EARLY PREDICTORS OF POST-STROKE MOTOR RECOVERY

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EARLY PREDICTORS OF POST-STROKE MOTOR RECOVERY

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LIST OF SYMBOLS AND ABBREVIATIONS

PREP/PREP2	Predict Recovery Potential prediction tool
PUE	Paretic upper extremity
PLE	Paretic lower extremity
EUH	Emory University Hospital
ERH	Emory Rehabilitation Hospital
GMH	Grady Memorial Hospital
AR	Acute inpatient rehabilitation
EMR	Electronic medical record
SAFE	Shoulder Abduction and Finger Extension manual muscle tests
E-SAFE	Estimated SAFE score
Acute E-SAFE	Estimated SAFE assessed in the acute hospital, closest to day-3 post-stroke
AR E-SAFE	Estimated SAFE assessed at evaluation in the acute rehabilitation setting
ARAT	Action Research Arm Test
E-ARAT	Estimated Action Research Arm Test
NIHSS	National Institutes of Health Stroke Scale
LOS	Length of hospital stay
ICH	Intracerebral hemorrhagic stroke
SAH	Subarachnoid hemorrhage
MCA	Middle cerebral artery
TIA	Transient ischemic attack
TBI	Traumatic brain injury
AD	Alzheimer’s disease

MS	Multiple sclerosis
ALS	Amyotrophic lateral sclerosis
CP	Cerebral palsy
CST	Corticospinal tract
M1	Primary motor cortex
PM	Premotor cortex
PMv	Ventral premotor cortex
PMd	Dorsal premotor cortex
SMA	Supplementary motor cortex
preSMA	Presupplementary motor cortex
S1	Primary somatosensory cortex
PPC	Posterior parietal cortex
SC	Spinal cord
CNS	Central nervous system
GABA	γ-aminobutyric acid
MRI	Magnetic resonance imaging
DWI	Diffusion weighted imaging
GRE	Gradient echo imaging
MNI	Montreal Neurological Institute
SPM12	Statistical Parametric Mapping software
SMATT	Sensorimotor area tract template atlas
JHU	Johns Hopkins University atlas
TMS	Transcranial magnetic stimulation
MEP	Motor evoked potential
EMG	Electromyogram

EEG	Electroencephalogram
PET	Positron emission tomography
ECR	Extensor carpi radialis muscle
FDI	First dorsal interosseous muscle
tPA	Tissue plasminogen activator
BMI	Body mass index
CART	Classification and regression tree
MCID	Minimal clinically important difference
ICC	Intraclass correlation coefficient
PPV/NPV	Positive predictive value/Negative predictive value
SPSS	IBM® Statistical Package for the Social Sciences
AROM	Active range of motion
9HPT	Nine-hole peg test
BBT	Box and block test
IRF-PAI (IRF)	Inpatient Rehabilitation Facility Patient Assessment Instrument
ISCCI	Ischemic stroke Charlson comorbidity index
CIMT	Constraint-induced movement therapy
WFL	Within functional limits
WNL	Within normal limits
CMS	Centers for Medicare and Medicaid Services
FY	Fiscal year
US	United States
NZ	New Zealand

SUMMARY

Stroke is a leading cause of long-term disability worldwide. Despite robust spontaneous biological recovery mechanisms and provision of intensive rehabilitation therapies, most stroke survivors experience persistent loss of upper extremity function which is directly related to reduced independence in activities of daily living and diminished quality of life. Identification of clinical, anatomical, or neurophysiologic indices that accurately predict the capacity for recovery post-stroke is crucial to facilitate precision-based medicine approaches for clinical management, including targeted therapeutic interventions. The Predict Recovery Potential (PREP2) prediction tool uses a combination of clinical measurements and neurological biomarkers to predict paretic upper extremity (PUE) motor outcomes but has yet to be externally validated in the US healthcare system. The primary study objectives were to: 1) evaluate external validation feasibility of PREP2 in the US; 2) retrospectively assess current care practices to determine the routinely collected measures that are most predictive of PUE functional outcome post-stroke; 3) evaluate the prognostic merit of biomarkers isolated from clinical neuroimaging. I hypothesized that our data would demonstrate that PREP2 will be feasible for external validation in healthcare settings in the US and that a combination of clinical measures and biomarkers extracted from clinical magnetic resonance imaging (MRI) would accurately predict level of PUE motor recovery post-stroke in patients who underwent acute inpatient rehabilitation (AR) post-stroke.

The studies were conducted via retrospective chart review for two cohorts of stroke patients over fiscal years 2016-2018. In Aim 1, I assessed prospective validation feasibility of the

PREP2 prediction tool in acute care settings in the US using a cohort of all stroke admissions to Emory University Hospital and Grady Memorial Hospital. In Aims 2 and 3, I assessed the ability of currently collected clinical measures and neurologic biomarkers isolated from clinical imaging to predict PUE motor outcomes post-stroke using a cohort of patients with similar clinical management across the continuum of stroke rehabilitation and recovery. This cohort of patients remained within the Emory University Hospital system for acute hospitalization, AR, and outpatient care, allowing longitudinal assessment to track recovery and to estimate the level of PUE motor function return. Institutional electronic medical record systems were utilized to extract metrics including demographic data, stroke characteristics, longitudinal documentation of post-stroke motor function, and metrics of stroke care management along the post-stroke care continuum. Clinically diagnostic MRI was used to create lesion masks which were spatially normalized and processed to obtain corticospinal tract (CST) lesion overlap in both primary motor (M1) and non-M1 CST projections. Metric associations were investigated with correlation and cluster analyses, Kruskal-Wallis tests, classification and regression tree (CART) analyses.

In Aim 1, we found that current stroke management allows for shoulder abduction finger extension manual muscle tests (SAFE score) to be obtained at therapy evaluations and for the National Institutes of Stroke Scale score to be extracted from the patient chart. On average, patients appropriate for CST integrity assessment remain in the acute care hospital setting at a time when CST function should be evaluated for PREP2 validation. In Aims 2 and 3, estimations of PUE strength extracted from the patient chart (E-SAFE) and clinical MRI-derived CST lesion overlap were associated with PUE functional outcome. Cluster analysis produced three distinct outcome groups and aligned closely to previous outcome

categories. Outcome groups significantly differed in E-SAFE scores and lesion overlap on cortical projections within the CST, in particular those emanating from non-M1 cortical areas. Exploratory predictive models using clinical MRI metrics, either alone or in combination with clinical measures, were able to accurately identify recovery outcome category for patients using assessments made during both the acute and early subacute phases of post-stroke recovery.

Results suggest that (1) prospective PREP2 validation studies are feasible in a US healthcare setting, (2) SAFE is an easy-to-acquire, readily implementable screening metric with high clinical utility for patients who undergo AR post-stroke, and (3) clinical MRI-derived biomarkers of both M1 and non-M1 contributions to CST integrity may offer unique insight into PUE motor outcome potential.

CHAPTER 1. INTRODUCTION

1.1 Stroke Background and Significance

1.1.1 Definition of Stroke

Stroke is most broadly defined as focal central nervous system (CNS) injury attributable to vascular etiology.[1,2] Stroke is divided into two main types, ischemic and hemorrhagic, both of which result in anoxic cell death but through different pathophysiologic mechanisms. Ischemic stroke, which accounts for 85% of strokes in the United States (US), is caused by an obstruction to cerebrovascular blood flow.[3–5] Blockage of any vessel supplying blood to the CNS deprives downstream nervous tissue of oxygen and glucose necessary for normal cell function, quickly resulting in energy depletion, ionic imbalance, and cell death.[4,6] The infarct core contains irreversibly damaged tissue, whereas injured, but surviving surrounding tissue is termed the penumbra. Hemorrhagic stroke accounts for the remaining 15% of strokes.[3] It may also be divided into two categories, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), defined by the area of hematoma formation, brain parenchyma or subarachnoid space, respectively.[5] Primary cell death in hemorrhagic stroke is initiated by anoxic sequelae similar to that of ischemic stroke, but may also result from mechanical damage due to compression of CNS tissues.[2] Focal damage to the CNS, regardless of stroke type, produces neurological deficit within specific physiologic systems due to the topographic nature of the CNS as well as the interconnectivity of functional regions within the brain.[1,7]

1.1.2 Significance of Stroke in the United States

Stroke is a leading cause of long-term disability in the US and worldwide.[3] Every year, approximately 800,000 strokes occur in the US; an estimated 7 million Americans over the age of 20 have had a stroke.[3] Stroke prevalence is increasing over time, with an estimated 20% rise between 2012 and 2030.[3] Improvements in stroke diagnostics and medical interventions have caused a decline in stroke mortality.[3] Current direct and indirect costs associated with stroke are estimated at over $100 billion per year, and these expenditures are predicted to triple by 2030.[3,8] The majority of these costs are incurred during highly variable inpatient hospital stays, the reimbursement for which is most commonly a fixed sum determined by diagnosis, incentivizing more efficient care strategies.[3,9–11] Taken together, the medical and financial burden of stroke-related, long-term disability will increase dramatically in the coming years unless advances to both increase the specificity of rehabilitative care and to improve post-stroke patient outcomes are made to address this major public health concern.[3]

1.1.3 Clinical Presentation of Stroke

Persons with stroke commonly present clinically with sudden onset of unilateral weakness, numbness, changes in vision, difficulty with speech, or loss of consciouness.[5,8] Resultant acute neurological dysfunction reflects both the size of injury and tissues involved.[15,161] However, differential diagnosis of stroke requires clinical imaging technologies to confirm and localize the position of the stroke and the affected vessels.[1]

Strokes occurring in cortical motor areas or descending motor tracts cause immediate, contralateral paresis.[7] Notably, about 80% of stroke patients have some degree of hemiparesis at stroke onset while more than half of patients have a persistent loss of hand function.[12–15] The prevalence of initial motor weakness correlates well with findings that approximately 50% of ischemic strokes are caused by occlusions in the middle cerebral artery (MCA), a vessel which supplies blood to much of the cortical territory involved in movement production: the primary motor, premotor, supplementary motor and somatosensory cortices, the basal ganglia, and the internal capsule.[7,16,17] Strokes localized to non-motor-contributing areas may also present acutely with motor impairment as a result of global downregulation of cortical excitability or compression of brain parenchyma due to edema or, in the case of hemorrhagic stroke, collection of blood products.[18–20] However motor impairment in these instances would be expected to largely resolve with the clearing of excess fluid accumulation and normalization of brain function.[20–22] Importantly, acute clinical measurement of paretic upper extremity (PUE) strength *does not differentiate* deficits that are caused by damage to motor areas from those resulting from damage to distant sites within the CNS. **This lack of differentiation highlights the necessity for rehabilitation providers to capitalize on quantitative metrics which elucidate the location of injured tissues and/or indicate the integrity of the motor system in order to accurately classify a patient's propensity for movement recovery post-stroke.**

1.2 A Brief Overview of the Anatomy and Physiology of Motor Function

1.2.1 Normal Anatomy and Physiology of Motor Function

Movements can be divided into three broad categories, reflexive, rhythmic, and voluntary motion, each requiring different amounts of descending control.[23] While the cortical descending motor system influences all types of movement, it is only required for goal-directed, voluntary motion.[23] In contrast, reflexes (e.g., knee jerk) and rhythmic movement (e.g., walking) may be influenced by cortical systems but are elicited in response to a stimulus by motor control networks in the spinal cord and brainstem and may therefore occur without input from cortical motor areas.[23]

The primary motor cortex (M1), also known as Brodmann's area 4, has been known as the final dispatch site for descending neural impulses which underlie complex, voluntary movement.[7,24] M1 lies in a headband-like shape in the frontal lobe, just anterior to the central sulcus, and has a generally-accepted somatotopic organization where areas controlling proximal joints, such as the shoulder, lie medially to those controlling distal joints, such as the wrist and hand.[7,25,26] M1 receives inputs from several cortical and subcortical areas mediating motor planning (premotor, supplementary motor and cingulate motor cortices, basal ganglia, and cerebellum) as well as somatosensory inputs from the parietal lobe.[7,27] See **Figure** 1.1. These varied network inputs illustrate the complex encoding, processing, and integration which must occur in M1 to execute a desired movement in context.[28]

The premotor cortex (PM) lies anteriorly to M1 along the lateral portion of the hemisphere in Brodmann's area 6 and also exhibits a somatotopic organization.[7] PM receives input

from supplementary motor areas (SMA) as well as parietal and prefrontal cortices which likely illustrates the role of premotor regions in integration and planning prior to motor execution.[7] PM regions are known to be involved in control of both the cognitive aspects of motor planning, including spatial attention, and the execution of movement itself.[24,29–32] Medial to the PM cortex, also in Brodmann's area 6, lies the SMA which receives inputs from parietal and temporal regions as well as structures of the basal ganglia and is thought to contribute to temporal specificity of muscle activation, particularly during reaching movements.[24,29,31,33] Though PM and SMA influence movement through their projections to M1, they also do so through direct projections to the spinal cord (SC) via the corticospinal tract (CST) enabling further influence on motor output.[29,33] See **Figure** 1.1.

1.2.1.1 The Corticospinal Tract is the Canonical Descending Motor Output Pathway

The CST is the canonical descending motor output pathway in mammals, directly linking cortical motor areas to the SC.[34] It is the primary tract responsible for the relay of signals that result in voluntary movement and has been found to be particularly integral in the generation of dexterous hand movements fundamental to functional fine motor control in both animals and humans.[34–36] The CST is the most direct and fastest conducting pathway between cortical motor areas and α motoneurons innervating upper extremity musculature and CST integrity has been implicated as a primary determinant in the recovery of fine motor control post-stroke.[7,34–37] See **Figure** 1.1.

Approximately 70% of the CST originates in motor areas: ~40% directly from M1, with additional contributions from premotor, supplementary motor, and cingulate motor areas.[7,27,38] The CST also encompasses projections from the primary somatosensory cortex

(S1) to the SC suppling sensory information that informs movement output, enabling precision in and refinement of motor control.[23]

Pyramidal neurons, whose cell bodies lie in layer V of M1, project myelinated axons downward through the internal capsule, the cerebral peduncle (midbrain), and pons. Approximately 85%-90% of pyramidal axons then decussate at the medullary pyramids and descend contralaterally within the lateral CST to the anterior horn of the SC, which has a somatotopic organization similar to that of M1.[7] Here, they primarily synapse directly onto cell bodies of α motoneurons which lie in motoneuronal cell columns in the ventral horn (lamina IX).[7] These α motoneurons then exit the SC, terminating on peripheral muscle fibers which act in aggregate to control distal motion.[7,39] These direct CST connections with α motoneurons, existent only in humans and certain primates, are proposed to enable differentiated motion and improved dexterity at the extremities. [24,33,38,40] Pyramidal axons from M1 also synapse on spinal interneurons which is thought to underlie synergistic muscle co-activation necessary for coordinated movement of an entire limb (e.g., reaching).[23] Though literature in human models is less definitive, studies using primate models have also illustrated the existence of pyramidal descending projections emanating from PM and SMA regions to be both monosynaptic (direct to α motoneurons) and disynaptic (indirect via spinal interneurons), which may illustrate that these non-primary motor areas may exert control over motor output in a similar manner to M1.[24,33] See **Figure** 1.1.

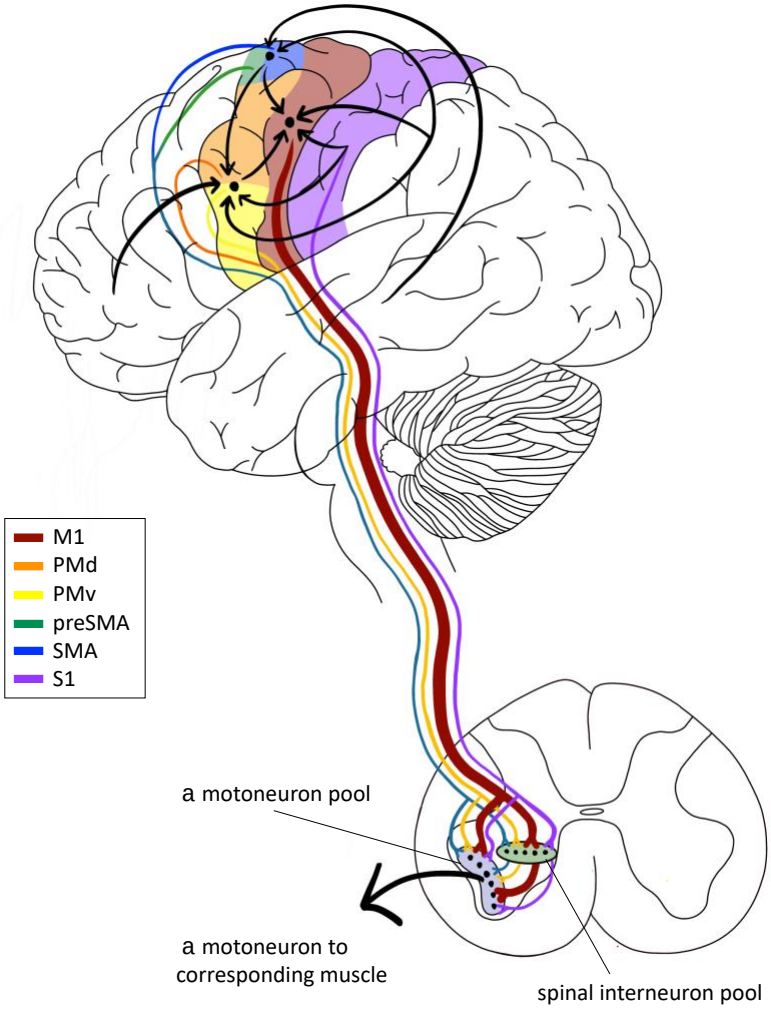

Figure 1.1 - The corticospinal tract (CST) is the most direct and fastest conducting pathway between cortical motor areas and α motoneurons innervating upper extremity musculature. The primary motor cortex (M1, red) receives inputs from several cortical and subcortical areas mediating motor planning as well as somatosensory inputs from the primary somatosensory cortex (S1, purple) and the posterior parietal lobe. The premotor cortex (PM encompasses: dorsal premotor, PMd, orange; and ventral premotor, PMv, yellow) receives input from supplementary motor areas (SMA, green; and presupplementary motor area, preSMA, blue) as well as parietal and prefrontal cortices. The SMA receives inputs from parietal and temporal regions. Though PM, SMA, and S1 influence movement through their projections to M1, they also do so through direct projections to the spinal cord (SC) via the CST. Pyramidal neurons of the CST synapse directly onto cell bodies of α motoneurons and onto interneurons in the SC. These α motoneurons then exit the SC, terminating on peripheral muscle fibers which act in aggregate to control distal motion. Adapted from Kandel, Schwartz, and Jessell, 2000 with assistance from Yasmine Bassil.

1.2.1.2 Subcortical Descending Motor Pathways

Though the motor system is generally organized so that voluntary motor commands are transmitted from top to bottom, there are numerous pathways between the cortical motor areas and subcortical structures that influence movement output such as the basal ganglia, cerebellum, and descending bulbospinal tracts emanating from the brainstem.[23,38]

The rubrospinal or dorsolateral brainstem pathway receives inputs from cortical motor areas and the cerebellum and consists largely of crossed fibers which project to the lower cervical and upper thoracic spinal segments.[23] Termination sites on interneurons in the intermediate zone of the SC are thought to facilitate and modulate movements of the upper extremities and are well-evidenced in primates but less definitive in human studies.[23,38,41–43]

The ventromedial brainstem pathway includes the tectospinal, vestibulospinal, and reticulospinal pathways.[23] The tectospinal pathway receives multisensory inputs and projects to the upper cervical SC to influence head movement whereas the vestibulospinal pathway receives inputs from the vestibular organs and the cerebellum, projecting throughout the medial spinal cord where it is thought to facilitate the maintenance of an upright body position.[23] The reticulospinal pathway emanates from the pons and medulla where it receives inputs from cortical motor areas, the cerebellum, and subcortical sensory systems.[23] The reticulospinal pathway descends ipsilaterally and projects to both interneurons and medial motoneuronal pools in bilateral cervical, thoracic and lumbar segments within the spinal cord to assist in preparation and coordination of movement via control of axial musculature.[23,38,41] However, in primate literature, the reticulospinal

pathway has also been shown to make both monosynaptic and disynaptic connections to α motoneurons controlling muscles of the forearm[44] and to facilitate excitation in intrinsic muscles of the hand, though less reliably and with lower amplitudes than the CST.[45]

These brainstem pathways, which run in parallel to the CST, in addition to uncrossed, ipsilateral fibers from the nonaffected hemisphere offer some functional redundance and may allow for partial recovery of motor function after stroke.[23,41–43,46,47]

1.2.2 Potential Physiologic Mechanisms for the Recovery of Motor Function

Spontaneous cellular repair processes post-stroke are thought to be explained by either upregulation/unmasking of redundant pathways or by the creation of new neuronal connections via collateral sprouting and synapse formation.[21] Though ipsilateral (uncrossed or subcortical) descending motor pathways have been suggested as possible alternate routes mediating motor recovery post-stroke, their primary function is not control of coordinated, distal movements, particularly of the upper extremity. Unsurprisingly, evidence implicating ipsilateral motor pathways with motor recovery post-stroke is mixed, complicated by nonuniform methodologies and contradictory findings.[21,34,38] At a purely anatomical level, most uncrossed fibers emanating from M1 innervate axial musculature and are therefore unlikely candidates for recovery of fine motor control.[7] Similarly, indirect corticobulbar motor pathways have modulatory roles in the temporal or spatial coordination of movement;[7] however, both their anatomical inputs from upper motor neurons and indirect connectivity with α motoneurons in the SC suggest these pathways

alone are unlikely candidates for restoration of normal dexterous movement patterns of the upper extremity and subsequent functional independence.[7]

Structural reorganization may be a more likely cellular basis for recovery of motor function post-stroke. Indeed, both pre-clinical and clinical evidence of focal lesions in cortical tissue governing hand movement have shown reappropriation of adjacent, surviving cortex for hand function after training.[48,49] While strokes in motor areas result in functional deficit, those localized within the CST seem to cause more severe and more permanent loss of motor function than lesions in other sites.[14,50–54] Animal lesion studies have shown that most axonal sprouting occurs in cortical areas, close in proximity to dendritic spines and neuronal cell bodies, which may be more energetically economical than repairing damage further from the nucleus but may also be a function of molecular signaling cascades, necessary from both pre- and postsynaptic cells.[14,55] This delimitation of structural cellular changes suggests that certain areas of the brain or distinct morphological regions of cells may be more readily primed for plastic reorganization after injury and may explain why damage to the CST is particularly devastating to the recovery of fine motor control. I will describe these processes of spontaneous cellular reorganization and repair in more detail in the following section.

