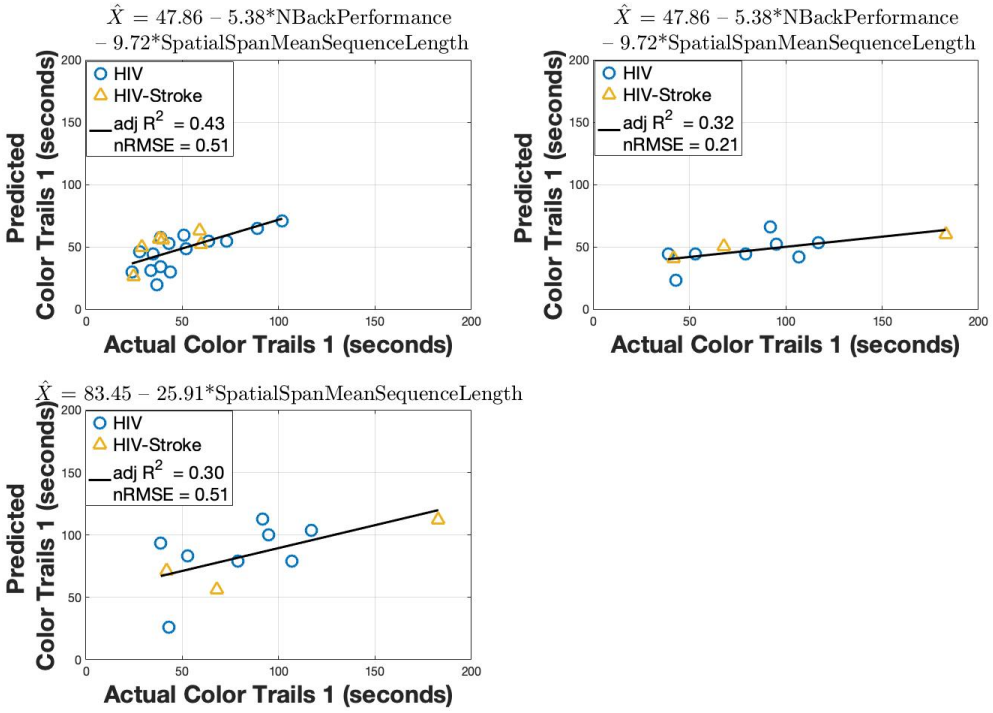

Figure 31: Color Trails 1 Non-dominant Limb Models

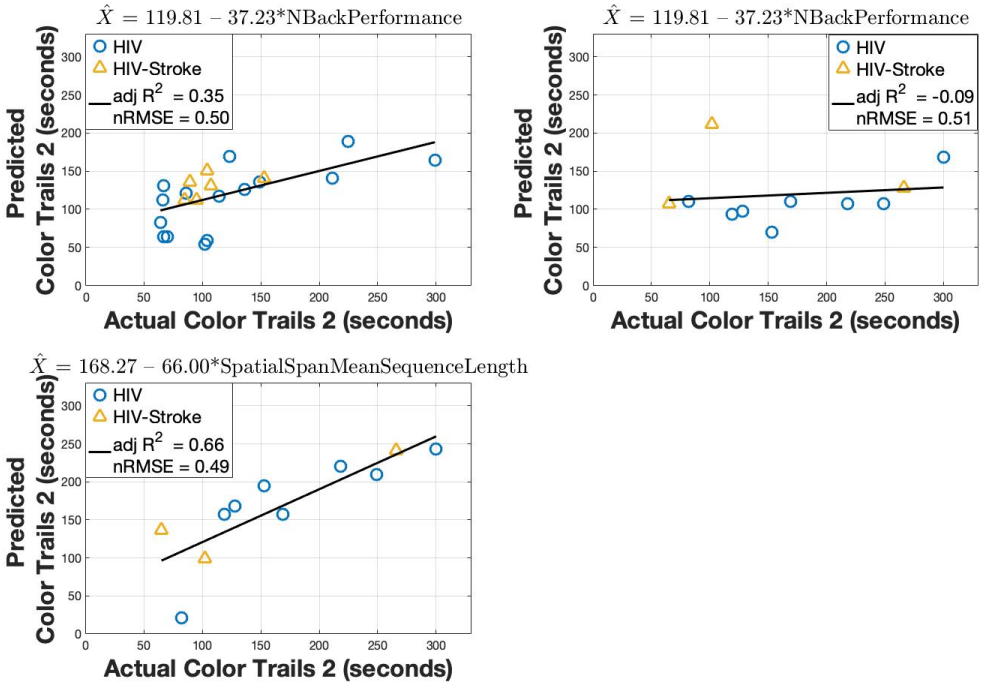

Figure 32: Color Trails 2 Non-dominant Limb Models

