UNIVERSITY OF CALIFORNIA,
IRVINE

Proprioception and motor learning after stroke – insights from neuroimaging studies

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Biomedical Sciences

by

Morgan L Ingemanson

Dissertation Committee:
Professor Steven C. Cramer, Co-Chair
Professor David J. Reinkensmeyer, Co-Chair
Associate Professor Michael A. Yassa

2017

DEDICATION

To my parents,
For their love and support.
Herre.

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ACKNOWLEDGMENTS

I am eternally grateful to my dissertation co-advisors and committee co-chairs – the dynamic duo – Dr. Steven Cramer and Dr. David Reinkensmeyer. Your immeasurable wisdom and guidance has molded me into the scientist I am today. Steve, never have I met someone with a zest for life so contagious. Your passion for research is unbridled, your humility is admirable, and your witticisms are unparalleled. I hope to emulate such qualities in my future career; perhaps more Seinfeld will help. Dave, your gamble on me as a wide-eyed rotation student without a glimmer of an engineering background was the pivotal moment that kicked off my graduate career. Your sense of wonder and innovation is inspiring, and your dedication to improving the lives of others is laudable. Thank you for taking a chance on me. It has been an honor, a pleasure, and a privilege to work alongside both of you. I hit the graduate school advisor jackpot, twice. THANK YOU.

I would also like to thank my committee member Dr. Michael Yassa for his valuable neuroimaging insights that have helped shape this dissertation. Your guidance has reminded me that motor learning is only a piece of the puzzle.

Financial support for these projects were provided by the National Center for Medical Rehabilitation Research (R01 HD062744), the National Institute of Neurological Disorders and Stroke (K24-HD074722), and the National Center for Advancing Translational Sciences, National Institutes of Health (UL1-TR001414, UL1-TR000153).

For their help on the projects discussed in this dissertation, I thank Justin Rowe, Vicky Chan, Professor Wolbrecht, Jeff Riley, and Jennifer Wu. I am especially grateful for my wonderful lab mates who have made coming to work feel less like work and more like play. Robert, Nina, Arshie, Vu, and Jessica, thank you for the quirky debates, the impromptu mimosas, and for teaching me how to use chopsticks.

Many, many thanks to my friends who have supported me through good times and bad. Lisa, Sarah, Maryann – without our weekly wine therapy, graduate school would not have been nearly as rosé colored. Thank you for dragging me out of the lab and to the pool. And of course, I must thank Brady, my eternal optimist, for filling my life with more laughs than I thought possible. Thank you for being my sounding board, my practice audience, and my calm during turbulent times.

I will never be able to thank my parents enough for their unwavering love and support. You have encouraged my ambition, you have fostered determination, and you have never let me settle for anything less than my best. In doing this, you instilled in me the confidence to chase my goals, full speed ahead. In times of doubt, you have been the positive reinforcement that puts me back on my feet. Tears well up knowing you are always behind me.

And finally, though she cannot possibly know how much of a help she has been, I would like to thank my cat, Nala, for her immeasurable emotional support and tolerance of my smothering love.

CURRICULUM VITAE

MORGAN L INGEMANSON

Education

2013 – 2017 Ph.D., Biomedical Sciences, University of California, Irvine; Irvine, CA
2009 – 2013 B.A., Neuroscience, Pomona College; Claremont, CA

Research Positions

2013 – 2017 Graduate Student Researcher, Department of Anatomy & Neurobiology
University of California, Irvine; Irvine, CA
Research Advisors: Steven C Cramer, MD; David J Reinkensmeyer, PhD

2011 – 2013 Undergraduate Researcher, Department of Neuroscience
Pomona College; Claremont, CA
Research Advisor: Jonathan Matsui, PhD

2011 Edmondson Fellow, Department of Pathology & Laboratory Medicine
University of California, Davis; Davis, CA
Research Advisor: Nam Tran, PhD

Peer-Reviewed Publications

Ingemanson ML, Rowe JB, Chan V, Riley J, Reinkensmeyer DJ, Cramer SC. Somatosensory system integrity predicts hand functional gains after stroke. (In review)

Ingemanson ML, Rowe JB, Chan V, Riley J, Reinkensmeyer DJ, Cramer SC. Neural correlates of proprioceptive deficits after stroke. (In review)

Wolbrecht ET, Rowe JB, Chan V, ***Ingemanson ML***, Cramer SC, Reinkensmeyer DJ. Finger weakness and individuation: Their correlation with each other, combined effect on hand function, and uncertain relationship to corticospinal tract injury. (In review)

Rowe JB, Chan V, ***Ingemanson ML***, Cramer SC, Wolbrecht ET, Reinkensmeyer DJ. Robotic assistance, motivation, and somatosensation during movement training after stroke. (In review)

Ingemanson ML, Rowe JB, Chen V, Wolbrecht ET, Cramer SC, Reinkensmeyer DJ. Use of a robotic device to measure age-related decline in finger proprioception. *Exp Brain Res*. 2016; 234(1):83-93.

Tran N, Godwin Z, Bockhold J, Passerini A, Cheng J, ***Ingemanson ML***. Clinical impact of sample interference on intensive insulin therapy in severely burned patients: A pilot study. *J Burn Care Res*. 2014; 35(6):533.

Publications in Preparation

Zhou R, ***Ingemanson ML***, Choi JJ, Wu KM, Kaur A, Erani F, Yang DZ, Khaturi N, Cassidy JM, Scacchi W, Dodakian L, McKenzie A, Lopes CV, Cramer SC. Testing of a novel, home-based augmented reality system in chronic stroke subjects.

Conference Abstracts

Cramer SC, Cassidy JM, ***Ingemanson ML***, Srinivasan R. (2017) Effect of corticospinal tract injury on motor cortex function and connectivity after stroke. *International Stroke Conference.*

Cramer SC, Zhou R, ***Ingemanson ML***, Choi JJ, Wu KM, Kaur A, Erani F, Yang DZ, Khaturi N, Cassidy JM, Scacchi W, Dodakian L, McKenzie A, Lopes CV. (2017). Targeted training of a motor-parietal circuit improves its behavioral output. *International Stroke Conference.*

Ingemanson ML, Rowe JB, Chan V, Reinkensmeyer DJ, Cramer SC. (2016) Specificity of neural system injury in relation to motor and proprioceptive deficits post-stroke. *Society for Neuroscience.*

Ingemanson ML, Rowe JB, Chan V, Wolbrecht EB, Reinkensmeyer DJ, Cramer SC. (2016) Sensory and motor system predictors of treatment gains after robotic retraining of finger movements post-stroke. *American Society of Neurorehabilitation.*

Ingemanson ML, Rowe JB, Chan V, Cramer SC, Reinkensmeyer DJ. (2016) Understanding treatment gains after robotic retraining of finger movements post-stroke. *University of California, Irvine, Institute for Clinical and Translational Science, Translational Research Day.*

Ingemanson ML, Rowe JB, Chan V, Cramer SC, Reinkensmeyer DJ. (2016) Robotic retraining of finger movements after stroke. *International Stroke Conference.*

Ingemanson ML, Rowe JB, Chan V, Wolbrecht EB, Reinkensmeyer DJ, Cramer SC. (2015) Brain activity in sensorimotor areas predicts treatment gains from robotic finger rehabilitation. *Organization for Human Brain Mapping*.

Ingemanson ML. (2013) Impaired hair cell development in the anterior lateral line of a *Danio rerio* small-eyed mutant. *Pomona College Experimental Thesis Symposium.*

Ingemanson ML, Tran N. (2011) Maintaining tight glycemic control with a hematocrit correcting point-of-care glucose meter. *University of California, Davis Edmondson Fellowship Symposium.*

Academic and Professional Honors

2016 First Place Oral Presentation Award
Department of Anatomy & Neurobiology Graduate Student Retreat
University of California, Irvine

2016	Professional Development Certificate Graduate Professional Success in Biomedical Sciences Program University of California, Irvine
2016	International Trainee Canadian Partnership for Stroke Recovery
2014	Honorable Mention, Graduate Research Fellowship Program National Science Foundation
2012 – 2013	Mortar Board National College Senior Honor Society Pomona College
2010 – 2012	Scholar Award Pomona College

Appointments, Committees, and Activities

2016 – 2017	Clinical Marketing Associate Evoke Neuroscience, Inc.
2015 – 2017	Scientific Writer The Loh Down on Science, LDOS MediaLab
2015 – 2017	Vice Chair University of California, Irvine SCRC High School Fellowship
2014 – 2017	TechTrek Instructor American Association of University Women, California
2011 – 2013	Program Coordinator Hugh Edmondson Research Fellowship, University of California, Davis
2010 – 2013	Varsity Swimming Pomona College

Professional Memberships

2016 – 2017	Society for Neuroscience
2016 – 2017	American Society of Neurorehabilitation
2015 – 2017	American Heart Association
2015 – 2017	Organization of Human Brain Mapping
2011 – 2013	Sigma Xi, Scientific Research Society

ABSTRACT OF THE DISSERTATION

Proprioception and motor learning after stroke – insights from neuroimaging studies

By

Morgan L Ingemanson

Doctor of Philosophy in Biomedical Sciences

University of California, Irvine, 2017

Professor Steven C. Cramer, Co-Chair

Professor David J. Reinkensmeyer, Co-Chair

Stroke is a leading cause of adult disability and patient response to treatment is highly variable. To understand this heterogeneity, the anatomical integrity and functional activity of the post-stroke motor system has been well investigated. In contrast, remarkably limited attention has been paid to somatosensory system counterparts in terms of predicting motor outcomes. Proprioception is known to be an integral aspect of motor control, and many rehabilitation strategies are built upon a somatosensory-induced Hebbian plasticity framework. Unfortunately, clinical assessments of proprioception often fail to yield meaningful behavioral data and neural correlates to post-stroke proprioception function are poorly understood. Behavioral and neuroimaging assessments of the somatosensory system, specifically proprioception, may yield valuable insight to the heterogeneity in therapy-induced motor gains. Therefore, the current dissertation aimed to 1) develop an objective and sensitive proprioception assessment; 2) characterize the neural correlates of post-stroke proprioception dysfunction; and 3) identify predictors of motor gains from a 3-week course of robotic finger therapy, taking into equal consideration somatosensory- and motor-derived variables. A proprioception assessment

designed with the Finger Individuating Grasp Exercise Robot (FINGER) was capable of detecting age-related and stroke-induced decline in finger proprioception and proved to be more sensitive than standard scales. Among a population of 30 subjects with chronic stroke, finger proprioception deficits were present contralesionally in 67% and bilaterally in 56%. Post-stroke proprioception status was best explained by anatomical injury to somatosensory networks and changes in cortical connectivity between ipsilesional primary motor cortex (iM1) and secondary somatosensory cortex (iS2). After a course of robotic therapy, subjects showed variable improvements in arm motor function. Behaviorally, baseline proprioception status best predicted treatment gains, outperforming baseline measure of motor behavior. Neurologically, a combined model of somatosensory network injury and iM1-iS2 cortical connectivity explained 56% of variance in treatment gains. The comprehensive approach described here demonstrates that proprioception is an integral aspect of post-stroke motor recovery. Importantly, these results are the first to directly support the concept of somatosensory-induced Hebbian-like learning within the context of robot-assisted motor rehabilitation for chronic stroke. The findings illustrate the importance of incorporating proprioception into rehabilitation strategies and clinical decision making.

INTRODUCTION

The human brain goes nearly unnoticed as it works wonders to fulfill the requirements of every-day life in an impeccably precise manner. These unique capacities are only fully esteemed when functions fail, such as after stroke. Nearly 800,000 new strokes occur each year in the U.S., leaving victims with an array of cognitive and physical impairments – from vision problems to aphasia, sensory impairments, and motor deficits – leading to a primary cause of adult disability in the United States [1]. The most common deficit after stroke, and the focus of the research composing this dissertation, is hemiparesis, especially of the upper limb. A motor deficit is present in approximately 80% of patients with stroke early on and in 50% at chronic time points, amounting to approximately two million stroke survivors in the United States with chromic arm impairment [2]. Due to the need for inpatient services, rehabilitation, and follow-up care, the projected total cost of stroke is estimated at $119 billion by year 2020 [1]. Hence, there is a great need for novel ways to reduce disability and more effectively allocate resources.

Although spontaneous recovery of motor function occurs after stroke, long-term recovery is often largely incomplete [3]. Historically, neurologists dedicated little time to facilitating recovery of motor deficits. Of post-stroke hemiplegia, Wilson noted: “Unless the first two or three weeks witness material change for the better, prognosis should be expressed in guarded terms …” [4]. More recently, a richer understanding of motor recovery has been gained. Spontaneous recovery is now known to display a nonlinear, logarithmic pattern, reaching a plateau in 95% of patients 3 months after stroke [5–7]. Sadly, for most patients, these plastic processes yield inadequate recovery [3]. Thus, many stroke therapies currently under study aim

not to salvage acutely threatened tissue, but instead to promote repair and restoration of function [8].

While many restorative therapies are under study, including robot-assisted training, one insight is clear: stroke is a very heterogeneous disease with substantial variability between patients and their response to therapy even under controlled settings [9]. The goal of a breakthrough stroke rehabilitation incites the need to first understand and characterize this vast heterogeneity. The ability to predict patient response to treatment would enable physicians to better match the right patients with the right therapy, improve customization of interventions for individual stroke survivors regarding their capacity for recovery, and facilitate development of new neurorehabilitation approaches. To this end, a number of neuroimaging methods have been examined to better understand, predict, and guide post-stroke restorative therapies.

In response to this growing interest in establishing stroke recovery biomarkers, the anatomical integrity and functional activity of the post-stroke motor system has been well investigated [10, 11] yet relatively limited attention has been paid to somatosensory system counterparts in terms of influencing motor outcomes. Proprioception is known to be an integral aspect to effective motor control within a neurologically intact system [12, 13]. Many rehabilitation strategies are built upon a Hebbian plasticity framework, which provides useful strategies for enhancing motor recovery after stroke [14]. More specifically, evidence from robot-assisted rehabilitation suggests that afferent input caused by moving a limb provokes plasticity in sensorimotor brain areas [15]. Assessments of the somatosensory system, specifically proprioception, may yield valuable insight to the heterogeneous response to therapy.

The studies composing this dissertation sought to characterize post-stroke proprioception and to evaluate the role that somatosensory function plays in motor recovery after robot-assisted movement training. Prior research has investigated these aims with regard to the motor system [10, 11, 16–18], but has yet to fully illuminate somatosensory counterparts. This is largely because clinical assessments of proprioception lack the objectivity, reliability, and sensitivity needed to yield meaningful behavioral data [19–22]. Without behavior metrics that accurately represent proprioception function, it is difficult to identify neurological correlates of dysfunction or to assess proprioception's role in motor recovery. Furthermore, neural correlates of proprioceptive deficits after central nervous system (CNS) injury remain poorly understood likely because somatosensory functions such as proprioception arise from a highly distributed network [23, 24]. In order to evaluate post-stroke proprioception, it was first necessary to develop a tool to accurately assess proprioception behavior. Moreover, in order to develop a predictive model of therapy-induced motor gains that addresses motor system and somatosensory system variables, functional magnetic resonance imaging (MRI) measures of both systems were used to characterize an individual's remaining neural resource before beginning a three-week course of robotic finger therapy. Rehabilitation of the fingers was selectively chosen due to the considerable neural resources these distal extremities have dedicated to proprioception in order to optimize motor control.

The first aim of this dissertation was to establish use of an exoskeletal robot to objectively and sensitively assess finger proprioception (Chapter 3). The second aim examined neural correlates of proprioception deficits after stroke, as measured by the robotic technique established in aim 1, and taking into account neural injury and function (Chapter 4). The third and final aim explored a Hebbian concept of motor learning and examined which combinations

of variables derived from the motor system and somatosensory system most strongly explained variance in the functional motor gains resultant from robotic therapy (Chapter 5). Together, this comprehensive approach provides strong evidence that measures of the somatosensory system are predictive of therapy-derived motor gains. It also demonstrates that a multivariate model incorporating measures of both neural injury and cortical function, rather than either alone, best explains post-stroke proprioception status and predicts patient outcome –findings previously established for the motor system only [11, 16, 17]. Importantly, these results are the first to directly support the concept of Hebbian-like learning derived from robot-assisted therapy. The data resulting from this doctoral work strongly suggest that neuroimaging-based somatosensory measurements should be incorporated into future research as well as clinical decision making in order to optimally pair patients with rehabilitation therapies.

CHAPTER 1

MOTOR LEARNING AFTER STROKE

"Stroke is not a killer but a chronic and progressive disabling disease," S. Thomas Carmichael writes [25]. Over the past two years, stroke has fallen from the third leading cause of death to the fifth [1]. Although this decline is welcome and indicates improved care in the acute setting, it has outpaced the decline in stroke incidence. Thus, more survivors than ever are faced with battling the chronically disabling disease. To make matters worse, stroke is an exceptionally heterogeneous disease. Despite research efforts, the ability to accurately predict recovery after stroke is ever evasive. Throughout the process of repair, patients demonstrate wide variability across multiple domains including infarct size and location, acute impairment, response to treatment, and long-term outcome [26]. Characterizing these and other factors is a critical element to understanding stroke heterogeneity.

The first part of this chapter briefly addresses the neuroplasticity processes implicated in stroke recovery while the second part addresses restorative therapies including robot-assisted rehabilitation. The third and final part of the chapter reviews known variables related to recovery of motor function during chronic stroke and associated neuroimaging methodology.

1.1 Mechanisms of Neural Plasticity Supporting Recovery of Function

Neural plasticity is the brain's ability to develop new or alter existing neuronal connections, acquire new functions, develop new anatomical structures, and acquire new behavioral states, all useful for post-stroke recovery of impairments [27–29]. The same principles of neuroplasticity that modulate changes within a neurologically intact system are also at work after neural injury [30, 31]. Subsequent to a cerebral infarct, two major phases of repair

can be distinguished wherein the brain undergoes endogenous and learning-dependent neuroplasticity in order to mitigate damage and support recovery [32]. The first phase, spontaneous recovery, starts within the first few days post-stroke and involves intrinsic repair mechanisms that enhance functional recovery even in the absence of therapy. After several weeks, spontaneous recovery plateaus and the brain reaches a stable but still modifiable chronic phase, during which restorative therapy-induced recovery of function can occur.

In human patients, some degree of spontaneous behavioral recovery is usually seen in the weeks to months following stroke [26]. The elemental properties of neural repair include axonal sprouting [33], neurogenesis [34, 35], and alterations in neuronal excitability [36–38]. For example, on a cellular level, recovery after stroke mirrors the mechanisms of learning and memory and is associated with long-term potentiation-like phenomena and dendritic spine morphogenesis [25]. On a molecular level, growth-promoting factors such as BDNF and NGF are expressed by neurons in the peri-infarct area, creating a favorable environment to support dendritic growth and synaptogenesis [14, 39]. Subsequently, outgrowth is modulated by inhibitory factors to prevent overconnectivity [27]. In addition to the peri-infarct area, these events can also be measured in homologous sites in the contralesional hemisphere and in remote regions functionally connected to the site of injury [26].

This natural occurrence of motor recovery is remarkably heterogeneous: the first voluntary movements after hemiplegic stroke can been seen anywhere from 6 to 33 days after stroke onset [40]. The most dramatic improvements occur in the first 30 days, as revealed by studies on arm disability wherein maximum function was achieved by 80% of patients within 3

weeks and by 95% of patients within 9 weeks [7]. Yet, for most patients, spontaneous recovery plateaus before levels of pre-stroke function are reached.

Fortunately, many of the same plasticity processes involved in spontaneous recovery can be initiated in the chronic phase [41]. The experience-dependent plasticity that supports motor learning in the damaged brain is believed to derive from the same basis for learning in the intact brain. For example, motor skill acquisition is associated with changes in gene expression, dendritic growth, synaptogenesis, and neuronal activity in the motor cortex and cerebellum [30, 31, 42, 43]. As revealed by fMRI, these changes can manifest as a shift in interhemispheric lateralization, altered activity of association cortices that are linked to injured areas, and reorganization of critical representation maps [26, 30]. On a system level, greater recovery has been linked to the return of activation in the primary sensorimotor cortex [44]. Ultimately, motor recovery after stroke involves developing new neural connections and acquiring new functions [45].

In summary, the best behavioral outcomes after acute and chronic stroke are associated with the greatest return of brain function towards the normal state of organization. Although there is a general consensus regarding the mechanisms of neuroplasticity that support recovery, researchers have yet to agree upon the best course of treatment for stroke. The events that support neural plasticity give insight to potential restorative therapies that might best facilitate optimal recovery.

1.2 Restorative Therapies for Promoting Recovery After Stroke

Although spontaneous motor recovery reaches a plateau before patients return to pre-stroke levels of function, initiating neuroplasticity in the chronic phase with the administration of

restorative therapies can yield additional gains. Unlike thrombolytic therapy, which indirectly improves motor function by salvaging acutely threatened tissue, restorative therapies aim to promote repair and restoration of function in surviving tissue.

A variety of restorative therapies have been found to improve motor function in animal models of stroke, including small molecules [46, 47], growth factors [48], cell-based therapies [49], and cortical stimulation [50]. Although promising within animal models, these therapies have had limited success thus far when explored in human trials [51–54]. Challenges with translating preclinical therapies to successful clinical trials include a more homogeneous injury in animal models [55], an incomplete model of the hand-reliant human experience in quadrupedal animals [26], and a difference in white matter brain composition between rodents (14%) and humans (50%) [56].