1.3 Neuroplasticity

1.3.1 Potential Mechanisms of Motor Recovery

Neuroplasticity refers to the capacity of the nervous system to adapt. Experience is a potent driver of neuroplasticity and is the focus of current gold-standard stroke rehabilitation interventions. But neuroplasticity is also often used to describe the spontaneous biological recovery mechanisms mentioned above. For purposes of discussion, I will separate the two concepts into experience-dependent plasticity, or that which is induced by use and therapeutic rehabilitation, and spontaneous biological recovery, occurring irrespective of therapeutic intervention post-stroke.

Persistent upper extremity motor impairment affects more than half of those with ischemic stroke.[14,36] Recovery of upper extremity motor function is a primary determinant of independence in activities of daily living.[15,56–59] Immediately post-stroke some amount of functional independence is lost for most patients (left y-axis, **Figure** 1.2). During the first 3- to 6-months post-stroke, most patients follow a typical recovery trajectory, provided they have a functional CST.[60,61] The course of functional motor recovery, depicted as the purple line in **Figure** 1.2, typically plateaus around 3-months post-stroke and is thought to be primarily regulated by molecular mechanisms underlying structural and functional reorganization within both lesioned and non-lesioned hemispheres.[34,62–64] This initial 3-month period constitutes the acute and early subacute recovery periods, where the acute period comprises the first 7 days post-stroke and the early subacute period is from day-7 to 3-months post-stroke.[65]

Stroke severity depends upon the extent of damage incurred by the initial injury and inflammatory response: processes of necrosis, apoptosis, inflammation, edema, dendritic spine and axonal degradation, and diaschisis (red bars, **Figure** 1.2).[14,55,66] However, these deleterious events also set off molecular cascades which induce cellular repair mechanisms associated with spontaneous biological recovery. These processes include angiogenesis, axonal sprouting, dendritic remodeling, synapse formation, glio- and neurogenesis and cell migration (blue/green bars, **Figure** 1.2).[14,55,67,68]

Infarction also triggers excitability changes mediated by alterations of neurotransmitter balance (right y-axis and orange line, **Figure** 1.2). Stroke instigates a massive discharge of glutamate, an excitatory neurotransmitter, into the surrounding tissues, resulting in additional excitotoxic cell death.[55,69] Neuroprotective increases in tonic (extrasynaptic) γ-aminobutyric acid (GABA) counteract initial hyperexcitability, followed by a gradual restoration of excitatory/inhibitory neurotransmitter balance and consequent increases in neuronal excitability toward pre-stroke levels.[14,36,70] These processes together are the ingredients for spontaneous biological recovery evidenced by functional reorganization and/or structural remodeling of cortical networks (both local and remote to the lesion location) that contribute to some recovery of function in the first 3-months post-stroke.

Experience-dependent plasticity occurs throughout all life stages. It is the method by which we obtain new motor skills and is a function of training and task practice. Training-induced gains in upper extremity function can still be made in the chronic phase of stroke (from 6-months post-stroke onward), but earlier therapeutic intervention yields greater improvements in upper extremity skills such as reaching, grasping, or pinching, all of which underlie functional independence in activities of daily living.[65,71–73] Therapeutic

interventions which target task-specific, experience-dependent plasticity are the foundation of contemporary post-stroke neurorehabilitation strategies. When these strategies are employed during a unique time of endogenous cellular repair and enhanced CNS reorganization, there is an interaction effect between cellular processes and behavioral activity.[68] **Thus, the timeframe of dynamic cellular and molecular processes offers the potential for a window of heightened experience-dependent plasticity to further enhance recovery of motor function post-stroke** (shaded yellow area, **Figure** 1.2).

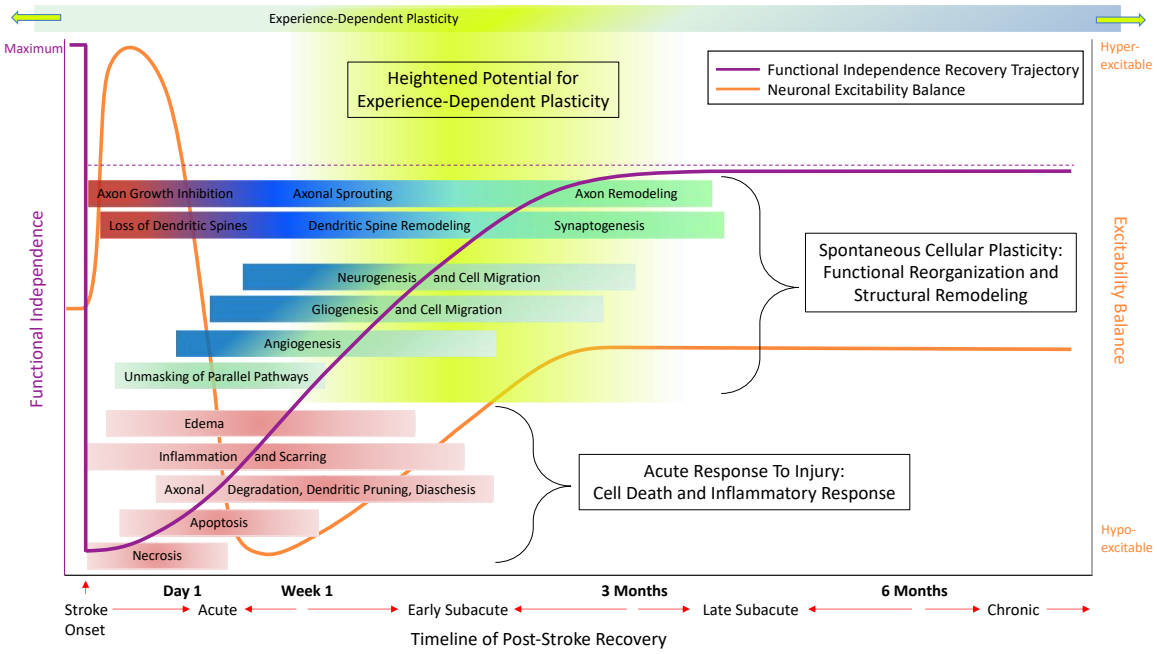

Figure 1.2 - The pathophysiology of post-stroke recovery is a dynamic process. Immediately post-stroke some amount of functional independence is lost for most patients (left y-axis and purple line) due to both the extent of damage to cerebral tissues and excitability changes mediated by alterations of neurotransmitter balance (right y-axis and orange line). Acute inflammatory responses, control of cortical excitability balance (orange line), and spontaneous cellular repair mechanisms promote return of functional independence (purple line). Though experience-dependent plasticity occurs across the life span, the interaction between dynamic cellular and molecular recovery processes and neurorehabilitation offers a potentially heightened window for experience-dependent plasticity to further enhance recovery of motor function post-stroke (shaded yellow area). Adapted from Stinear and Byblow, 2014.

1.3.2 Timing is Critical

Precision of therapeutic intervention during this period of increased, spontaneous, structural plasticity post-stroke is critically important. While the potential for heightened experience-dependent plasticity is an enticing target to either speed or potentially increase the amount of motor recovery potential for patients' post-stroke, this period must be approached with careful attention to the parameters of neurorehabilitation intervention. The time sensitive nature of neuroprotection and neurorecovery processes need to be better understood to determine how and when to optimally intervene in order to maximize recovery of motor function post-stroke. Notably, mechanisms which enhance structural plasticity may also subvert precision of newly forming connectivity within physiologically distinct domains, yielding maladaptive motor recovery results.[14,55,74]

In functional terms, both human and animal studies indicate that training must occur with time and dose specificity; forced overuse too soon after stroke can result in reduced functional gains.[14,75] In human studies, high intensity doses of constraint-induced movement therapy (CIMT) delivered within the first month post-stroke yielded significantly less improvement at 3-months post-stroke than lower intensity control doses of CIMT (therapy began in this study, on average, 9 days post-stroke and was delivered for 2 weeks).[75] A similar interaction effect is observed regarding cortical excitability balance and the timing specificity of therapeutic training. In humans, lower levels of cortical excitability, as measured by transcranial magnetic stimulation (TMS) resting motor threshold, have been found to correlate with poorer hand dexterity in chronic stroke.[76] But early periods of hyperexcitability may be no more ideal for functional training. In animal models, maximization of upper limb use during early periods of hyperexcitability has

shown deleterious effects, while establishing a time buffer (3-5 days) between stroke and induction of agents that increase neuronal excitability was shown to be critical to enhance functional recovery of the forelimb.[14,69,77] In some instances, early hypoexcitability reversal has even been shown to exacerbate the extent of infarct core.[14,69,77] Clearly, the approach to neurorehabilitation in the acute and early subacute periods post-stroke must be delivered with great time specificity if we are to improve the trajectory of functional motor recovery. But newly formed connectivity must also be specific to tissues involved in sensorimotor control if it is to support motor function recovery. To leverage cellular repair processes, rehabilitation therapy must target plasticity in the synapses associated with functional movement. Fortuitously, mechanisms of structural and functional plasticity are responsive to, and therefore may be guided by, neurorehabilitation paragigms.[14,68]

The sensitivity of the repair processes occurring during the period of spontaneous biological recovery post-stroke leaves us with newfound appreciation for the importance of acute and early subacute neurobiomarkers. Such biomarkers may improve patient-specific care based upon more precise identification of injury severity, location of damaged tissue, and the temporal transition from neuroprotective to neurorecovery phases of spontaneous cellular repair processes. The next frontier of stroke rehabilitation will need to identify biomarkers sensitive to the type and timing of therapy delivery to maximize functional gain and identify which patients will benefit from specific therapeutic approaches.

1.4 Predicting Post-Stroke Functional Motor Recovery

1.4.1 Biomarkers of Post-Stroke Motor Function are Needed in the Clinic

Rehabilitation therapy is the treatment most integral to motor recovery, however delivery of services and quality of care during this critical period lack uniformity, precision, and effectiveness.[10,36,63] Though historically the strongest predictor of outcome post-stroke has been severity of initial injury, there is no clear consensus regarding which measures are most relevant to motor recovery and which are most appropriate to set therapeutic goals or establish discharge criteria.[21,65,78] This makes sense if we recall that acute clinical measurement of PUE lacks the specificity to differentiate damage to motor areas from damage to distant brain tissues.

Rehabilitation clinicians do not currently have the tools necessary to accurately predict recovery of motor function, the performance of which is imperative for regaining independence after stroke.[3,21,78,79] Therapists commonly create functional goals based upon baseline scores on clinical outcome measures, which are valuable to track progressive recovery, but are not predictive metrics.[80,81] Moreover, there is no strong evidence to suggest that rehabilitation therapists are able to predict motor recovery outcomes using common clinical assessments.[63,82] In fact, a study investigating physical therapists' recovery prediction accuracy at 72 hours post-stroke showed that even experienced therapists' early predictions are only slightly above chance, even when outcomes were coarsely binned into *no recovery*, *some recovery,* or *full recovery* groups.[82] These results highlight that, in the acute phase of stroke, patients who can initially present similarly may have vastly different functional outcomes.[82–84] To date, little evidence exists supporting the

use of novel therapies such as virtual reality training, repetitive TMS, or robotics therapies to increase the level of the plateau observed at 3-months, though data are beginning to emerge supporting therapy's ability to increase the rate of recovery post-stroke.[63,85] **Biomarkers providing early, accurate prediction of recovery of motor function post-stroke would enable precision-based rehabilitation strategies to improve outcomes, speed recovery, and reduce disability.**[79,86] **However, existing tools to predict recovery of motor function have yet to be validated in the US healthcare system.**

1.4.2 Non-invasive Biomarkers May Predict Functional Outcomes Post-Stroke

While animal studies have demonstrated that cortical reorganization and white matter plasticity underlie functional gains, the invasive nature of methods such as intracortical stimulation, genetic manipulation, or tissue excision and staining precludes its use in humans.[34,48,87,88] However, technologies that noninvasively measure tract integrity, cortical volume, and/or cerebral activation patterns, offer new insights into structural underpinnings of functional changes seen post-stroke in clinical populations.[87,89–91]

Imaging modalities such as magnetic resonance imaging (MRI), TMS, electroencephalography (EEG), and positron emission tomography (PET) provide noninvasive evidence linking functional recovery and structural reorganization within the human brain post-stroke.[21,49,92] For example, TMS has been widely employed to probe functional integrity in descending motor pathways after stroke, while structural MRI has been similarly used to identify how damage to anatomic structures correlates with motor outcomes.[21,50,52,76,93–95]

Using MRI, the structural integrity of the descending motor system can be quantified by measuring both the location and extent of stroke lesion overlap with the CST.[52,54,84] Several studies have shown that poorer motor outcomes post-stroke are correlated with a greater extent of lesion encroachment with the CST.[50,51,53,54] Structural MRI may offer some of the strongest evidence to predict motor recovery post stroke, outperforming the use of clinical bedside measures alone.[54,84,86,96]

Models using a combination of clinical measures and neurological biomarkers, e.g. CST integrity, can predict stroke outcomes and patient response to therapy.[10,79,97,98] More precise measurement of both the structure and function of motor tracts better depicts the physiological extent of injury and may improve our understanding of the propensity for neuroplastic reorganization and functional recovery.[87,96,99] This precision is of particular importance for those with initially-lower levels of volitional control as these patients exhibit the most heterogeneous recovery patterns.[79,84,100] Reperfusion of penumbral tissue in addition to reversible factors such as edema, inflammation, and globally-decreased neuronal excitability may all play a role in masking the true extent of early functional disability due to irreversible neuronal damage as opposed to that caused by reversible repair processes.[18–21] Unfortunately, studies leveraging MRI are often conducted using MRI scanners with higher magnetic field strengths, which are not widely available at hospitals within the US. Both the scarcity of research-grade scanners and the associated increase in medical cost due to additional imaging scans may be prohibitive to widespread adoption of such tools. However, creation of MRI processing pipelines to extract prognostic biomarkers from standard-of-care, diagnostic clinical imaging increases the generalized utility of using structural images as predictive neurobiomarkers post-stroke.

1.4.3 Developing Biologically-Informed Models of Post-Stroke Recovery in Humans

The use of predictive tools is supported by the literature suggesting the most robust predictive models use a combination of neurological biomarkers.[10,79] The consensus from the Stroke Recovery and Rehabilitation Roundtable indicates that clinical outcome measures alone are insufficient to comprehensively predict outcomes for the full spectrum of stroke severity.[79] Though early functional deficit may indicate a propensity for future recovery, clinical measures have been found to account roughly for only half the variance in motor outcomes.[101] Similarly, the extent of initial neuronal injury has been found to be a major prognostic indicator for functional recovery, but when used in isolation, lesion characteristics such as size and location provide limited information to predict long-term recovery of function post-stroke.[84,102,103] **Therefore, the combination of clinical metrics of PUE strength (measuring function) and clinical MRI (measuring structural integrity of the CST) offers a strong foundation for a model aiming to predict level of upper extremity motor recovery post-stroke.**

Previous work has established the utility of a predictive model which categorizes the level of expected motor recovery based upon functional and structural integrity of the corticospinal tracts.[61,84,100,104] The Predict Recovery Potential (PREP/ PREP2) prediction tool, developed in New Zealand (NZ) and employed in the first week post-stroke, has been shown to correctly predict 90-day PUE outcome for 75-80% of patients.[63,100,104] While initial studies measured outcome at 3-months post-stroke, prediction accuracy remained at approximately 80% at 2-year follow up evaluation.[105] PREP2 combines objective clinical assessments and neurophysiologic indicators of corticomotor function to provide clinically-relevant information and guide personalized treatment.[63,100,104] In earlier

iterations of the model, MRI biomarkers of CST structural integrity, using high-resolution MR-based diffusion-weighted imaging, were employed to improve prognostic accuracy.[84,100] Biomarkers of CST structural integrity have been omitted from PREP2 for accessibility reasons, not because prediction accuracy was any less robust.[100] PREP2 has been shown to have superior accuracy over predictions made by experienced therapists and those made by other models.[63,82] Further, it has been shown to improve therapist confidence in their clinical decision making, and resulted in shorter average length of stay (LOS) by approximately 1 week in inpatient hospital settings in NZ.[61,100,104] Despite the clear promise of PREP2 to improve post-stroke rehabilitation care, it has yet to be externally validated in the US healthcare system.

New Zealand operates a free, public healthcare infrastructure in which universal access serves to narrow health disparities.[106,107] NZ also utilizes a unique identifier for each patient (national health index number), facilitating transfer of information with patients as they move through the continuum of post-stroke care.[106,107] In contrast, the US healthcare system is more fragmented; many facilities are privately owned and operated and are more siloed in their patient care strategies and management systems.[108] Medical spending in the US is more than double that of NZ.[109] Reimbursement structures within the US are moving toward bundled payment models per diagnosis, incentivizing more efficient medical management and shorter lengths of hospital stays.[3,10,108] Despite its high healthcare spending, the US has poorer metrics of population health including higher burden of chronic disease.[109] Correspondingly, the incidence of stroke in the US is approximately 30% higher than in NZ.[3,110] Given the differences in healthcare delivery systems, payer models, and population health, it is not clear that the tools used in one environment will

work equivalently in another. Therefore, one of the primary study objectives is to evaluate external validation feasibility of PREP2 in two representative, urban, academic hospital systems in the US.

1.4.4 PREP2 Prediction Tool, Explained

The current PREP2 prediction tool is illustrated in **Figure** 1.3.[100] Patients receive a SAFE score evaluation at or before day-3 post-stroke. SAFE is comprised of two manual muscle tests, (S)houlder (A)bduction and (F)inger (E)xtension, each scored on a 0-5 scale according to Medical Research Council grading system, where lower scores denote less strength. SAFE is the sum of the two manual muscle test scores and is therefore scored on a 0-10 scale. For those patients with a SAFE score ≥ 5, patient age and SAFE score are used to designate participants into either "Excellent" or "Good" recovery prediction groups.

For patients with a SAFE score < 5, TMS, a form of focal, noninvasive brain stimulation applied over the M1 in the stroke-affected hemisphere, is utilized between day-3 and day-7 to assess the functional integrity of the descending CST. Functional integrity is measured by the presence or absence of motor evoked potentials (MEPs). MEPs are measured with electromyography (EMG) of the extensor carpi radialis (ECR) and first dorsal interosseous (FDI) muscles, a wrist extensor and index finger abductor, respectively. MEP responses must be reproducible with consistent latencies appropriate for each muscle.[111] TMS results are binarized into Motor Evoked Potential positive (MEP+) and negative (MEP-) designations.[63,99,100,111]

MEP+ participants are also predicted to have "Good" motor recovery.[100] This rationale is physiologically-based as detectable MEPs in response to excitation of pyramidal neurons in M1 indicate a functional pathway between cortex and muscle, i.e. less damage to critical CST fibers and less necessity for structural cellular repair. Finally, MEP- participants are separated into "Limited" and "Poor" recovery groups by evaluating the National Institutes of Health Stroke Scale (NIHSS) score taken on day-3. The NIHSS is a validated and commonly used clinical assessment of global stroke severity.[112] The NIHSS measures cognition and language deficits, visual and sensory impairment and neglect, and coordination abnormalities, in addition to motor weakness; performance on each of 13 items is rated on an ordinal scale with a maximum score of 42, where lower scores indicate less severe stroke symptoms.[112]

PUE motor recovery outcome is measured via the Action Research Arm Test (ARAT), a validated, sensitive, and reliable test, commonly used in stroke related research to measure upper extremity motor function. The ARAT assesses four subgroups of action: grasp, grip, pinch and gross arm movement. Performance on each item is rated on a 4-point ordinal scale ranging from 3-0, higher scores denote greater function with a maximum score of 57.[113,114] ARAT scores at 90 days post-stroke either confirm or refute the PUE recovery prediction. Each of PREP2's four recovery prediction categories lend themselves to a framework for clinical decision making and care planning, see **Figure** 1.3 below.[100,104]

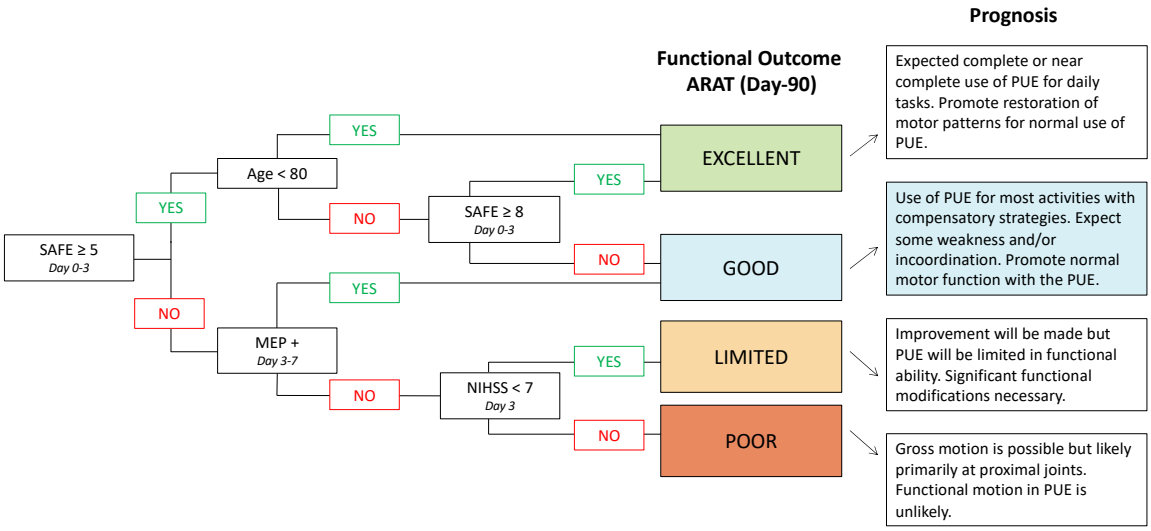

Figure 1.3 - The PREP2 prediction tool. Using shoulder abduction and finger extension manual muscle tests (SAFE), patient age, corticospinal tract integrity (MEP+), and National Institutes of Health Stroke Scale (NIHSS) score, PREP2 predicts paretic upper extremity (PUE) functional motor outcome at 3-months poststroke with 75% accuracy. Figure adapted from Stinear et al, 2017.

1.5 Project Overview

In order to improve post-stroke rehabilitation treatment, there is a clear need to identify key biomarkers which precisely measure structure and function of sensorimotor tracts and to test the fidelity of PREP2 in the US. Therefore, the study endeavored to answer the following research questions: 1) What is the feasibility of conducting external validation studies of PREP2 in the US healthcare system? 2) What routinely collected clinical measures are most predictive of PUE functional outcome post-stroke? 3) What is the prognostic merit of biomarkers of CST structural integrity isolated from clinical neuroimaging?

As a necessary first step to assess prospective validation feasibility of the PREP2 prediction tool in acute care settings in the US, I conducted a retrospective chart review of all stroke admissions to Emory University Hospital (EUH) and Grady Memorial Hospital (GMH) over fiscal years (FY) 2016-2018. I extracted demographic and clinical information to critically appraise similarities and differences in patient characteristics and stroke care management between US and NZ health care systems.