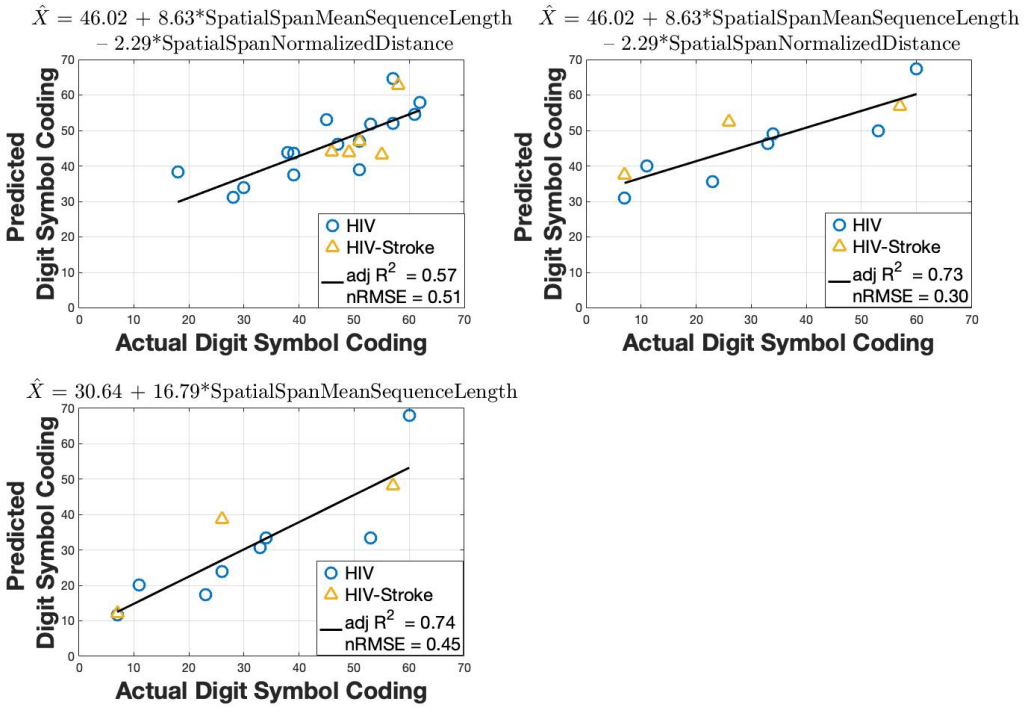

Figure 33: Digit Symbol Coding Non-dominant Limb Models

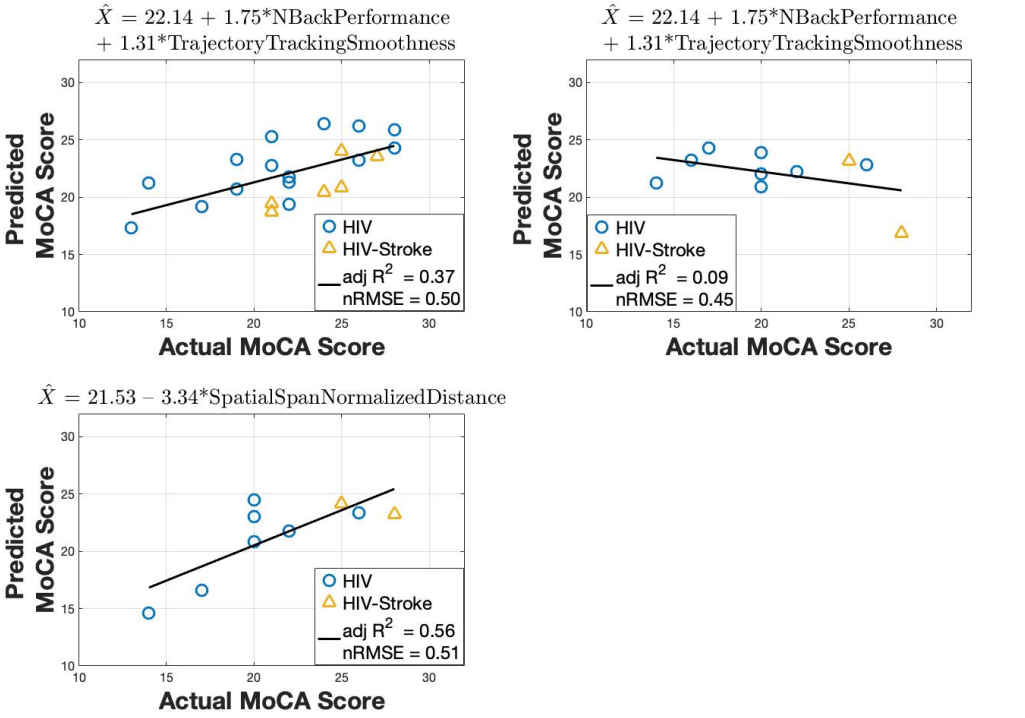

Figure 34: MoCA Non-dominant Limb Models

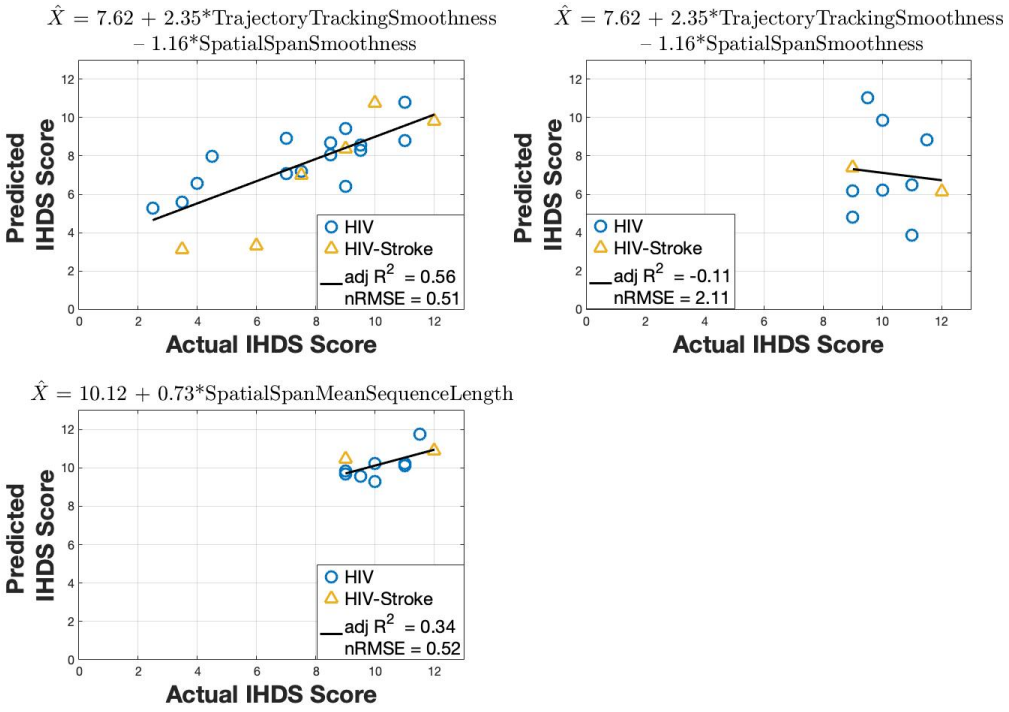