The difficulty in translating preclinical restorative therapies to humans has left physical rehabilitation interventions as the standard approach for improving motor function after stroke [6]. Individuals typically receive intensive hands-on therapy for several months after stroke to treat hemiparesis and improve independence. A number of therapy forms, durations, and intensities have been studied, with no clear result as to differences in efficacy across schools of approach [8]. Some methods have entailed bilateral training [57], exercises in a gravity-reduced environment [58], or constraint-induced movement therapy [59, 60]. Although such therapies have demonstrated some degree of clinical utility, the optimal training techniques for facilitating reorganization have remained unclear. Challenges with quantifying dose and comparing content of therapies have impeded improvements in understanding the mechanistic underpinnings of rehabilitation science.

Robotics have increasingly been used to implement activity-based therapy in the context of stroke. Robotic devices allow physicians and researchers to precisely quantify dose, type, and consistency of rehabilitation therapy [9]. They also have the potential to allow more therapy with less supervision, improving rehabilitation cost-benefit profiles [61]. The primary therapy paradigm tested is active assistance [62–66], a clinical term that refers to exercises in which the patient attempts a movement (active) and in which a robotic device helps complete the movements if the patient is unable (assistance). Such active assistance may improve motor recovery by enhancing proprioceptive input and inducing a Hebbian-like learning paradigm [9], but this has yet to be directly explored in the context of stroke rehabilitation.

1.3 Predicting Upper Limb Treatment-Induced Gains After Stroke: A Motor System Story

Even within well-controlled robot-assisted rehabilitation studies, significant variability in individual response to treatment is observed [11, 15, 67] and the heterogeneity of stroke remains a major focus of ongoing research. Clinical factors such as age [68, 69], depression [70–72], and comorbidities such as diabetes [73], hyperglycemia , and hypertension [74] are known to negatively impact recovery. While important to consider in developing a post-stroke prognosis, these factors explain only a small amount of inter-subject variation and are unable to reliably predict outcomes [75, 76]. Thus, researchers have turned to other elements such as baseline impairment and neuroimaging-derived metrics of neural injury and neural function to characterize inter-individual differences. Notably, the vast majority of studies have investigated these features solely for the motor system [10, 11, 16–18]; somatosensory system counterparts

have remained largely uninvestigated. The utility of motor-derived variables in predicting motor outcomes post-stroke is the focus of this chapter section.

Baseline Impairment: Traditionally, the most commonly used prognostic indicator of spontaneous recovery, response to treatment, and long-term outcome have been measures of impairment. Baseline impairment of the motor system in particular has been commonly cited as a predictor of recovery and is currently used to guide post-stroke rehabilitative care. Overall, less severe baseline motor impairment in the acute setting has been correlated with greater treatment-related gains [77], shorter length of inpatient stay [78], and less severe impairment as discharge [79, 80]. Clinical behavior metrics of motor status in the acute phase have also demonstrated moderate utility in predicting chronic phase motor status [68]. Moreover, in the chronic phase, some studies have observed a linear relationship between baseline impairment and treatment-induced motor gains [81, 82] while others suggest a second order function wherein patients at the mild and severe ends of the impairment spectrum improve the least [83]. Yet, regardless of the mathematical function used to describe this relationship, baseline motor impairment fails to comprehensively elucidate the heterogeneous response to stroke [84].

Magnetic Resonance Imaging: Measures that characterize the structure of the biological target have shown promise in providing insight into the capacity for recovery beyond baseline clinical behavior metrics [77]. Brain mapping with MRI is a non-invasive approach for assessing structural integrity of the motor system after stroke. Lesion volume has had moderate success in predicting post-stroke outcome, such that larger infarcts and thus a greater degree of neural injury are associated with both greater baseline impairment and poorer long-term outcome [85, 86]. However, the relationship between infarction load and chronic post-stroke hemiparesis has

not been consistently observed across studies [87, 88], suggesting that plastic brain reorganization after stroke attenuates the effect of infarct volume on purposive limb movement.

In comparison to lesion size, a system-specific approach that takes into account lesion location has demonstrated enhanced utility in explaining degree of motor impairment and predicting rehabilitation gains. Structural measures such as gray matter density, gray matter volume, and gray matter injury in primary and secondary motor regions have been used to predict response to treatment [11, 17, 89]. Additionally, the degree of damage to the descending corticospinal tract (CST) from the primary motor cortex (M1) appears to be a particularly important factor for limiting upper limb recovery [90]. Assessing CST integrity can be achieved via Diffusion Tensor Imaging (DTI), an MRI-based neuroimaging technique. DTI estimates the anisotropy of water diffusion, expressed as fractional anisotropy (FA), to map the location and orientation of axon bundles [91]. Quantifying FA within the CST has helped explain the degree of motor impairment and muscle weakness in subjects with chronic stroke [92, 93]. Yet, performing white matter tractography in stroke patients often proves challenging, particularly in a heterogeneous sample, due the complete interruption of white matter tracts within the boundaries of large infracts. One workaround for this problem is calculating lesion load to a normal (canonical) CST generated from DTI tractography in neurologically intact subjects. This method has been shown to perform comparably to calculating lesion overlap using tracts generated from patients' own brains [11, 94, 95]. Quantified injury of the CST positively correlates with motor impairment after chronic stroke [92, 96] and has demonstrated improved prediction value of treatment-induced motor gains compared to baseline impairment and infarct volume [11, 16, 93, 95, 97].

Functional Magnetic Resonance Imaging: One of the limitations of structural neuroimaging is that it provides no information regarding how surviving tissues are working – or if they are working at all. Thus, a growing number of studies have explored the functional activation and connectivity of neural regions in an attempt to characterize the post-stroke brain. Functional MRI (fMRI) enables researchers to visualize brain regions activated in response to a task and to quantify how that activity changes in response to neural injury or therapeutic intervention. This is accomplished with the blood oxygenation level-dependent (BOLD) contrast, which is a relative ratio of deoxygenated to oxygenated hemoglobin reflecting neuronal activity. When a specific neural region becomes active, a local increase in deoxygenation occurs as oxygen is extracted. This is closely followed by an increase in cerebral blood flow, resulting in more oxygenated blood supplied to the region than is used by the active neurons. The net effect is a local decrease in deoxygenated hemoglobin and an increase in fMRI BOLD signal. These data can be used to measure regional activation as well as cortical connectivity, an indication of how functionally connected spatially remote regions are [98]. Functional MRI is therefore a non-invasive method for assessing brain function with high spatial resolution, enabling researchers to visualize how patterns of brain activity change in response to neural injury.

Studies utilizing fMRI to measure cortical activation and connectivity of motor circuits have provided insight into post-stroke motor behavior. After stroke, moving the paretic limb activates primary and secondary motor regions in both the ipsilesional (i.e., the lesioned hemisphere, located contralateral to the paretic limb) and contralesional (i.e., the neurologically intact hemisphere, located ipsilateral to the paretic limb) hemispheres. This pattern of activation is either not observed or observed to a much more unilateral extent in healthy individuals [99], and greater bilateral activation post-stroke is associated with greater motor impairment [44, 100,

101]. Conversely, normalization of brain activation patterns, marked by a shift in interhemispheric balance towards the ipsilesional motor cortex, is correlated with therapy-induced gains [15, 102–104]. Furthermore, functional connectivity has been valuable in predicting motor recovery after stroke. Increases in functional connectivity of the supplementary motor area and the contralesional and ipsilesional motor cortex have been shown to correlate with therapy-induced upper-extremity motor function [11, 105]. Collectively, these studies emphasize that changes in the functional activity and connectivity of the motor cortex can be induced in the chronic stroke phase to support motor recovery.

Electroencephalography: Electromagnetic measures of brain function after stroke via electroencephalogray (EEG) also demonstrate utility as predictors of long-term outcome. EEG is a low-cost, safe, and highly accessible methodology for rapid, non-invasive, bedside examination of brain function. Convergent evidence supports the value of a network-based approach for understanding the relationship between dysfunctional neural activity and behavioral deficit after stroke [106]. This is true for connectivity metrics derived from MRI, as previously discussed, and also for EEG-based measures of connectivity. EEG coherence between electrodes overlying brain regions of interest is a quantification of similarity of EEG signals in terms of wavelength phase and amplitude difference. It has been widely adopted as a surrogate marker of communication between cortical neural sources [107]. Many studies of post-stroke motor function have assessed coherence in the high beta frequencies (20-30 Hz) as this is the frequency bandwidth most strongly associated with function of the motor system [108, 109]. In a recent study from the Cramer lab, resting-state coherence between M1 and the rest of the cortex in the high beta band was shown to be a robust marker of baseline motor status, a biomarker of change in motor status across rehabilitation therapy, and a predictor of gains from therapy for subjects

with chronic stroke [110]. Thus, EEG measures of cortical connectivity may have value as biomarkers of cortical function and plasticity after stroke.

Multimodal Approach: Recent studies suggest a multimodal approach, particularly those that include measure of neural injury and function across multiple assessment modalities, best characterize stroke heterogeneity [11, 16, 18, 110, 111]. In the pivotal study by Stinear and colleagues, a predictive model of chronic stroke recovery that combined both a functional and structural measure of CST integrity outperformed models that included either measure alone [16]. The same group has extended these findings to predict upper limb recovery in an acute stroke setting via the PREP algorithm [18]. Aligned with these results, a recent study out of the Cramer lab reports that restorative therapy after chronic stroke was best predicted by a model including neural injury and function, represented by CST injury and interhemispheric M1 functional connectivity, respectively [11]. These studies clearly illustrate that the strongest predictive models include both structural and functional measures of brain state. Yet, multivariate studies to date have almost exclusively focused on characterizing variables of brain injury and function as they pertain to the *motor* system. The working hypothesis behind the studies described here is that a model that incorporates *somatosensory* system counterparts might lead to better insight to post-stroke recovery potential.

CHAPTER 2

PROPRIOCEPTION AND THE SENSORIMOTOR SYSTEM

The planning, execution, and optimal control of motor behaviors are complex neural processes that are in part dependent on correct sampling of multiple sensory modalities. Somatosensation, an umbrella term for the process of converting external stimuli into internal sensory impulses, plays a large role in movement production. The somatosensory system mediates a range of sensations – touch, pressure, vibration, limb position, heat, cold, and pain – that are transduced by receptors within skin, tendon, or muscle and conveyed to the brain. Particularly critical to the effective motor control needed to support activities of daily living is proprioception: the sense of position, motion, or force generated by the body [112]. Without correct processing and translation of proprioceptive input, motor outputs are abnormal or inaccurate. Thus, there is a tight link between sensory processing and movement production.

The first part of this chapter reviews the neuroanatomy of proprioception. The second part highlights the importance of proprioception function in motor control and discusses the theoretical role of proprioception in a Hebbian model of post-stroke motor rehabilitation. The third part reviews current state of knowledge regarding post-stroke proprioception characterization. The fourth and final part addresses shortcomings in clinical assessments of proprioception function and how a robotic approach might overcome them.

2.1 Neuroanatomy of Proprioception

The complex neurobiological machinery that supports somatosensation can be divided into functionally distinct subsystems that utilize their own sets of peripheral receptors and central pathways. One subsystem originates in specialized receptors that are associated with muscles,

tendons, and joints and is responsible for proprioception. Comprehensively, proprioception enables the ability to sense the position of one's limbs and other body parts in space. Yet in its classical definition, proprioception has several sub-components. Position sense refers to the ability to sense the static position of a joint or limb in space without the use of vision. Kinesthesia refers to the sense of movement of a limb of body part.

For most of the 20th century, sources of proprioceptive input were believed to be located in the joints themselves [113]. Today, it is understood that the peripheral receptors for proprioception, called mechanoreceptors, are primarily found in muscle, tendon, ligament, and joint capsule [114]. These mechanoreceptors depolarize in response to tissue deformation to transduce neural signals that provide sensory information on intrinsic and extrinsic joint loads. Four types of mechanoreceptors are dispersed throughout articular tissues [115]: a) Ruffini receptors behave as both static and dynamic receptors based on their low-threshold, slow-adapting characteristics and are thought to mediate the sensation of joint motion; b) Pacinian corpuscles are exclusively classified as dynamic receptors due to their rapidly adapting nature; c) Golgi tendon organs are stimulated at the extremes of joint motion; d) free nerve endings become active when articular tissues are subjected to damaging mechanical deformation. Additionally, muscle spindles are a type of mechanoreceptor found in skeletal muscle that contribute to proprioception [116]. Muscle spindles are comprised of three types of intrafusal fibers that differentially inform the CNS regarding muscle length or rate of change in length [117, 118]. These different types of mechanoreceptors have distinct response profiles to the same type of stimulus, which allows more discrete sensory information concerning mechanical stimuli to be transmitted to the CNS [119]. Afferent fibers that mediate proprioception project into the medical aspect of the dorsal roots and enter the dorsal horn of the spinal cord. From there, many

afferents form synaptic connections with second order neurons located in deeper layers of the dorsal horn, which ascend through the ipsilateral spinal cord [120]. Thus, integration of sensory input received from all parts of the body begins at the level of the spinal cord and is conveyed to all three levels of motor control: the cerebral cortex, brain stem, and spinal reflexes [121].

Ascending pathways to the cerebral cortex provide the conscious appreciation of joint position sense and kinesthesia. Specifically, coded signals from peripheral receptors ascend to the cortex via the dorsal column-medial lemniscal tract, relaying through the ventral posterior lateral (VPL) nucleus of the thalamus [120]. Most of the axons arising from neurons in the VPL project to cortical neurons located in layer 4 of the primary somatosensory cortex (S1), located in the postcentral gyrus of the parietal lobe [122]. From S1, there are a number of ways in which proprioception afferents gain access to circuits that initiate voluntary movements. Evidence from animal and human research shows that S1 and M1 are interconnected through rich fiber pathways [123, 124]. These connections are thought to help modulate the relationship between sensory and motor components of sensorimotor processes [125–127]. Neurons in S1 also project to other parietal areas which, in turn, supply inputs to neurons in primary motor and premotor areas of the frontal lobe [115]. Higher order cortical centers are also involved in processing proprioception information. One such area is the secondary somatosensory cortex (S2), which lies in the upper bank of the lateral sulcus. S2 receives somatosensory projections directly from the VPL and also indirectly, i.e., from S1 [128]. Connectivity mapping has shown that subregions of S2 in the human parietal operculum are densely connected to the pre-central gyrus and premotor cortex, suggesting that S2 has a functional role in sensory-motor integration processes like incorporating sensory feedback into motor actions [129].

2.2 The Role of Proprioception in Motor Control

Within a neurologically intact system, proprioception is responsible for relaying perturbations or changes in the external environment and also for modulating activity of motor neurons via descending efferent commands [130]. Contemporary theories of neuromuscular control emphasize the significance of proprioception in the planning of all motor output [114]. Convergent evidence demonstrates that proprioception provides a unique sensory component to optimize the control and regulation of coordinated movements, motor learning, and error correction during movements [12, 13, 131–133]. For example, disrupting proprioception signaling in neurologically healthy participants via tendon vibration produces consistent errors of wrist movement trajectories [134]. This integrated sensorimotor system is particularly noteworthy for hand and finger function given the large hand representation in the sensorimotor cortex [135].

Proprioception is believed to play a critical role in the Hebbian synapse, a widely used model for the process of learning in biological and artificial networks [136, 137]. This model proposes that greater neural plasticity is achieved when afferent input is optimally coupled to efferent commands [136]. Hebbian mechanisms are engaged when presynaptic and postsynaptic neurons are coincidently active and when neurotransmitter release occurs within a few tens of milliseconds after a multi-input-stimulated postsynaptic action potential [138, 139]. Following stroke, such coincident activity could reinforce that appropriate pre- and post-synaptic elements within a surviving circuit (or within a new circuit formed by axonal sprouting) are functioning correctly [27]. These coincidentally active connections are selected for retention or strengthening and contribute to behavioral recovery. Mounting evidence supports a fundamental role for Hebbian mechanisms in producing activity-dependent changes in synaptic strength in models of

learning and memory [140]. Likewise, it is thought that specific forms of use-dependent rehabilitative training can influence rewiring and functional outcome of motor behavior after stroke [141–143].

One type of use-dependent training believed to support Hebbian-like plasticity is robot-assisted rehabilitation. As discussed in Chapter 1, robotics have been a recent focus of attention with regard to their efficacy in inducing recovery of motor function post-stroke. The common conception of how robot-assisted training might facilitate motor recovery after CNS injury is based on a Hebbian-like theory of learning. It can be conceptualized mathematically as: $\Delta O = f(\sum_{N} M * S)$ such that correlated motor output (**M**) and sensory input (**S**) summed over many movement attempts (**N**), is the driving force for use-dependent change in motor outcome (**ΔO**). The function ***f( )*** expresses the presence of patient-specific neurological limits, partially dictated by the anatomy of the injury, on what practice can achieve in terms of recovered motor function. Given these principles, robot-assisted movement training could ostensibly enhance motor learning after stroke by finishing movements that patients initiate but are unable to complete, thereby intensifying joint, muscle, and cutaneous sensory input that is correlated with the patient's motor output.

Direct evidence for Hebbian-like mechanisms of motor recovery after stroke is lacking. Overall, the principle of Hebbian plasticity has received limited direct study in the context of post-stroke rehabilitation in part due to difficulty in designing a robotic device that would facilitate such studies. To investigate this model of motor learning, a robotic training device would need to enhance the sensory input associated with movement in order to strengthen functional connections between somatosensory neurons and motor output neurons in the cortex.

However, patient effort is considered crucial to increasing motor-plasticity during rehabilitation therapy [144, 145] and thus, voluntary motor movements on behalf of the patient would be required. Achieving this is a challenge robot-assisted therapies often face, as there is a possibility of the robot 'taking over' movement practice from the patient and allowing the patient to reduce their effort at the task [146, 147]. Additionally, time-correlated activity of efferent and afferent signals is critical to the Hebbian theory of learning. Robotic enhancement of somatosensation would need to occur in tight timing correlation with a patient's voluntary motor output.

An additional challenge to studying Hebbian-like recovery of motor function induced by a robotic device is the ambiguous understanding of the post-stroke somatosensory system. Somatosensory-induced brain plasticity is believed to support recovery of motor function [148], yet little is known about how sensory function predicts response to robot-assisted training. Researchers agree that it is especially important to assess proprioceptive function after central nervous system injury when the goal is to rehabilitate motor functions [149]. The neuroimaging methodologies that have so thoroughly investigated neural injury and function of the motor system have yet to fully extend to the somatosensory system. A better understanding of the relationship between somatosensory networks and motor recovery may allow researchers to confirm that robotic rehabilitation works in a Hebbian-like manner (i.e., is dependent on intact somatosensory pathways), and thereby lead to more accurate prediction of patient response to therapy. It might also lead to more suitable rehabilitation strategies in clinical settings and better matching the right patients with the right types of therapy.

2.3 Characterizing Post-Stroke Proprioception: An Incomplete Picture

Although the functional anatomy of proprioception in the peripheral and central nervous systems has been well studied in neurologically intact systems, post-stroke proprioception has not been fully characterized. Given that proprioception information is conveyed to the spinal cord, brain stem, and cerebral cortex using diffuse networks, it is unsurprising that proprioception deficits are particularly common after stroke. These sensory impairments are usually paralleled by motor deficits [150].

The field of stroke rehabilitation has seen several attempts to identify the percentage of stroke survivors with impaired somatosensation. Proprioceptive impairment is thought to occur in the contralesional upper limb in 50% or more of patients with stroke [151–158]. However, individual studies vary widely on the incidence of somatosensory dysfunction from 11% [159] to as high as 85% [160]. Regarding proprioception, Carey and Matyas found 49% of post-acute stroke survivors had impaired limb position sense, [155] whereas studies with chronic subjects have reported impaired proprioception ranging from 27% [161] to 52% [162]. Although the ipsilesional limb is typically thought of as the “unaffected” limb after stroke, ipsilesional proprioception deficits have also been observed [154, 163], yet the incidence of bilateral proprioception deficits is debated. Variation in incidence reports likely reflects the variation in assessment methodology, population under study, and the phase of recovery during which patients were investigated.

While the incidence of proprioception dysfunction is debated, researchers consistently agree upon the importance of assessing proprioception after stroke. Proprioception is critical to overall patient outcome, demonstrated via correlations between proprioception deficits and

length of hospitalization, increased mortality rates, detrimental effects on personal safety after discharge, and diminished quality of life [22, 153, 164–167]. Tyson and colleagues observed in their sample of 102 stroke patients that somatosensory deficits were related to functional mobility, independence in activities of daily living, balance, and weakness [161]. In sum somatosensory deficits, and proprioception impairments in particular, have an important negative effect on motor and functional performance [168].

Several neuroimaging studies have aimed to identify the neurological underpinnings of proprioception deficits after stroke. A direct lesion to S1 or along the primary afferent sensory pathway is likely to result in some level of somatosensory dysfunction [169]. Many studies have observed proprioception impairments after lesions to brain regions known to be involved in sensory processing such as the thalamus [170, 171], posterior limb of the internal capsule [172], and S1 and the posterior parietal cortices [172, 173]. The voxel-wise association between lesion location and somatosensory deficits in patients after stroke has also been explored. One recent study revealed that lesions in the sensory fibers of the superior thalamocortical radiation and the parietal operculum were associated with proprioception deficits in the arm and hand of 38 patients with acute stroke [174]. Yet, from the limited number of studies conducted so far, there is still limited certainty in optimal approaches to identifying a specific association between lesion site and proprioception function [175].

Neuroimaging studies have also investigated functional changes in somatosensory brain regions after stroke. One common finding after unilateral stroke is a shift in interhemispheric balance of activation from ipsilesional to contralesional sensorimotor areas. In parallel to studies of laterality shifts in M1 discussed in Chapter 1, the larger the imbalance between the S1's in

subjects with chronic stroke, the poorer motor task performance [176]. Resolution of S1 imbalance (i.e., a return to a state of normal functional activation) is associated with sensorimotor recovery [26, 177]. Regional analyses of S1 activity also support this conclusion, as a close relationship between increases in therapy-induced hand function and increases in ipsilesional S1 peak activation has been observed [178]. Similarly, fMRI activity in ipsilesional S2 has been linked with improved hand function after rehabilitation therapy [179]. Thus, sensory network activity appears to be closely related to sensory function and therapy-induced motor gains seen after stroke.