To assess the ability of currently collected clinical measures and neurologic biomarkers isolated from clinical imaging to predict PUE motor outcomes post-stroke, I conducted a retrospective chart review for a subset of patients with similar clinical management across the continuum of stroke rehabilitation and recovery. This subset of patients remained within the Emory University Hospital system for acute hospitalization, acute inpatient rehabilitation, and outpatient care, allowing longitudinal assessment to track recovery and to estimate the level of PUE motor function return. Longitudinal assessment of motor

recovery in this subset of individuals is the closest model to the NZ system available within a retrospective study design.

A prospective evaluation of PREP2 metrics was planned however, due to the research restrictions resulting from the COVID-19 global pandemic, the project shifted to a retrospective design to evaluate current standards of clinical care and assess potential prospective validation of PREP2. I tested the hypotheses that PREP2 would be feasible for prospective validation and that a combination of clinical metrics and biomarkers of structural CST integrity obtained from clinical neuroimaging would accurately predict PUE motor recovery outcome post-stroke in US health care systems by pursuing the following specific aims:

1.5.1 Aims and Hypotheses

1.5.1.1 Aim 1

To assess the feasibility of PREP2 external validation studies in a representative US hospital system. I performed a retrospective study of all stroke admissions to EUH and GMH over FY 2016-18 to determine if, when, and to what extent, the core elements of PREP2 were collected.

Hypothesis 1: Current standards of post-stroke care management at both EUH and GMH would support future external validation of PREP2 as measured by consistent documentation of objective assessments of PUE strength and National Institute of Health Stroke Scale (NIHSS) within 3 days of admission.

1.5.1.2 Aim 2

To evaluate which current, standard-of-care clinical measures are most predictive of PUE functional outcome post-stroke. I extracted demographics, stroke characteristics, and longitudinal documentation of post-stroke motor function from institutional electronic medical records for a subset of patients with common post-stroke clinical recovery management. I assessed relationships between clinical measures and PUE recovery outcome and used clinical measures to predict PUE motor outcomes for patients who underwent AR post-stroke.

Hypothesis 2: Early clinical measures of post-stroke PUE strength would be the standard-of-care measures that are most predictive of PUE motor recovery outcomes for patients with initially higher levels of strength. However, no standard-of-care clinical measures, when used in isolation, would accurately characterize recovery outcomes for those with initially lower levels of PUE strength.

1.5.1.3 Aim 3

To characterize the associations and predictive utility of structural biomarkers of CST integrity isolated from clinical neuroimaging with PUE functional outcome post-stroke. Using the same cohort of patients discussed in Aim 2, I extracted biomarkers of CST structural integrity from clinical neuroimaging, assessed relationships with PUE recovery outcome, and used those biomarkers to refine predictions of PUE motor outcomes.

Hypothesis 3: Clinical neuroimaging-based measures of CST structural integrity would be associated with PUE motor recovery outcome and would improve the accuracy of outcome category predictions made using clinical measures alone for patients with initially lower PUE strength scores.

CHAPTER 2. SPECIFIC AIM 1

Prospective validation of the PREP2 upper extremity outcome prediction tool is feasible in a US healthcare setting

This chapter is reproduced with minor edits from:

Saltão da Silva, MA; Stinear, C; Wolf, S; Borich, M. *Prospective validation of the PREP2 upper extremity outcome prediction tool is feasible in a US healthcare setting* (In review, Clinical Rehabilitation).

2.1 Introduction

Stroke is a leading cause of long-term adult disability worldwide.[3] Most patients experience persistent loss of upper extremity function which is directly related to reduced independence in activities of daily living and diminished quality of life.[10,59,115,116] Early, accurate prognosis of motor outcomes would improve the quality of stroke management and enable more efficient allocation of high value rehabilitation services, which emphasize better patient outcomes per dollar spent on care rather than a larger volume of services delivered.[117,118]

Predictive models of stroke outcomes using a combination of clinical assessments and objective neurological biomarkers have been developed and validated in other healthcare systems.[65,84,100,119] The Predict Recovery Potential (PREP2) prediction tool uses a combination of clinical measurements and neurological biomarkers to predict paretic upper extremity (PUE) motor outcomes. It was developed and internally validated in New Zealand (NZ), but has yet to be externally validated in the United States (US).[100] The stroke population in NZ is similar to that of the US in terms of age and stroke characteristics; however, differences in health care delivery models between NZ and the US may limit the feasibility of prospective validation and generalization of findings.[3,8,106,110] The primary purpose of this study was to retrospectively assess current acute stroke care management practices to determine the feasibility of prospective validation of PREP2 in a US healthcare setting. We hypothesized that if a retrospective audit cohort showed patient characteristics, acute inpatient length of stay, and rehabilitation evaluation timelines were similar to previous studies in international settings, then prospective validation of PREP2 would be feasible in a US healthcare setting.

2.2 Methods

2.2.1 Study Population

We conducted a retrospective chart review of all stroke admissions at Emory University (EUH) and Grady Memorial (GMH) Hospitals, two representative, urban, academic, comprehensive stroke care centers in the US, between September 1, 2016 and August 31, 2018 (fiscal years (FY) 2016 – 2018). EUH and GMH provide optimal sites to evaluate PREP2 validation feasibility due to their broad demographic coverage, certification as comprehensive stroke centers, and longstanding affiliation with the National Institute of Health Stroke Network.

2.2.2 Selection Criteria

Eligible patients were identified using previously established inclusion and exclusion criteria which were used to establish patient eligibility for Aims 1-3.[100] Major inclusion criteria included: first ever or recurrent, ischemic or intracerebral hemorrhagic stroke; new upper extremity weakness beginning at or after current stroke onset; age 18 years or over.[100]

The Stroke Coordinator at EUH provided the study team with a list of all stroke admissions during FY 2016-2018. At GMH, a search was conducted via the Epic Clarity database in collaboration with an IRB-assigned Clinical Intelligence Developer using the following ICD codes: any code beginning with G45 or I60-I69.

Upper extremity weakness was determined by chart documentation from the admitting physician, in consultation notes from the neurohospitalist team, and was confirmed by occupational and physical therapy evaluation documentation. Exclusion criteria included the diagnosis of non-intracerebral stroke such as transient ischemic attack (TIA), subarachnoid hemorrhage, stroke secondary to traumatic brain injury (TBI), tumor resection, other surgical procedure, cerebellar stroke, or stroke in patients with history of malignant neoplasm of the brain. Certain comorbidities which may confound motor recovery results were also excluded: 1) neurodegenerative diseases (both motor and cognitive) such as dementia or Alzheimer's disease (AD), multiple sclerosis (MS), or amyotrophic lateral sclerosis (ALS); 2) major psychiatric or substance abuse disorder diagnoses; 3) cerebral palsy (CP). Due to the retrospective nature of the study and permission for waived consent, patients with cognitive or communication impairment, which might compromise the ability for informed consent, were included in the present study. Patients with contraindications to transcranial magnetic stimulation (TMS) or magnetic resonance imaging (MRI) were not excluded as in previous PREP2 studies, but are instead noted as feasibility-related findings. **Figure** 2.1 represents the workflow for patient selection.

This study received local Institutional Review Board approval and patient consent was waived.

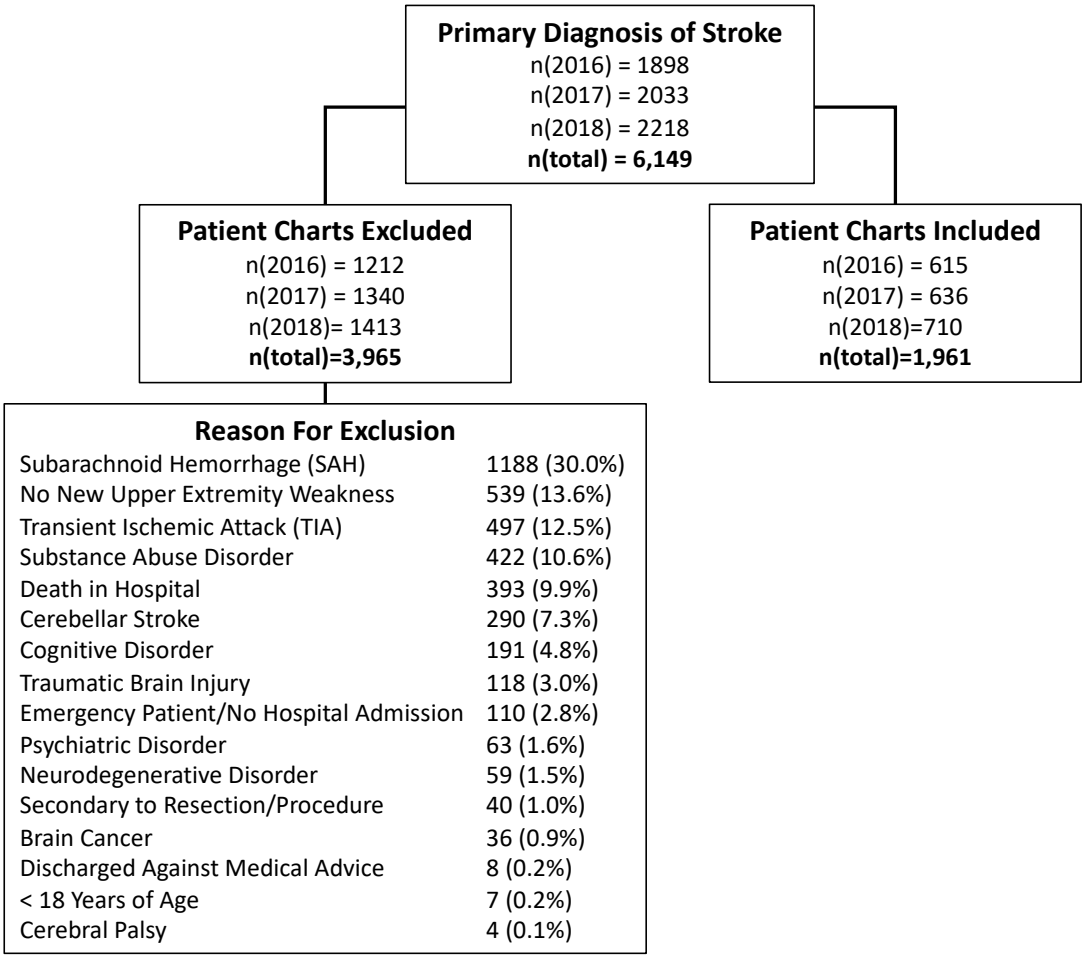

Figure 2.1 - Patient selection criteria. Methodological workflow of the chart review for of 6,149 patients with stroke admitted to Grady Memorial Hospital (GMH) or Emory University Hospital (EUH) in fiscal years 2016-2018. Charts were scanned to confirm stroke diagnosis and to review inclusion and exclusion criteria (inclusion criteria: ≥ 18 years of age, first-ever or recurrent ischemic or hemorrhagic stroke, new upper extremity muscular weakness at or after onset of current stroke). Full data extraction was conducted for the 1,961 patients deemed appropriate for study inclusion.

2.2.3 Data Extraction, Interpretation, and Analysis

Institutional electronic medical record systems, Cerner Powerchart (EUH) and EPIC (GMH), were utilized to extract core metrics and the timeline on which they were gathered: 1) shoulder abduction and finger extension manual muscle tests (SAFE score); 2) patient age; 3) National Institutes of Health Stroke Scale (NIHSS) score. In addition, stroke specific variables and demographic data were obtained including stroke type and hemisphere, length of inpatient stay, and contraindications to transcranial magnetic stimulation (TMS). See **Table** 2.1 and **Figure** 2.2 for more detail.

If an objective SAFE score was not available in clinical documentation, an estimated SAFE score was calculated using available assessments of PUE strength. Shoulder abduction is achieved through activation of the middle fibers of the deltoid and the subscapularis, innervated by the axillary and suprascapular nerves, respectively, which arise from nerve roots of the fifth and sixth cervical segments of the spinal cord (C5-C6).[120,121] If shoulder abduction was not documented, measurement of shoulder flexion, deltoid strength, or proximal strength were used as alternative tests with preference for shoulder flexion as the muscles involved (anterior fibers of the deltoid and coracobrachialis) are innervated by nerves emanating from C5-C7 spinal cord segments.[120,121] Finger extension is achieved through activation of the extensor digitorum, extensor indicis and extensor digiti minimi, all of which emanate from the deep branch of the radial nerve (nerve root segments C6-C8).[120,121] If finger extension was not documented, measurement of wrist extension, grip strength, or distal strength were used as alternative tests for finger extension with similar preference for substitution of wrist or elbow extension measurements due to the extensor's

shared, radial nerve innervation.[120] Further detail regarding estimated SAFE score calculation is available in the SAFE Estimation Key (**APPENDIX A**.).

If the NIHSS was assessed more than once, the assessment performed closest to inpatient day 3 was used. Statistical approach consisted of descriptive analyses to summarize the distribution of variables of interest for the study cohort.

2.3 Results

2.3.1 Patient Characteristics

Of 6,149 patients admitted with stroke during the study time interval, 1,961 (31.9%) met study inclusion criteria. The most common reason for exclusion was subarachnoid hemorrhage (1188/3965, 30.0%). Participant characteristics are provided in **Table** 2.1 and shown in comparison with NZ data. The median patient age in the US was 8 years younger than in NZ (64 and 72 years, respectively) with similar age ranges. 49.0% of patients in the US audit cohort were female. 50.7% had left hemisphere strokes. The US cohort had a higher percentage of hemorrhagic stroke (US = 23.4%, NZ = 10.1%), a higher percentage of severe strokes as measured by NIHSS scores (NIHSS Scores ≥ 16 in US = 17.8%; in NZ = 4.8%). The US cohort also had greater impairment in PUE strength post-stroke. For the 1,593 patients with an estimable SAFE score, 646 had a SAFE < 5 (40.6%) compared with in 31.9% in the NZ research cohort.

Table 2.1 - Research population comparison: New Zealand vs. United States cohorts

Participant Characteristics	NZ Research Cohort[100] (n = 207)	US Audit Cohort (n = 1961)
Median Age (Range)	72 (18 - 98)	64 (18 - 106)
Sex		
Female	104 (50.2%)	960 (49.0%)
Male	103 (49.8%)	1001 (51.0%)
Stroke Type		
Ischemic	186 (89.9%)	1503 (76.6%)
Hemorrhagic	21 (10.1%)	458 (23.4%)
Stroke Hemisphere		
Left	99 (47.8%)	994 (50.7%)
Right	108 (52.2%)	891 (45.4%)
Bilateral	-	69 (3.5%)
Not Specified	-	7 (<1%)
NIHSS/ Stroke Severity Distribution		
Mild (0 - 4)	112 (54.1%)	712 (36.3%)
Moderate (5 - 15)	85 (41.1%)	639 (32.6%)
Severe (≥ 16)	10 (4.8%)	348 (17.8%)
Not Tested	-	262 (13.4%)
SAFE Score		
SAFE ≥ 5	141 (68.1%)	947 (48.3%) *
SAFE < 5	66 (31.9%)	646 (32.9%) *
Not Estimable	-	368 (18.8%)

*1568/1593 SAFE scores were estimated

2.3.2 Validation Feasibility

Current standards of acute stroke care are depicted in **Figure** 2.2. NIHSS measurement occurred on day 2.4 (SD = 1.2 days, median = 3 days, range = 0-16 days). NIHSS scores were recorded for 1,699/1,961 participants (86.6%). The average time to therapy evaluation was 3.4 days (SD = 4.5 days, median = 2 days, range 0-71 days) and SAFE scores were estimable from therapy evaluations for 1,593/1,961 participants (81.2%). 552/1,961 (28.1%) participants had incomplete datasets due to missing NIHSS scores, inestimable SAFE scores, or both. The average length of acute care stay (LOS) for the entire cohort was 11.2 days (SD = 12.9 days, median = 7 days, range 0-190 days) while the average LOS for those with SAFE < 5 was 16.7 days (SD = 16.6 days, median = 12 days, range 0-190 days).

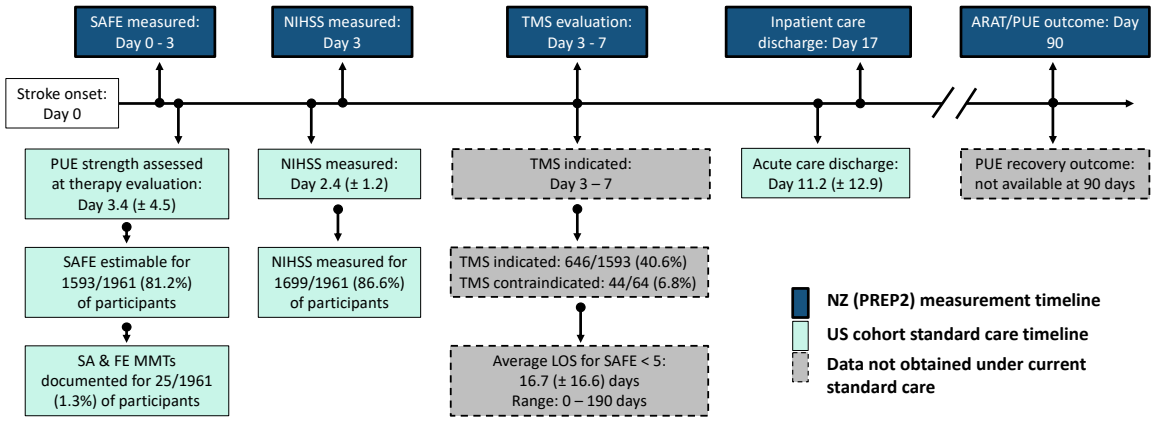

Figure 2.2 - Timeline supports successful prospective implementation for early predictive biomarkers post-stroke. PREP2 metrics include patient age; shoulder abduction and finger extension manual muscle tests (SAFE score); National Institutes of Health Stroke Scale (NIHSS) score); corticospinal tract integrity classified with motor-evoked potential status (MEP status); paretic upper extremity (PUE) functional outcome. SAFE is measured serially on days 0-3 post-stroke until a prediction can be made. NIHSS scores are measured on day-3 for those with SAFE < 5. Transcranial magnetic stimulation (TMS) is also indicated for those with SAFE < 5. TMS is used to assess the functional integrity of the descending corticospinal tract (CST) through electromyographic (EMG) measurement of the presence or absence of MEPs. TMS assessment is conducted between days 3-7 post-stroke. Action Research Arm Test (ARAT) is used at 90 days post-stroke to determine PUE functional outcome. All days reported for US cohort represent mean (± standard deviation).

2.4 Discussion

Prospective validation of the PREP2 prediction tool in a US setting is feasible based upon our findings. Current stroke management allows for SAFE score, NIHSS, and TMS assessment of corticospinal tract function at the appropriate times for PREP2, but does not allow for day-90 follow-up to evaluate the accuracy of PREP2 predictions. Therapy evaluations occur, on average, at an appropriate time for SAFE score measurement. NIHSS is obtained serially at GMH and new initiatives at EUH have also made this additional evaluation standard practice. Patients appropriate for TMS assessment are still in the acute care hospital at a time when corticospinal tract function should be evaluated.

Objective measurement and documentation of predictors of upper extremity outcomes were infrequent. Measurement and documentation of SA and FE manual muscle tests were completed 1% of the time by therapy providers. If PREP2 is validated in a US setting, then a principled implementation strategy will be needed to support SAFE score and corticospinal tract function evaluation for the use of PREP2 in routine clinical care.[122]

Atlanta cohort demographic data are similar to US and NZ national data, but some differences were noted. The relative percentage of hemorrhagic strokes was higher in our cohort which may be driven by the strength of the neurovascular surgical specialty care teams at EUH and associated high numbers of hemorrhagic strokes. When compared to those reported in the PREP2 data, patients in our cohort were younger, had more severe strokes, and demonstrated greater initial PUE weakness. The difference in severity may be explained by our inclusion of patients with cognitive or communication impairment who were not eligible for research participation in NZ due to reduced capacity for informed

consent. Future prospective external validation studies should be cognizant of potential differences in patient characteristics, and that the proportion of individuals in each outcome category may change as a result. Future external validation studies may need to update the PREP2 prediction tool to achieve optimal accuracy in new health care settings and patient populations.[117,123]

The retrospective study design employed has strengths and limitations. An advantage of this retrospective audit is that patients did not need to provide informed consent at the time of their admission, thus providing a dataset that may be a more accurate representation of the general stroke population. The study design also provided access to current standards of clinical care within a large study cohort. However, the retrospective design also required estimation of SAFE scores for nearly all participants. This approximation likely introduces some measurement error to current findings and may have affected estimations of the number of patients requiring TMS assessment. Generalizability of current findings may also be limited. EUH and GMH may not be representative of other US healthcare settings due to differences in stroke care management standards across US hospitals. However, another US healthcare setting recently reported acute care lengths of stay similar to those observed in the present study, indicating that the PREP2 assessment timeline might also be feasible in other US settings.[124]

Validation of outcome predictions requires follow up evaluation of patients to test the accuracy of the prediction tool. However, long-term (≥ 90 days) follow up of patient outcomes by early clinical decision makers in the context of stroke rehabilitation is virtually nonexistent within the current, fractured US healthcare delivery model. Further, logistical challenges associated with collecting in-person objective outcome assessments

emphasize a potential, important role of virtual assessments to increase ease of patient tracking across the continuum of stroke recovery. Systemically, the quantification of quality of care and of patient outcomes are not well defined, studied, or reported in stroke rehabilitation, which presents a major barrier to delivery of high value care in the US.

2.5 Conclusions

Validation, implementation, and impact evaluation of prediction tools have the potential to enhance care standards and enable higher value care for patients after stroke in the US healthcare system. Findings indicate that prospective validation of PREP2 is potentially feasible in US healthcare settings.

CHAPTER 3. SPECIFIC AIM 2

Paretic upper extremity strength at acute rehabilitation evaluation predicts motor function outcome after stroke

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3.1 Introduction

Stroke is a leading cause of long-term adult disability worldwide.[3] Most patients experience persistent upper extremity motor impairment.[14,36] Recovery of paretic upper extremity (PUE) motor function is a primary determinant of functional independence in activities of daily living and quality of life.[15,56–59] The majority of motor recovery occurs early after stroke, typically plateauing around 3-months post-injury, and is thought to be regulated by molecular mechanisms underlying structural and functional reorganization and the restoration of excitatory and inhibitory neurotransmitter balance within both lesioned and non-lesioned hemispheres.[14,34,36,62–64] These processes together are the ingredients for spontaneous biological recovery that contribute to recovery of function in the first 3-months post-stroke (**Figure** 1.2).