Figure 35: IHDS Non-dominant Limb Models

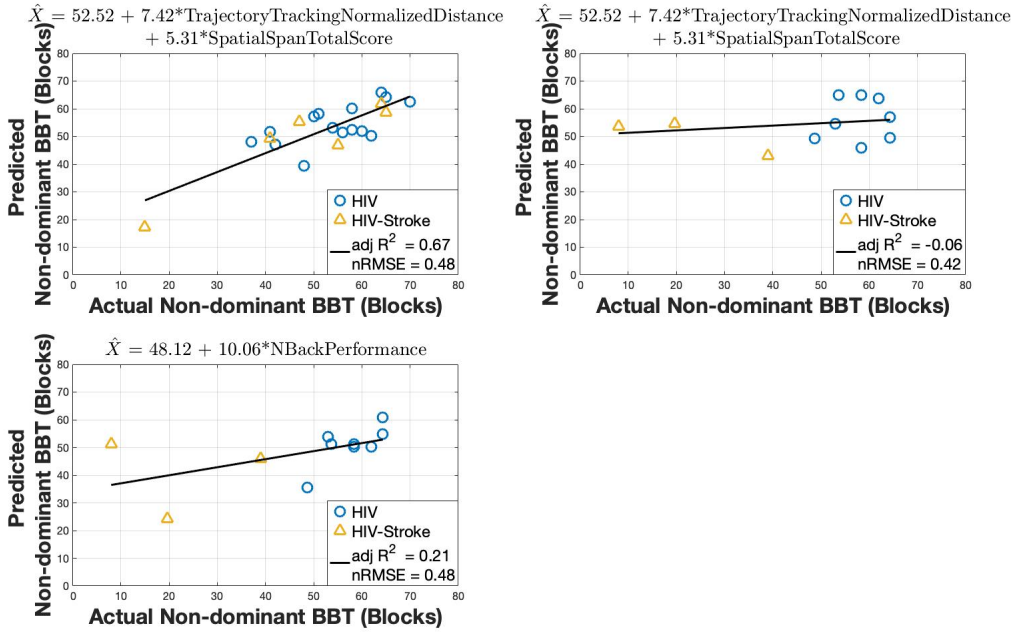

Figure 36: Box and Blocks Non-dominant Limb Models

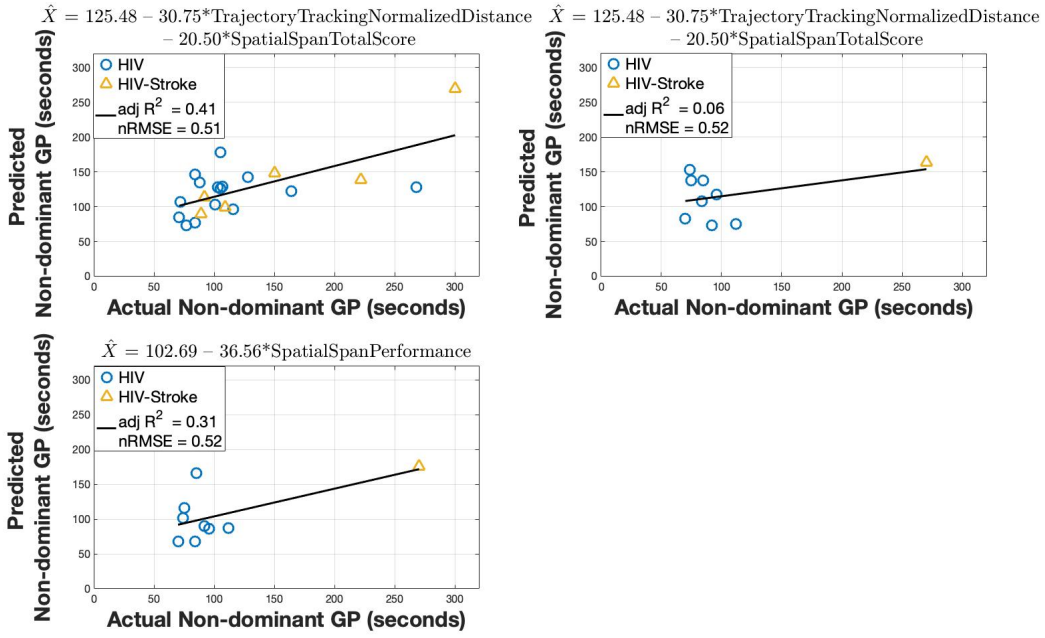