From a behavioral standpoint, the relationship between proprioception function and motor recovery is not as easily defined. Some studies have reported a significant correlation between these two variables [180, 181], while others have not [40, 182, 183]. For example, Wade et al. evaluated 25 prognostic factors and reported that initial motor deficit and loss of position sense in the arm were both significant correlates of motor function recovery of the hemiplegic upper arm [181]. In contrast, Katrak et al. found that proprioception in the upper arm was not correlated with recovery of hand movement of function over a 3 month period [182]. These mixed results may be due to the differences in proprioception measures, the specific body part assessed, and heterogeneity in subject populations. Because of the complexity of the central sensory system, studies employing objective behavioral mapping techniques and multimodal imaging will yield the most useful data in elucidating the role of somatosensation in recovery from brain damage [125].

2.4 Assessing Proprioception

Although physicians and therapists agree on the importance of assessing proprioception function after stroke [184], current methods used to evaluate proprioception are riddled with problems. In a survey among 172 clinicians, 98% routinely provided treatment in sensory impairments, yet fewer than 30% reported use of standardized measurements for somatosensory assessments [185]. Moreover, seemingly 'standardized' somatosensation assessments have in fact been found to be not standardized [21, 22]. On a whole, clinical assessments of proprioception remain crude and are known to have low sensitivity and high variability [21, 154], floor effects [19] and poor inter-rater reliability [20, 21, 158, 166]. This variation and subjectivity of somatosensory testing undoubtedly contributes to the challenges with defining the frequency of discriminative somatosensory loss.

Given the complexity of proprioception, it has been difficult to develop a single measure that can capture proprioception acuity. Many somatosensory testing batteries exist, such as the Fugl-Meyer sensory scale [186], Nottingham Sensory Assessment (NSA) [22, 187], and Rivermead assessment of somatosensory performance (RASP) [22, 162]. Although these batteries demonstrate improved standardization and reliability, variation across studies may still be influenced by measures used, body parts tested, time post-stroke when studies are performed, and the populations investigated. This was demonstrated in a recent publication that systematically reviewed the possibilities of assessing proprioception [188]. A total of 57 studies were included in the report, from which 32 different methods for assessing proprioception were described. Variations came with respect to measuring different proprioception subsenses (i.e., active versus passive position, motion detection, or direction discrimination), measuring different joints, and the use of different types of equipment and values [188].

A sensitive, reliable, and purely objective tool would overcome many of the challenges that clinical assessments face. Robots have potential to fulfill this role. Robotic devices have been developed to quantify sensorimotor impairments in the upper arm, wrist, and hand following stroke [151, 189–193]. Perhaps the most widely used robotic assessment of proprioception is executed by KINARM (BKIN Technologies Ltd.). The KINARM device applies mechanical loads at the shoulder and/or elbows in order to move a subject's impaired upper limb into different positions along the horizontal plane. Subjects then mirror these positions with their other (free) arm with vision occluded [194]. Prior studies utilizing such devices have revealed that stroke and traumatic brain injury patients frequently have sensory deficits despite receiving normal scores on traditional clinical assessments [151, 189, 193]. Though this approach is a marked improvement from clinical assessments in terms of reliability, sensitivity, and granularity, it poses a problem in that the ipsilesional ("unimpaired") limb is assumed to have fully intact proprioception. Yet in fact, the ipsilesional limb is known to display proprioception deficits post-stroke [154, 163].

In order to investigate the degree of proprioception loss from post-stroke pathology, a sensitive and objective behavioral assessment of proprioception that does not rely on the ipsilesional limb for mirror matching is essential. Such an assessment would not only facilitate the characterization of post-stroke proprioception, it would also provide an independent behavioral variable that could be used to evaluate proprioception's predictive power for therapy-induced motor gains.

CHAPTER 3

USE OF A ROBOTIC DEVICE TO MEASURE AGE-RELATED DECLINE IN FINGER PROPRIOCEPTION

Abstract

Age-related changes in proprioception are known to affect postural stability, yet the extent to which such changes affect the finger joints is poorly understood despite the importance of finger proprioception in the control of skilled hand movement. We quantified age-related changes in finger proprioception in 37 healthy young, middle-aged, and older adults using two robot-based tasks wherein participants' index and middle fingers were moved by an exoskeletal robot. The first task assessed finger position sense by asking participants to indicate when their index and middle fingers were directly overlapped during a passive crisscross movement; the second task assessed finger movement detection by asking participants to indicate the onset of passive finger movement. When these tasks were completed without vision, finger position sense errors were 48% larger in older adults compared to young participants ($p < 0.05$); proprioceptive reaction time was 78% longer in older adults compared to young adults ($p < 0.01$). When visual feedback was provided in addition to proprioception, these age-related differences were no longer apparent. No difference between dominant and non-dominant hand performance was found for either proprioception task. These findings demonstrate that finger proprioception is impaired in older adults and visual feedback can be used to compensate for this deficit. The findings also support the feasibility and utility of the FINGER robot as a sensitive tool for detecting age-related decline in proprioception.

Introduction

Proprioception, the sense of how our bodies are positioned, is a critical component of voluntary movement control and is important for generating smooth, coordinated movements and for maintaining upright posture and balance [195]. Muscle spindles [118, 196], cutaneous receptors [197], and joint mechanoreceptors [198, 199] provide proprioceptive feedback to the central nervous system that is essential for determining the position of distal body segments [132]. Not surprisingly, functionally deafferented individuals suffer profound disturbances in arm and hand function [12, 200], postural control [201], and locomotion [202].

A number of investigations have provided evidence that proprioception is affected by healthy aging and have focused on the ability of older individuals to detect passive motion or reproduce experimentally pre-determined joint positions in the lower limb [203–205]. It has also been well documented that these changes in lower extremity proprioception contribute to the decreases in postural stability often associated with healthy aging [206, 207]. Collectively, these data have been taken as evidence of compromised proprioceptive acuity that is thought to contribute to age-related postural instability [208], which lends to an increased risk of falls in older adults [209, 210].

Evidence also exists that upper limb static position sense is impaired in older adults, as demonstrated by an object-based spherical hand grasp-matching task [211] and by limb position reproduction tasks about the elbow [212, 213] and wrist [214]. Additionally, passive movement detection thresholds about the wrist joint are up to twice as high in older compared to young healthy participants [215]. However, little is known regarding the effect of age on proprioception the finger joints, despite the importance of proprioceptive feedback for coordinated hand and arm

control that is of critical use in activities of daily living and in maintaining functional independence [151, 152]. This age-related decline in joint position sense acuity needs further characterization, including direct measurement of finger joint proprioception.

To our knowledge, there are only a few tests designed to assess position sense in finger joints [211, 216, 217]. Clinical assessments of proprioception are commonly based on discriminating the upward or downward position of a passively moved finger [21, 184]. While traditional evaluations of sensory function often include proprioceptive tasks [184] and have proven useful in evaluating the condition of patients with stroke [155] and other impairments, these assessments are frequently insensitive, unreliable, subjective, and found to lack standardization [21, 22]. In contrast, robotic assessments are quantitative, sensitive, and can detect motor and sensory deficits in patients who receive normal scores on traditional clinical assessment measures [61, 189, 218]. For example, KINARM is a device that measures and perturbs shoulder and elbow joint positions and has provided reliable quantitative assessments of deficits in limb position sense for patients with stroke and traumatic brain injury [151, 152, 213, 219]. The largest study to date that assessed systematic aging-related declines in position sense with robotics used the robot to move one arm passively to a location in space, then asked the participant to match the location of the arm [213]. Several age-related declines in shoulder and elbow proprioception were identified, including variability and absolute error. Extending the use of robotics to assessing proprioception in healthy individuals can improve understanding of the effects of healthy aging on human proprioception and dexterity.

In this study, we examined finger proprioception in healthy participants through the use of a novel exoskeleton robot called FINGER. FINGER is capable of individually assisting both

the index and middle fingers through a natural grasping motion [220]. Each finger is individually guided by an 8-bar mechanism that controls the orientation and position of the proximal phalanx and the position of the middle phalanx, thus providing a naturalistic curling motion around the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints (Fig. 3.1). We designed a novel finger proprioception task, as well as a second task that mimics current neurological practice, and used them to assess young, middle-aged, and older adults. We hypothesized that older participants would generate larger errors in the passive finger position sense test and have delayed proprioceptive reaction times compared to younger participants. Additionally, we hypothesized that adding visual feedback of the hand being tested during these tasks would help participants to compensate for any proprioception errors. As a secondary aim, we also compared the two proprioception tasks across each participant's dominant and non-dominant finger joints to determine if a relative hand advantage for proprioceptive processing was present.

Methods

Subject Enrollment

Healthy participants, aged 22-87 years were recruited. Exclusion criteria included any history of hand injury (such as wrist, hand, or finger fractures or the presence of surgical hardware) or pathology (such as diabetes, stroke, or arthritis). Handedness was determined using the Edinburgh Handedness Inventory [221]. The local ethics committee approved this study and written informed consent was obtained from each participant prior to participating, following procedures established by the University of California Irvine Institutional Review Board.

Experimental Design with FINGER

The experiment took place across a single session and involved use of the exoskeleton rehabilitation robot, FINGER (Fig. 3.1) [220]. FINGER is capable of individually moving both the index and middle fingers through a natural grasping motion. Each finger can be individually guided by an 8-bar mechanism that controls the orientation and position of the proximal phalanx and the position of the middle phalanx. Each 8-bar mechanism has a single degree-of-freedom and is actuated by a high bandwidth and low-friction linear electric actuator. In designing FINGER, a regression analysis was used to determine the angular relationship between the middle and proximal phalanges for 7 healthy motion capture participants, using a second-order polynomial equation (Fig. 3.2) [220]. As the relationship between the PIP and MCP joints has been quantified and movement of these joints is highly correlated, for simplicity we reference error with regard to the MCP joint. However, position sense assessments reported here are thought to derive from both the PIP and MCP.

In this experiment, we used the FINGER robot to actively move the participant’s passive index and middle fingers through a crisscross motion (Fig. 3.2). All movements followed minimum jerk trajectories calculated to take the desired finger from its starting point to its target point over the course of 5 seconds, with fingers moving at a MCP angular velocity of 0.24 radians per second. For all crisscrossing movements, FINGER moved participants' index and middle fingers in opposing directions and always came to pause with the fingers separated by 30% of the natural range of motion (ROM) for these two fingers. Thus, at only one point in time during each crisscross movement were the participants' index and middle fingers directly aligned. The rate of change of the separation distance between the fingers was identical for all crisscrossing movements (Fig. 3.2). However, the position in space where the fingers were

directly aligned varied for each crisscross movement. In order to achieve this, FINGER alternated between symmetric and asymmetric finger movement paths (Fig. 3.2). During symmetric movements, the index and middle fingers made mirrored movements through 30% ROM; during asymmetric movement paths, one finger moved through a larger range than the other to create different finger velocity profiles. The magnitude of asymmetry varied between 10-70% ROM before fingers came to rest separated at 30% ROM, with the various asymmetric movement paths presented in a pseudo-randomized order. A pause time with duration pseudo-randomized to be between 0-3 seconds followed each crisscrossing movement in order to generate crisscross finger motions that were non-periodic and therefore unpredictable to participants through use of timing strategies.

Two proprioception tasks were performed using the same robot-controlled finger motions generated by FINGER: a finger overlap task and a movement onset task. For each task, a total of 12 crossover movements occurred over approximately 2 minutes. Participants first performed the finger overlap task, then each was assessed to confirm that they understood the overlap task, and then they performed the movement detection task on either their dominant or non-dominant hand. All experimental procedures were then repeated with their other hand. The order of hand testing was counter-balanced across participants. The timing sequence of each finger movement and each rest period was identical within and across participants. All participants wore noise-canceling headphones throughout testing to neutralize any sound emitted from FINGER.

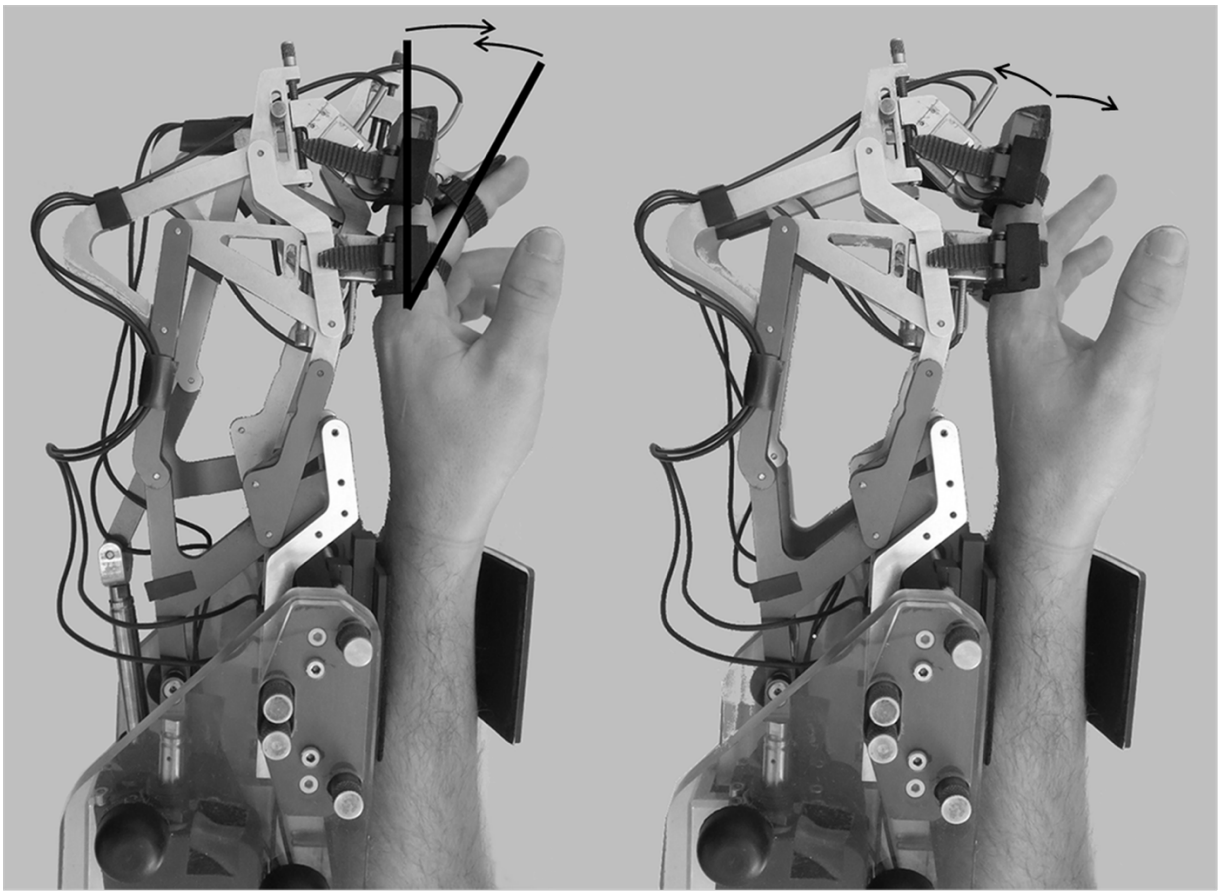

Figure 3.1. FINGER robot with two 8-bar finger curling mechanisms and two actuators that allow for naturalistic grasping motions by controlling the angle and position of the proximal phalanx and the position of the middle phalanx. The index and middle fingers attach to the robot and are guided through crisscross finger movements during the proprioception tasks; movement stops and reverses directions when fingers are separated at 30 % of range of motion (defined by *bold lines*).

Passive Finger Position Sense: Overlap Task

Passive finger position sense was measured with a finger overlap task. During the overlap task, all participants were properly fitted into FINGER and asked to relax their hand. Test trials were repeated if any evidence of active movement was observed. Participants were instructed to press the spacebar on a keyboard with their free hand when they perceived their index and middle fingers from their test hand were directly overlapped on top of one another. Participants completed the overlap task under two different feedback conditions: first with visual access to their hand and then with vision occluded. Error was defined as the amount of finger separation, measured in degrees about the MCP, that existed when the participant indicated they felt their index and middle fingers were directly overlapped. Error included angles with both negative and positive degrees, as responses occurred both before and after fingers were directly overlapped (0°). However, unless otherwise stated all analyses report group errors as averages of absolute errors.

Following completion of the overlap task, participants completed an assessment to evaluate their comprehension of the overlap task. Participants who were able to describe the desired finger position when they tapped the spacebar using specific keywords (such as "overlapped", "aligned", and "in parallel") were deemed cognitively aware and compliant of the overlap task instructions. This assessment also had participants indicate if they could feel their fingers 1) start moving, 2) stop moving, or 3) cross over during the overlap task. These three questions referenced the index and middle fingers separately and were answered yes/no. The entire assessment was completed for both the dominant and non-dominant hands, directly after concluding the overlap task with vision occluded for each hand.

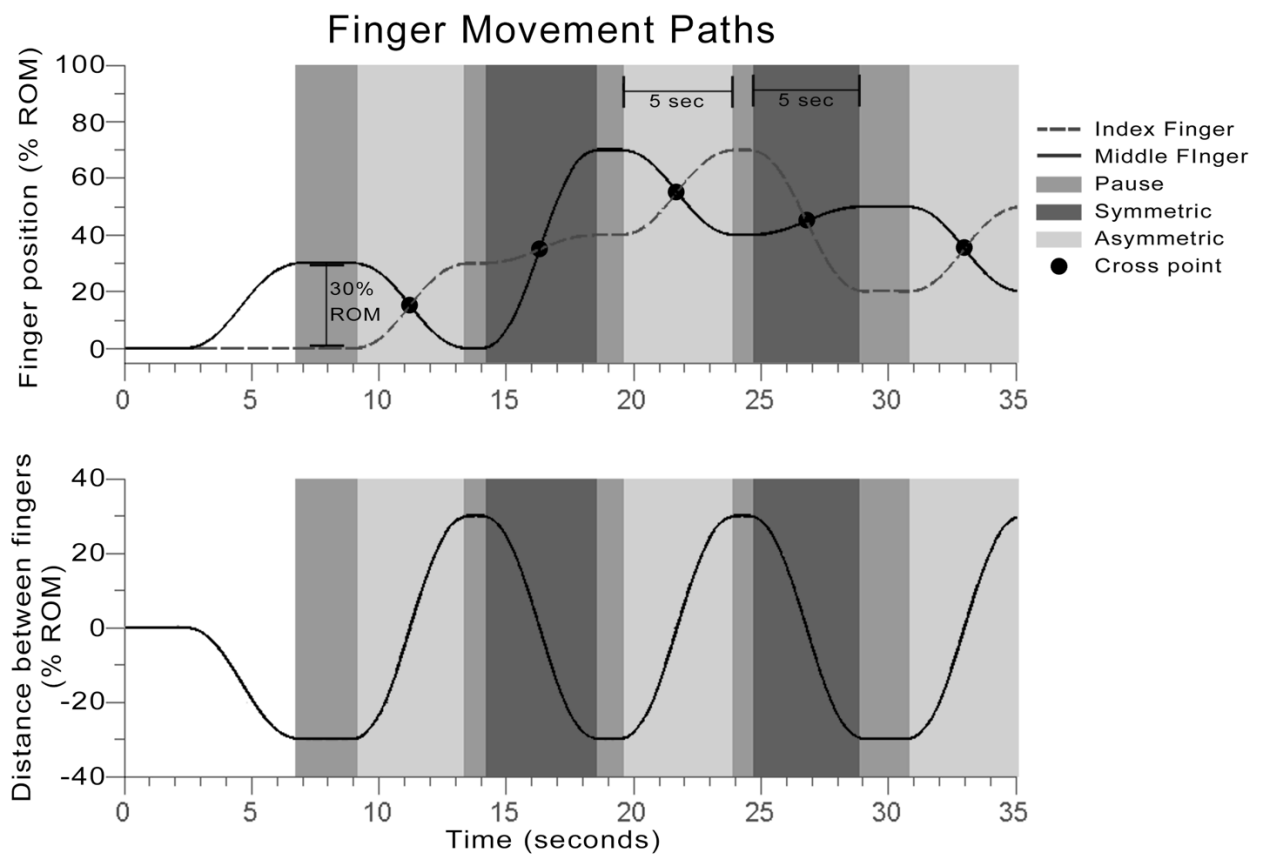

Figure 3.2. Example index and middle finger movement paths during proprioception tasks generated by the FINGER robot. FINGER moved participants' index and middle fingers in opposing directions to create crisscross motions. One crossover event occurred during each crisscross movement wherein the index and middle fingers were directly overlapping. The position in space where the crossover event occurred varied for each crisscross movement; to create this effect, the fingers alternated between symmetric and asymmetric movements. Each crisscross movement occurred over 5 seconds, followed by a pseudo-random 0-3 second pause. During the pause, index and middle fingers were separated at 30% of the ROM by FINGER. Varying finger velocity profiles and pseudo-random pause times created non-periodic crisscross movements that participants could not predict using timing strategies.

Passive Movement Detection: Movement Onset Task

Passive movement detection was measured with a movement onset task. During passive movement detection testing, which was a form of reaction time test, participants were instructed to press the spacebar on a keyboard with their free hand when they first perceived any passive movement in their fingers. Participants completed the movement onset task under two different feedback conditions: first with visual access to their hand and then with vision occluded. Performance was quantified as the amount of time delay, in milliseconds (ms), between the onset of robot initiated finger movement and the moment the participant pressed the spacebar to indicate perceived motion.