Therapeutic interventions that target task-specific, experience-dependent plasticity induction are the foundation of contemporary post-stroke neurorehabilitation strategies. Early therapeutic intervention promotes recovery of PUE skills such as reaching, grasping, or pinching, all of which underlie functional independence in activities of daily living.[71–73] When these strategies are employed during a unique time of endogenous cellular repair and enhanced central nervous system reorganization, there is an interaction between cellular processes and behavioral activity.[68] Thus, the timeframe of dynamic cellular and molecular processes offers an enticing target to augment motor recovery for patients' post-stroke (shaded yellow area, **Figure** 1.2). Critically, this period coincides with the timeframe of acute inpatient rehabilitation (AR), the setting in which the majority of post-stroke rehabilitation services and expenditures occur, thereby emphasizing the importance of

delivering precision-based therapeutic interventions in AR that are effective in targeting task-specific plasticity to enhance recovery of PUE motor function.[3,9–11]

Early, accurate prognosis of motor outcomes would inform the delivery and specification of rehabilitative services individualized to the patient. While a codified set of measures that predict a patient's PUE functional outcome is lacking within the US healthcare system,[79] predictive models of stroke outcomes have been developed in healthcare systems in other countries.[65,84,100,119] The Predict Recovery Potential (PREP2) prediction tool, developed and internally validated in New Zealand (NZ), predicts PUE motor outcomes using a combination of clinical assessments and objective neurological biomarkers.[100] Implementation of the PREP2 prediction tool into clinical practice in NZ resulted in therapist-led modifications to clinical decision-making that were directly informed by outcome predictions.[104] For example, therapists decreased the amount of passive movement in PUE therapy sessions for patients with good predicted outcomes.[104] Improved therapist confidence contributed to modifications in therapeutic planning and progression, resulting in reduced lengths of inpatient hospitalization while demonstrating equivalent PUE motor outcomes at 90 days compared to when the tool was not used.[104]

NZ operates a free, public healthcare infrastructure with a unique identifier for each patient (national health index number), facilitating transfer of information with patients as they move through the continuum of post-stroke care.[106,107] In contrast, the United States (US) healthcare system is structurally fragmented and facilities are often siloed in their patient care strategies and management systems.[108] Therapists treating patients in AR settings in the US often lack access to therapeutic records at other time points along the care continuum. This limits knowledge of a patient's recovery trajectory before AR but, perhaps

more importantly, probably prohibits longitudinal tracking to evaluate patient outcomes. Such differences in international healthcare delivery models create a barrier to the execution of high fidelity PREP2 validation studies and may subsequently limit the generalization of findings.[3,8,106,110] To date, two studies investigated PREP2 metrics in a healthcare system outside of NZ, but initial data collection occurred on a timeline that coincides more closely to AR admission in the US (initial strength measurements made for patients approximately 1- to 2-weeks post-stroke).[125,126] Prediction accuracy in both studies was similar but lower than in the NZ cohort (~60% overall vs. NZ accuracy=75%).[100,125] The lower accuracy may be explained by only including participants admitted to inpatient rehabilitation, by omission of biomarkers of functional corticospinal tract integrity, and by delayed initial strength measurement.[125,126] However, the lower observed accuracy also emphasizes the need to identify measures that can be collected at admission to AR that more accurately predict stroke outcome.

Accordingly, there is a need to identify measures made at later timepoints of recovery that may better predict stroke outcome in the subacute stage. There is also a need to address the inherent challenges with implementation of prediction tools reliant on early patient assessments. Therefore, the primary objective of this study was to retrospectively assess current care practices to determine which routinely collected measures are most predictive of PUE functional outcome post-stroke in patients undergoing AR. We chose an observational, retrospective study design because we were most interested in identifying rapidly implementable, standard-of-care metrics that could predict PUE outcomes and guide care in AR settings. We hypothesized that measures routinely collected as part of standard clinical care post-stroke would predict PUE outcome category.

3.2 Methods

3.2.1 Study Population and Eligibility Criteria

We conducted a longitudinal retrospective chart review of a subset of patients admitted with a primary diagnosis of stroke who received care in the Emory University Hospital (EUH) system, a representative, urban, academic, comprehensive stroke care center in the US, between September 1, 2016 and August 31, 2018. We selected cases using previously established inclusion and exclusion criteria.[100] Major inclusion criteria included the following: first ever or recurrent, ischemic or intracerebral hemorrhagic (ICH) stroke; new upper extremity weakness beginning at or after current stroke onset; age of ≥18 years.[100] Major exclusion criteria are detailed in Chapter 2. In addition, individuals were required to have remained within the EUH system for acute hospitalization, acute inpatient rehabilitation at Emory Rehabilitation Hospital (ERH), and Emory outpatient therapy through at least 90 days post-stroke to permit longitudinal assessment of PUE recovery outcomes and reduce the heterogeneity of post-stroke care for the study cohort across the continuum of recovery. A single patient did not begin outpatient care until approximately 1-year post-stroke (428 days) but was included in the analysis. Since the plateau of motor recovery typically occurs around 90 days post-stroke, measurement of functional outcome at a time point after that time point would enable an approximation of day-90 PUE functional outcome. Lastly, patients were required to have received diagnostic magnetic resonance imaging (MRI) while at EUH as a separate inclusion criterion associated with a parallel investigation. Patients were identified from an existing stroke database and by reviewing records of ERH admits and Emory outpatient records. This study received Emory University Institutional Review Board approval and patient consent was waived.

3.2.2 Data Extraction, Interpretation, and Analysis

Clinical metrics including demographic information, stroke characteristics, care continuum metrics, and provider documentation of post-stoke motor function were extracted from Cerner Powerchart, the institutional electronic medical record (EMR) system of the Emory Healthcare system. Data were extracted longitudinally across acute hospitalization, acute inpatient rehabilitation, and outpatient therapy through at least 90 days post-stroke.

Identified stroke characteristics extracted included: stroke type, location, imaging obtained, and stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS).[112] If the NIHSS was measured more than once, the assessment performed closest to inpatient day-3 was used. Care continuum metrics included length of hospitalizations, duration in outpatient therapy, and time to therapy evaluation(s). Provider documentation of PUE strength and post-stroke disability included manual muscle test scores, sensation, coordination, language impairments, and measures of mobility. These metrics were recorded serially by different providers within the care continuum including physicians, physical therapists, occupational therapists, and speech language pathologists (**Table** 3.1).

Shoulder abduction (SA) and finger extension (FE) manual muscle tests were used to calculate a SAFE score (/10) for each patient.[84,100,127] If an objective SAFE score was not available in clinical documentation, an Estimated SAFE score (E-SAFE) was calculated using available assessments of PUE strength with preference given to strength of muscles with similar spinal cord segmental innervation as detailed in Chapter 2.[120,121] Assessments of shoulder flexion, shoulder extension, deltoid muscle strength, or proximal strength were used as alternative tests for shoulder abduction with preference given to shoulder flexion

or deltoid strength. Assessments of wrist extension, grip strength, or distal strength were used as alternative tests for finger extension with preference given to wrist extensors. If the SAFE (or E-SAFE) score was documented more than once during acute hospitalization, the assessment performed closest to inpatient day-3 was used, in accordance with previous work.[99,84,100] In the AR setting, the SAFE (or E-SAFE) score performed closest to ERH admission was used. See **APPENDIX A**. for more detail on SAFE estimation.

Additional clinical and demographic information was extracted to evaluate the potential effects of non-stroke variables on PUE motor recovery outcomes. Demographic information included prior living situation/familial support and pre-stroke UE dominance. Clinical information included comorbidities commonly correlated with stroke prevalence and calculation of the ischemic stroke Charlson comorbidity index (ISCCI) for all patients.[128,129] Mobility status for all patients was estimated using selected items of the Inpatient Rehabilitation Facility Patient Assessment Instrument (IRF-PAI).[130] The IRF-PAI is a standardized metric used to measure quality of care and to determine service reimbursement in rehabilitation settings beginning in 2019.[130] IRF-PAI scores for sit to stand and ambulation (10-ft, level surface) were estimated via medical record review by a licensed physical therapist who was trained in administration of the IRF-PAI and blinded to study outcomes. Standard scoring of the IRF-PAI uses a 6-point ordinal scale; a score of 6 indicates the patient is able to complete the task with no assistance; a score of 1 indicates the patient contributes no effort to perform the activity.[131] For the purposes of this study, when the item was not performed due to patient refusal or for medical safety reasons, the patient received a score of 0.

The Action Research Arm Test (ARAT) was the primary dependent variable to quantify PUE functional outcome for each patient. The ARAT is a validated, sensitive, and reliable test, commonly used in stroke-related research to measure level of upper extremity function.[132] Due to the retrospective nature of the study design, ARAT scores were estimated from therapy documentation at approximately 90 days post-stroke in accordance with the grading criteria for each test. Estimated ARAT (E-ARAT) scoring was conducted by two licensed, clinical neurologic therapists who were otherwise blinded to study findings. Rehabilitation provider notes were evaluated in detail to extract the following measures, where available, for each patient: clinical assessments of PUE muscle and grip strength, coordination, active and passive range of motion, observational movement analysis, therapeutic activity, exercises performed, rehabilitation goals, Nine-Hole Peg Test (9HPT) and Box and Block Test (BBT) scores as compared to matched, normative values.[133–137] Each clinician independently reviewed the EMR and determined maximal and minimal scores for each ARAT test item, creating a score range for every patient. E-ARAT for every patient was calculated by taking each clinician's median score and averaging the two values. See **APPENDIX B**. for more detail, patient examples, and the ARAT scoring sheet.

3.2.3 Statistical Methodology

Descriptive analyses were performed to summarize the distribution of variables of interest for the entire cohort. Non-parametric correlation analyses (Spearman's rho, r_S) were performed to evaluate the relationship between clinical metrics extracted and level of PUE

motor function at 3-months post-stroke (E-ARAT scores). The interrater reliability of the E-ARAT scores was assessed with an intraclass correlation coefficient (ICC), calculated using a two-way mixed effects model, considering people effects to be random and item effects to be fixed.[132,138]

A k-means cluster analysis was performed using E-ARAT scores to identify PUE outcome groups similarly to hypothesis-free classification analyses conducted in previous studies.[84] The cluster analysis was repeated using two, three, and four clusters and a minimal clinically important difference (MCID) of 12 points on the ARAT as the minimum distance between cluster centers to identify the maximum number of meaningfully different outcome groups.[84,139] Independent-samples means comparisons were then conducted using Kruskal-Wallis tests to identify differences in clinical metrics between outcome groups.

To explore which factor(s) may predict outcome cluster group, a classification and regression tree (CART) analysis was conducted. Gini was used to maximize homogeneity of child nodes with respect to the value of the target variable. All clinical metrics including stroke characteristics, comorbidities, SAFE scores, sensation, coordination, language impairments, and measures of mobility were available as inputs using a maximum tree depth of 1, a minimum terminal node size of 3, and automated pruning to avoid over-fitting. A CART analysis is a form of machine learning and does not require a minimum number of cases per variable, as is the case for traditional regression modelling. Therefore, this analytical approach was deemed appropriate for exploratory analyses with our limited sample size. Positive (PPV) and negative (NPV) predictive values, sensitivity, and specificity of the resulting decision tree were also calculated.

Tests were two-tailed with significance set to $p<0.05$. Significance values were adjusted for multiple comparisons using Bonferroni correction with a two-tailed significance level of $p=0.0017$ for correlation analyses (0.05/29 comparisons) and $p=0.02$ for t-tests (0.05/3 comparisons). All statistical analyses were conducted using IBM® Statistical Package for the Social Sciences (SPSS).

3.3 Results

Thirty-four patients (median age (range): 64 (36-84) years, female: 14) admitted to EUH with acute stroke, discharged to inpatient rehabilitation at ERH, and continued outpatient therapy at Emory during fiscal years 2016-2018 met study eligibility criteria. Patient characteristics are summarized in **Table** 3.1. Interrater agreement for E-ARAT scores was high (ICC=0.846, 95% CI: 0.69–0.92, $p<.0005$). A true SAFE score could only be calculated for 21 of the 272 (7.7%) of provider evaluations examined and were estimated for the remaining 92.3% of assessments.

Table 3.1 - Patient demographics, comorbidities, and stroke data

Demographics	**Median (range)/ Count (% total)**
Age at stroke onset, years*	64 (36-84)
Race African American Caucasian	 19 (55.9%) 15 (44.1%)
Sex Female Male	 14 (41.2%) 20 (58.8%)
Living situation With family With friend/roommate Alone	 28 (82.4%) 4 (11.8%) 2 (5.9%)
Comorbidities	
BMI[a], kg/m2*	29 (18.9-43.2)
CDC BMI[a] classification Normal Overweight Obesity (Class 1-3)	 9 (26.5%) 13 (38.2%) 12 (35.3%)
Smoker (current or former)*	3 (8.8%)
Hypertension*	24 (70.6%)
Hyperlipidemia*	13 (38.2%)
Previous stroke* Residual upper extremity weakness	16 (47.1%) 3 (8.8%)
Type II diabetes mellitus*	12 (35.3%)
Cardiac history*	7 (20.6%)
Chronic kidney disease*	5 (14.7%)
White matter disease, any* Mild Moderate Severe/Extensive	24 (70.6%) 12 (35.3%) 8 (23.5%) 4 (11.8%)
Ischemic stroke Charlson comorbidity index (/19)*	1 (0-5)

Stroke Information	
Type*	
Ischemic	24 (70.6%)
Hemorrhagic	8 (23.5%)
Ischemic with hemorrhagic transformation	2 (5.9%)
Stroke hemisphere*	
Right	12 (35.3%)
Left	17 (50.0%)
Bilateral	5 (14.7%)
Stroke location*	
Subcortical only	15 (44.1%)
Mixed cortical and subcortical	14 (41.2%)
Brainstem only	4 (11.8%)
Mixed subcortical and brainstem	1 (2.9%)
NIHSS*[b]/Stroke severity distribution	
Mild (0 - 4)	6 (17.7%)
Moderate (5 - 15)	17 (50.0%)
Severe (≥ 16)	5 (14.7%)
Not Tested	6 (17.7%)
Pre-stroke dominant upper extremity affected*	23 (67.7%)
Medical intervention*	
tPA[c]	3 (8.8%)
Mechanical thrombectomy	2 (5.9%)
Hemi-craniectomy	4 (11.8%)
Impairment	
E-SAFE[d] score (/10)*†	
Acute E-SAFE[d]	5 (0-8)
AR[e] E-SAFE[d]	6 (0-10)
Sensory impairment*	
Acute	18 (52.9%)
AR[e]	12 (35.3%)
Coordination impairment*	
Acute	30 (88.2%)
AR[e]	20 (58.8%)
Language impairment*	
Acute	17 (50.0%)
AR[e]	20 (58.8%)
IRF Sit-to-stand (/6)*	

Acute AR[e]	3 (0-4) 3 (0-4)
IRF Ambulation (/6)* Acute AR[e]	 1 (0-4) 1 (0-4)
Hospital and Rehabilitation Duration	
Acute hospital LOS[f], days	6.5 (1-27)
AR[e] LOS[f], days	19.5 (6-35)
Outpatient therapy duration, days	88.5 (29-314)
Number of outpatient occupational therapy visits	21.5 (7-54)

(a) Body mass index (BMI); (b) National Institutes of Health Stroke Scale (NIHSS); (c)Tissue plasminogen activator (tPA); (d) Estimated SAFE (E-SAFE); (e) Acute inpatient rehabilitation (AR); (f) Length of stay (LOS)
*Data were available to the CART analysis
† SAFE was estimated for 251/272 (92.3%) of provider evaluations examined

3.3.1 Correlation Analyses

Spearman's correlation analyses revealed the E-SAFE assessment performed closest to inpatient day-3 during acute hospitalization (Acute E-SAFE) was correlated with E-ARAT score (r_s=0.59, n=34, p=0.0002) (**Figure** 3.1**a**). The median time to Acute E-SAFE assessment was 3.0 days (range=0-12 days). The E-SAFE scores taken upon admission to AR (AR E-SAFE) were also correlated with E-ARAT score (r_s=0.73, n=34, p<0.00005) (**Figure** 3.1**b**). The median time to AR evaluation from stroke onset was 7.0 days (range = 2 - 27 days). The median time to E-ARAT assessment was 90.5 days (range = 69 - 428 days). The median time to assessment not including the single patient with only 1-year follow up data was 90.0 days (range = 69 - 149 days). IRF-PAI sit-to-stand and ambulation scores measured during acute hospitalization showed no significance to E-ARAT scores (Acute IRF-PAI sit-to-stand p=0.16; Acute IRF-PAI ambulation p=0.12). Neither IRF-PAI sit-to-stand nor ambulation scores at admission to AR remained significantly correlated with E-ARAT after correction for multiple comparisons (Bonferroni correction yielded a two-tailed significance threshold of p=0.0017; AR IRF-PAI sit-to-stand p=0.021; AR IRF-PAI ambulation p=0.004). Similarly, no IRF-PAI measure of mobility remained significantly correlated with E-SAFE scores after Bonferroni correction.

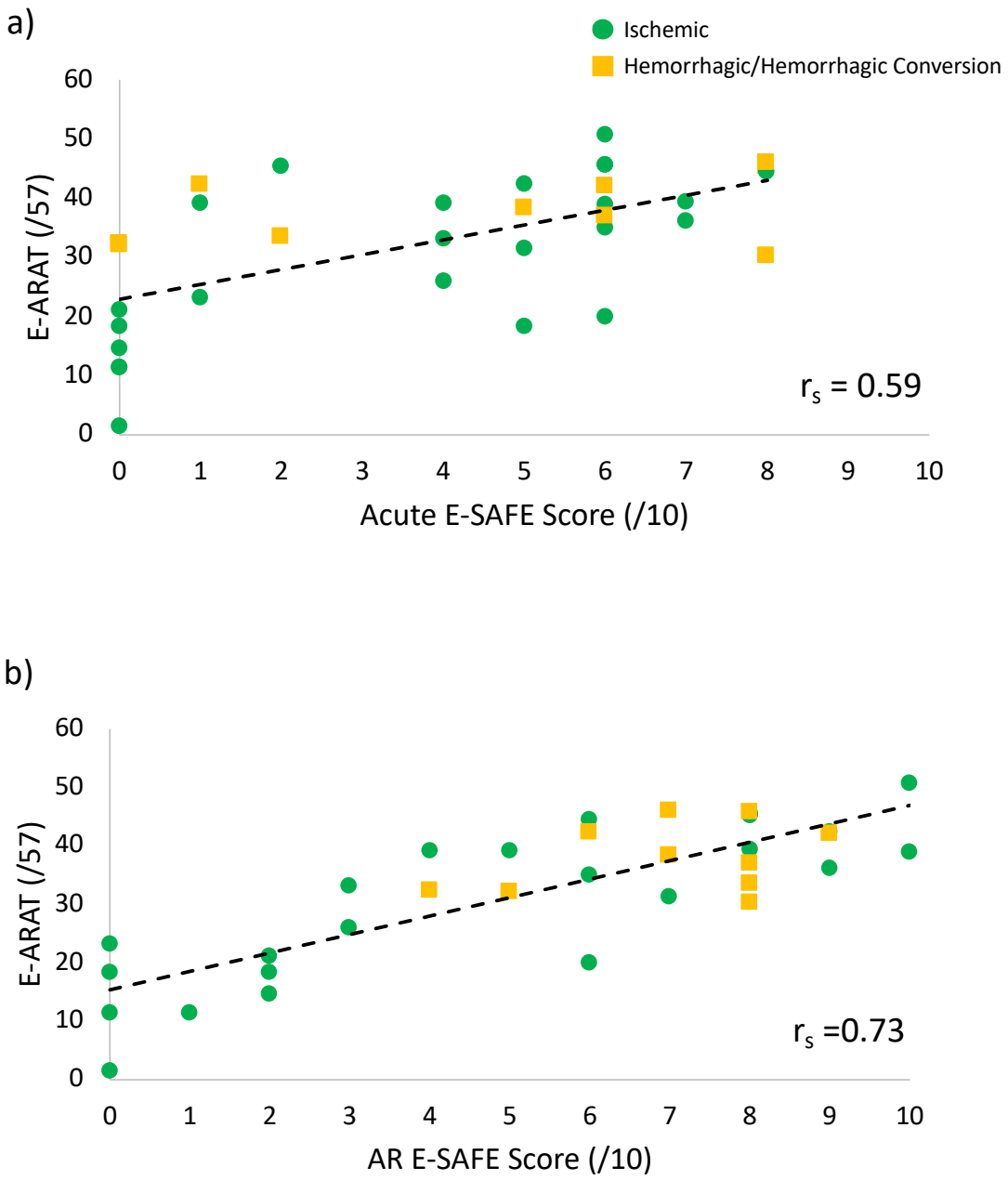

Figure 3.1 - E-SAFE score is associated with E-ARAT score at acute and AR timepoints. a) Acute E-SAFE post-stroke is moderately correlated with E-ARAT score. r_s = 0.59, n = 34, **p < 0.01 level. b) AR E-SAFE is strongly correlated with E-ARAT score. r_s = 0.73, n = 34, **p < 0.01 level. Ischemic strokes denoted with green circles; Hemorrhagic strokes depicted with orange squares.

3.3.2 Cluster Analyses

Cluster analyses using two, three, and four groups all resulted in a significant difference between clusters (ANOVA $p<0.001$ for all cluster iterations). See **Figure** 3.2. The three-cluster analysis produced distinct groups with centers at least 12 points (MCID) apart on the E-ARAT; however the four-cluster analysis failed to produce separation of at least one MCID between the highest scoring cluster centers (four-cluster analysis centers: 1.50, 18.36, **35.39, 45.10**).[139] Cluster cutoff scores align closely to previous predicted stroke outcome categories with PREP2[100] (**Figure** 3.3). Based on similarities in cluster group score ranges, group nomenclature for our cohort was defined as *Good*, *Limited*, and *Poor*, corresponding to the ARAT score ranges identified in PREP2.[100]

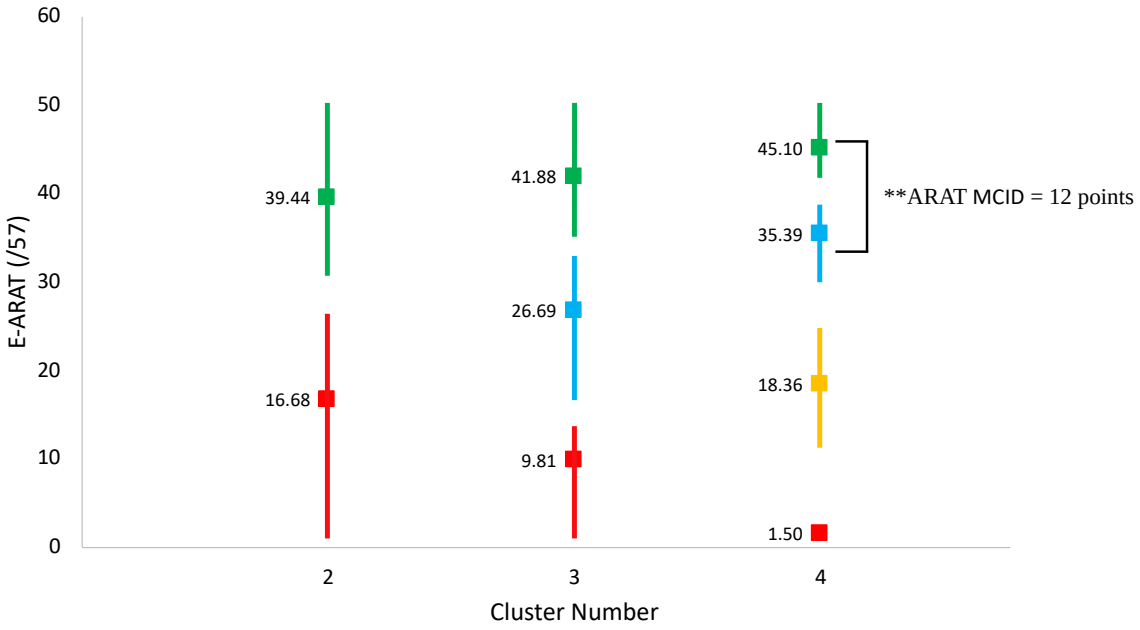

Figure 3.2 - Cluster analysis results. Analyses using two, three, and four groups all resulted in a significant difference between clusters (ANOVA $p<0.001$ for all cluster iterations). The three-cluster analysis produced distinct groups with centers at least 12 points (MCID) apart on the E-ARAT; however, the four-cluster analysis failed to produce separation of at least one MCID between the highest scoring cluster centers (three-cluster analysis centers: 9.81, 26.69, 41.88; four-cluster analysis centers: 1.50, 18.36, 35.39, 45.10).