Figure 37: Grooved Pegboard Non-dominant Limb Models

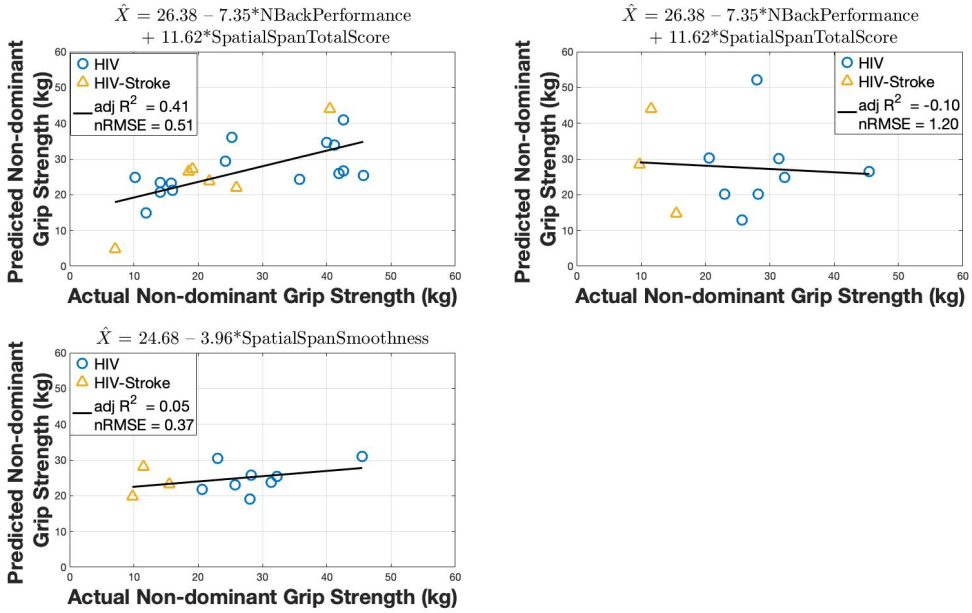

Figure 38: Grip Strength Non-dominant Limb Models

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