Statistical Analysis

Statistical analyses were conducted using JMP 11 software, were 2-tailed, and used $\alpha=0.05$. Normally distributed data and data that could be transformed to a normal distribution were analyzed using parametric statistics, otherwise non-parametric statistics were used.

Participant performance on the overlap task and on the movement onset task was analyzed separately. Initial analyses examined the effect of age on finger proprioceptive ability. An omnibus mixed effect model, with participants as a random effect and age group category as a fixed effect, was performed to assess the main effect of age on each of the proprioception tasks. The main effects of visual feedback condition and hand dominance were also evaluated to elucidate any differences between the three age groups according to hand dominance and according to the presence or absence of visual feedback. Post hoc analyses were performed using Fisher's Least Significant Difference test. Within group analyses were performed using a mixed effect model, with participants as a random effect and visual feedback condition and hand

dominance as fixed effects. Post hoc analyses were again performed using Fisher's Least Significant Difference test.

Results

We recruited 37 healthy adult volunteers aged 20 years and above. The measurements were acquired from three groups of adults: 12 young participants (average age: 24.5 ± 1.6 years (mean ± SD), range: 22-28, 5 males), 12 middle-aged participants (average age: 44.5 ± 9.4 years, range: 30-60, 3 males), and 13 older participants (average age: 73.3 ± 6.8 years, range: 67-87, 8 males). Of the 37 participants, 35 were right-handed. Performance on the overlap task and the movement onset task was collected under four different conditions: dominant hand with vision, dominant hand without vision, non-dominant hand with vision, non-dominant hand without vision. Not all participants completed the four different testing conditions as the full protocol was incorporated in stages; the number of participants for each test is given within Figs. 3.3 and 3.4.

Overlap Task Results

Results from the assessment immediately following the overlap task revealed that all participants understood the instructions for the overlap task and attempted to press the spacebar when their index and middle fingers were directly overlapped. Likewise, 95% of participants were able to feel their index and middle fingers start moving, stop moving, and crossover during the task. Only one participant in the middle-aged group was unable to feel their index finger start moving; one participant in the older age group reported they could not feel their fingers cross over. Although these participants reported lack of somatosensation, each did demonstrate

comprehension of the overlap task, and so data from all participants are included in the following statistical analyses.

For participant average absolute errors, a difference in performance on the overlap task was found to exist as a main effect of age ($F_{(2,31)}$=5.74, p=0.007, Fig. 3.3A); the main effect for visual feedback condition was trending ($F_{(1,99)}$=2.83, p=0.09); and the main effect for hand dominance was not significant ($F_{(1,88)}$=0.10, p=0.75). Given our hypothesis that vision would help participants compensate for any deficits in proprioception, we proceeded with one-way ANOVAs to evaluate any main effect of age for the four test conditions: dominant hand, dominant hand+vision, non-dominant hand, non-dominant hand+vision (Fig. 3.3). Difference in overlap error according to age was detected for both hands when participants completed the task with vision occluded (dominant hand: $F_{(2,34)}$=4.84, p=0.01; non-dominant hand: $F_{(2,33)}$=3.53, p=0.04). Post-hoc tests for the dominant hand revealed the older age group made significantly larger errors than the young ($t_{(34)}$=2.05, p=0.04) and middle-aged groups ($t_{(34)}$=3.04, p=0.004). For example, the older participants made on average 48% larger finger position sense errors compared to young participants. Similarly, post-hoc tests for the non-dominant hand indicated the older group made larger errors than the young ($t_{(33)}$=2.04, p=0.04) and middle-aged groups ($t_{(33)}$=2.46, p=0.02). Conversely, a difference in overlap error according to age was not detected when participants completed the task with visual feedback (dominant hand+vision: $F_{(2,25)}$=0.78, p=0.47; non-dominant hand+vision: $F_{(2,25)}$=1.73, p=0.19). The overlap task mixed-effects model did not indicate a significant interaction for categorical age groups and visual feedback condition ($F_{(2,99)}$=0.52, p=0.6).

Overlap error can also be evaluated by computing signed averages, wherein negative and positive errors reveal if participants responded before or after their fingers were directly overlapped, respectively (Fig. 3.3B). Signed average overlap errors were calculated for each age group (young: -3.2 ± 2.9° (mean ± SD); middle-aged: -0.01 ± 3.9°; older: 2.6 ± 6.3°). Across all age groups and task conditions, 49% of participants made negative signed average overlap errors, indicating that participants anticipated the moment their fingers would cross.

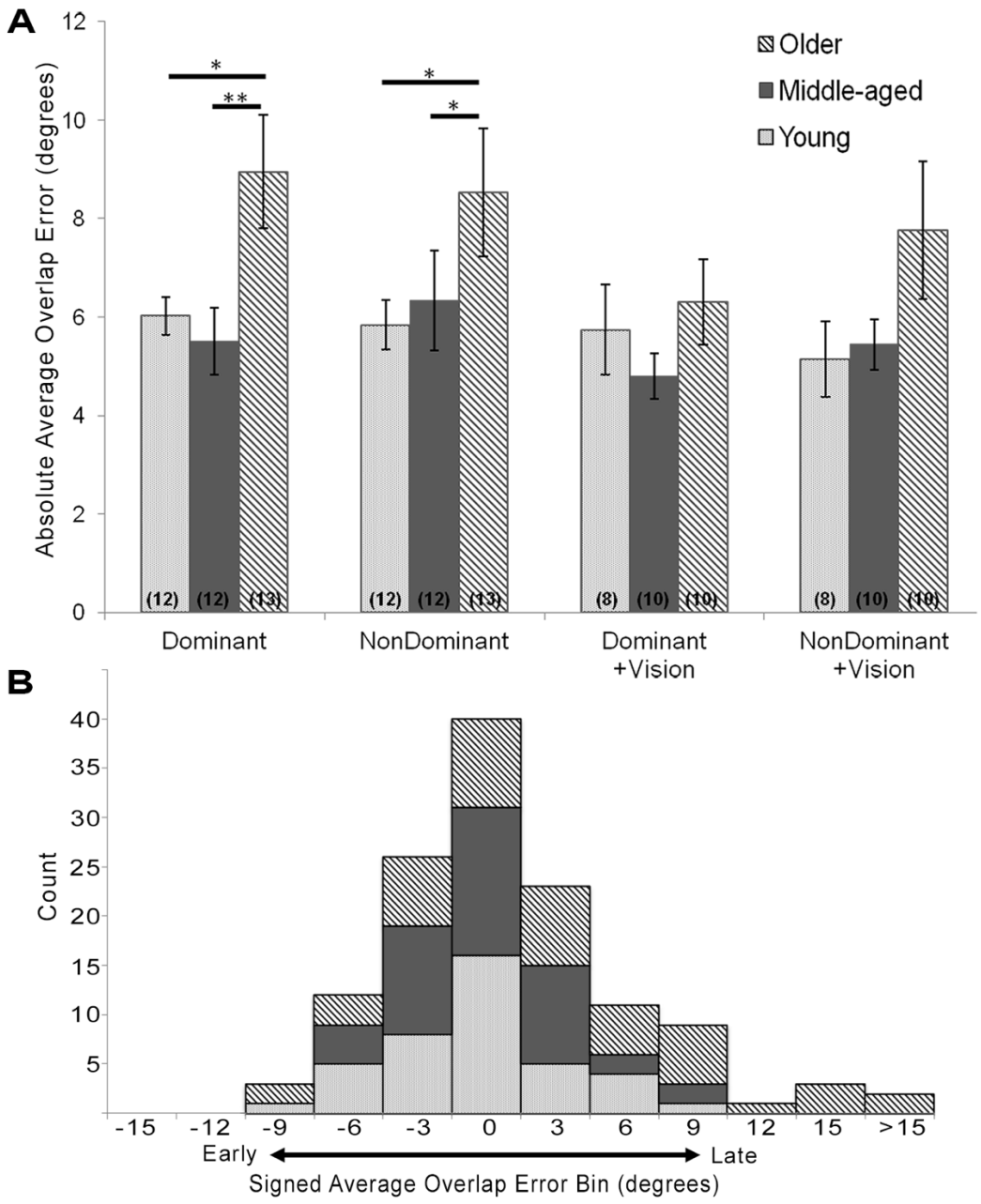

Figure 3.3. **(A)** Average absolute error, in degrees about the MCP, made on the overlap task for the dominant and non-dominant hands, with and without vision. The older age group performed significantly worse than the young and middle-aged groups for both the dominant and non-dominant hands without vision. However, no difference existed between the age groups when participants were permitted visual feedback of their hand. Numbers in parentheses indicate the number of participants tested for each condition. Error bars are standard error. * = $p<0.05$. ** = $p<0.01$. **(B)** Histogram distribution of signed average errors made on the overlap task.

Movement Onset Task Results

For participant average movement onset detection times, a difference in performance on the movement onset task was found to exist as a main effect of age ($F_{(2,25)}$=4.16, p=0.03, Fig. 3.4) and a main effect of visual feedback condition ($F_{(1,82)}$=6.01, p=0.01); the main effect for hand dominance was not significant ($F_{(1,82)}$=2.83, p=0.10). Using the same age group divisions from the overlap task analyses, subsequent one-way ANOVAs were performed to detect any differences among age groups for the four testing conditions (Fig. 3.4). A main effect of age was found for both hands when participants performed the movement onset task with vision occluded (dominant hand: $F_{(2,25)}$=4.74, p=0.02; non-dominant hand: $F_{(2,25)}$=4.29, p=0.02). Post-hoc tests for the dominant hand revealed the older age group had significantly longer reaction times than the young age group ($t_{(25)}$=3.08, p=0.005). For example, proprioceptive reaction time was 78% longer in older adults compared to young adults. Likewise, post-hoc tests for the non-dominant hand indicated the older group had significantly longer reaction times than the young age group ($t_{(25)}$=2.90, p=0.007). Conversely, a difference in movement onset detection time according to age was not detected when participants had visual input during the task (dominant hand+vision: $F_{(2,25)}$=1.84, p=0.18; non-dominant hand+vision: $F_{(2,25)}$=0.59, p=0.56).

Moreover, the movement onset task mixed-effects model indicated a significant interaction for categorical age groups and visual feedback condition ($F_{(2,81)}$=4.31, p=0.02). Within-group analyses indicated a significant main effect for vision for the young age group ($F_{(1,22)}$=13.03, p=0.002), but not for the middle-aged or older age groups. A paired t-test revealed detection times for the young age group with visual feedback were longer than those without visual feedback ($t_{(22)}$=3.6, p=0.002).

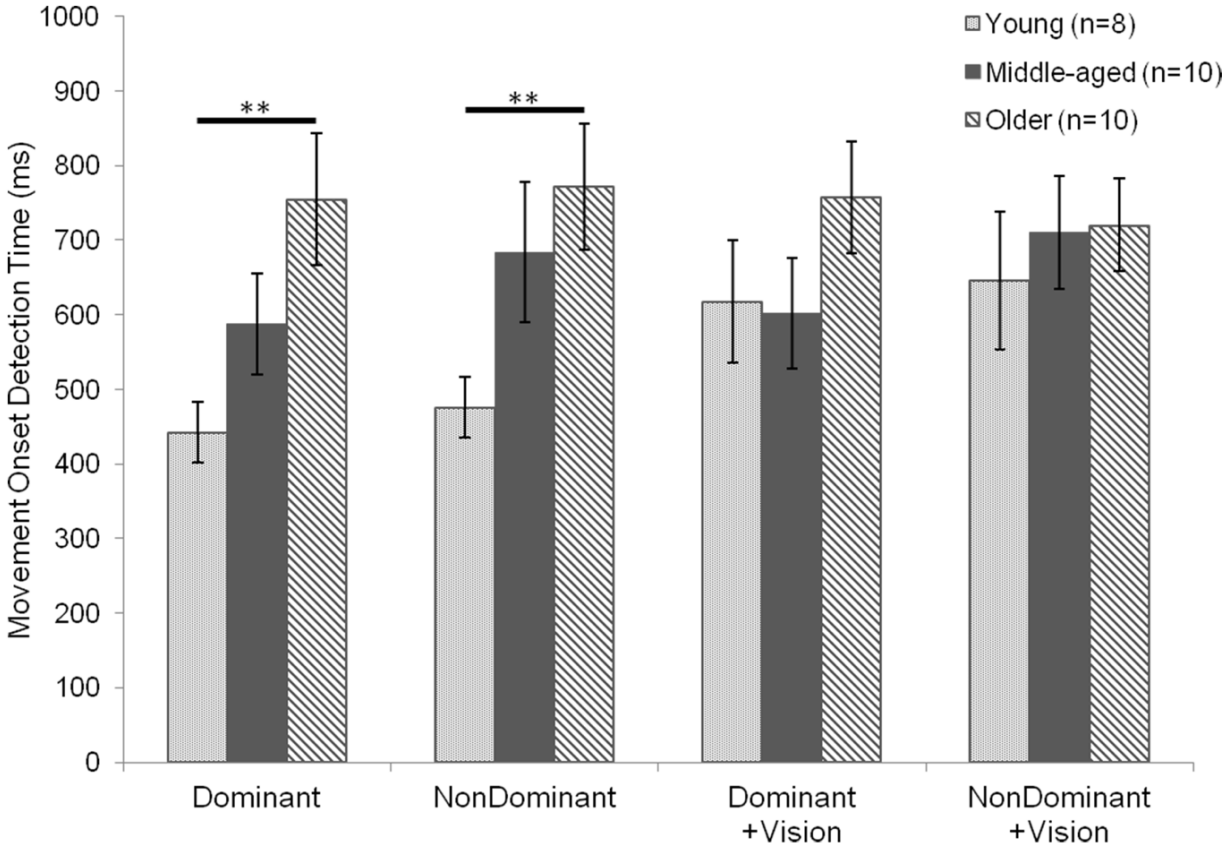

Figure 3.4. Mean time to detect finger movement onset during the movement onset task for the dominant and non-dominant hands, with and without vision. The older age group performed significantly worse than the young age group for both the dominant and non-dominant hands without vision. However, no difference existed among the groups when participants were permitted visual feedback while completing the task. Error bars are standard error. ** = $p<0.01$

Discussion

The primary aim of the present study was to evaluate age-related changes in finger joint position and movement sense by means of a novel robotic proprioception assessment. We hypothesized that passive finger movement tasks with FINGER would detect diminished proprioceptive ability in older adults compared to younger adults. Our results from 37 individuals aged 22-80 years revealed significant age-related declines in PIP and MCP joint proprioception. In the case of the overlap task, wherein index and middle fingers were passively moved in opposing directions and participants indicated when their fingers were directly overlapped, older participants demonstrated diminished finger position sense and made 48% larger errors than young healthy participants (Fig. 3.3). Moreover, the movement onset task also showed that older participants were 78% slower in detecting the onset of passive finger movements than young participants (Fig. 3.4). These proprioceptive deficits were masked when older participants were permitted vision of their hand. Additional assessments indicated hand dominance did not affect finger proprioception in either task. These results describe a decline of finger proprioception and finger proprioception reaction time with normal aging, a finding of concern to our aging population given that finger joint proprioceptive ability strongly relates to precise control of hand movements performed during activities of daily living.

The results presented here support the view that age-related proprioception decline is a generalized phenomenon that older adults experience throughout multiple effector systems of the body. These data are the first to provide strong evidence that finger joint position sense and movement onset detection are significantly impaired in healthy older adults, a finding that supports observations of generalized declines in proprioceptive ability with aging. Previous research indicates lower limb proprioception, specifically position sense of toes, ankles, and

knees [209], decreases with normal aging. Declines in active and passive joint movement of the elbow and wrist have been detected in the elderly at comparable rates reported for the lower limb [212–215]. For example, in an arm position-matching task, errors in hand-based position sense parameters increased 36% across adulthood [213]. The present findings report a similar decline in proprioception of the finger joints. It is important to note, however, that task design likely has a significant influence in evaluating joint position sense, and thus direct comparisons across protocols are difficult. What is clear is that age-related proprioceptive impairment is pervasive across limbs, including the fingers.

Age-Related Changes Affecting Finger Proprioception

Numerous peripheral and central level neurophysiological factors might account for the observed age-related changes in proprioception [222]. A general loss of sensitivity affecting stretch-sensitive mechanoreceptors [223], age-related alterations in cutaneous receptors, decreased density of Meissner and Pacinian corpuscles per unit of skin area [224], and a decline in joint mechanoreceptors [225] likely contribute to the impaired dynamic position sense detected in the older participants.

In addition to these probable contributions from the peripheral nervous system, it is likely that some component of age-related decline in proprioceptive function is related to changes in the central nervous system [206]. This could theoretically be due to some combination of elementary sensory signaling or cognitive decline. Regarding the latter, joint position errors made by the elderly can be modulated by the amount of proprioceptive processing required [212, 226, 227], suggesting task type and experimental design can indeed impact the severity of proprioceptive impairments detected. In the current study, the overlap and movement onset tasks

do not rely on proprioceptive memory (as in ipsilateral remembered matching) or interhemispheric transfer (as in mirroring tasks). Thus, we suggest that the proprioception assessments presented here are independent of cognitive attentional resources available to older individuals and likely reflect the neurophysiological underpinnings of finger proprioception for different age groups.

Advantages of Proprioception Testing with FINGER

Joint position sense is usually assessed in patients with stroke [151, 158] or as a test for sensory deficits due to aging or disease [228, 229]. Robotic devices can quantitatively assess sensorimotor dysfunction with heightened sensitivity in these populations [61]. For example, robotic assessments have revealed patients frequently have deficits in motor and sensory functions despite receiving normal scores on traditional clinical measures [189]. Additionally, seemingly ‘standardized’ somatosensation assessments have in fact been found to be subjective and have poor inter-rate reliability [21, 22], deeming traditional proprioceptive measurements both unreliable and insensitive. As this study sought to detect minor differences in proprioceptive ability that may exist between healthy individuals as a function of age, we designed proprioception tasks using FINGER. Using this finger-curling robot allowed us to design two passive proprioception tasks.

Various tasks designed to measure the ability to sense joint movement have been developed. An early study in motion sense found that compared to young adults, older participants were less capable of sensing motion of the metacarpophalangeal and metatarsophalangeal joints in the absence of vision [230]. Movement detection thresholds have also been studied in relation to normal aging for lower limb joints, such as the ankle [231, 232]

and knee [203, 233]. More recently, robotics have been employed to enhance acuity in studies addressing kinesthesia in the elbow and wrist joints [151, 193, 213, 215, 218, 219]. The present study is the first to our knowledge to extend conventional measurements of passive movement detection to the finger joints using robotics.

The overlap task was designed to address the intrinsic dual functionality of proprioception, which refers to both position sense and movement detection. The ability to monitor position during motion has been termed “dynamic position” sense. Traditional position sense studies have had participants mirror a static position with their free limb [212]. While employing robotics in this setting has introduced objective scoring [151, 193, 213, 215], testing paradigms that incorporate sense of position and sense of movement are challenging to design. The overlap task presented here introduces a quantitative assessment for dynamic finger position sense (Figs. 3.1, 3.2). Because sense of position and sense of movement are both important in proprioception and strongly contribute to fine motor control during voluntary movement execution [234, 235], we suggest the overlap task, which tests both senses, provides enhanced insight to the decay of proprioceptive ability as a result of normal aging. Indeed, this task detected decreased proprioception in the older age group compared to both the young and middle-aged groups and therefore proved to be a more sensitive probe than the movement onset task, which characterizes sense of movement alone and did not consistently detect a difference between the older and middle-aged groups.

Role of Feedback Condition on Proprioception

In a number of highly skilled motor activities, responses to kinesthetic stimulus rather than a visual one would seem beneficial since the kinesthetic route is faster to process [236–239].

Despite this, kinesthetic cues are rarely the only means through which one perceives movement. On both the overlap task and movement onset task, our older age group demonstrated impaired proprioception compared to the young group without vision, but performed comparably when vision was included. Previous studies have confirmed the importance of vision in the control of posture under challenging conditions [240–242] and suggest that the visual system is relied upon to compensate for diminished proprioception in the lower limbs and upper limbs [200]. It is likely that visual input plays a similar compensatory role in the finger joints, which allows older participants to complete proprioception tasks indistinguishably from younger participants.

It is well-known that reaction times generally increase with aging and this effect is seen in response to stimuli across all sensory modalities [243–245]. Thus, it may seem possible that such aging-related increases in reaction time would map onto increases observed in overlap error, making it possible that the observed deficit was due to prolonged reaction time rather than impaired proprioception per se. It is important to note that by design, the overlap task is inherently independent of reaction time because it is anticipatory by nature. Longer preparatory intervals are known to reduce reaction time [245]; given that participants could anticipate the timing that their slowly moving fingers would cross, this preparatory interval was extended during the overlap task. Thus, 49% of participants made signed average overlap errors that were negative (Fig. 3.3B). The prevalence of negative errors on the overlap task reveals that participants anticipated the crossover event and sometimes reacted too early. The overlap task is therefore anticipatory in nature and delays in reaction time due to aging are unlikely to confound the results presented here.