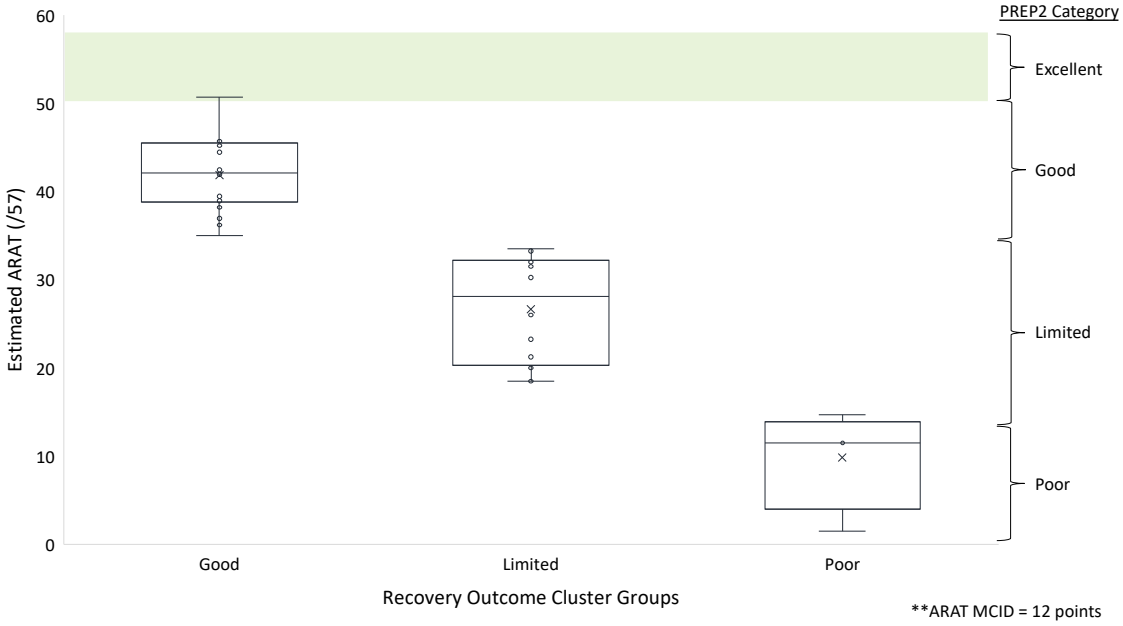

Figure 3.3 - Three-cluster analysis produced distinct outcome groups with centers at least 12 points (MCID) apart on the E-ARAT. Cluster centers denoted with "x" in the figure. Three cluster cutoff scores align closely to previous predicted stroke outcome categories with PREP2, therefore group nomenclature for our cohort was defined as *Good*, *Limited*, and *Poor*, corresponding to previously identified ARAT score ranges.

3.3.3 Kruskal-Wallis Results

The Kruskal-Wallis test showed a significant difference in Acute E-SAFE scores between outcome groups, $H(2)=14.32$, $p=0.001$. Post-hoc pairwise comparisons revealed that Acute E-SAFE score was higher for those in the *Good* cluster than those in both the *Limited* and *Poor* clusters (*Good-Limited* median difference=3, $p=0.035$; *Good-Poor* median difference=6, $p=0.002$) (**Figure** 3.4**a**, **Table** 3.2). The AR E-SAFE score was similarly found to be significantly different between groups, $H(2)=17.47$, $p<0.0005$. Post-hoc pairwise testing revealed that AR E-SAFE score was higher for the *Good* cluster group than both *Limited* and *Poor* groups (*Good-Limited* median difference=4.5, $p=0.007$; *Good-Poor* median difference=7.5, $p=0.001$) (**Figure** 3.4**b**, **Table** 3.2).

No clinical variables (denoted by a * in **Table** 3.1) differentiated the *Limited* from *Poor* outcome groups. Lengths of stay in both acute and rehabilitation hospitals were not significantly different between groups, nor was the duration of outpatient therapy or number of outpatient visits. **Table** 3.2 contains outcome cluster patient data.

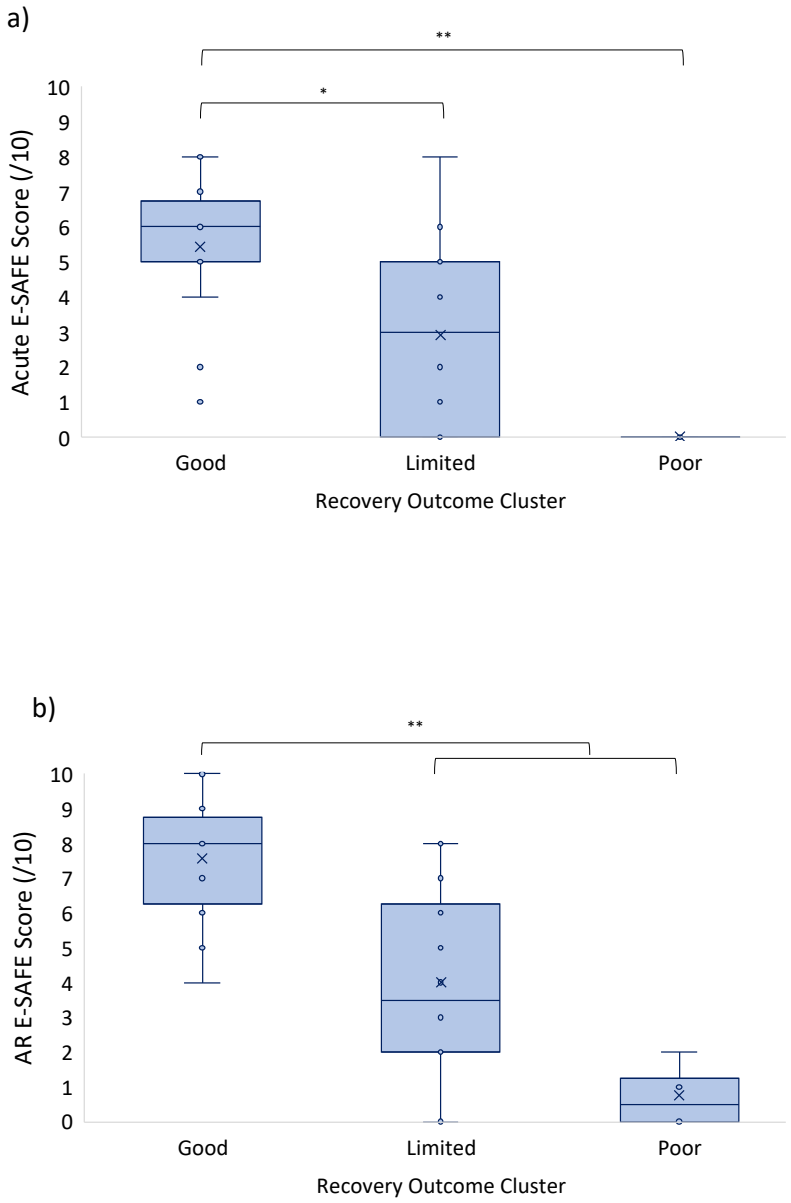

Figure 3.4 - E-SAFE is higher for those in the Good recovery group. a) Acute E-SAFE is higher for those in the *Good* outcome group over *Limited* and *Poor* outcome groups. *Good-Limited* p=0.035, *Good-Poor* p=0.002. b) AR E-SAFE is higher for those in the *Good* outcome group over *Limited* and *Poor* outcome groups. *Good-Limited* p=0.007, *Good-Poor* p=0.001. All p values reported represent adjusted significance; *p<0.05 level, **p<0.01 level.

Table 3.2 – PUE outcome cluster group data

PUE Recovery Outcome Group	**Good** Median (range)	**Limited** Median (range)	**Poor** Median (range)
Number of Patients (% total)	18 (52.9%)	12 (35.3%)	4 (11.8%)
E-ARAT[a] Score* (/57)	42.25 (35-50.75)	28.13 (18.50-33.50)	11.50 (1.50-14.75)
Acute E-SAFE[b] Score* (/10)	6 (1-8)	3 (0-8)	0 (0-0)
AR[c] E-SAFE[b] Score* (/10)	8 (4-10)	3.5 (0-8)	0.5 (0-2)
Acute LOS[d] (EUH), days	7 (2-25)	6.5 (2-27)	6 (1-23)
AR LOS[d] (ERH), days	19 (6-35)	20 (7-35)	19.5 (17-25)
Outpatient therapy duration, days	99.5 (44-314)	82 (37-271)	71 (29-157)
Number of outpatient visits	20.5 (12-50)	23.5 (11-54)	18 (7-22)

(a) Estimated ARAT (E-ARAT); (b) Estimated SAFE (E-SAFE); (c) Acute inpatient rehabilitation (AR); (d) Length of stay (LOS)
*Variables show statistical differences between groups

3.3.4 CART Analysis

The exploratory CART analysis yielded a decision tree selecting AR E-SAFE to classify patients with 70.6% accuracy (correct classification for 24 of 34 patients) (**Figure** 3.5). Patients were classified as having a *Good*, *Limited* or *Poor* outcome, but the decision tree failed to differentiate between *Limited* and *Poor* outcomes. For the *Good* outcome group, the PPV of the decision tree was 75.0% (18 of the 24 *Good* PUE outcome predictions were true, 6 were lower than predicted (had a *Limited* category outcome)) and the sensitivity was 100.0% (all 18 *Good* outcomes were predicted to be *Good*). The largest error was introduced for those with lower strength at admission to ERH (AR E-SAFE<4) where the accuracy was 60.0% (6 of the 10 *Limited* outcome predictions were true, 4 were lower than predicted (had a *Poor* category outcome)). For the *Limited* outcome group, the PPV was 60.0% (6 of the 10 *Limited* outcome predictions were true) and the sensitivity was 50.0% (6 of the 12 *Limited* outcomes were predicted to be *Limited*). For the *Poor* group, the PPV and sensitivity were both 0.0%. All inaccurate predictions were higher than the achieved outcome (i.e., 6 individuals predicted to be in the *Good* outcome group achieved an E-ARAT within the *Limited* outcome score range).

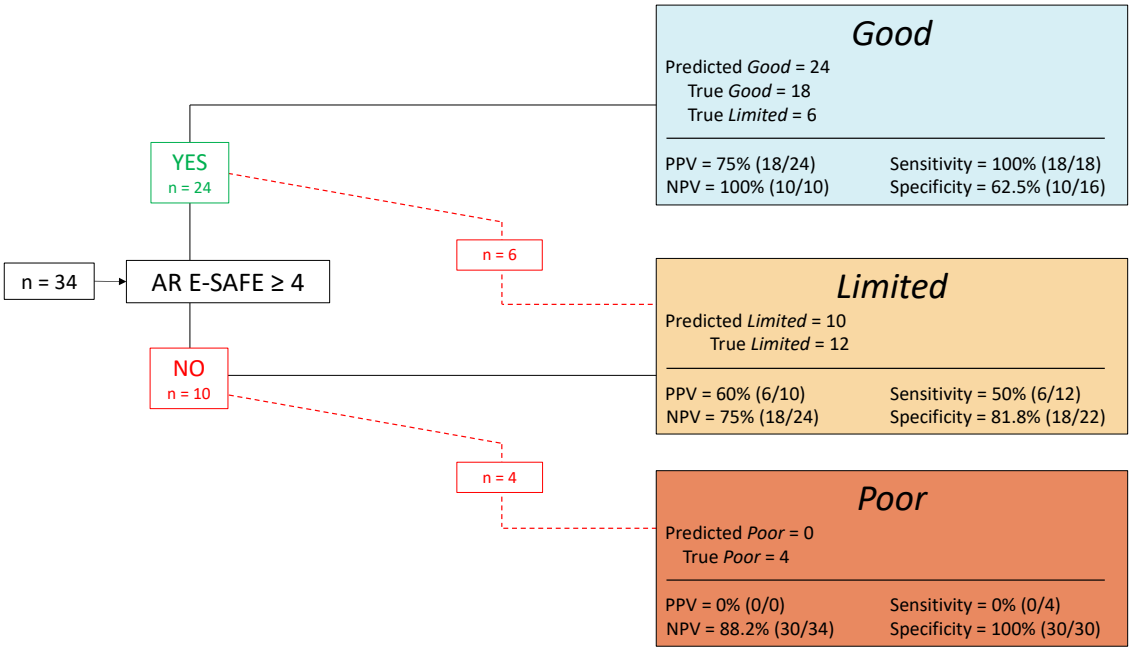

Figure 3.5 - AR E-SAFE predicts PUE outcome category with 70% accuracy. Clinical metrics alone fail to differentiate between *Limited* and *Poor* outcomes but predict the difference between *Good* and *Limited or Poor* outcomes only. All inaccurate predictions were of a higher outcome group than achieved.

3.4 Discussion

The current study findings reveal that PUE E-SAFE score, measured both acutely and at AR admission, are associated with PUE motor recovery outcome post-stroke, that categorization of PUE outcomes is consistent with previous studies, and that predictive models using AR E-SAFE can identify *Good* from *Limited*/*Poor* recovery outcome categories in patients undergoing AR. However, standard clinical metrics were unable to differentiate between *Limited* and *Poor* outcomes.

3.4.1 Upper Extremity Strength is Strongly Associated with Recovery of PUE Motor Function

E-SAFE score emerged as the metric with the strongest association with PUE outcome at 90 days post-stroke in keeping with previous studies.[127] This finding was true when measured early during acute hospitalization (day-3 post-stroke) and during the early subacute phase (AR admission). These findings may be unsurprising as E-SAFE score is a gross measure of baseline impairment and initial impairment has repeatedly been found to be the most powerful predictor of functional motor outcome.[140–143] SAFE is an objective, easy-to-administer clinical metric of key muscle strength further supporting its use as a screening tool in the acute and subacute stages of recovery. In AR settings, SAFE score may be important to obtain and document as an initial screening tool for expected PUE functional recovery outcome, particularly when EMRs are not shared between care facilities or when detailed acute hospitalization records are not available. Importantly, objective quantification is preferred to other qualitative documentation terminology commonly used by therapists (e.g., “within functional limits”) as these terms are imprecise

and unclear for other providers. We observed that only 7% of provider evaluations collected objective SAFE measurements. To implement SAFE scores into routine clinical care, a structured training strategy should be considered to ensure standard measurement and documentation.[122,144]

Sit-to-stand and ambulation status measured using the IRF-PAI showed no significance to E-ARAT. This may be due, in part, to the IRF-PAI scoring system which corresponds to necessary level of assistance rather than strength, movement quality, or specified use of an assistive device.[130] Therefore, the lack of association between measures may be due to measurement differences, in particular, to the lack of precision in the IRF-PAI, though the lack of association may also be due to physiologic differences in upper and lower extremity control and recovery mechanisms.[46,145–147]

3.4.2 Categorization of PUE Recovery Outcome Group is Consistent with Previous Studies

Our cluster analysis resulted in E-ARAT cutoff scores which were highly consistent with categories identified with prospective ARAT assessments in PREP2.[100] The current cohort of individuals admitted to AR had worse outcomes overall than the NZ cohort. Surprisingly, only one patient would have been classified by the PREP2 decision tool as having an *Excellent* recovery outcome (E-ARAT ≥50),[84,100] possibly due to study selection criteria which limited our cohort to those requiring therapeutic intervention in an AR setting. Though discharge decisions are multifactorial and not solely dependent on PUE status, it may be the case that most individuals that would be predicted to have an *Excellent*

PUE outcome are discharged to home from acute hospitalization rather than to AR, reflecting a robust filter within the US healthcare system which reserves the resource of AR for those who require a higher level of therapeutic intervention.

3.4.3 Predictive Models Can Identify Good from Limited/Poor Recovery Outcome Categories

In our cohort, functional PUE recovery after stroke was estimated with 70% accuracy using AR E-SAFE alone. The E-SAFE score cutoff selected by the CART analysis in our decision tree is one point lower than in the PREP2 prediction tool (E-SAFE ≥4 vs. SAFE ≥5).[100] We may expect that strength cutoff scores would decrease with time with time post-stroke as it should reflect progression of recovery. Unlike in PREP2 studies, if little to no PUE strength is available by the second week post-stroke (AR E-SAFE<4), our data suggest that a patient will achieve less than a *Good* recovery outcome without the need for further outcome potential clarification by assessing motor evoked potential status. However, a higher AR E-SAFE score does not guarantee a *Good* recovery outcome (PPV=75%). These preliminary data show promise for the creation and validation of a predictive tool with clinical utility at admission to AR in the US healthcare system but further research will be necessary to ensure these findings remain valid within a larger patient cohort.

Two studies have evaluated PREP2 metrics in healthcare settings outside of NZ and gathered initial SAFE scores in a timeline consistent with that of AR E-SAFE measurement in our cohort.[125,126] Interestingly, both studies reported initial SAFE score medians for

Limited and Poor outcome groups of <4, suggesting that similar modification of cutoff scores may be necessary to achieve optimal accuracy in new health care settings and patient populations.[117,123,125,126] Because SAFE score continues to demonstrate strong predictive potential and has been successfully implemented in both New Zealand and Sweden, future studies should seek first to validate existing prediction tools, with high fidelity to the original metrics and timeline, with the knowledge that cutoff score modification may be necessary.[117,122,123,144,148]

3.4.4 Limitations

This retrospective study design has strengths and limitations. The most significant limitation of the retrospective design is that it necessitated estimation of most SAFE scores and estimation of ARAT performance for all patients. This approximation likely introduces some measurement error to current findings though E-ARAT scores demonstrated excellent inter-rater reliability between experienced neurologic therapists. Further, our retrospective data provided access to current standards of clinical care and recovery outcomes within the study cohort, thus yielding a dataset that may be a more accurate representation of the recovery experience of individuals post-stroke. An additional limitation to the retrospective design is that we were unable to control for differences in the content of therapy provided at each stage of post-stroke care. However, individuals who receive therapy in the same rehabilitation settings should receive a similar dosage and type of therapeutic intervention, thereby reducing heterogeneity. Further, patients in our cohort had statistically similar therapy duration across the continuum of care. Lastly, the

generalizability of current findings may also be limited due to the small sample size and an uneven distribution of individuals across categories that resulted in underrepresentation of patients in both *Limited* and *Poor* outcome categories. Though our exploratory CART analysis yielded a decision tree that accurately predicts outcome for 70% of individuals, the small sample size and category distribution may lead to overfitting of the model. Though results are promising, further investigation and validation using a larger sample size will be necessary.

3.5 Conclusions

Tailoring therapeutic intervention to expected motor outcomes is a common theme in neurorehabilitation, yet there remains an opportunity to increase the personalization of treatment and enable recovery to an individual's physiologic potential. Our findings suggest that patients who undergo AR post-stroke demonstrate heterogeneous levels of impairment and functional outcomes while highlighting the clinical utility of the SAFE score as a simple, easy-to-acquire, readily implementable screening metric that could guide clinical decision-making in AR. Exploratory predictive modeling suggests PUE functional outcome after stroke may be accurately predicted using AR SAFE score. In an era of precision medicine, the early and intentional use of these clinically-feasible metrics may allow for improved care plan development and optimized allocation of rehabilitation resources. Taken together, these observations support the notion that clinical information routinely collected after stroke is associated with level of recovery of PUE function and, if

optimized, have the potential to inform and improve the delivery of therapeutic interventions post-stroke.

CHAPTER 4. SPECIFIC AIM 3

Clinical imaging derived metrics of corticospinal tract structural integrity are associated with post-stroke motor outcomes: a retrospective study

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4.1 Introduction

Stroke is a leading cause of long-term adult disability in the United States (US).[3] Early, accurate prediction of recovery of motor function post-stroke would enable precision-based rehabilitation strategies to improve outcomes and reduce disability.[79,86] However, current clinical practice lacks objective tools necessary to accurately predict motor recovery and deliver optimally-targeted interventions.[3,21,78,79]

The majority of motor recovery occurs early after stroke, typically plateauing around 3-months post-injury, and is thought to be primarily regulated by molecular mechanisms underlying structural and functional reorganization of the motor system within both lesioned and non-lesioned hemispheres.[14,34,36,63] The corticospinal tract (CST) is the canonical descending motor output pathway responsible for generating voluntary movements and is particularly important for fine motor control of dexterous distal movements in both animals and humans.[34–36] Approximately 40% of the CST originates directly from the primary motor cortex (M1), while an additional ~30% of the CST is comprised of tracts originating from non-M1 motor areas such as premotor cortex (PM), supplementary motor cortex (SMA), and cingulate motor areas.[7,27,38,149] Pyramidal cells within M1 generate signals for execution of movements in context.[28] PM and cingulate regions are known to be involved in control of both the cognitive aspects of motor planning (including spatial attention) and the execution of movement itself, while the SMA is thought to contribute to temporal specificity of muscle activation, particularly during reaching movements.[24,29–33] The CST also encompasses projections from the primary somatosensory cortex (S1) to the SC suppling sensory information that informs movement output, enabling precision and refinement of motor control.[23] Stroke-induced disruption of

the CST often results in functional impairment of the hand and upper limb and is known to particularly affect the recovery of fine motor control.[14,51,54] Prior studies have shown associations between paretic upper extremity (PUE) motor recovery and disruptions of M1 contributions to the CST post-stroke.[50,51,53,54] More recently, other studies have evaluated differential contributors to CST structural integrity with inconclusive results.[29,50,52,95,150,151] Thus, less is currently known about the relevance of non-M1 projections within the CST to specific elements of PUE motor recovery.

Models to predict PUE motor recovery outcome have been developed and implemented in other healthcare systems.[65,84,100,119,122,148] The Predict Recovery Potential (PREP2) prediction tool, developed and internally validated in New Zealand (NZ), predicts PUE motor outcomes using a combination of clinical assessments and objective neurological biomarkers.[100] PREP2 employs transcranial magnetic stimulation (TMS) of M1 to measure CST functional integrity and the National Institutes of Health Stroke Scale (NIHSS) score to differentiate functional prognosis in the subset of individuals with initially low PUE strength.[100,112] TMS assessment is not currently standard-of-care in US hospitals however, clinical neuroimaging is routinely used to diagnose stroke in the US and can be used to quantify structural integrity of the CST.

Using magnetic resonance imaging (MRI), the structural integrity of the descending sensorimotor system can be quantified by measuring both the location and extent of stroke lesion overlap with the CST and has been used to identify how damage to anatomic structures relates to post-stroke motor outcomes.[50,52,76,84,95,99] Several studies have shown that poorer motor outcomes are correlated with a greater extent of lesion encroachment with the CST.[50,51,53,54] Interestingly, structural MRI may outperform the use of clinical

bedside measures of PUE strength or functional impairment,[54,84,86,96] but most of these studies employed research-grade MRI with higher resolution compared to standard-of-care clinical MRI.[52] In the absence of both TMS and research-grade MRI, routine acute clinical MRI may offer alternative estimates of lesion overlap and anatomical integrity. In fact, studies using clinical MRI have emerged providing high quality evidence for imaging-derived prediction of motor return post-stroke, but have yet to combine those standard-of-care MRI metrics with clinical measures to predict functional outcome.[51,52,86,95,98]

Previously, we observed that estimated shoulder abduction and finger extension (E-SAFE) PUE strength from assessments at admission to acute inpatient rehabilitation (AR) could predict PUE motor recovery outcomes with 70% accuracy but that clinical metrics alone were unable to distinguish between *Limited* and *Poor* recovery outcome groups.[152] Further, most previous work has not evaluated MRI prognostic utility for hemorrhagic stroke.[51,52,98] Accordingly, there is a need to investigate possible markers of CST integrity that differentiate outcomes for both ischemic and intracerebral hemorrhagic strokes and is of particular importance for those patients with initially-lower levels of volitional control who exhibit the most difficult to predict recovery patterns.[52,61,100,153]

The primary objective of this study was to retrospectively investigate associations between clinical MRI-based metrics of CST status and PUE motor recovery in patients that completed AR post-stroke. We hypothesized that clinical MRI-based measures of lesion disruption to M1 and non-M1 contributions to the CST would be associated with PUE functional outcome at ~90 days post-stroke. Our exploratory hypothesis was that metrics of lesion-based CST disruption would improve the predictive accuracy of PUE motor

recovery outcome over use of clinical metrics alone, particularly for those with initially lower levels of PUE strength.

4.2 Methods

4.2.1 Study Population and Selection Criteria

As detailed in Chapter 3, we conducted a longitudinal retrospective chart review of a subset of patients admitted with stroke who received care in the Emory University Hospital (EUH) system, between September 1, 2016 and August 31, 2018. Inclusion and exclusion criteria have been described in previous chapters.[152] Individuals were required to have remained within the EUH system for acute hospitalization, acute inpatient rehabilitation at Emory Rehabilitation Hospital (ERH), and Emory outpatient therapy through at least 90 days post-stroke to permit longitudinal assessment of PUE recovery outcomes. Lastly, patients were required to have received clinically diagnostic MRI during their acute stroke workup at EUH. This study received Emory University Institutional Review Board approval and patient consent was waived.

4.2.2 Data Extraction, Interpretation, and Analysis

4.2.2.1 Clinical Variables

As previously described, clinical metrics including demographic information, stroke characteristics, care continuum metrics, and provider documentation of post-stoke motor

function were extracted from Cerner Powerchart, the institutional electronic medical record (EMR) system of the Emory Healthcare system.[152]

Provider documentation of PUE strength and post-stroke disability were recorded serially including manual muscle test scores, sensation, coordination, language impairments, and measures of mobility. E-SAFE scores were calculated for each patient calculated using available assessments of PUE strength. If the E-SAFE score was documented more than once during acute hospitalization, the assessment performed closest to inpatient day-3 was used; in the AR setting, the E-SAFE score performed closest to admission was used, in accordance with previous work.[84,100,99,152] Estimated Action Research Arm Test (E-ARAT) scores were used as the primary dependent variable to quantify PUE functional outcome for each patient. [100,132,152] E-ARAT was estimated from therapy documentation at approximately 90 days post-stroke in accordance with the grading criteria for each test.[132,152] As described in Chapter 3, three-cluster cluster analysis produced distinct outcome groups with centers at least 12 points apart (the minimal clinically important difference) on the E-ARAT and were defined as *Good*, *Limited*, and *Poor* PUE outcome groups, corresponding to diminishing levels of PUE function.[152]

4.2.2.2 Image Processing and Lesion Mapping

Standard-of-care clinical MRI were obtained from the Department of Radiology at EUH. Stroke topography was determined using diagnostic, clinically-obtained T2-weighted images. Diffusion weighted images (DWI) were utilized for ischemic strokes and gradient echo images (GRE) were used for hemorrhagic strokes in order to maximize visual contrast

and improve the specificity of lesion identification. Scans performed closest to the date of admission were used when multiple MRI sequences were acquired during the acute inpatient stay. Lesion masks were created in ITK-SNAP version 3.8.0[154] by a member of the research staff who was otherwise blinded to participant outcomes. Lesions were traced in a slice-by-slice manner in the axial plane using a semi-automated segmentation process. In this process, a scalar "speed" image was created to delineate between structures of interest.[154,155] Active contour segmentation was then guided by both the speed image and manually-placed initialization seeds.[155] Traces were manually adjusted as necessary in the sagittal and coronal planes to ensure accuracy of the three-dimensional segmentation. Once drawn, lesion mask location and extent were independently verified visually and with neuroradiology documentation. A board-certified vascular neurologist (S.B.) provided additional consultation to ensure accuracy of lesion masks. Lesion volume was automatically calculated by ITK-SNAP software.[154]

T1-weighted images (anatomical scans), T2-weighted images (pathological scans), and lesion masks (lesion map) were used as inputs for spatial normalization into standard Montreal Neurological Institute (MNI) space using Statistical Parametric Mapping software (SPM12).[156,157] SPM's combined normalization-segmentation process was employed via the associated clinical toolbox using the 2mm T1-weighted MNI152 template, a standard template bounding box ([−90 −126 −72; 90 90 108]), and $2mm^3$ voxel size.[156–158] Validation of normalization in standard stereotaxic space was then visually confirmed to ensure proper alignment of cortical boundaries, subcortical anatomical landmarks, and drawn lesions.

4.2.2.3 CST Lesion Overlap Calculation

The spatially normalized lesion mask for each participant was processed through custom MNI ROI overlap software to obtain CST lesion overlap using the sensorimotor area tract template (SMATT) atlas.[159,160] The SMATT atlas delineates contributions to the CST emanating from six cortical seed regions: M1; ventral and dorsal premotor areas (PMv and PMd); supplementary and pre-supplementary motor areas (SMA and preSMA); and primary somatosensory cortex (S1).[159] SMATT was created using a slice-by-slice thresholding technique in both right and left hemispheres to minimize tract overlap while conserving tract volume.[159] Data analysis output included voxel sizes for each tract, the number of voxels disrupted by the lesion, and percent tract lesion overlap. The lesion load output was individuated by seed region (M1, PMv, PMd, SMA, preSMA, and S1), therefore a whole CST lesion overlap percentage (CST overlap) was calculated by summing the number of voxels in each tract, the number of voxels overlapped by the region and dividing the two metrics. This calculation was conducted using tract voxel numbers for the affected hemisphere, as there are slight differences in CST size between right and left hemispheres.[159] A non-M1 CST lesion overlap percentage was calculated using similar methodology, but omitting overlap data from the M1 CST only. CST lesion overlap percentage was also calculated using the Johns Hopkins University white matter tractography atlas (JHU).[161] The JHU atlas has been employed more often in tractography studies, so was used to comparatively assess SMATT atlas utility.[52,161]

4.2.2.4 Statistical Methodology

Descriptive analysis was performed to summarize the distribution of variables of interest for the entire cohort. Non-parametric correlation analyses (Spearman's rho, r_S) were performed to evaluate the relationship between CST lesion overlap metrics, lesion volume, and level of paretic upper extremity motor function at 3-months post-stroke (E-ARAT scores). Parametric correlation analyses (Pearson's correlation coefficient, r) were performed to evaluate the relationship between continuous MRI variables. Independent-samples means comparisons were then conducted using Kruskal-Wallis tests to identify differences in MRI metrics between outcome groups. To explore which MRI-derived factor(s) may predict outcome cluster group, a classification and regression tree (CART) analysis was conducted. Gini was used to maximize homogeneity of child nodes with respect to the value of the target variable. Clinical and MRI metrics including all tract overlap percentages from both SMATT and JHU atlases, lesion volume, stroke characteristics, patient age, patient comorbidities, E-SAFE scores, sensation, coordination, language impairments, and measures of mobility were available as inputs using a maximum tree depth of 2, a minimum terminal node size of 3, and automated pruning to avoid over-fitting. Positive (PPV) and negative (NPV) predictive values, sensitivity, and specificity of the resulting decision tree were also calculated.

Tests were two-tailed with significance set to $p<0.05$. Significance values were adjusted for multiple comparisons using Bonferroni correction with a two-tailed significance level of $p=0.0083$ for correlation analyses (0.05/6 comparisons and $p=0.02$ for t-tests (0.05/3 comparisons). All statistical analyses were conducted using IBM® Statistical Package for the Social Sciences (SPSS).

4.3 Results

Thirty-four patients (median age: 64 (36-84) years, female: 14) admitted to EUH with acute stroke, discharged to inpatient rehabilitation at ERH, and continued outpatient therapy at Emory during fiscal years 2016-2018 met study eligibility criteria. Twenty-five patients were diagnosed with ischemic stroke (70.6%), 8 with hemorrhagic stroke (23.5%), and 2 with ischemic stroke with hemorrhagic conversion (5.9%). Twelve strokes (35.3%) were localized in the right hemisphere, 17 (50.0%) in the left hemisphere, and 5 (14.7%) had bilateral involvement. Twenty-nine (85.3% of strokes) had subcortical involvement; 4 (11.8%) were localized to the brainstem. Seven patients (20.6%) had previous clinical stroke while 24 (70.6%) had some degree of white matter disease. A lesion heat map for all 34 participants is depicted in **Figure** 4.1**.** The median time to AR-SAFE evaluation was 7 days (range = 2-27 days). The median time to MRI was 1 day (range = 0-6 days). The median time to E-ARAT assessment was 90.5 days (range = 69-428 days). Additional patient characteristics are summarized in **Table** 3.1 (Chapter 3).

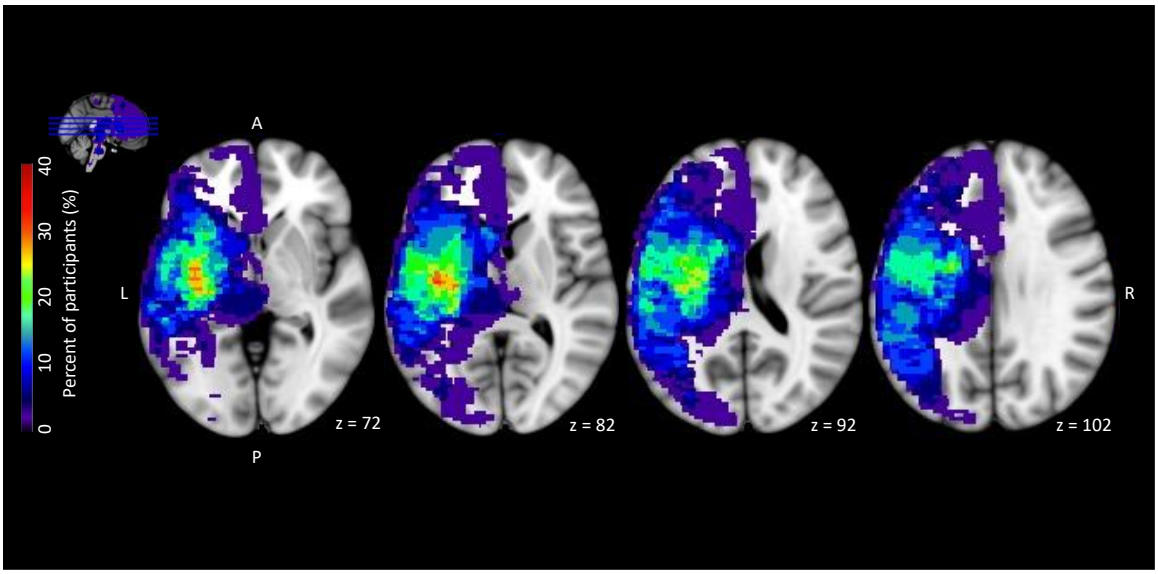

Figure 4.1 - Stroke lesion overlap heat map for all 34 participants. All lesions were flipped onto the left hemisphere for display. For the 5 participants with stroke involvement in bilateral hemispheres, the hemisphere contralateral to the affected PUE was used for stroke location purposes. Color bar on the right maximum value 40% = 13 participants (maximal overlap voxel = red).

4.3.1 Correlation Analyses

Spearman's correlation analyses revealed the SMATT CST overlap to be moderately negatively correlated with E-ARAT (SMATT CST r_s (32) = -0.443, p = 0.0087), (**Figure** 4.2**a**). The JHU CST overlap was also significantly correlated with E-ARAT, though less strongly (JHU CST r_s (32) = -0.361, p = 0.036), (**Figure** 4.2**b**). JHU CST and SMATT CST overlap were highly and significantly correlated (r (32) = 0.919, p < 0.0001). Lesion volume was not associated with E-ARAT scores (lesion volume r_s (32) = -0.071, p = 0.69). Measures of lower extremity function in acute and AR settings showed no association to either CST lesion overlap metrics or lesion volume.

Further correlation analyses were conducted to evaluate which regions within the SMATT atlas were most highly correlated with the E-ARAT. PMv overlap percentage was the only tract that remained significantly correlated after adjusting for multiple comparisons (r_s (32) = -0.457, p = 0.0066) (See **Table 4.1**).

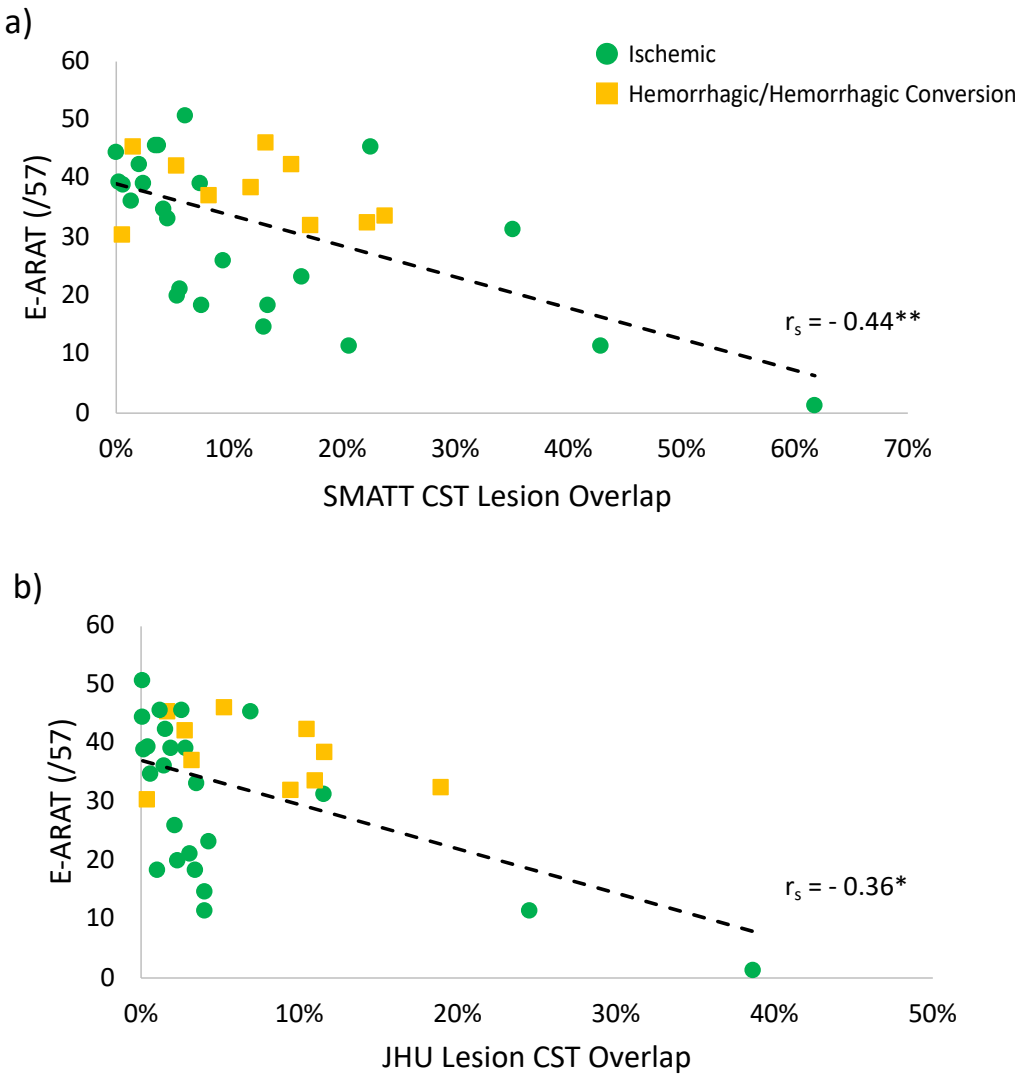

Figure 4.2 - CST lesion overlap is associated with E-ARAT scores. a) SMATT CST Lesion overlap is moderately correlated with E-ARAT score; (r_s = -0.44, n = 34, **p = 0.0087). b) JHU CST-Lesion overlap is weakly correlated with E-ARAT score; (r_s = -0.36, n = 34, *p = 0.036). *Correlation is significant to the 0.05 level (2-tailed); **Correlation is significant to the 0.01 level (2-tailed).

Table 4.1 - SMATT tracts correlate with E-ARAT scores and distinguish between PUE outcome groups (n=34)

SMATT Tract	**Spearman Correlations**	**Kruskal-Wallis Results**	**Pairwise comparisons** (median difference in % overlap, p^a)
SMATT CST	r_s (32) = -0.443, p = 0.0087*	H(2) = 11.41, p = 0.003*	*Good-Poor*: 20.25, p^a=0.007** *Good-Limited*: 7.55, p^a=0.072†
M1	r_s (32) = -0.344, p = 0.046*	H(2) = 7.84, p = 0.02*	*Good-Poor*: 25.25, p^a=0.024**
PMd	r_s (32) = -0.413, p = 0.015*	H(2) = 12.15, p = 0.002**	*Good-Poor*: 32.10, p^a=0.002** *Limited-Poor*: 23.76, p^a=0.073†
PMv	r_s (32) = -0.457, p = 0.0066**	H(2) = 13.66, p = 0.001**	*Good-Poor*: 53.28, p^a=0.005** *Good-Limited*: 10.36, p^a=0.018**
preSMA	r_s (32) = -0.414, p = 0.015*	H(2) = 10.65, p = 0.005**	*Good-Poor*: 29.08, p^a=0.004** *Limited-Poor*: 22.79, p^a=0.084†
SMA	r_s (32) = -0.375, p = 0.029*	H(2) = 11.54, p = 0.003**	*Good-Poor*: 28.88, p^a=0.004**
S1	r_s (32) = -0.381, p = 0.026*	H(2) = 7.02, p = 0.03*	*Good-Poor*: 18.79, p^a=0.057†

* Correlation is significant; ** Correlation remained significant after Bonferroni correction. All p-values reported for pairwise comparisons (last column) represent adjusted significance (p^a). † Approaching significance after Bonferroni correction.

4.3.2 Kruskal-Wallis Results

The Kruskal-Wallis tests showed significant differences between outcome groups for all SMATT tract lesion overlap percentages. Post-hoc pairwise comparisons revealed that almost all significant differences were between *Good* and *Poor* outcome groups. Only PMv lesion overlap revealed a significant difference between *Good* and *Limited* outcome groups (*Good-Limited* median difference = 10.36%, p = 0.018) (**Figure 4.3a**), though SMATT CST lesion overlap showed a non-significant trend for a difference between *Good* and *Limited* outcome groups after Bonferroni correction (SMATT CST *Good-Limited* median difference = 7.55%, p = 0.072). **See Table 4.1, pairwise comparisons.** No MRI variable significantly differentiated the *Limited* from *Poor* outcome groups, though overlap percentages from 2 non-M1 CST contributors, PMd and preSMA, were both approaching significance after Bonferroni correction (PMd *Limited-Poor* p = 0.073, preSMA *Limited-Poor* p = 0.084) (**Figure 4.3b-c**). Lesion volume was not significantly associated with PUE outcome category ($H(2) = 2.06$, p = 0.36).