One should also consider the role of reaction time in the movement onset task. It is logical that reaction time does play a role in the movement onset task, as it is in essence a test of proprioceptive reaction time. However, the results from the movement onset task are likely indicative of more than a simple delay of reaction time with age. For example, if these results revealed a delay in reaction time alone, there should be a difference between older and young age groups regardless of visual feedback condition. This is not the case, as all age groups performed similarly on the movement onset task when they were permitted visual access to their hand (Fig. 3.4). One may be tempted to attribute the similar performances amongst the groups when visual feedback was permitted to the young participants' seemingly slowed reaction times. Indeed, visual feedback significantly increased movement onset detection time for the young age group, but this is not an atypical observation. Visual responses are known to have slower processing times compared to those of kinesthesia [236–239]. Moreover, visual input tends to dominate input from somatosensory modalities [246]. For the young participants, a tendency to depend on visual feedback of the hand rather than proprioception when performing this task resulted in slower response times than when they completed the task without vision, thereby requiring them to utilize their highly attuned proprioceptive abilities. It is likely that the older age group also relied on visual feedback to complete this task when given the opportunity. Yet, the older age group did not demonstrate a significant main effect for visual feedback condition. This suggests that proprioceptive abilities for elderly individuals were diminished and therefore rendered the slower processing time of visual input undetectable. By any means, given the potential confounds of reaction time on the movement onset task, the overlap task is perhaps a more ideal way to parse out the effects of delayed reaction time from the effects of age-related decline in finger proprioception.

Lack of Asymmetry Due to Hand Dominance

Studies regarding static position sense about the elbow have indicated asymmetries in younger individuals with the non-dominant arm exhibiting an enhanced ability to utilize limb position feedback [247]. Interpreted as a specialization of the non-dominant hemisphere system for position-related proprioception processing [206, 248], this finding has been seen in older adults for conditions requiring interhemispheric transfer of proprioceptive information (i.e. static limb matching tasks) [212–214]. Although a lifetime of dominant hand use may suggest enhanced dynamic movement onset detection for dominant limbs, dynamic movement reproduction does not differ between the two arms [222, 249] nor does passive movement onset detection in wrist joints differ according to hand dominance for elderly participants [215]. Likewise, in the present study the main effect of hand dominance failed to reach statistical significance for the overlap and movement onset tasks. This suggests that decay in proprioceptive ability with natural aging is generalized to both upper limbs. Moreover, it highlights the influence of task design in detecting kinesthetic asymmetries.

The results of this study extend our current understanding of the extent of age-related proprioception declines and confirm that such declines are general phenomena affecting the most distal part of the upper extremity. Additionally, they introduce two novel robotic techniques for quantitatively assessing dynamic position sense in the finger joints, one being free of possible reaction time confounds. These results may also have clinical value. The functional consequences of impaired finger joint proprioceptive ability strongly relate to precise control of finger movements performed during activities of daily living [250, 251]. This is particularly relevant for our aging society where physiological declines in finger proprioception are naturally

occurring, and may also be useful for understanding diseases in which sensory function is affected such as stroke.

CHAPTER 4

NEURAL CORRELATES OF PROPRIOCEPTIVE DEFICITS AFTER STROKE

Abstract

Proprioception of the fingers is essential for motor control. Reduced proprioception after stroke is linked to increased length of hospitalization and mortality. However, the neural correlates of proprioceptive deficits after stroke remain incompletely understood, in part due to weaknesses of clinical proprioception assessments. The current study examined the neural basis of finger proprioceptive deficits after stroke, hypothesizing that a model incorporating neural injury and neural function of the somatosensory system would be key. Finger proprioception was measured using a robot in 27 subjects with chronic stroke, among whom measures of neural injury (damage to gray and white matter, including corticospinal and thalamocortical sensory tracts), neural function (activation and connectivity of cortical sensorimotor areas), and clinical status (demographics and behavioral measures) were also assessed. Impairment in finger proprioception was present contralesionally in 67%, and bilaterally in 56%. Robotic measures of proprioceptive deficits were found more sensitive than standard scales and were specific to proprioception function. Multivariate modeling found that contralesional proprioceptive deficits were best explained by combining a measure of neural function (S2-M1 connectivity) with a measure of neural injury (total sensory system injury, r^2=0.63, p=0.0006). Proprioceptive impairment of the fingers occurs frequently after stroke and is best measured using a quantitative device such as a robot. Anatomical injury to somatosensory networks and functional connectivity between S2-M1 best explained proprioception performance. With this neural circuitry identified, it is possible to develop more effective neurorehabilitation therapies.

Introduction

Proprioception of the fingers is central to human behavior. Proprioceptive deficits may be present in 50% or more of patients with stroke [151, 154, 165] and can be present in both ipsilesional and contralesional limbs after unilateral infarct [154]. Reduced proprioception after stroke is associated with longer hospitalization, increased mortality, and diminished quality of life [154, 165, 168].

The goal of the current study was to understand key factors underlying inter-subject differences in finger proprioception after stroke, findings that could inform approach to therapy. Simply measuring injury to sensory areas incompletely explains proprioception deficits after stroke [175]. The primary hypothesis, therefore, was that proprioception deficits would be best explained by a model combining measures of neural injury and neural function, given increasing evidence that both forms of measurement are needed to most robustly explain variance in behavioral outcomes after stroke [11, 16, 17]. A new method for measuring sensory system injury, lesion overlap with the thalamocortical sensory tract, was examined.

A key consideration in this study was the method by which proprioception is measured. Bedside tests of proprioception are subjective and non-standardized [154], plus have low sensitivity, high variability, floor effects, and low reliability [19, 20, 154, 158, 166]. Robotic devices have been shown to better quantify arm sensory impairments following stroke [151, 190, 193] but to date have not been used to measure post-stroke proprioceptive deficits in finger joints, an afferent data stream critical to human function [135]. Towards this, we developed and employed a novel exoskeletal robotic device that measures finger proprioception with high sensitivity [220, 252].

Methods

Subject Enrollment

Twenty-seven subjects with unilateral chronic stroke were recruited. Key inclusion criteria were age 18-80; radiologically confirmed stroke >6 months prior; arm motor deficit (contralesional Box & Blocks score at least 10% <ipsilesional hand) with preserved contralesional hand movement (Box & Blocks score ≥3). Subjects were excluded if they had significant cognitive impairment or another diagnosis affecting hand function. Proprioception data collected for a previously published normative study [252] using identical methods in 25 healthy age-matched subjects were used as control data. The local ethics committee approved this study, and written informed consent was obtained from each subject prior to participating following procedures established by the University of California Irvine Institutional Review Board.

Proprioception Assessment

Passive finger position sense was measured using the FINGER (Finger Individuating Grasp Exercise Robot) exoskeleton robotic device [220, 252], which guides index and middle fingers through motion around metacarpophalangeal and proximal interphalangeal joints, allowing for individual finger guidance. The robot slowly (up to 13 degrees/second) moved the index and middle fingers in opposing directions during a series of 12 non-periodic finger-crossing movements, of different distances and angular velocities, in pseudorandom order. For each finger-crossing movement, subjects were instructed to press a keyboard spacebar when they perceived their index/middle fingers were directly aligned relative to one another. This task spanned two minutes for each hand, with ipsilesional hand tested first. The angular distance between the metacarpophalangeal joints when the spacebar was pressed was calculated for each

finger-crossing movement. Proprioception error reported here reflects the average error across the 12 finger-crossing movements for each hand of each subject.

Prior to testing each hand, subjects performed passive range of motion exercises using the FINGER robot to ensure no pain or discomfort. The examiner then walked through a practice round with each subject, confirming that they understood and could demonstrate the task. Next, appropriate attention and cognitive status were confirmed by requiring that each subject could correctly repeat full task instructions to the examiner.

The robot-guided finger-crossing movements during the task were relatively slow, and as a result identification of direct finger alignment was not dependent on reaction time, as subjects were able to anticipate the moment of finger crossing. This was demonstrated in our previous study of unimpaired control subjects, wherein about half of the proprioception errors were made before and half following direct finger alignment [252]. Thus, this proprioception task with the FINGER robot measures ability to integrate proprioceptive information during relatively slow movement of the fingers to detect direct finger alignment.

Subject Characteristics

Demographics/History: Medical history was obtained, including handedness [221].

Sensorimotor Behavior: Stroke severity was assessed with the NIH Stroke Scale (NIHSS). Motor status was evaluated with the Action Arm Research Test (ARAT), Box & Blocks Test (B&B), Nine Hole Peg Test (NHPT; number of seconds to complete the task, maximum score 60s) and Finger Tapping Test (FT; number of finger taps over 10s). The motor and sensory Fugl-Meyer (FM) arm assessments were obtained.

Image Acquisition

On a 3T Philips MRI, high-resolution T1-weighted images were acquired using a 3-dimensional MP-RAGE sequence (150 slices, $1mm^3$ voxels). T2 FLAIR images were also acquired. Four runs of BOLD fMRI were acquired using a T2*-weighted gradient-echo sequence (TR=2,000 ms, TE=30 ms, each run with 48 brain volumes=96 s), during which subjects were visually guided to alternate 24 seconds rest with 24 seconds active 0.5 Hz index and middle finger flexion/extension movements while wearing a non-actuated plastic exoskeleton similar to the robotic interface used during the proprioception task. An investigator observed movements during scanning ensured compliance.

Brain Injury

Grey Matter Injury: Using MRIcron (www.mccauslandcenter.sc.edu/crnl/mricron/) , each participant's infarct was outlined by hand on the T1-weighted MRI image, informed by FLAIR image, in a standardized manner as described previously [95]. Stroke masks were transformed into Montreal Neurological Institute (MNI) standard stereotaxic space using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL, https://fsl.fmrib.ox.ac.uk/). Stroke masks for participants with right-sided lesions were flipped about the midsagittal plane.

Degree of overlap between cortical regions of interest (ROIs) and each stroke mask was calculated. Using Marsbar [253], sphere ROIs representing hand M1, hand S1, and secondary somatosensory cortex (specifically operculum parietal (OP) 4, denoted here as S2) [129] were generated. Percent stroke mask overlap with each ROI was calculated for each subject.

White Matter Injury: Because fiber tracking with diffusion tensor imaging (DTI) can be problematic in brain regions affected by stroke, white matter injury for each subject was

quantified by examining the extent to which each infarct overlapped with white matter tract templates generated from healthy controls. Injury to the corticospinal tract (CST) was measured as percent overlap between each subject's infarct and the normal CST, as described previously [97].

As part of the current study, we devised a new method for measuring sensory tract injury. Injury to the thalamocortical sensory tract (TST, Fig. 4.1) was measured as amount of overlap in MNI stereotaxic space between the normal TST and each subject's infarct. The normal TST was developed with diffusion tensor imaging (DTI) from 17 healthy control subjects (Fig. 4.1) [97]. To create the normal TST tract, control subject images in native space were first corrected for eddy current distortions and head motion artifacts using FSL. FSL's BEDPOSTX program was then used to generate probability distributions of diffusion parameters at each voxel, including modeling for diffusion of crossing fibers along two directions. With the thalamus as the seed region, connectivity-based segmentation was used to assign each voxel in the seed some probability of being connected to each of various targets, including the post-central gyrus. Subject-specific masks of thalamic regions with highest probability of connection to the post-central gyrus were generated. Each mask was visually inspected and compared to an anatomical atlas [122], confirming that they were located in the approximate region classically defined as VPL. Next, probabilistic tractography was performed in each subject using the dorsal two-thirds of the post-central gyrus as the seed region, the VPL as a waypoint target mask, and a mid-sagittal slice as an exclusion mask. The resulting individual subject tracts were binarized, transformed into MNI space, summed, and thresholded to include only voxels that were common to the tracts of $\geq$6 subjects. Similar to methodology used to calculate percent injury to CST [11, 17, 254], injury to the TST was calculated as the percent injury to the normal TST. This was

accomplished by overlaying stroke masks in MNI space with the normal TST tract. Because of seed point locations, values for white matter injury for subjects with infarcts inferior to the thalamus were omitted from statistical analyses.

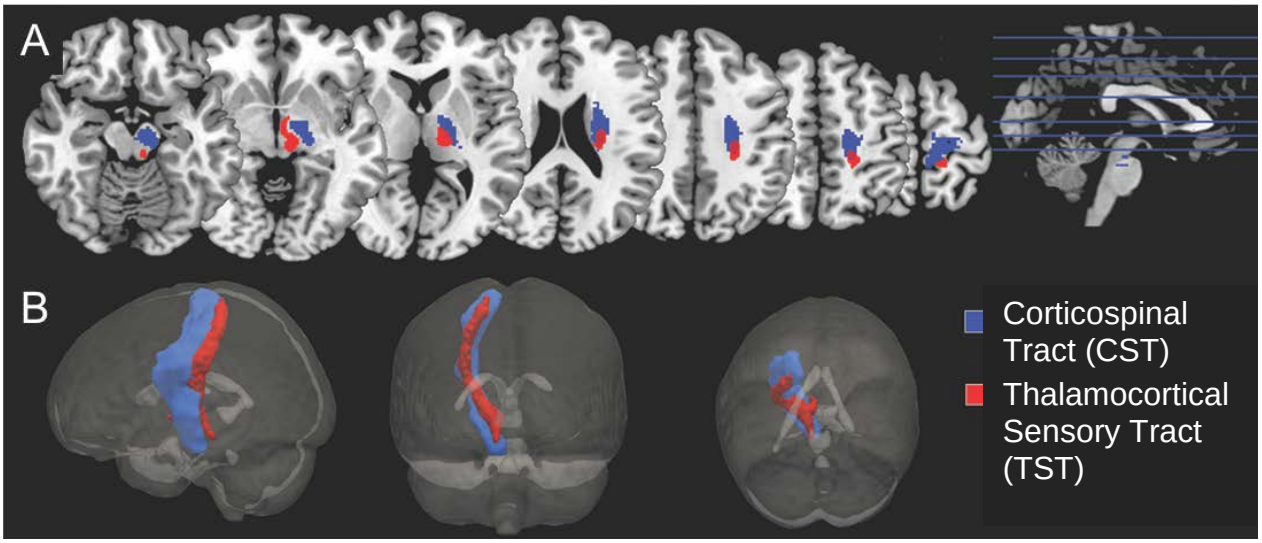

Figure 4.1. CST and TST tracts generated from probabilistic tractography of DTI data from healthy control subjects. Blue tract is CST; red tract, TST. **(A**) tracts are overlaid on a T1-weighted MRI template. **(B)** glass brain visualization of the tracts.

Total System Injury: A comprehensive measure of system injury within the stroke-affected hemisphere was calculated for the sensory system and the motor system. To quantify total sensory system injury, S1, S2, and TST percentage injury measures were each standardized, then values were averaged for each subject (Fig. 4.2). For total motor system injury, standardized injury measures to M1 and CST were averaged.

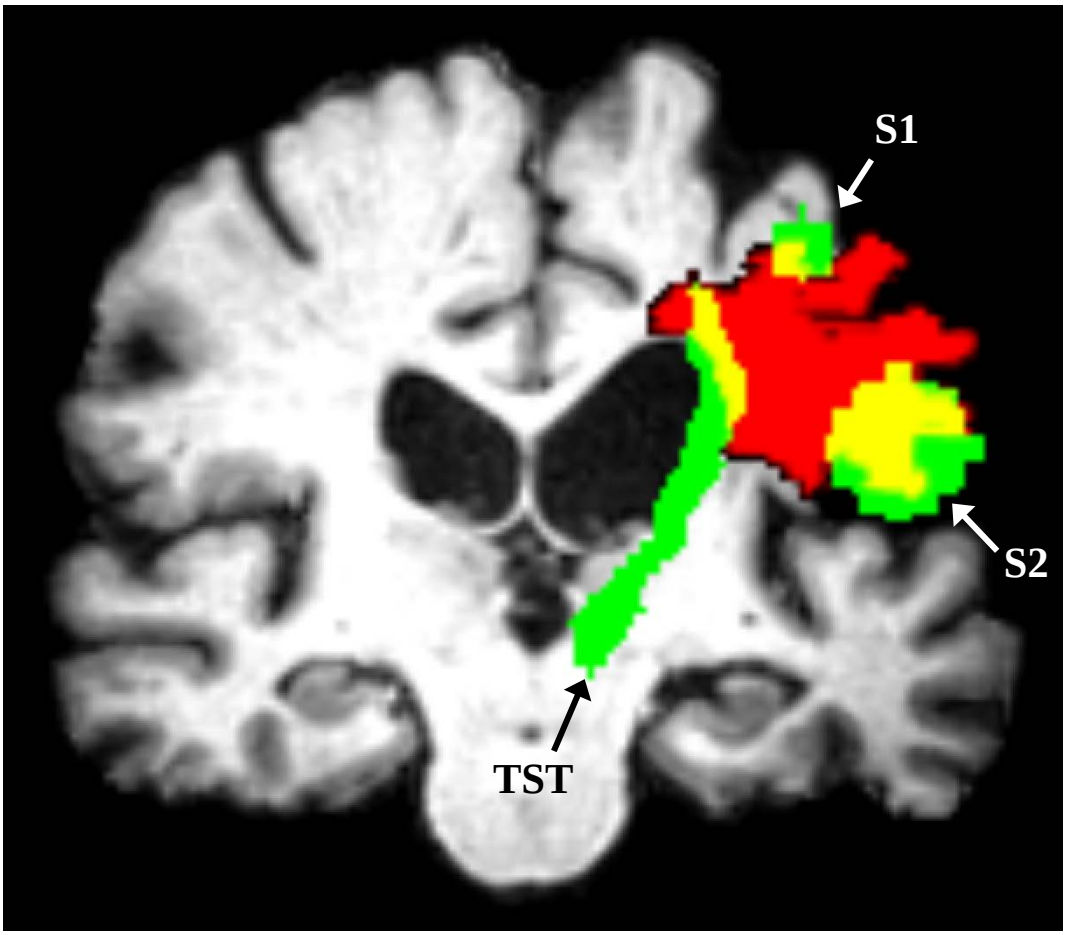

Figure 4.2 Total Sensory System Injury is an aggregate metric of primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and thalamocortical sensory tract (TST) injury. Percentage injury of these individual regions (shown in green) was calculated via lesion overalap (lesion shown in red; overlap shown in yellow) and standardized, then averaged for each subject to create a comprehensive anatomical injury metric for the somatosensory system.

Cortical Function

Two measures of regional brain function were extracted from fMRI images: (1) activation volume and (2) peak activation beta (contrast) estimate, each measured in contralesional and ipsilesional M1, S1, and S2. To do so, functional data from the four BOLD fMRI runs were preprocessed using the Statistical Parametric Mapping 12 (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing steps included realignment to the first image, coregistration to the mean EPI image, normalization to the standard MNI EPI template, and spatial smoothing (FWHM = 6 mm). Data were visually inspected for head movement and were rejected for subjects with >2mm head displacement.

For statistical analysis, the fMRI data were modeled as a boxcar convolved with a hemodynamic response. A high-pass filter of 128 s was used to remove low signal changes. Functional run data were inspected for outliers due to excessive head motion (>1 mm translation or >0.2 radians rotation between each volume) and signal noise ($Z > 3$ from the mean image intensity) using the Artifact Detection Tool (http://www.nitrc.org/projects/artifact_detect). Outliers were de-weighted during statistical analysis. Single-subject t-maps (task versus rest) were generated using $p < 0.001$ uncorrected for multiple comparisons. Activation volume and contrast estimates were then extracted in SPM12 using small volume correction for M1, S1, and S2 ROIs on each brain side.

Cortical Connectivity

Connectivity was assessed as the temporal correlation using an ROI-ROI approach. After the fMRI data were preprocessed in SPM12, intra- and interhemispheric functional connectivity metrics were calculated using the CONN toolbox [255]. Time courses were filtered between

0.008 and 0.13 to minimize low-frequency drift and high-frequency noise. Within-subject realignment parameters, outliers, and main session effects were included as first-level covariates. Functional connectivity was evaluated between ipsilesional M1 and contralesional M1, ipsilesional S1, and ipsilesional S2 (iM1-cM1, iM1-iS1, and iM1-iS2, respectively); between ipsilesional S1 and contralesional S1, and ipsilesional S2 (iS1-cS1, iS1-iS2, respectively); and between ipsilesional S2 and contralesional S2 (iS2-cS2). Primary analysis of S2 examined OP 4, as above, but OP 1 [256] was also examined to enable secondary hypothesis testing. Fisher-transformed correlation coefficients were extracted for each connection in each subject.

Statistical Analysis

The frequency of proprioception impairment for the contralesional and ipsilesional hand of subjects with stroke was defined using a 2-SD criterion of abnormality based on performance of age-matched controls. To evaluate between-group (contralesional, ipsilesional, and control) differences, a mixed-effect model with subject as a random effect and group as a fixed effect was performed; post hoc analyses used Fisher's LSD or paired t-tests.

Bivariate screening was performed to identify measures that best accounted for inter-subject variability in contralesional proprioception error. Normally distributed data and data that could be transformed to a normal distribution were analyzed using parametric statistics, otherwise nonparametric statistics were used. Analyses were two-tailed with $\alpha=0.05$ and used JMP software (version 9.0.0, SAS Institute). For each of the 5 main categories (two of which are clinical measures, *demographics/medical history* and *sensorimotor behavior*; two of which are measures of neural function, *cortical function*, and *cortical connectivity*; and one of which is a measure of neural injury, *brain injury*), results of bivariate screening determined whether any

individual assessment survived as a correlate of proprioception error and would be advanced to multivariate modeling.

A forward stepwise multivariate linear regression approach (0.1 to enter, 0.15 to leave the model) was used to understand inter-subject proprioceptive variability, advancing the most significant predictors from each category identified in bivariate screening (as long as bivariate screening showed $p<0.1$).

Results

Behavioral data from 27 subjects with unilateral chronic stroke were available for analysis (Table 4.1). All completed testing except two who could not complete MRI (claustrophobia). Two subjects were excluded from cortical function and connectivity analyses due to excessive head motion during scanning, while five subjects were excluded from white matter injury analysis due to lesion location below the thalamus.

Table 4.1. Characteristics of Subjects with Stroke

Variable	Value	
Demographics/medical history		
Age, mean yr±SD	58±14	
Gender, M/F	19/8	
Hand dominance, R/L/A	24/3/0	
Diabetes mellitus, yes/no	6/21	
Hypertension, yes/no	15/12	
Hypercholesterolemia, yes/no	15/12	
Geriatric Depression Scale, mean±SD	4.07±3.73	
Time poststroke, median mo [IQR]	30 [9-44]	
Stroke type, ischemic/hemorrhagic	18/9	
Stroke hemisphere, L/R	13/14	
Stroke in dominant hemisphere, yes/no	13/14	
NIHSS, normal = 0	2.41±2.25	
Sensorimotor Behavior, mean±SD	***Contralesional***	***Ipsilesional***
ARAT, normal = 57	32.74±22.41	
FM Arm Motor, normal = 66	45.9±11.7	
FM Arm Sensory, normal = 12	10.89±2.42	12.00±0.00
B&B score	22.2±18.0	55.9±8.2
NHPT score	54.6±10.7	25.1±7.9
FT score	14.4±12.3	47.2±10.2
Brain injury		
Infarct volume, cm^3, mean±SD	20.6±23.4	
M1 injury, yes/no	5/20	
M1 % injury, mean±SD	10.1±21.1	
S1 injury, yes/no	7/18	
S1 % injury, mean±SD	17.0±30.8	
S2 injury, yes/no	9/16	
S2 % injury, mean±SD	11.6±24.7	
CST injury, yes/no	18/2	
CST % injury, mean±SD	34.3±28.7	
TST injury, yes/no	17/3	
TST % injury, mean±SD	7.5±6.7	
Total motor system injury	0.9±0.8	
Total sensory system injury	0.05±0.7	

Cortical function, mean (SD)	***Contralesional***	***Ipsilesional***
M1 activation volume, voxels	24.9±34.1	51.4±39.2
S1 activation volume, voxels	36.0±33.5	53.3±39.9
S2 activation volume, voxels	107.8±89.5	132.8±108.5
M1 activation, contrast estimate	2.0±1.9	3.7±2.0
S1 activation, contrast estimate	2.1±1.1	2.8±1.5
S2 activation, contrast estimate	2.4±1.5	2.3±1.7
Cortical connectivity, mean (SD)		
iM1-cM1 correlation coefficient	0.18±0.21	
iM1-iS1 correlation coefficient	0.45±0.19	
iM1-iS2 correlation coefficient	0.09±0.19	
iS1-cS1 correlation coefficient	0.14±0.20	
iS1-iS2 correlation coefficient	0.08±0.21	
iS2-cS2 correlation coefficient	0.27±0.21	

A = ambidextrous; ARAT = Action Arm Research Test; B&B = Box & Blocks; c = contralesional; CST = corticospinal tract; F = female; FM = Fugl-Meyer; FT = Finger Tapping; i = ipsilesional; IQR = interquartile range; L = left; M = male; M1 = primary motor cortex; NHPT = Nine Hole Peg Test; NIHSS = NIH stroke scale; R = right; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SD = standard deviation; TST = thalamocortical sensory tract.

Proprioception Error

Subjects with stroke successfully completed the robotic proprioception assessment, most showed deficits in both hands, and this methodology was found to be correlated with, but more sensitive than, standard clinical scales of sensory function.

Subjects with stroke were excellent at detecting finger-crossing movements during the proprioception task, with 25/27 detecting all 12 finger-crossing movements, similar to the proportion of healthy controls (23/25) who detected all 12 finger-crossing movements. There was little floor effect, as only a single subject with stroke scored the maximum error. Subjects with stroke made both early and late responses during the task (Fig. 4.3A), indeed half (50.8%) of all errors preceded finger crossing, mirroring findings in healthy subjects [252].

In neurologically intact control subjects, error for the dominant hand was 7.3±3.8°; for the non-dominant hand, 6.8±3.0°. There was no significant difference between the two hands ($p=0.40$) and so for subsequent analyses, control error refers to average of dominant and non-dominant hands. In subjects with stroke, proprioception error for the contralesional hand was 16.2±6.4° (mean±SD); for the ipsilesional hand, 13.3±5.4°. Proprioception performance for the contralesional hand and ipsilesional hand were positively correlated (Fig. 4.3B, $r=0.65$, $p=0.0002$). The main effect of group was significant ($p<0.0001$) as were post hoc pairwise comparisons: contralesional errors were greater than ipsilesional errors ($p=0.006$) as well as controls ($p<0.0001$), and ipsilesional errors were greater than controls ($p<0.0001$).

Impaired proprioception was detected for the majority of subjects with stroke: 67% had contralesional impairments, 63% had ipsilesional impairments, and 56% had bilateral impairments. By comparison, by the FM sensory scale, only 7/27 (26%) had contralesional arm

sensory impairment and 0 had ipsilesional arm sensory impairment; the NIHSS sensory subscale showed sensory deficits in 12/27 (44.4%). Notably, robot-assessed proprioception deficits were specific to sensory function, as contralesional proprioception error correlated with clinical sensory assessments (FM sensory score: $r=-0.39$, $p=0.046$; NIHSS sensory subscore: $r=0.47$, $p=0.01$) but not with clinical motor assessments (FM motor score: $p=0.19$), or other clinical metrics (NIHSS language subscore: $p=0.55$; NIHSS attention subscore $p=0.20$; Geriatric Depression Scale score: $p=0.37$).

Given that proprioception testing of one hand required metacarpophalangeal joint flexion of the opposite hand to press the spacebar, it is important to assess the relationship between proprioception error of the tested hand and motor status of the opposite hand. There was a weak relationship between contralesional hand proprioception error and ipsilesional FT score ($r=-0.43$, $p=0.03$). However, this correlation explained only 18% of variance in contralesional proprioception error and was not significant when age was accounted for, a covariate previously demonstrated to be of importance when assessing proprioception using FINGER in a healthy population [252]. Moreover, the trial-to-trial variance in proprioception testing had no relationship with finger motor status of ipsilesional hand ($p=0.8$). Proprioception error in the ipsilesional hand was not related to motor status (FT score) of the contralesional hand.

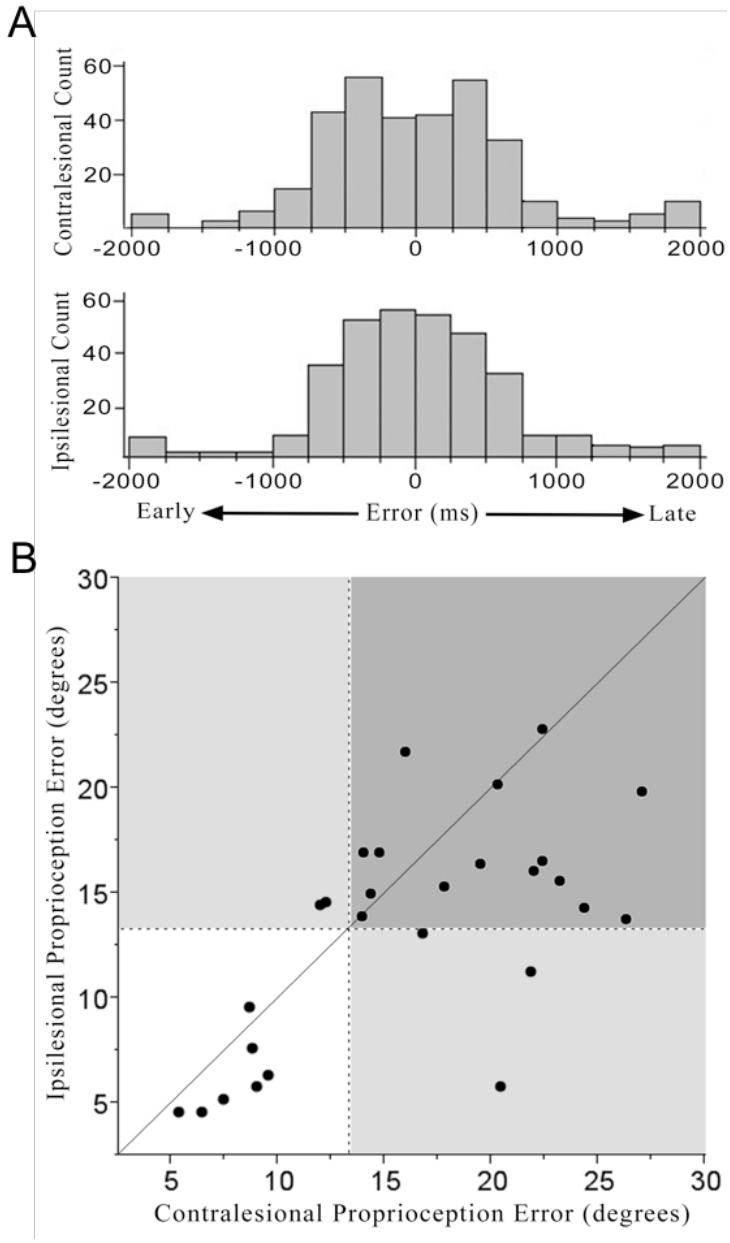

Figure 4.3. The primary method for measuring proprioception error was magnitude, and this can be further understood by also considering timing of proprioception errors. **(A)** Distribution of error times (time between when the two fingers moved by the robot actually crossed and when the subject reported them as crossed), for each hand. Amount of early versus late responses did not differ according to hand tested (p=0.78). **(B)** Magnitude of proprioceptive error (number of actual degrees separating the two fingers when the subject reported them as crossed). These errors were classified as abnormal when >2SD beyond normative values from healthy age-matched controls (dashed lines). Impaired performance for the contralesional hand is indicated to the right of the vertical dashed line, while impaired performance for the ipsilesional hand is indicated above the horizontal dashed line. The solid diagonal line indicates equal contralesional and ipsilesional hand impairment. A total of 56% patients had bilateral impairment.

Correlates of Proprioceptive Error

Bivariate screen found significant correlates of proprioception error in four categories (Table 4.2), with NIHSS (*demographics/medical history*), ARAT (*sensorimotor behavior*), Total Sensory System Injury (*brain injury*), and iM1-iS2 functional connectivity (*cortical connectivity*) most significant within their categories; no cortical activation measures were significant. Notably, when connectivity between iM1-iS2 was calculated using the OP 1 subdivision of S2 instead of the OP 4 subdivision, iM1-iS2 connectivity no longer correlated with contralesional proprioception error ($p=0.54$). Excluding subjects with ≥50% damage to cortical ROIs [257] had no significant effect on bivariate correlations.

Table 4.2. Bivariate Correlations with Contralesional Proprioception Error

Variable	*Correlation with Contralesional Proprioception*	
	r	***p***
Demographics/medical history		
Age	0.38	0.048
Gender, M/F	0.38	0.047
Hand dominance, R/L/A	0.22	0.27
Diabetes mellitus, yes/no	0.04	0.84
Hypertension, yes/no	0.05	0.81
Hypercholesterolemia, yes/no	0.33	0.09
Geriatric Depression Scale	0.17	0.37
Time post-stroke	-0.36	0.06
Stroke type, ischemic/hemorrhagic	0.15	0.76
Stroke hemisphere, L/R	0.10	0.61
Stroke in dominant hemisphere, Y/N	0.07	0.74
NIHSS	0.39	0.04
Sensorimotor Behavior		
ARAT	-0.42	0.03
FM Arm Motor	-0.26	0.19
FM Arm Sensory	-0.39	0.046
B&B	-0.27	0.17
NHPT	0.32	0.11
FT	-0.13	0.49
Brain injury		
Infarct volume	-0.13	0.52
M1 injury, yes/no	0.18	0.39
M1 % injury	0.19	0.36
S1 injury, yes/no	0.09	0.67
S1 % injury	0.14	0.52
S2 injury, yes/no	0.19	0.36
S2 % injury	-0.05	0.80
CST injury, yes/no	0.33	0.15
CST % injury	0.24	0.30
TST injury, yes/no	0.44	0.049
TST % injury	0.37	0.10
Total motor system injury	0.37	0.10

Total sensory system injury	0.63	0.003
Cortical function		
iM1 activation volume	0.08	0.72
cM1 activation volume	0.13	0.57
iS1 activation volume	0.23	0.30
cS1 activation volume	0.16	0.49
iS2 activation volume	-0.03	0.88
cS2 activation volume	0.11	0.62
iM1 activation: contrast estimate	0.04	0.83
cM1 activation: contrast estimate	0.03	0.88
iS1 activation: contrast estimate	0.01	0.98
cS1 activation: contrast estimate	0.16	0.47
iS2 activation: contrast estimate	-0.18	0.43
cS2 activation: contrast estimate	0.15	0.51
Cortical connectivity		
iM1-cM1 connectivity	0.10	0.64
iM1-iS1 connectivity	-0.002	0.98
iM1-iS2 connectivity	-0.43	0.04
iS1-cS1 connectivity	-0.001	0.99
iS1-iS2 connectivity	-0.08	0.70
iS2-cS2 connectivity	-0.12	0.58

A = ambidextrous; ARAT = Action Arm Research Test; B&B = Box & Blocks; c = contralesional; CST = corticospinal tract; F = female; FM = Fugl-Meyer; FT = Finger Tapping; i = ipsilesional; L = left; M = male; M1 = primary motor cortex; NHPT = Nine Hole Peg Test; NIHSS = NIH stroke scale; R = right; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; TST = thalamocortical sensory tract.

Multivariate Modeling

When the strongest correlates from each of the four categories with a significant finding on bivariate screening were entered into a model, two terms survived: Total Sensory System Injury (p=0.002, Fig. 4.4A) and iM1-iS2 functional connectivity (p=0.01, Fig. 4.4B). The resultant multivariate model containing these terms explained 63% of variance in proprioception error for the contralesional hand of subjects with stroke (p=0.0006).

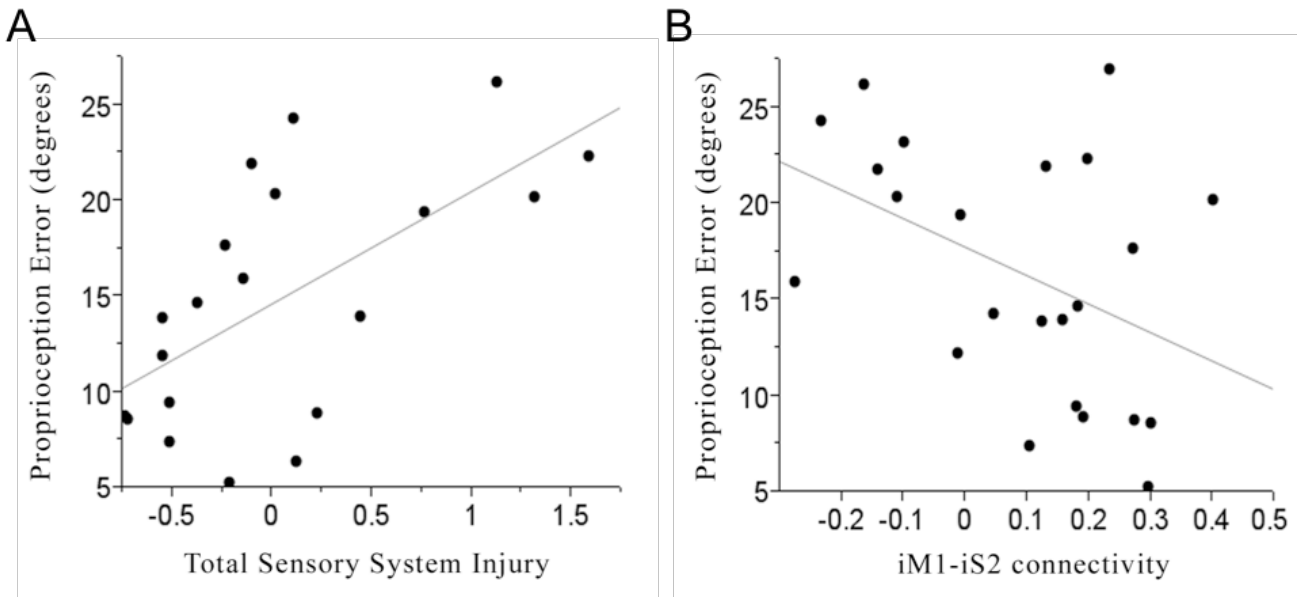

Figure 4.4. For subjects with stroke, **(A)** smaller total sensory system injury (r=0.63, p=0.003) and **(B)** greater ipsilesional M1-ipsilesional S2 functional connectivity (r=-0.43, p=0.04) were each associated with smaller contralesional finger proprioception error.

Discussion

Proprioception of the fingers is essential for motor control and human behavior. Reduced proprioception after stroke is linked to increased length of hospitalization, mortality, and personal safety issues [154, 165, 168]. However, the neural correlates of proprioceptive deficits after stroke remain incompletely understood, in part due to weaknesses of clinical approaches to measuring proprioception and sensory system injury. These issues were addressed in the current study, including a new method for measuring injury to the thalamocortical sensory tract in individual patients (Fig. 4.1B). The FINGER robot was used to measure contralesional finger proprioception deficit, present in 67%. Sensory system injury was measured in aggregate and included measures of S1, S2, and TST injury (Fig 4.2).

The current study found that 67% of subjects with stroke have contralesional finger proprioceptive deficits, consistent with prior reports focused on the arm [151, 154, 165]. These robotic measures of proprioceptive deficits were specific, correlating with scores on sensory but not motor, cognitive, or other scales. Historically, proprioception assessment has been deemed subjective, insensitive, non-standardized, and unreliable [19, 20, 154, 158, 166]. Robotic methods have been advanced but with limitations, for example, the KINARM robot [151, 194] requires participants to move the ipsilesional arm into a position that mirrors the static position held by the contralesional arm, which attains robotic precision but requires transcallosal processing of sensory signals plus precise ipsilesional limb sensorimotor function. This confound was avoided with the current approach, which was found to be valid in relation to two clinical scales of sensory impairment. A robotic assessment such as with the FINGER robot provides a continuous and linear measurement, features that have advantages for behavioral studies [258]. Finger proprioceptive deficits were also present in the ipsilesional fingers in 63% of subjects

(Fig. 4.3B), which may reflect post-stroke disturbances of interhemispheric signal transfer [16, 259].

Proprioceptive deficits in contralesional fingers varied widely. This variability was best explained by a multivariate model that incorporated measures of neural injury (less severe total sensory system injury) and neural function (greater iM1-iS2 functional connectivity). These results emphasize the importance of incorporating both neural injury and neural function to understand behavioral status in chronic stroke. This combined approach explained far more variance in proprioception error (63%) than any single measure did (≤32%, Table 4.2). Including measures of both injury and function to understand behavior is consistent with preclinical [30] and human motor studies [11, 16, 17] and here extends this model for understanding behavior after stroke to sensory systems.

To date, relatively little is known about the specific association between lesion location and proprioceptive dysfunction [174, 260]. One challenge to understanding this relationship may be that sensory functions such as proprioception arise from a highly distributed network [23, 24, 135], and so a single regional sensory system injury measure may provide insufficient insights. In the current study we examined an aggregate measure of total sensory system injury (Fig. 4.2), including both white matter and grey matter injury, and this was superior to any single regional sensory system injury measure for explaining proprioception (Table 4.2, Fig. 4.4A). White matter injury was measured using a new method, lesion overlap with the TST, via a canonical tract generated *a priori* that aimed to model the sensory component of the superior thalamic radiation [174] (Fig. 4.1), injury to which has been linked to post-stroke sensory deficits [174, 261]. Gray matter injury within total sensory system injury was measured as lesion overlap with

regions representing hand area of S1 and S2. Integrity of S1 has been previously shown to have an impact on proprioceptive function [260]. The S2 region, which responds bilaterally to somatosensory stimuli and has distinct subdivisions [129, 256, 262], has received increased attention as important to understanding somatosensory deficits after brain injury [259, 263]. Results emphasize the value of measuring both gray matter and white matter injury to best understand stroke effects on a widely distributed system.

The aspect of neural function that best explained proprioception performance was a measure of functional connectivity, reflecting strength of temporal synchrony of blood oxygen level-dependent signals between spatially remote brain regions, which has increasingly been used to investigate behavioral state post-stroke though not proprioception. In the current study, a single instance of connectivity, between iM1-iS2, was identified as a correlate of proprioception error, such that stronger regional connectivity was associated with better proprioception performance (Fig. 4.4B). Notably, this connectivity metric was significant only when the OP 4 subregion of S2 was evaluated; OP 4 has a strong anatomical and functional connection with S1 and with M1 and is thought to play a key role in sensory-motor integration [256]. In comparison, the OP 1 sub-region of S2 has strong connections with anterior inferior parietal cortex, is responsible for complex functions such as tactile working memory and perceptual learning [264]; connectivity between ipsilesional M1 and OP 1 sub-region of S2 did not survive bivariate screen ($p=0.54$).

Strengths of the current study include use of a sensitive and quantitative robotic assessment of proprioception, and examination of multiple classes of candidate explanatory variables. A population with a wide range of sensorimotor deficits was evaluated, increasing the

likelihood that results generalize. The study is limited by modest sample size, which is further complicated by incomplete testing in some subjects, e.g., due to claustrophobia. Also these results require validation in an independent sample size. Together, results indicate that finger proprioception impairment post-stroke is common, bilateral, and best modeled by measures of neural injury and neural function.