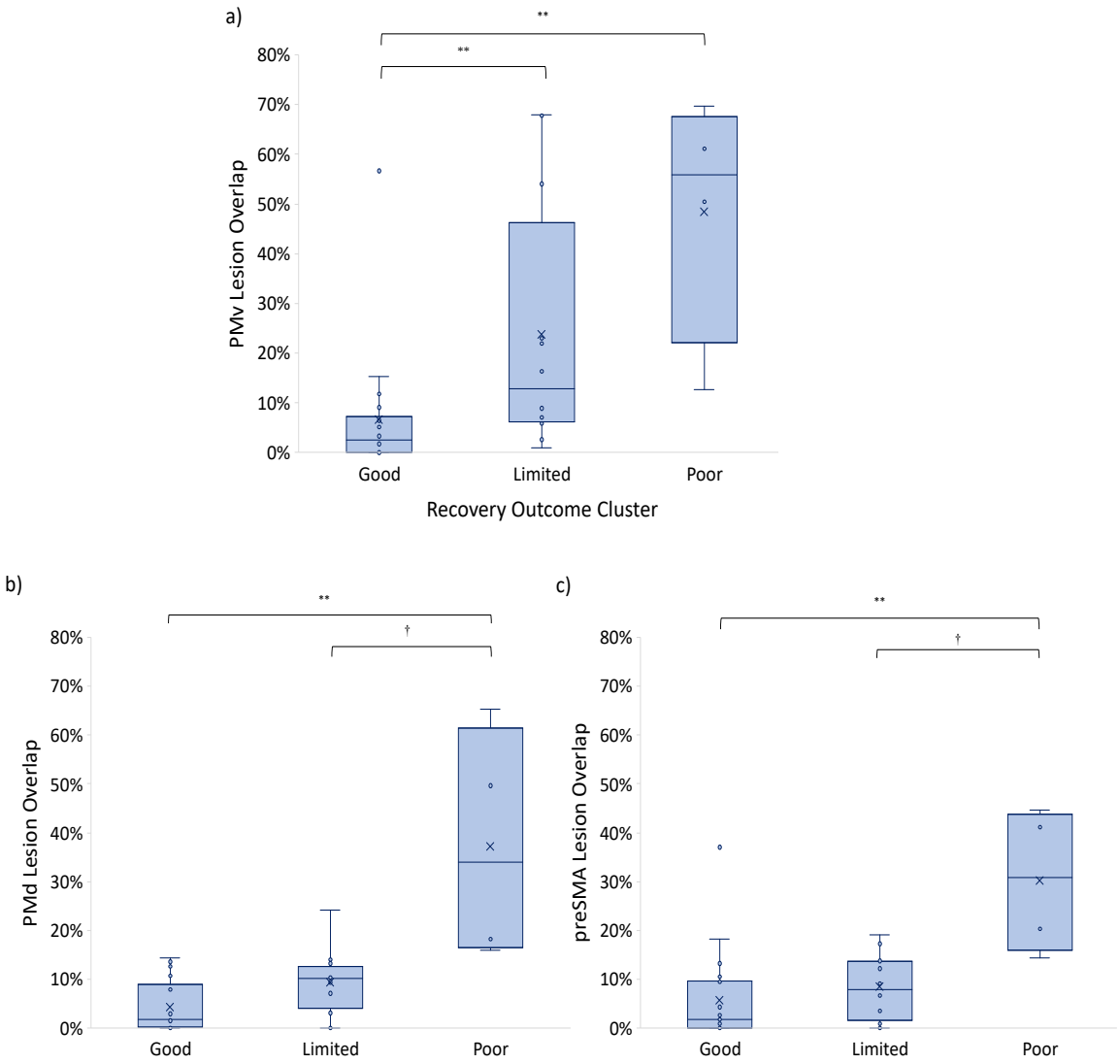

Figure 4.3 - CST lesion overlap is smaller for those in the *Good* recovery group. a) PMv lesion overlap % is lower for those in the *Good* outcome group over those in both the *Limited and Poor* outcome groups. *Good-Limited* p=0.018, *Good-Poor* p=0.005. b) PMd lesion overlap % is lower for those in the *Good* outcome group over those in the *Poor* outcome group and showed a non-significant trend for a difference between *Limited* and *Poor* outcome groups. *Good-Poor* p=0.002, *Limited-Poor* p=0.073. c) preSMA lesion overlap % is lower for those in the *Good* outcome group over those in the *Poor* outcome group and showed a non-significant trend for a difference between *Limited* and *Poor* outcome groups. *Good-Poor* p=0.004, *Limited-Poor* p=0.084. All p values reported represent adjusted significance; Cluster centers denoted with "x" in the figure; horizontal bars represent medians *p<0.05 level, **p<0.01 level; †Approaching significance after Bonferroni correction.

Figure 4.4 depicts representative lesions overlaid on the SMATT atlas template for 2 individuals from different outcome groups. Participant A (**Figure** 4.4 **top right, middle, left**) achieved a PUE outcome in the *Good* category. Participant B **Figure** 4.4 **bottom right, middle, left**) achieved a PUE outcome in the *Limited* category. **Right**, **Middle**, and **Left** slices depict the axial, coronal, and sagittal slices, respectively. Stroke lesions are depicted in light red with dark red outline. Individual contributions to the CST are color coded (see figure key). Both individuals had similar whole CST lesion overlap (participant A = 9.51%, participant B = 11.97%) but participant A had higher relative contribution of M1 CST lesion overlap (Participant A M1 overlap = 18.87%, non-M1 overlap = 9.28%; Participant B M1 overlap = 1.94%, non-M1 overlap = 12.46%).

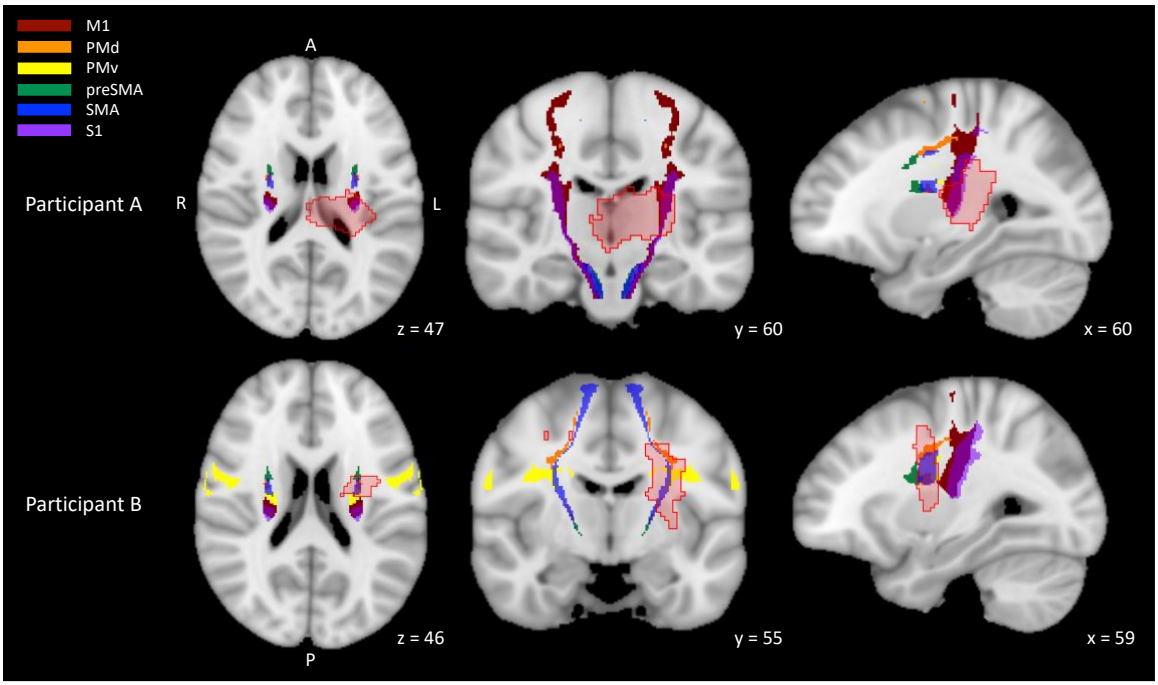

Figure 4.4 - Representative stroke lesions and SMATT corticospinal tract (CST) templates. CST templates have been differentiated by contributing region: primary motor cortex (M1, dark red), dorsal premotor cortex (PMd, orange), ventral premotor cortex (PMv, yellow), presupplementary motor cortex (preSMA, green), supplementary motor cortex (SMA, blue), primary somatosensory cortex (S1, purple). Stroke lesions are depicted in light red with dark red outline. Participant A (top (right, middle, left)) achieved a PUE outcome in the *Good* category. Participant B bottom (right, middle, left) achieved a PUE outcome in the *Limited* category. Right, Middle, and Left slices depict the axial, coronal, and sagittal slices, respectively. Both individuals had similar whole CST lesion overlap (A = 9.51%, B = 11.97%) but participant A had higher relative contribution of M1 CST lesion overlap (A M1 overlap = 18.87%, participant B M1 overlap = 1.94%).

4.3.3 CART Analyses

When only MRI-derived metrics were made available for an exploratory CART analysis, it yielded a decision tree selecting SMATT PMd tract overlap < 15% and SMATT PMv tract overlap ≤ 15% to classify patients. The resulting decision tree was 79.4% accurate when decision tree predictions were tested against the outcome cluster classification (correct classification for 27 of 34 patients) (**Figure** 4.5**a**). SMATT PMd tract overlap < 15% distinguished those in the *Poor* outcome group from *Limited* or *Good* outcome groups with 80% accuracy (4 of the 5 *Poor* PUE outcome predictions were true). The largest error was introduced when distinguishing *Limited* from *Good* outcome groups where PMv overlap ≤ 15% only did so accurately for half those in the *Limited* outcome group. Most inaccurate predictions were higher than the achieved outcome (i.e., 5 individuals predicted to be in the *Good* outcome group achieved an E-ARAT within the *Limited* outcome score range). However, 1 individual predicted to be in the *Poor* outcome group achieved an E-ARAT within the *Limited* outcome score range and 1 individual predicted to be in the *Limited* outcome group achieved an E-ARAT within the *Good* outcome score range. The resulting decision tree was 75% accurate in outcome group prediction for those with ischemic stroke (18 of 24 patients with ischemic strokes were correctly classified) and 90% accurate in outcome group prediction for those with hemorrhagic stroke (9 of 10 patients with any hemorrhagic involvement were correctly classified). See **Figure** 4.5**a** for further statistics on predictive values, sensitivity, and specificity.

When all clinical and MRI metrics were made available to the CART analysis as potential predictors of PUE outcome, it yielded a decision tree selecting AR E-SAFE, patient age, and SMATT CST overlap to classify patients with 88.2% accuracy (correct classification for 30 of 34 patients) (**Figure** 4.5**b**). For those with AR E-SAFE < 4, all of whom had ischemic strokes, SMATT CST lesion overlap > 18% delineated *Poor* from *Limited* outcome groups with 90.0% accuracy (correct classification for 9 of 10 patients). However, similar error as in (**a)** was introduced for those with higher strength at admission to AR (AR E-SAFE > 4) where patient age > 75 years was selected to differentiate *Good* from *Limited* outcome groups but only did so accurately for half those in the *Limited* outcome group. All inaccurate predictions were higher than the achieved outcome (i.e., 3 individuals predicted to be in the *Good* outcome group achieved an E-ARAT within the *Limited* outcome score range; 1 individual predicted to be in the *Limited* outcome group achieved an E-ARAT within the *Poor* outcome score range). The resulting decision tree was 91% accurate in outcome group prediction for those with ischemic stroke (22 of 24 patients with ischemic strokes were correctly classified) and 80% accurate in outcome group prediction for those with hemorrhagic stroke (8 of 10 patients with any hemorrhagic involvement were correctly classified). See **Figure** 4.5**b** for further statistics on predictive values, sensitivity, and specificity.

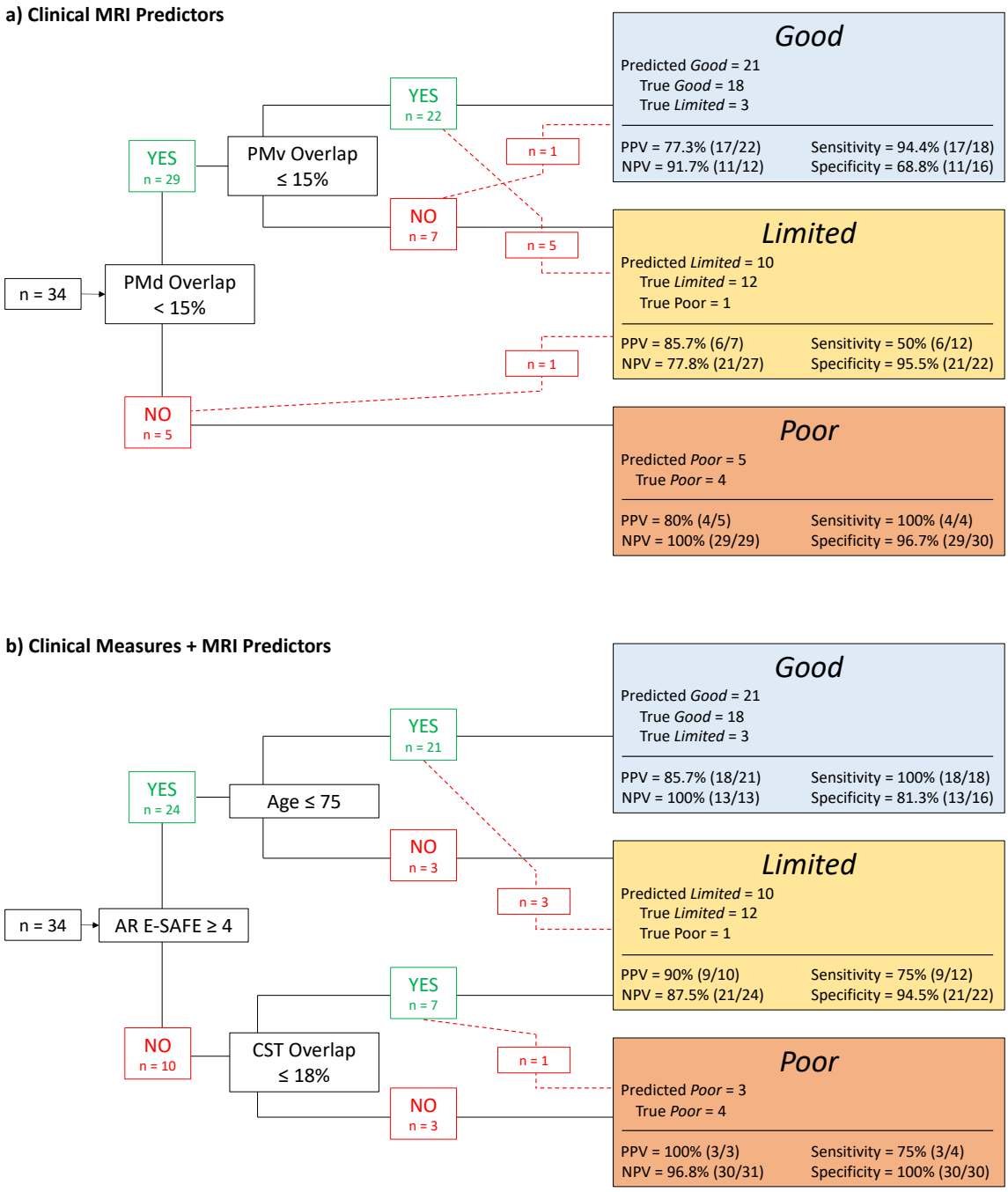

Figure 4.5 - Clinical MRI-based metrics of acute post-stroke CST status identified recovery outcome category in patients undergoing AR. a) PMd and PMv tract overlap predicts PUE outcome category with 79% accuracy. b) AR E-SAFE, patient age, and CST lesion overlap % predicts PUE outcome category with 88% accuracy.

4.4 Discussion

Current study findings revealed that clinical MRI-derived CST lesion overlap was associated with PUE motor outcome post-stroke and that cortical projections within the CST, beyond those emanating from M1, were able to distinguish between PUE motor outcome groups. Further, results suggest that exploratory predictive models using clinical MRI metrics, either alone or in combination with clinical measures, can accurately identify recovery outcome category for patients during both the acute and early subacute phases of post-stroke recovery that underwent AR post-stroke.

4.4.1 Clinically-Derived Lesion Overlap of CST were Associated with Recovery of PUE Motor Function

Clinically-derived lesion overlap percentages for both the entire CST and specifically for the PMv CST contribution emerged as metrics with significant associations to PUE outcome at 90 days post-stroke. This observation is in agreement with previous studies employing higher-resolution MRI that showed functional PUE outcome was correlated with extent of injury to both M1[95] and non-M1 tracts,[29,50,95,162] suggesting that lower-resolution clinical scans may provide imaging-based information with prognostic utility for PUE motor outcome post-stroke. Our results indicate there may be advantages to evaluating the structural status of tracts outside of M1 CST and are in agreement with those from a recent study wherein connectivity between M1, premotor, supplementary motor and parietal areas was necessary for more robust PUE recovery post-stroke and was particularly important for those with greater motor impairment.[151] Also in keeping with findings from previous studies,[50,95] lesion volume was not significantly associated with PUE outcome

suggesting lesion location may be a more important factor contributing to PUE motor function than total lesion volume.

Current findings suggest that PUE functional outcome level is likely to be higher when there is a smaller extent of CST injury, in particular when PMv descending CST injury is minimal. The PMv has been implicated in proper anticipatory shaping of the hand for grasping actions in both non-human primates and humans and several subtests of the ARAT require grasping an object to complete the task.[30,163,164] Further, studies in non-human primates have shown that CST projections from PMv differentially terminate in upper cervical segments to potentially provide a unique contribution to control of the head, neck, and/or shoulder musculature necessary for reaching tasks.[27,30] Additionally, intracortical stimulation of the area within PMv with the densest direct connectivity to upper cervical segments elicited movement in the thumb and fingers.[27,30] Thus, stroke-related disruption of these direct PMv CST projections may underlie specific deficits resulting in poorer execution of functional reaching and grasping tasks that affect PUE recovery outcome level.

Our results underscore the relevance of contributions to the CST from cortical motor areas beyond M1, though most differences elucidated by individual contributing tracts in our study were between the highest- and lowest-functioning outcome groups. However, closer inspection of group differences in CST lesion overlap revealed that with the exception of one patient, individuals with greater than 20% disruption to PMd had a *Poor* outcome. These findings are in concert with another recent study wherein PMd lesion load was found to be the most robust neuroimaging predictor of 6-month PUE motor impairment.[29] Authors from that study posited that the significant influence of PMd projections on motor

recovery post-stroke may be due to the similar relative size of CST projections from M1 and PMd and their similar activation during complex motor tasks.[29]

PMd is commonly thought to be a motor planning center because of its known contributions to cognitive aspects such as spatial attention and working memory and its many projections to M1.[30,32] PMd receives inputs from supplementary motor areas as well as parietal and prefrontal cortices, likely illustrating some role in integration and planning prior to motor execution.[30] However PMd also acts to control the execution of movement and contributes to descending motor signals both indirectly via its connections with M1 and directly through its CST projections.[30,32] In non-human primates, PMd CST projections have been shown to terminate on propriospinal interneurons[24] and subsequent studies showed that a majority of PMd neurons exhibited activity tuned to both target location and arm use during planning periods for reach and grasp actions.[30,38,165] PMd connectivity with propriospinal interneurons may therefore be an anatomic basis enabling the sensorimotor integration necessary for proper motor planning during reaching movements. Though the termination site of these direct projections are less clear in humans, animal literature has shown that direct projections from PMd to the spinal cord terminate not only on propriospinal interneurons but also descending subcortical motor networks and in the region of α motoneurons, implying a more complex modulatory role in motor execution, one that has a major impact on motor performance.[30,38,165]

In a previous study,[84] a single participant achieved minimal actual recovery of PUE motor function though the predicted outcome by an earlier iteration of PREP was expected to be notable (equivalent of a Good outcome in later studies). This individual displayed acute weakness (SAFE < 5) but was MEP+ during TMS assessment of M1 CST functional

integrity.[84] The authors speculated that part of the rationale for the overestimation of PUE outcome was due to "isolated and complete" damage to the premotor cortex which would not have been detectible using M1 CST based lesion analysis nor TMS assessment targeting M1.[84] Our findings support the notion that disruption to non-M1 motor areas may influence post-stroke recovery, particularly in patients with more profound PUE impairment, and highlight the potential utility of further investigating projections within the CST beyond those from M1.

4.4.2 Clinical MRI-Based Metrics of Acute Post-Stroke CST Status Identified Recovery Outcome Category in Patients Undergoing AR

Clinical MRI-derived CST lesion overlap may offer an earlier indication of PUE outcome (as early as 24h post-stroke) than previously established clinical measures of PUE strength.[152] Despite previous work using clinical MRI showing that M1 CST bore the strongest association with PUE outcomes,[52] here we demonstrated that lesion overlap in non-M1 CST contributors (PMd and PMv tracts) were able to distinguish PUE outcome groups and did so with similar predictive accuracy for both ischemic and hemorrhagic stroke. When considering the clinical utility of outcome predictors, accurate assessments available during acute hospitalization may be preferable for early clinical decision making to optimize resource management. In the timeframe of acute hospitalization, our findings indicated that non-M1 projections within the CST offered the strongest predictor of PUE outcome suggesting that prospective evaluation of clinical MRI-based CST metrics is

warranted to determine if lesion involvement in M1 and/or non-M1 cortical projections is predictive of PUE recovery.

CST lesion overlap improved predictions using clinical metrics alone. In our cohort, PUE outcome predictions made using a combination of clinical measures and MRI biomarkers (AR E-SAFE, patient age, CST lesion load) showed improved PUE outcome prediction accuracy over use of either clinical metrics or MRI metrics alone. Our findings are in close agreement with a recent study that found that the combination of initial PUE impairment, patient age, and PMd CST structural integrity was a strong predictor of 6-month PUE impairment.[29] The current findings are in line with previous findings showing: 1) PUE strength is a gross measure of baseline impairment that provides a general indication of the capacity to generate force required for functional task performance; 2) both initial impairment and patient age are predictors of functional motor outcome;[140–143] 3) CST structural integrity provides insight into the underlying neural resources available for spontaneous biological recovery and experience-dependent plasticity in addition to more specific information regarding resources for sensorimotor control, motor planning, sequencing, and execution.[141,143] Quantifying CST structural integrity post-stroke may be particularly important for those with initially-lower levels of volitional control as the resolution of early strength deficits is likely to be significantly influenced by CST tract status.[61,79,84,153] Lesions localized within the CST are frequently associated with more severe, persistent loss of PUE motor function than lesions in other sites suggesting that certain areas of the brain and/or neuronal cell constituents may be more amenable to spontaneous biological recovery and/or plastic reorganization after stroke.[14,50–54] Disruption of CST from non-M1 cortical contributors may cause a loss of unique

modulatory function carried out by those descending fibers rather than a total loss of premotor cortical function, as these areas also project directly to M1. However, there is not yet a functional parcellation distinguishing contributions of descending vs. M1 projections of the PM to motor control. Therefore, structural biomarkers that quantify disruption to M1 and non-M1 CST projections may offer the specificity necessary to differentiate PUE functional recovery outcome categories however, they do not yet allow us the specificity to predict loss of specific domains of motor planning, execution, or refinement. Additional studies are needed to further characterize potential tract-based biomarkers of domain-specific motor recovery.

4.4.3 Limitations

Our retrospective study design has strengths and limitations. An advantage of the retrospective study design is that it allowed for critical appraisal of current standards of clinical care and recovery outcomes within the study cohort, thus our dataset may more accurately represent the true recovery experience for patients post-stroke. However, the retrospective design also required estimation of measurements including E-ARAT performance, the primary outcome measure in our study. Although estimation may introduce some measurement error to current findings, we previously showed good inter-rater reliability for the estimation approach suggesting results were not subjected to systematic bias. It was also not possible to control for differences in the content of therapy provided at each stage of post-stroke care which may limit generalizability in comparison

with previous studies. However, individuals received therapy in the same rehabilitation setting and should have received a similar dosage and type of therapeutic intervention.

Lower-resolution clinical MRI data processing can introduce error during the normalization process as co-registration to a high-resolution standard template may result in imprecise alignment with neuroanatomic structures and diminished accuracy of lesion boundary localization. The template image and tract atlas[52] used for normalization in our study was derived from scans of 152 young, healthy individuals (mean age = 25 years) which may be less analogous to our cohort of individuals (mean age = 62 years) than an age-matched template due to known age-related changes.[166,167]

We adopted a conservative threshold for statistical significance, which may have increased the likelihood of type 2 error given the size of the study cohort. Therefore, we also chose to report non-significant trends in the results. In seeking a clear MRI metric that differentiates between *Limited* and *Poor* outcomes, further prospective research with a larger cohort size may be warranted. Lastly, though our exploratory CART analysis yielded decision trees that accurately predicted outcome for between 79-88% of individuals, the small sample size and category distribution may have led to overfitting of the model. It is also important to note that the substantial improvement in prediction accuracy seen over use of clinical measures alone[152] may be due, in part, to the increase in maximum tree depth from 1 level to 2 levels. Prediction improvement specifically attributable to the addition of CST lesion load is due to the differentiation of *Limited* from *Poor* outcome groups for those with AR E-SAFE < 4, which improves decision tree accuracy by properly identifying *Poor* PUE outcome for 3 individuals previously predicted to have a *Limited* outcome. Further

investigation and validation using a larger sample size will be necessary to confirm the preliminary study findings.