CHAPTER 5

SOMATOSENSORY SYSTEM INTEGRITY PREDICTS HAND FUNCTIONAL GAINS AFTER STROKE

Abstract

Somatosensation is important for motor learning but has received limited attention in post-stroke motor rehabilitation. In the context of robotic therapy designed to enhance proprioceptive feedback via a Hebbian model, we hypothesized that variability in motor gains would be predicted by baseline somatosensory integrity. In 30 patients with chronic stroke, behavioral performance, neural injury, and cortical function were quantified for the somatosensory and motor systems. Patients then received a 3-week robot-based therapy targeting finger movements. Hand function improved after treatment (Box&Blocks score increase of 2.8 blocks, p=0.001) but with substantial variability (4.7 block SD); 9 subjects showed improvement exceeding the minimal clinically important difference (6 blocks), while 8 subjects showed no improvement, all of whom had >2 SD greater proprioception deficit vs. 25 controls. In terms of baseline behavioral assessments, a somatosensory measure (finger proprioception assessed robotically) best predicted treatment gains, outperforming motor measures. When measures of neural injury and neural function were examined to explain variability in treatment response, somatosensory-related variables were again the strongest predictors. A multivariate model combining total sensory system injury and sensorimotor cortical connectivity (between ipsilesional primary motor and secondary somatosensory cortices) explained 56% of variance in treatment-induced hand functional gains (p=0.002). Proprioceptive ability and measures of somatosensory network injury and function best explained inter-subject differences in treatment-related hand function gains. These results underscore the importance of baseline somatosensory

integrity over the more commonly emphasized baseline motor ability for improving hand function after stroke, and provide insights for individualizing rehabilitation therapy.

Introduction

Persistent functional deficits after stroke, particularly in the arm, are common, often profound in magnitude, and are an increasing health care problem in the United States [265]. A number of rehabilitation therapies have been developed to address such deficits, however, patients vary substantially in their response to treatment [9, 266]. The ability to predict a patient's response to a treatment targeting upper extremity function would enable physicians to better match patients with an effective form of therapy, increasing statistical power in clinical trials and optimizing resource allocation in clinical practice.

In an effort to understand this variability, studies have evaluated extent of neural injury and features of neural function prior to therapy [10, 11, 16–18], most often with a focus on the motor system. However, the somatosensory system may also be important for improving hand function. In the intact CNS, proprioception plays a critical role in motor learning [267] and motor control [12, 13], with proprioceptive signals reaching numerous cerebral cortex regions [149] and modulating motor neuron activity [130]. In cats [268] and primates [269–272], injury to CNS somatosensory structures produces few motor deficits but substantially slows/reduces acquisition of new motor skills. In humans, there has been limited study of how stroke-related injury to CNS somatosensory structures affects motor recovery.

To address this issue, we designed a robotic rehabilitation therapy that adopted a framework based on principles of Hebbian plasticity, a widely used model for learning [136, 137] that emphasizes improved neuronal plasticity through repeated and optimally timed

efferent-afferent interactions and that can provide useful strategies for enhancing post-stroke motor recovery [14]. Here, robotic assistance was used to maximize time-correlated proprioception input in response to voluntary motor output, focusing on the fingers given their high density of proprioceptive sensors and large cortical representation [135]. We hypothesized that if a Hebbian process drove sensorimotor plasticity for this this training approach, then therapeutic effects should depend on baseline integrity of both somatosensory and motor systems.

In a trial of 30 patients using this approach, hand functional gains were found to be significant but highly variable across patients [273]. Consistent with our hypothesis, these gains depended on proprioceptive capability of the fingers measured behaviorally at baseline, assessed using a robotic finger position matching paradigm.

The primary goal of the current report was to determine if somatosensory integrity considered more comprehensively–not just behaviorally, but also in terms of injury to and neural function of the somatosensory system–survive as predictors of the hand functional gains observed in this study when considered alongside baseline motor system measures. That is, we sought to identify the somatosensory and motor factors that most reliably predict which patients will, and will not, achieve hand functional gains in order to explain the wide variance in response to this Hebbian-based intervention. Our primary hypothesis was that baseline assessments of the somatosensory system would be the strongest predictors of treatment gains. A secondary hypothesis was that measures of both neural injury and neural function would be needed to best explain inter-subject variability, consistent with previous studies examining neural predictors of therapeutic benefit for other therapies [11, 16–18].

Methods

Patient Enrollment

Subjects with unilateral chronic hemiparetic stroke gave informed consent to be part of a study of robotic-assisted finger therapy (ClinicalTrials.gov ID# NCT02048826), as approved by the University of California, Irvine Institutional Review Board. Inclusion and exclusion criteria (Table 5.1) aimed to capture patients with chronic hemiparetic stroke across a wide range of motor deficits at a time point when motor status after stroke was stable, i.e., at a plateau [7]. The subjects described here are the same as those discussed in Chapter 4 for identifying the neurological underpinnings of proprioception; the current report is focused on predicting treatment-induced hand functional gains.

Table 5.1. Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Age ≥ 18, ≤ 80 years	Contraindication to MRI
Stroke with onset 6 months prior	Severe cognitive impairment
Residual hand motor deficit (B&B stroke-affected hand ≤ 10% non-affected hand)	Concurrent diagnosis affecting arm/hand function
Preserved voluntary hand movements (B&B ≥ 3 blocks over 60 sec)	Hand motor status not at stable plateau (Δ B&B >6 between baseline visits)

B&B = Box and Blocks Test

After enrollment, medical history and sensorimotor behavioral status were assessed. Next, measurements were made in four categories of candidate neural predictors: (1) neural injury; plus three categories of neural function (2) cortical function, (3) cortical connectivity, and (4) EEG coherence. Patients then underwent a 3-week course of robotic therapy. The primary endpoint was the change from baseline to 1 month post-therapy in the Box & Blocks (B&B) score, a measure of manual dexterity [274] classified in the International Classification of Function [275].

Robotic Therapy

Careful consideration of prior successful randomized, controlled studies with robotic therapy devices was used to guide an ideal approach for studying Hebbian-like plasticity induced via robotic rehabilitation. Lessons learned from studies with the BiManuTrac device [276], HWARD device [15], and the pioneering arm-training robot MIT-MANUS [62, 63] have indicated an ideal approach may be to: 1) focus on distal training, 2) incorporate robot assistance that intensely stimulates proprioceptive afference, and 3) allow a high frequency of movement, while also requiring high levels of motor output from the patient. Because the fingers have a well-developed neuro-muscular system to which the brain has dedicated significant resources [120], and finger function is an integral part of activities of daily living, the exoskeletal finger curling robot FINGER was developed with the aforementioned features for use in these studies [220].

During the 3-week period, subjects underwent nine 1-hour treatment sessions of robotic finger therapy, performing approximately 8,000 total training movements. Therapy sessions consisted of playing a game similar to Guitar Hero®, the 3rd largest video game franchise in history, wherein subjects made repeated grasp movements of the index finger, middle finger, or

both of the affected hand using the FINGER robot. Game play required subjects to play along with a song by attempting to hit streaming notes by flexing one or both of these fingers, as specified by note color, to a desired angle then stopping at the correct moment; this required the participant to stop finger flexion inside of a narrow target at the very time when the scrolling musical note was passing. After successfully hitting a note, the subjects were then required to extend their fingers back to a neutral position before the game would give a point, then proceed to the next note.

The robotic therapy approach employed a Hebbian approach by using active assist mode to ensure appropriate proprioceptive feedback in a narrow and physiologically appropriate time window [220]. During each individuated natural finger grasping motions, the FINGER robot helped both finger flexion and extension in active assist mode, and was programmed to provide assistance only for patient-initiated movements; participants were randomized into high and low assistance groups, but this did not affect change in B&B [273] and so participants are combined in current analyses. The assistive forces provided by the robot guided fingers along a physiological spatiotemporal trajectory using a compliant position controller, thereby increasing the amount and temporal precision of proprioceptive feedback in a manner that was time-correlated with attempted motor activity. To reduce slacking the robot only provided these forces if the participants initiated the movements themselves as determined using the robot's force sensors. This precise "assist-as-needed" control strategy was made possible by a high level of control fidelity, achieved by using a high bandwidth of force control and very low friction via lightweight, high-speed, ungeared linear actuators using an 8-bar mechanism, with further friction reduction achieved through feed-forward control compensation.

Measures of Sensorimotor Behavior

A single, licensed physical therapist performed all clinical behavioral assessments. In addition to the B&B score, the stroke-affected arm was also characterized at baseline with other tests (Table 5.2) that included Action Arm Research Test (ARAT) [277], Upper-Extremity Fugl-Meyer Scale (FM) [83], Nine Hole Peg Test (NHPT) [278], and Finger Tapping (FT) test [279]. Clinical assessments of sensory function included the light touch and proprioception sub-scores of the FM scale [186].

The FINGER robot not only provided therapy, but also was used to assess proprioception of the index and middle fingers on the stroke-affected hand. As described previously in Chapter 3, the FINGER robot can be used to evaluate passive finger position sense via a series of 12 non-periodic finger-crossing movements wherein the index and middle fingers are slowly moved in opposing directions. For each finger-crossing movement, subjects pressed a keyboard spacebar to indicate the moment when they perceived their fingers were directly aligned relative to one another. Error, defined as the angular distance between the two metacarpophalangeal joints when the spacebar was pressed, is presented here as the average error across the 12 finger-crossing movements (Table 5.2).

Neuroimaging Metrics

Many of the neuroimaging metrics employed in Chapter 4 are utilized within the present study to generate possible predictors of response to therapy. For a detailed review of methodology, see Chapter 4 Methods.

Brain Injury: On a 3T Philips MRI, high-resolution T1-weighted and T2-FLAIR images were acquired. Measures of infarct volume, grey matter injury, and white matter injury were

derived from MRI images (Table 5.2). These metrics include injury to M1, S1, S2, CST, TST, total motor system injury, and total sensory system injury.

Measures of Cortical Function: Four runs of BOLD fMRI were acquired at baseline. During image acquisition, patients wore a plastic distal arm exoskeleton similar to the robotic therapy interface and viewed a video from the robotic therapy Guitar Hero® game. The video guided the paretic hand to alternate between rest and active 0.5 Hz index and middle finger grasp-release movements similar to those made during therapy with the FINGER robot. Three measures of brain function were extracted for M1, S1, and S2 ROIs on each brain side (Table 5.2): (1) activation beta (contrast) estimate, (2) activation volume, and (3) activation volume Laterality Index, a measure of hemispheric dominance ranging from +1 (activation only in the ipsilesional hemisphere) to -1 (activation only in the contralesional hemisphere; calculated according to Fernández *et al*. [280].

Measures of Cortical Connectivity: Functional connectivity was assessed from the BOLD fMRI images with an ROI-ROI approach. Ipsilesional and contralesional ROIs were used to extract the following Fisher-transformed correlation coefficients for each subject: iM1-cM1, iM1-iS1, iM1-iS2, iS1-cS1, iS1-iS2, iS2-cS2 (Table 5.2).

Measures of EEG Coherence: Three minutes of awake, eyes-open, resting-state brain activity was acquired by dense array surface EEG using the 256-lead Hyrdocel net (Electrical Geodesics, Inc.). Data were preprocessed to remove extra-brain artifacts as described previously [281, 282]. Resting-state connectivity was estimated from EEG coherence in the high beta (20-30 Hz) frequencies using electrodes overlying M1, S1, or S2 as the seed region (Table 5.2).

Statistical Analysis

Normally distributed data and data that could be transformed to a normal distribution were analyzed using parametric statistics, otherwise nonparametric statistics were used. Analyses were two-tailed with α=0.05 and used JPM-11. A paired t-test was used to evaluate the effects of robotic therapy on motor function from baseline to 1-month post therapy. Linear regression was used to identify behavioral measures related to treatment-induced hand functional gains. Comparisons with 25 age-matched healthy controls used data described in Chapter 3.

To identify measures of neural injury and neural function that predict motor gains, a bivariate screen evaluated each variable within the four neurological-based categories (brain injury, cortical function, cortical connectivity, and EEG coherence). Results of bivariate screening determined whether any individual variable in a category survived as a predictor of hand functional gains and would be advanced to multivariate modeling. The most significant predictors from each category identified in bivariate screening (as long as bivariate screening showed $p<0.1$) were advanced into a forward stepwise multivariate linear regression approach (0.1 to enter, 0.15 to leave the model) in order to best predict treatment-induced hand functional gains.

Results

Data from 30 subjects were available for analysis (Table 5.2). All 30 subjects had 100% compliance with therapy. All completed testing except for four who could not complete MRI (claustrophobia), three who could not complete EEG (cap incompatibility with hair accessories), and three who were not administered the robotic proprioception test (protocol implemented in stages). Three subjects were excluded from fMRI-derived analyses due to excessive head motion during scanning, while five subjects were excluded from white matter injury analysis due to lesion location extending into brainstem.

Overall, patients showed statistically significant hand functional gains from therapy as measured by the primary endpoint, ΔB&B at 1 month post-therapy. Measurement of the B&B score at baseline was stable, with a non-significant difference of 0.6 ± 1.9 blocks (mean ± SD p=0.09) seen between the two baseline measurements taken 6 days apart. However, the change from average baseline to 1 month post-therapy was significant (ΔB&B: 2.8 ± 4.7 blocks, p = 0.001), with substantial variability in treatment response: 9 subjects improved by 6 or more blocks, the minimal clinically important difference (MCID) for B&B [283], while 8 subjects failed to show any improvement in B&B score.

Table 5.2: Independent Variables: Baseline Values and Correlation with Motor Gains

Measure	Baseline Value	Correlation with motor gains: r	p
Demographics/medical			
Age, mean yr (SD)	57.8 (13.18)	-0.03	0.88
Gender, F/M	10/20	0.14	0.47
Hand dominance[a], R/L/A	27/3/0	0.11	0.56
Diabetes mellitus, yes/no	6/24	0.04	0.84
Hypertension, yes/no	15/15	0.13	0.50
Hypercholesterolemia, yes/no	16/14	0.03	0.89
Time poststroke, mean mo (SD)	37.24 (46.67)	0.31	0.08
Stroke type, ischemic/hemorrhagic	19/11	0.30	0.47
Stroke hemisphere, L/R	14/16	0.07	0.72
Stroke in dominant hemisphere, yes/no	15/15	0.04	0.82
NIHSS, normal = 0	2.3 (2.18)	0.22	0.25
Geriatric Depression Scale	3.76 (3.66)	-0.06	0.72
Sensorimotor Behavior, mean (SD)			
Proprioception error	16.15 (6.41)	-0.60	0.001
ARAT, normal = 57	33.97 (21.99)	0.48	0.01
FM Motor[b], normal = 66	46.4 (11.63)	0.27	0.15
B&B Score	22.97 (18.11)	0.31	0.09
NHPT Score	54.72 (10.30)	0.24	0.20
FT Score	13.66 (13.05)	0.31	0.11
FM Sensory[b], normal = 12	10.87 (2.33)	0.29	0.13
Light touch subscore[b], normal = 4	3.4 (1.04)	0.30	0.11
Proprioception subscore[b], normal = 8	7.47 (1.55)	0.32	0.09
Neurological Variables:			
Brain injury			
Infarct volume, mean cm^3 (SD)	19.85 (23.30)	0.18	0.36
M1 % injury, mean (SD)	9.69 (20.81)	0.38	0.07
S1 % injury, mean (SD)	16.31 (30.34)	0.37	0.08
S2 % injury, mean (SD)	11.18 (24.34)	0.18	0.39
Cortex % injury, mean (SD)	1.27 (2.22)	0.12	0.56
CST % injury, mean (SD)	32.44 (29.16)	0.09	0.70
TST % injury, mean (SD)	36.01 (28.84)	0.02	0.92
Total Motor System Injury	0.77 (0.51)	0.38	0.09
Total Sensory System Injury	0.79 (0.44)	-0.49	0.03
Cortical function, mean (SD)			
iM1 activation volume	51.39 (39.22)	0.36	0.10
cM1 activation volume	24.89 (34.08)	-0.18	0.42

iS1 activation volume	53.27 (39.90)	0.20	0.38
cS1 activation volume	36.02 (33.47)	-0.13	0.57
iS2 activation volume	132.75 (108.47)	0.22	0.32
cS2 activation volume	107.84 (89.45)	-0.02	0.92
iM1 contrast estimate	3.71 (2.05)	0.31	0.16
cM1 contrast estimate	1.98 (1.91)	-0.16	0.49
iS1 contrast estimate	2.79 (1.52)	0.29	0.20
cS1 contrast estimate	2.07 (1.14)	-0.26	0.23
iS2 contrast estimate	2.29 (1.67)	0.20	0.38
cS2 contrast estimate	2.44 (1.52)	-0.14	0.53
M1 Laterality Index	0.55 (0.60)	0.28	0.20
S1 Laterality Index	0.25 (0.77)	0.60	0.01
S2 Laterality Index	0.02 (0.79)	0.20	0.39
Cortical connectivity, mean (SD)			
iM1-cM1 connectivity	0.17 (0.21)	0.01	0.96
iM1-iS1 connectivity	0.45 (0.19)	0.09	0.68
iM1-iS2 connectivity	0.09 (0.19)	0.46	0.03
iS1-cS1 connectivity	0.14 (0.20)	0.18	0.40
iS1-iS2 connectivity	0.08 (0.21)	0.45	0.03
iS2-cS2 connectivity	0.27 (0.21)	0.22	0.30
EEG Beta coherence, mean (SD)			
iM1-cM1	0.19 (0.10)	-0.31	0.12
iM1-iPr	0.23 (0.06)	0.17	0.38
iM1-iPf	0.14 (0.11)	-0.22	0.27
iS1-cS1	0.19 (0.11)	-0.46	0.02
iS1-iPr	0.46 (0.08)	-0.03	0.87
iS1-iPf	0.07 (0.07)	0.04	0.83
iS2-cS2	0.24 (0.15)	-0.25	0.22
iS2-iPr	0.20 (0.08)	-0.01	0.95
iS2-iPf	0.17 (0.11)	-0.31	0.12

[a] Handedness determined using the Edinburgh Handedness Inventory [221]
[b] Fugl-Meyer assessment was for upper extremity only

A = ambidextrous; ARAT = Action Arm Research Test; B&B = Box & Blocks; c = contralesional; CST = corticospinal tract; F = female; FM = Fugl-Meyer; FT = Finger Tapping; i = ipsilesional; L = left; M = male; M1 = primary motor cortex; NHPT = Nine Hole Peg Test; NIHSS = NIH stroke scale; Pf = prefrontal cortex; Pr = parietal cortex; R = right; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; TST = thalamocortical sensory tract.

Behavioral Factors Related to Treatment-Induced Hand Functional Gains

Better proprioception at baseline was associated with larger treatment gains, such that subjects with smaller proprioception error prior to therapy had greater hand functional gains after therapy ($r=-0.60$, $p=0.0008$, Fig. 5.1). This relationship does not simply reflect the link between proprioception and motor status, as at baseline proprioception error was not significantly related to B&B score ($p=0.2$), or to other motor assessment. Furthermore, proprioception error remained a significant predictor of functional hand gains (ΔB&B) even when specifically controlling for baseline motor status (baseline B&B score) using partial correlation ($r=-0.59$, $p=0.002$). Intact proprioception at baseline was necessary to achieve hand functional gains, as all eight subjects who failed to show any improvement in B&B score had proprioception errors at least 2 SDs greater than those measured in the 25 age-matched healthy controls.

Baseline motor status also predicted treatment-induced hand functional gains, but with weaker predictive value as compared to baseline proprioception status. For example, baseline score on B&B showed only a trend for predicting ΔB&B ($r=0.31$, $p=0.09$). Among the four other baseline motor assessments, only the ARAT score was found to significantly predict motor gains ($r=0.48$, $p=0.007$), though this was a weaker predictor as compared to proprioception.

In secondary analyses, other behavioral measures, such as depression score ($r=-0.06$, $p=0.7$) and NIHSS score ($r=-0.21$, $p=0.3$) were not significantly associated with hand functional gains (Table 5.2).

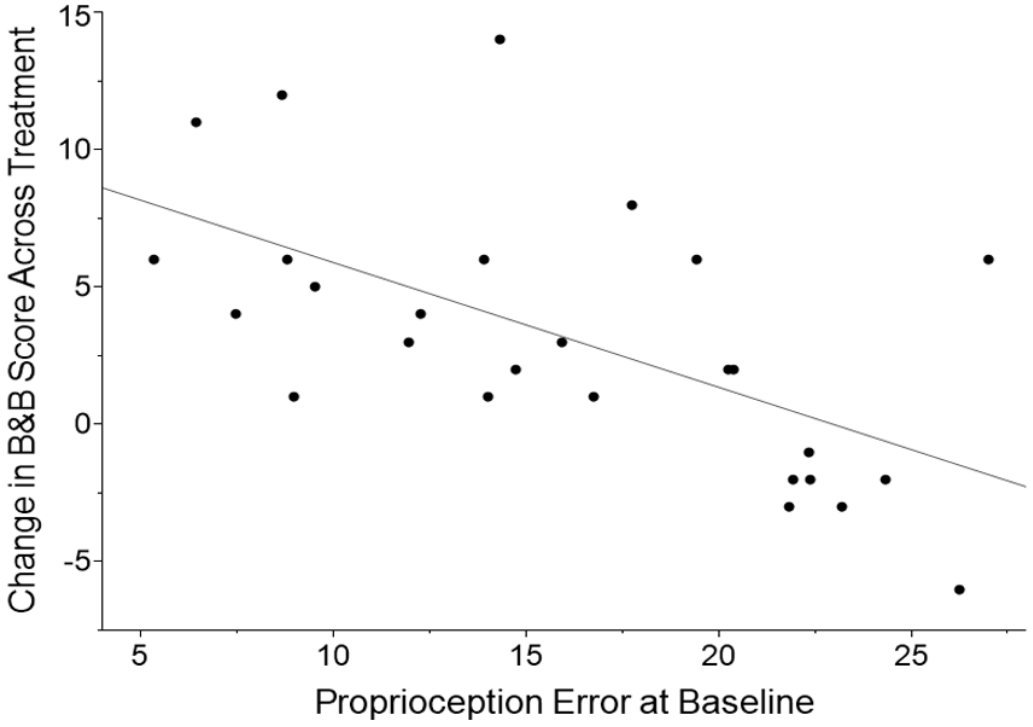

Figure 5.1 Better proprioception function at baseline predicted treatment-related gains in hand function (r=-0.60, p=0.0008), defined as change in B&B score from baseline to 1 month post-therapy. Proprioception error is the number of degrees separating index and middle fingers at the time when the subject reported them as directly aligned; smaller error is indicative of better proprioception function.

Neurological Factors that Predict Treatment-Induced Hand Functional Gains

Measures of neural injury and neural function in somatosensory and motor systems at baseline were examined to better understand how proprioceptive integrity was associated with larger treatment gains. On bivariate screening, all four categories of neural injury/function had at least one variable that significantly predicted treatment-induced hand functional gains (Table 5.2), with the most significant being Total Sensory System Injury ($r=-0.49$, $p=0.03$), for brain injury; S1 Laterality Index ($r=0.60$, $p=0.01$), for cortical function; iM1-iS2 functional connectivity ($r=0.46$, $p=0.03$), for cortical connectivity; and iS1-cS1 coherence ($r=-0.46$, $p=0.02$), for EEG coherence. Excluding patients with ≥50% damage to cortical ROIs had no effect on these findings.

When these four variables were entered into a forward stepwise model, two survived: a measure of neural injury (Total Sensory System Injury, $p=0.004$; Figure 2A) and a measure of neural function (cortical connectivity, i.e., iM1-iS2 functional connectivity, $p=0.04$; Figure 2B). The multivariate model containing these two terms explained 56% of variance in treatment-induced hand functional gains ($r=0.75$, $p=0.002$; Table 5.3, Figure 5.2C).

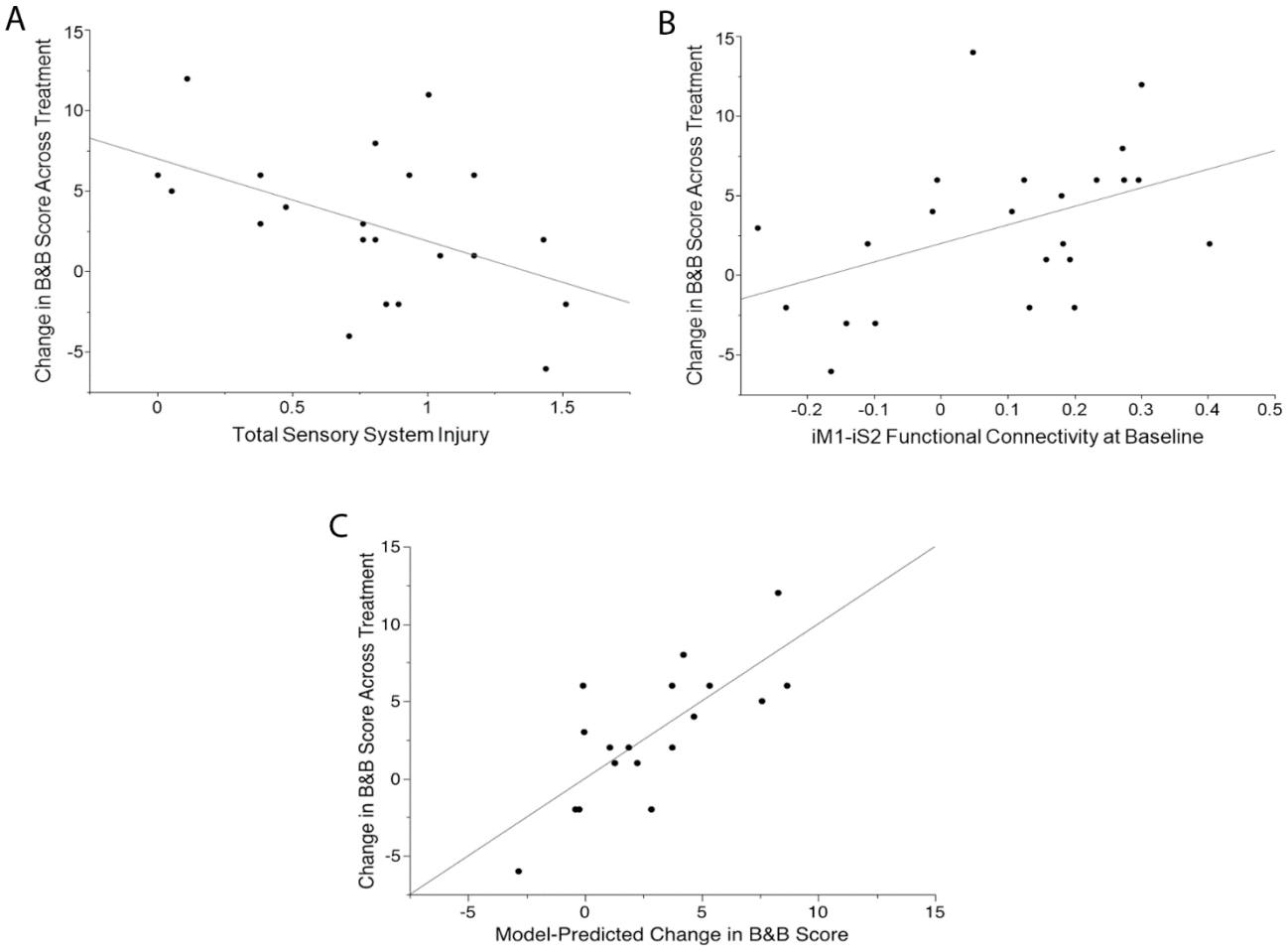

Figure 5.2. (**A**) Smaller Total Sensory System Injury (r=-0.49, p=0.03) and (**B**) greater ipsilesional M1-ipsilesional S2 (iM1-iS2) functional connectivity (r=0.46, p=0.03) each significantly predicted larger treatment-related gains in hand function (change in B&B score from baseline to 1 month post-therapy). Total Sensory System Injury is an aggregate measurement of injury to TST, S1, and S2. **(C)** Change in hand function predicted by the final model in relation to actual change.

Table 5.3. Multivariate Predictor Model

Variable	Estimate	Standard Error	95 % CI	*p*
Intercept	6.403	1.614	–	0.001
Total Sensory System Injury	-5.481	1.617	-8.92 to -2.03	0.004
iM1-iS2 connectivity	8.254	3.854	0.04 to 16.47	0.04

For the final model, r=0.75 (p=0.002).

iM1 = ipsilesional primary motor cortex; iS2= ipsilesional secondary somatosensory cortex

Discussion

Stroke is a leading cause of disability, due in part to reduced hand function, as upper extremity paresis is present in 76% of patients [2], and 50% of patients have upper extremity proprioception deficits 6 months after stroke [284]. A number of rehabilitation therapies aim to improve hand function. Patients show wide differences in response to such therapies, in part reflecting variability in injury and neural function [11, 16–18], emphasizing the need for improved methods to match patients with a manner of rehabilitation therapy tailored to their needs. The current study provided 30 patients with robot-assisted finger training that optimized proprioception feedback using a Hebbian-based mechanism of sensory feedback. These are some of the first controlled data to support a Hebbian hypothesis for robot-assisted training, the other being a study of a hand robot in which the group receiving a higher dose of active assistance during training showed greater arm gains [15]. However, treatment gains in the current study were highly variable. Behaviorally, differences in treatment gains were best explained by proprioception status, and indeed intact proprioception at baseline was necessary to achieve any motor gains. When the neural basis of inter-subject differences in treatment gains were examined, the best predictors consistently came from somatosensory rather than motor measures,

and included measures of both neural injury and neural function. Together, these findings provide useful insights towards the goal of individualizing rehabilitation after stroke.

Better proprioception at baseline was the strongest behavioral predictor of motor gains (Table 5.2; Fig. 5.1). This is consistent with a study by Vidoni and Boyd, who found that among 12 patients with chronic stroke, deficits in proprioception predicted behavioral change associated with 100 trials (two hours) of tracking training [285]. The link between proprioception and treatment-related gains in the current cohort was also described in our report of clinical trial results [273]; here we extend that finding by comparing with predictive value of other sensory measures as well as motor measures. Indeed, the relationship between baseline proprioception and subsequent treatment-related hand function gains was independent of any association that baseline motor behavior had with treatment-related gains: proprioception error did not correlate with any baseline motor measure and remained a significant predictor of gains even after controlling for baseline motor status. Furthermore, all eight subjects who failed to show any improvement in B&B score had proprioception errors at least 2 SDs greater than those found in 25 age-matched healthy controls (see Chapter 3). Together, these experimental findings are consistent with clinical observations, e.g., that somatosensory deficits after stroke are associated with poorer outcomes in motor function, longer hospitalization, increased mortality, and diminished quality of life [153, 154, 165, 168]. In a meta-analysis of stroke studies, Meyer et al found proprioception was related to arm functional status [286]. These findings are concordant with evidence that proprioception provides a unique component for optimizing motor control [12, 13, 131, 132] and supports the idea that the Hebbian framework attempted in the current intervention supported motor gains.

A major aim of this study was to identify the neural basis for inter-subject differences in treatment-related gains in hand motor function. The data indicate that measures of both somatosensory and motor systems have predictive value, but emphasize greater predictive value for somatosensory system injury and function as compared to the motor system measures (Table 5.2). The two variables that were retained in the final multivariate model, Total Sensory System Injury and iM1-iS2 functional connectivity, were derived from somatosensory and sensorimotor systems (Table 5.3). These findings are consistent with behavioral findings, where a somatosensory measure, proprioception, was the best predictor of treatment-related gains in hand function. Total Sensory System Injury is an aggregate measure that includes TST, S1, and S2 injury. These anatomical regions have been shown to have an impact on somatosensory function [175] yet, the Total Sensory System Injury aggregate measure demonstrated superior predictive value than any element alone (Fig. 5.2A; Table 5.2). This finding suggests that the motor learning induced here was dependent on preserved anatomical integrity of a distributed somatosensory network, and emphasizes the value of comprehensive injury metrics incorporating both grey matter and white matter. Previous studies of CNS somatosensory system injury in animals are consistent with current findings but to our knowledge there has been limited study to date beyond lesions to post-central gyrus. Sakamoto et al [268] removed primary sensory cortex unilaterally in cats and found that while there was no obvious difference in limb use, learning of a new forelimb motor skill contralateral to the lesion was reduced. Lesions to post-central gyrus produce little if any deficits in the control of limb movements [269–272], but learning of a new motor behavior is either slowed or decreased, whether lesions are small [272] or large [269, 270].

The final multivariate model also contained a measure of neural function, connectivity between iM1 and iS2 (Fig. 5.2B). This highlights the importance of sensorimotor processing in motor rehabilitation targeting hand function. S2 has a strong anatomical and functional connection with S1 and M1, and is known to play a key role in sensorimotor integration [256]. This finding suggests that the robot-assisted therapy used here, with its emphasis on bolstering afferent signals, required intact functional interactions between higher order sensorimotor regions, as subjects with weaker iM1-iS2 connectivity were less successful in achieving gains in hand motor function. The emergence of both a neural injury and a neural function measure in the final predictive model is in line with preclinical [30] and clinical studies [11, 16–18] that emphasize neural injury and function as key determinants of post-stroke functional outcome.

Strengths of the current study include examination of somatosensory system and motor system status, and consideration of multiple classes of neural candidate predictor variables in parallel. Baseline measures of the primary endpoint were very stable (0.6 blocks between baseline measurements). The potential to study a Hebbian-based intervention was enabled by several features of FINGER robot design, and by targeting fingers, which are highly innervated with respect to proprioception [135]. Weaknesses of the study include the fact that data could not be collected from some subjects for each neuroimaging technique. A measure of peripheral nerve sensory function was not available but might have influenced results. Results reported here might be specific to the Hebbian-based learning targeting finger movements as provided by the FINGER robot, and results might not generalize to treatments that make less demand on finger proprioceptive function. The multivariate model identified here explained 56% of variance in outcome (Table 5.3), and while this exceeds performance of any single neural measure (up to 36%, see Table 5.2), additional factors need to be identified to explain remaining variance.

Stroke is an extremely heterogeneous disease. Gains from rehabilitation therapies are maximized when content of therapy is appropriately matched to an individual patient's behavior, injury, and brain state. The current findings indicate that proprioception is important to achieving hand function gains with a Hebbian-based robot-assisted therapy. Consistent with this finding, variability in treatment gains was best explained by measures of CNS somatosensory system injury and function. The current findings may be useful to define approaches to individualize rehabilitation therapy and thereby maximize treatment-related gains.

CHAPTER 6

SUMMARY AND CONCLUSIONS

Stroke is a highly heterogeneous disease, not only in its initial presentation but also in the extent of spontaneous recovery and response to restorative therapies. With 50-70% of survivors experiencing long-term motor deficits, new approaches are needed to improve motor function. Progress can be made in the form of developing new therapies or identifying new biomarkers of motor recovery that could help guide treatment and explain patient heterogeneity. With regard to the latter, recent research has illuminated advantages of a multimodal approach for understanding interindividual differences in therapy-induced motor gains. An emphasis has been placed on structural and functional neuroimaging of the motor system. Though this is a striking improvement over behavioral assessments alone, it fails to incorporate the other half of sensorimotor function: proprioception. Sensory information underlies the planning of all motor output, and without intact proprioception, one cannot optimize motor control. Indeed, somatosensory-induced brain plasticity is the working hypothesis for how robot-assisted rehabilitation training might induce recovery of motor function. Literature findings are convergent that it is especially important to assess proprioception status after central nervous system injury when the goal is to rehabilitation motor functions. Despite this, nothing is known about how proprioception predicts response to robot-assisted training. Previous attempts to do so have been limited by inadequate methodology for evaluating proprioception behavior. Therefore, the salience of the current studies lies in the development of a sensitive, objective, and granular approach to assessing proprioception function and the utilization of a multimodal approach that incorporates neural injury and function metrics of the somatosensory system in addition to the

oft-investigated motor system. Specifically, this dissertation set out to define the role of proprioception in robot-assisted motor therapy.

The aim of the first study (Chapter 3) established the use of an exoskeletal robot, FINGER, to objectively and sensitively assess finger proprioception. Within a neurologically intact population, the FINGER robot was able to detect age-related declines in finger proprioception for young (22-28 years), middle-aged (30-60 years), and older adults (>65 years). Proprioception errors were 48% larger in older adults than in young adults, yet when visual feedback was permitted during testing these age-related differences subsided. The experimental paradigm utilized a passive finger position sense task wherein subjects indicated a direct overlap of their index and middle fingers during a finger-crossing movement. This assessment addressed the intrinsic dual functionality of proprioception, such that both position sense and movement detection were reflected in task performance. This study characterized the extent of age-related proprioception decline for the first time in finger joints. Moreover, this study introduces a novel robotic technique for objectively and sensitively assessing dynamic position sense in the finger joints with a continuous and linear measurement. It is a particularly pertinent tool given that the functional consequences of impaired finger joint proprioceptive ability strongly relate to precise control of finger movements performed during activities of daily living.

The second study (Chapter 4) examined the neural basis of finger proprioception deficits after stroke. Historically, this has been a difficult objective in part due to weaknesses of clinical proprioception assessments and challenges in conceptualizing sensory system neural injury. Thus, this study utilized the FINGER robot proprioception assessment and identified contralesional proprioception impairments in 67% of chronic stroke subjects and bilateral

deficits in 56%. Robotic measures were specific to proprioception function and were more sensitive than clinical assessments. To characterize these deficits, variables belonging to 5 categories (demographics/medical history, sensorimotor behavior, brain injury, cortical function, and cortical connectivity) were examined. A new method of measuring thalamocortical sensory tract (TST) integrity was developed to quantify injury to the somatosensory system. An aggregate measure of TST, S1, and S2 injury – termed Total Sensory System Injury – was superior to any single neural injury measure for explaining proprioception impairment. A multivariate model incorporating this neural injury measure and an aspect of neural function, namely iM1-iS2 functional connectivity which plays a key role in sensory-motor integration, best explained proprioception behavior. The findings illuminate key neurological underpinnings of proprioception worthy of consideration for future studies investigating the role of proprioception in Hebbian-induced plasticity.

The third and final study composing this dissertation (Chapter 5) moved beyond characterizing post-stroke proprioception and attempted to define the role of proprioception as it pertains to achieving functional gains from robot-assisted motor therapy. To stimulate somatosensory-induced brain plasticity, a robot-assisted rehabilitation therapy was designed with the FINGER robot to assist subjects in individually moving their index and middle fingers in naturalistic curling motions. The therapeutic goal was to strengthen functional connections between somatosensory neurons and motor output neurons in the cortex, and thus baseline proprioception metrics were hypothesized to have value in predicting therapy-induced motor gains. Patients showed significant motor gains due to therapy and baseline proprioception status, as measured by the FINGER robot, was the best sensorimotor behavioral predictor. To identify neurological factors that predict motor gains, variables of neural injury, cortical function, cortical

connectivity, and cortical coherence pertaining to the motor and somatosensory system were examined for their predictive value. A multivariate model of neural injury and function explained 56% of variance in outcome, far more than any single neurological measure alone. The two neurological variables that composed this model were Total Sensory System Injury and iM1-iS2 functional connectivity, the same two variables previously identified as neural correlates to proprioception. Notably, all somatosensory-related variables outperformed their motor system counterparts. A novel finding of this study was that for the first time, proprioception behavior and neurological underpinnings were used to best predict motor outcome. This study confirms that somatosensory function, specifically proprioception, is critical for motor learning induced with a Hebbian-based, robot-assisted therapy.

Implications and Future Directions

Taken together, the studies composing this dissertation contribute novel and corroborative data towards the need to incorporate proprioception measures into therapeutic decision-making after stroke. The data demonstrate that proprioception is an integral aspect of post-stroke motor learning. For the first time, robot-assisted motor rehabilitation has been shown to be dependent on the neurological integrity of the somatosensory system, extending proprioception's predictive value far beyond general outcome measures.

Future neuroimaging studies attempting to understand the variability in stroke or response to therapy would benefit from incorporating somatosensory system metrics. In the present study, somatosensory variables were more significant predictors of motor outcome than oft-cited motor variable predictors. This may be a reflection on the type of therapy used in the studies described here, as it was designed to amplify somatosensory-induced neuroplasticity. Or,

these results may be specific to the fingers – a system with many resources allocated to proprioception. Until neuroimaging studies fully address somatosensory system variables, the robust influence of proprioception of the motor learning process (or lack thereof) will remain unclear.

Additionally, future studies should address the feasibility of rehabilitating the proprioceptive system itself. There is preliminary evidence to suggest that conventional and robot-assisted sensory re-education training leads to positive improvement in upper-limb proprioception in acute [287] and chronic patients [167, 288–290]. Despite this, the number of studies examining proprioception dysfunction is small and future work with large sample sizes is needed to corroborate these effects. Moreover, because this field is still in its infancy, the treatment programs that yield the most effective outcomes remain an open question. This would be an exceptionally worthwhile investigation, given that the data reported here demonstrate that intact proprioception is critical to achieving motor gains.

The studies described here also have direct clinical implications. They illuminate the striking need for an objective and sensitive assessment of dynamic proprioception in a clinical setting. If properly designed, a simple in-clinic proprioception test could help physicians pair patients with the best therapy options. For example, proprioception status could ostensibly be incorporated into an algorithm for predicting the potential for recovery of motor function after stroke. One might imagine a clinical operations paradigm wherein stroke survivors first complete a proprioception assessment and, depending on somatosensory system status, move forward to sensory rehabilitation prior to engaging in motor rehabilitation. More efforts should be made toward developing an in-clinic option for objectively and sensitively assessing proprioception, as

this type of insight cannot currently be gained from the clinical proprioception assessments currently available.

Conclusions

In summary, proprioception is critical to improving motor function in a chronic stroke population. Neuroimaging-derived measures of somatosensory system injury and function are the strongest determinants of likelihood of recovery with a robot-assisted rehabilitative therapy. No comparative measure of the motor system exhibited such utility. The data also highlight the utility of an objective and sensitive proprioception assessment and the ability to identify neurological correlates to proprioception behavior if accurate measures are acquired. Given the clear functional impact of somatosensory deficits after stroke, further research is warranted as to more specific rehabilitative training paradigms designed to foster recovery of sensorimotor function. These studies will hopefully spur support for examining somatosensory-related neuroimaging and behavioral metrics in large, restorative therapy clinical trials.

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APPENDIX I

LIST OF ABBREVIATIONS AND DEFINITIONS

ANOVA	analysis of variance
ARAT	action arm research test
B&B	box and blocks score
BOLD	blood oxygen-level dependent
c	contralesional i.e., the neurologically intact hemisphere, located ipsilateral to the paretic limb
CNS	central nervous system
CST	corticospinal tract
DTI	diffusion tensor imaging
EEG	electroencephalography
EPI	echo-planar imaging
FA	fractional anisotrophy
FINGER	finger individuating grasp exercise robot
FM	Fugl-Meyer assessment
fMRI	functional magnetic resonance imaging
FT	finger tapping test
i	ipsilesional i.e., the lesioned hemisphere, located contralateral to the paretic limb
IQR	inter-quartile range
M1	primary motor cortex
MCP	metacarpophalangeal joint
MNI	Montreal Neurological Institute

MRI	magnetic resonance imaging
NHPT	nine hole peg test
NIHSS	NIH stroke scale
OP1	parietal operculum area 1
OP4	parietal operculum area 4
Pf	prefrontal
PIP	proximal interphalangeal joint
Pr	parietal
ROI	region of interest
ROM	range of motion
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SD	standard deviation
Total Motor System Injury	Aggregate measure of injury to M1 and CST
Total Sensory System Injury	Aggregate measure of injury to S1, S2, and TST
TST	thalamocortical sensory tract
VPL	ventral posterior lateral nucleus