4.5 Conclusions

The current findings support the notion that clinical information routinely collected after stroke in conjunction with clinical MRI derived biomarkers of CST integrity are associated with level of recovery of PUE function. Prospective studies are suggested to determine the predictive utility of including clinical imaging-based biomarkers of white matter tract structural integrity in predictive models of post-stroke recovery. In an era of precision medicine, biologically-informed algorithms that accurately predict recovery outcome may allow for improved care plan development, patient management, and optimized allocation of rehabilitation resources.

CHAPTER 5. DISCUSSION

5.1 Project Summary

Early, accurate prediction of recovery of motor function post-stroke would enable precision-based rehabilitation strategies to improve outcomes and reduce disability. Existing tools to predict recovery of motor function have yet to be tested in the US healthcare system.[79] Therefore, the purpose of this dissertation was to evaluate external validation feasibility of PREP2 in US healthcare systems and to determine the utility of readily implementable clinical measures and structural CST biomarkers to predict PUE functional outcomes in individuals post-stroke. The previous chapters demonstrated the feasibility of conducting external validation studies of the PREP2 prediction tool[100] in US healthcare systems with strict fidelity to the original metrics and timelines. In addition, the predictive utility of both the SAFE score and of biomarkers of CST structural integrity isolated from clinical neuroimaging was demonstrated using data comprised solely of current standard-of-care practices.

In Chapter 1, I provided background on the significance of stroke as a major public health concern due to its prevalence, cost, and long-term impact on upper extremity motor function, a primary determinant of independence and quality of life for stroke survivors.[3,8,13,15,57–59] I provided a brief overview of the pertinent anatomy and physiology of the motor system and discussed physiologic mechanisms for both spontaneous biologic recovery and experience-dependent plasticity in sensorimotor regions, highlighting the time sensitivity for rehabilitative efforts post-stroke and emphasizing the need for clinically accessible tools to accurately predict recovery of motor function.[14,36,55,70] I reviewed the

well-evidenced PREP2 prediction tool which has yet to be externally validated in the US healthcare system.[100] I discussed relevant differences between NZ and US healthcare systems which may act as a barrier to future studies seeking to implement PREP2 metrics in the US and reviewed evidence for alternative biomarkers of CST integrity that may be more readily implemented in the US healthcare system.[3,52,98,109,110] Finally, I provided scientific rationale informing both the dissertation aims and proposed hypotheses.

Chapter 2 presented data to determine the feasibility of prospective validation of PREP2 in a US healthcare setting. We retrospectively reviewed all stroke admissions at EUH and GMH between FY 2016 – 2018, extracting metrics including demographic data, inpatient length of stay, PUE strength, NIHSS scores, and the timeline of measures made from institutional electronic medical record systems.

Based upon our findings, prospective validation of the PREP2 prediction tool in a US setting is feasible with little disruption to current care practices. Current stroke management allows for SAFE score to be obtained at therapy evaluations and for NIHSS to be extracted from the patient chart. Further, on average, patients appropriate for TMS assessment remain in the acute care hospital setting at a time when CST function should be evaluated for PREP2 validation.[100] However, objective measurement of predictors of upper extremity outcomes were infrequent, TMS is not part of standard care in the US, current care practices do not allow for day-90 follow-up to evaluate the accuracy of PREP2 predictions, and clinician resistance to change will need to be formally addressed to ensure successful implementation of biologically-informed prediction tools. If PREP2 is prospectively validated in a US setting, then a principled implementation strategy will be needed.

In Chapter 3, we investigated current care practices to determine the routinely collected clinical measures that are most predictive of PUE functional outcome post-stroke in patients undergoing AR. In this chapter, we assessed patients who received care in the EUH system post-stroke via longitudinal chart review. Serial assessments of PUE strength were estimated using available shoulder abduction and finger extension manual muscle test documentation (E-SAFE). E-ARAT was used to quantify 3-month PUE functional outcome.

Study findings revealed that PUE E-SAFE, measured both acutely and at AR admission, is associated with PUE motor recovery outcome. The cluster analysis produced three distinct outcome groups which aligned closely with previously identified outcome categories[100] and outcome groups significantly differed in Acute E-SAFE and AR E-SAFE. Notably, exploratory predictive models using AR E-SAFE alone were able to identify *Good* from *Limited* or *Poor* recovery outcome categories in patients undergoing AR, classifying patient outcome with 70.6% accuracy. However, standard clinical metrics were unable to differentiate between *Limited* and *Poor* outcomes.

Chapter 4 examined associations between clinical MRI-based metrics of CST structural integrity and PUE motor recovery in the same cohort of patients evaluated in Chapter 3. Clinically diagnostic MRI was used to create lesion masks which were then spatially normalized into standard MNI space.[155–157,159] The normalized lesion mask was processed through custom software to obtain CST lesion overlap using an atlas that delineates contributions to the CST emanating from six cortical seed regions.[159] This enabled assessment of how lesion presence in both M1 and non-M1 CST projections relates to post-stroke PUE motor outcomes.

Study findings revealed that clinical MRI-derived CST lesion overlap is associated with PUE motor outcome post-stroke and that cortical projections within the CST, in particular those emanating from non-M1 cortical areas, can distinguish between PUE motor outcome groups, though they did not statistically differentiate between *Limited* and *Poor* outcome groups, as was hypothesized. Further, exploratory predictive models using clinical MRI metrics, either alone or in combination with clinical measures, were able to accurately identify recovery outcome category for patients during both the acute and early subacute phases of post-stroke recovery.

Taken together, our results suggest that **(1)** prospective PREP2 validation studies are feasible and warranted in a US healthcare setting**, (2)** SAFE is an easy-to-acquire, readily implementable screening metric with high clinical utility for patients who undergo AR post-stroke, and **(3)** clinical MRI-derived biomarkers of both M1 and non-M1 contributions to CST integrity may offer unique insight into PUE motor outcome potential. Though promising, further investigation and prospective validation using a larger patient cohort in multi-center trials will be necessary to confirm these preliminary study findings.

5.2 Generalizing Results

While a prospective evaluation of PREP2 metrics was initially planned, the project shifted to a retrospective design due to the research restrictions resulting from the COVID-19 global pandemic. The retrospective design created new opportunities for unique evaluation of current standards of clinical care within the study cohort, thus yielding a dataset that may be a more accurate representation of the recovery experience of individuals post-stroke than would be assessed in a prospective study. Evaluation of current standards of care also enabled a focus on clinically-feasible measures. These measures may be implemented with minimal disruption to care practices and could therefore enable a higher likelihood of clinical adoption, maximizing the utility and generalizability of our findings. However, the retrospective design, study parameters, concentration on patients who underwent care in an AR setting post-stroke, and focus on CST-mediated motor control also limits generalizability in additional important ways: 1) the CST is not the only motor pathway controlling the upper extremities; 2) our predictions are confined to PUE motor recovery and we are specifically limited in our ability to predict recovery of lower extremity function; 3) our findings don't include patients that experienced an *Excellent* outcome; 4) differentiation between *Limited* and *Poor* recovery outcome groups using structural CST is inconclusive; and 5) practice standards may have evolved since the end of fiscal year 2018.

5.2.1 The CST is Not the Only Motor Pathway

As discussed briefly in Chapter 1, the CST may be the most direct and largest contributor to skilled hand movement, but it is not the only descending pathway which exerts control on voluntary movement of the upper extremity.[22,45]

The CST's direct connectivity with α motoneurons has been suggested to underlie independent finger motion and increased dexterity as these direct connections seem to exist only in certain primates and humans.[24,33,38,40] In contrast, animals demonstrating disynaptic connections from cortical motor areas to α motoneurons through spinal interneurons or subcortical descending motor systems tend to demonstrate motor control of the extremities with limited ability to differentiate motion at the digits.[33] Direct cortical connections to α motoneurons are proposed to widen the potential degrees of freedom available for movement of the extremities, increasing the potential for differentiated motion, therefore enabling improved dexterity.[33] However, brainstem motor pathways are also known to play a large role in the control of movement and may allow for partial recovery of upper extremity motor function after stroke.[23,41–43,46,47]

In their seminal 1968 papers, Lawrence and Kuypers investigated disruption to both cortical and subcortical descending pathways on the motor function in macaques. They demonstrated that upper extremity movement is not exclusively controlled by CST signaling pathways, though it does seem responsible for fine motor control of the upper limbs, and further, that the rubrospinal pathway plays an important role in independent upper extremity use during reach and grasp tasks.[41–43] If subcortical pathways in humans contribute similarly to the control and recovery of upper extremity movement post-stroke,

it may partially explain findings from this study wherein individuals with strokes localized in the pons demonstrated poorer PUE recovery outcomes (all 3 patients with pontine stroke had an E-ARAT score ≤ 20, corresponding to *Limited* and *Poor* outcome groups). This may be logical as strokes at or below the level of brainstem would impact both cortical and subcortical descending motor pathways and would therefore be more likely to result in greater long-term motor dysfunction. Moreover, stroke-induced disruption to descending projections from cortical motor areas may affect function both through the loss of more direct CST projections to the SC and through disruption of inputs to brainstem motor pathways.

The distribution of projections from primary, premotor, and supplementary motor cortices to brainstem motor pathways may also play a role in the post-stroke recovery of voluntary movement of the upper extremity. Work in non-human primates has shown that primary and premotor cortical regions differ in their corticobulbar projections, both in density and in termination laterality.[168] Projections originating in M1 tended to be less dense and to terminate on the contralateral reticulospinal tract whereas projections originating in premotor areas were more dense and primarily terminated on ipsilateral reticulospinal pathways.[168] While corticobulbar projection pathways and the distinct roles of subcortical tracts are not as clearly defined in humans, more precise identification of tracts disrupted by the stroke lesion may also help improve prediction of specific elements of PUE motor return.

Human tractography studies have begun to evaluate the relationship between upper extremity motor impairment and changes in subcortical descending pathways with conflicting results.[169–172] While increased metrics of tract integrity in the ipsilesional

rubrospinal pathway was associated with better PUE motor recovery for those with initially mild to moderate impairment, individuals with chronic stroke showed similar metrics of tract integrity to be inversely related to more severe hand impairment.[170,172] Specifically, higher values of tract integrity in ipsilesional rubrospinal and contralesional reticulospinal tracts have been shown in those with the most severe, chronic post-stroke hand impairment.[170,171] Though these results are somewhat contradictory, they do support the notion that upregulation of subcortical descending networks play a role in stroke recovery when descending control from the CST is compromised.

When contextualized by primate studies which suggest that subcortical pathways provide less selective movement control while the CST enables more fractionated control of the extremity, we may imagine that post-stroke impairment outcomes are likely related to the relative preservation of both cortical and subcortical descending motor networks. Therefore, the inclusion of MRI metrics that quantify the structural integrity of subcortical motor networks in addition to the CST may increase the generalizability of these findings but also allow for improved precision in prediction of post-stroke PUE motor outcomes.

5.2.2 Outcome Predictions are Limited to PUE Motor Function

It is important to note that the recovery outcomes predicted in this work are limited to PUE motor function and do not refer to a more expansive definition of systems-wide recovery. Further, our definition of PUE outcome is based upon scoring of a single measure which assesses motor function, the ARAT.[113] The ARAT measures capacity for function which provides limited in insight into real world ability. Thus, we must be cautious to assume that

the measures we assessed would predict more or less disability post-stroke as we did not measure disability or independence in ADLs directly. Though we assessed an array of clinical information to evaluate the potential effects of non-motor variables on PUE motor recovery, our data does not allow for assessment of broader sensorimotor outcome and, in particular, we are unable to elucidate functional motor outcomes of the lower extremity.

In this dissertation, early sit-to-stand and ambulation status, measured using the IRF-PAI, showed no significant association with either E-SAFE scores or E-ARAT, nor did we find correlations between these measures of lower extremity function with either lesion volume or CST lesion load metrics. However, we did not measure lower extremity functional recovery at 90 days post-stroke, so are unable to make firm conclusions regarding the relationships between paretic lower extremity (PLE) functional motor outcome and measures of upper extremity impairment, function, or metrics of CST integrity.

5.2.3 Findings Don't Include Patients that Experienced an Excellent Outcome

Our cohort in Aims 2 and 3 is limited to individuals who underwent care in an AR setting and as such, is limited to *Good, Limited* and *Poor* PUE outcomes. It was initially surprising that only one individual admitted to AR would have been classified by the PREP2 decision tool as having an *Excellent* recovery outcome (E-ARAT ≥50) as we expected that the potential for an *Excellent* outcome exists for individuals discharged to AR if they receive a higher dose of individualized therapy early post-stroke.[84,100] This may be due to study selection criteria which limited our cohort to those requiring therapeutic intervention in an AR setting as it is possible that most individuals who would be predicted to have an

Excellent PUE outcome are discharged to home from acute hospitalization rather than to AR due to lower levels of initial PUE impairment or early resolution of PUE impairment. Results from Aims 2 and 3 should therefore be applied cautiously to individuals who may be may be predicted early during stroke recovery to have an *Excellent* PUE outcome, as they may lack generalizability for that outcome category. Further, prediction tools applied in the AR stage may only be applicable to patients that achieve a less than *Excellent* PUE motor function recovery outcome.

5.2.4 Differentiation Between Limited and Poor Outcome Groups Using Structural CST is Inconclusive

Results from this dissertation do not conclusively demonstrate that either clinical measures or clinical imaging biomarkers of CST integrity can clearly distinguish between patients expected to have *Limited* and *Poor* recovery outcomes. While the data suggest that a combination of these neuroimaging biomarkers and clinical measures may provide the most accurate prediction of outcome, it will require prospective investigation with larger sample sizes and equal distribution of individuals in outcome groups, including those with an *Excellent* outcome. There may also be an opportunity to expand neuroimaging analyses to allow for differentiation of these most severely impaired individuals through study of compensatory reorganization by surviving networks.

5.2.5 Practice Standards May Have Evolved Since the Timeframe Studied

The time period assessed (fiscal years 2016-2018) was chosen at the start of the project (late 2017). It was intended to pertain only to Aim 1 methodology, as Aims 2 and 3 were originally planned as prospective studies, and was meant to encompass a time period sufficient to comprehensively assess standard care practices at the time. It is possible that practice standards may have changed somewhat in the intervening time period (September 1, 2018 – present) including possible Covid-19 pandemic-specific shifts in practice. One known change was the implementation in June 2019 of NIHSS measurement at EUH upon each shift change for the duration of acute hospital stay. While this specific change in practice is in fact favorable for PREP2 validation study feasibility, there may be others that could limit the generalizability of our findings to some extent. Thus, conclusions drawn should be interpreted within the context of clinical care practices specific to individual hospital and rehabilitation facilities.

5.3 Potential Implementation Barriers

Validation, implementation, and impact evaluation of prediction tools have the potential to enhance care standards and enable higher value care for patients after stroke in the US healthcare system. Taken together, the results described above demonstrate the promise of predictive tools and that it is possible to conduct validation studies in clinical care settings in the US practices however, several barriers to successful implementation were identified that warrant further consideration.

5.3.1 Lack of Access to TMS in Most US Healthcare Settings

TMS isn't currently available at most hospitals in the US. TMS units are costly ($20,000-$30,000 per unit) and require training for clinicians prior to use. Further, TMS assessment is not currently a reimbursable service, thus time spent on TMS evaluation would not be fiscally productive for the hospital. However, it is important to remember that results from NZ demonstrated that implementation of the PREP2 prediction tool in clinical practice resulted in reduced lengths of inpatient hospitalization by approximately 1-week with equivalent long-term PUE motor outcomes.[104] In the context of Medicare's diagnosis-related group (DRG) reimbursement structure, wherein hospitals are paid a predetermined fee per hospitalization regardless of the costs associated with care, hospitals are continually incentivized to increase their operating efficiency.[11] The cost of TMS units may therefore be absorbed by the cost savings to the hospital. In light of this potential, a clear cost-benefit analysis should also be assessed in validation and implementation studies in the US in order to increase the likelihood of support from hospital leadership.

Therapists may be the most likely providers to perform TMS in a clinical setting given that the results from outcome prediction tools are directly relevant to therapeutic planning. Furthermore, therapists generally perform comprehensive evaluations, including special tests, to inform their differential diagnoses and treatment strategies. However, TMS is not currently taught as part of curricula for either physical therapy or occupational therapy programs in the US. Those conducting validation studies may want to propose the addition of training in advanced technologies (i.e., TMS and MRI) that index the functional and structural integrity of the CST and have been shown to be powerful predictors of outcome.[52,84,95,100] Adding TMS as an evaluative modality to training program curricula in

the future may enable more rapid and wide-spread adoption of this technology and would offer clinicians an additional tool to improve patient assessment.

5.3.2 Robust Systems of Information Transfer Between Healthcare Settings are Needed

Another important implementation consideration is how to best facilitate transfer of predictive information from one clinical setting to another so that clinicians may use it effectively. The fractured nature of the US healthcare system is an impediment to implementation of predictive tools as medical records containing detailed therapy notes are often not shared between healthcare settings. Therapists in outpatient settings are rarely privy to acute hospitalization records after stroke; even therapists in inpatient rehabilitation settings may not receive a full reporting of therapeutic evaluation and interventions in the acute setting. However, practical use of prediction tools requires the transfer of this information and will necessitate better communication between providers in different settings. In lieu of a universal electronic medical record in the US, this may be more immediately remedied by ensuring that administrative transfer of patient information between healthcare facilities includes comprehensive therapeutic records rather than a single statement regarding functional patient status at the time of transfer or discharge.

5.3.3 Objective Measurement of Impairment Needs Improvement

Objective measurement and documentation of predictors of upper extremity outcomes were rare in our cohort. In the study cohort in Aim 1, measurement and documentation of

SA and FE manual muscle tests were completed ~1% of the time by therapy providers in the acute hospital setting. In the cohort from Aims 2 and 3, we observed that only 7% of provider evaluations across the spectrum of post-stroke recovery collected objective SAFE measurements. It should be noted that the predictive merit of SA and FE manual muscle tests have been documented in the literature for over 10 years however, according to our findings this has not translated to use in clinical practice.[99,127,173] Instead of quantitative measurement of specific muscle weakness, qualitative terminology such as "within functional limits" or "within normal limits" was often used to document strength, function, or progress. These terms are imprecise and unclear for other providers (and for third-party payers) limiting the utility of therapeutic assessments and the ability to precisely track patient recovery over time. If PREP2, SAFE scores, or any other assessment of PUE strength are to be validated and implemented into routine clinical care in a US setting, a structured training strategy should be considered to ensure standardized measurement and documentation.[122,144]

5.3.4 Resistance to Change in Clinical Practice Must be Addressed

If prospective studies are successful in replicating earlier findings and validating the use of predictive measures in clinical practice in the US, implementation studies must then be conducted to assess the logistics of putting such prediction tools to use. While ramping up for prospective evaluations of PREP2 metrics pre-pandemic, I had the opportunity to present this work to therapists in a variety of healthcare settings. Though there were individual providers excited by the promise of implementing new evidence into clinical practice, the majority expressed some amount of resistance to new care paradigms. In the healthcare sector, one which sees an ever quickening pace of new science, provider

responses have important bearing on the translation of evidence-based practices.[174] Further, resistance to change does not define a single category of attitude and may be better thought of as a spectrum from aggressive resistance to commitment.[174,175] This resistance is highly nuanced and highlights the clear need for future research to include cross discipline collaboration with implementation scientists and change management professionals as behavioral modification in clinical practice may prove to be a more significant obstacle than anticipated. Experts in behavioral change may exploit strategies to increase clinical staff engagement, to create protocols shaped by stakeholder input, and to inspire clinical adoption of new tools, all of which will be critical to establish evidence-based predictive tools in contemporary clinical practice.[174]

5.4 Tailoring Therapy to the Individual is a Physiologic Necessity

5.4.1 Post-stroke Therapeutic Intervention is Ripe for Precision-Therapy Enabling Tools

Our findings from Aims 2 and 3 suggest that patients who undergo AR post-stroke demonstrate heterogeneous levels of impairment and functional outcomes. Tailoring therapeutic intervention to expected motor outcome is a common theme in neurorehabilitation, yet there remains a major opportunity to increase the personalization of treatment strategies. The use of clinical measures to guide therapeutic intervention is common practice in spinal cord injury rehabilitation, however stroke rehabilitation lacks similar metrics and guidelines.

Greater prognostic specificity may allow for prescription of optimal therapeutic paradigms, ones that allow therapists to differentiate therapeutic interventions and goals based upon the expectation of motor recovery or motor compensation as the likely patient outcome.[81] During this important stage of post-stroke recovery however, therapists don't differentiate goals based upon expected independence due to restoration of normal movement patterns (functional recovery) vs. independence due to use of alternative limbs or muscle activation patterns (functional compensation).[81] To be clear, therapy documentation in our studies did contain information about compensatory movement when present, but whether there was an expectation of compensatory pattern resolution was notably absent from clinical notes. This is in keeping with the lack of evidence suggesting that rehabilitation therapists are able to predict motor recovery outcomes using common clinical assessments[63,82] but may be logical when we recall that acute clinical measurement of paretic extremity strength lacks the specificity to differentiate damage to motor areas from damage to distant brain tissues.[20–22]

This lack of specificity has significant implications for clinical practice. As an incidental finding during qualitative review of therapy documentation for SAFE score estimation and E-ARAT scoring, we found that nearly 75% of individuals in our study cohort with *Limited* or *Poor* outcomes (ARAT $\leq$ 34) received treatment wherein therapeutic goals and activities targeted improvement of individuated finger motion. However, this may have limited effectiveness as there is little evidence to suggest that these individuals have the capacity to regain fine motor dexterity.[84,100,104,176] This is a real-world example of where the use of outcome prediction tools may serve to improve both the personalization of therapy and the recovery trajectory for individuals post-stroke.

A recent study evaluating the effect of timing of an additional intensive bout of PUE training found that most functional improvement plateaued around 6-months post-stroke and confirmed that the vast majority of gains were made within the first 90-days.[34,62–64,177] The additional delivery of intensive task-specific training consisted of a "standardized, yet highly individualized, shaping protocol" based in task-specific training in ADLs and leisure activities.[177] When the additional therapy was conducted during the first 3 months post-stroke (at a time coinciding with AR and outpatient therapy in our cohort for Aims 2 and 3) participants improved significantly more than controls[177] indicating that this highly individualized therapy, when given at earlier timepoints, may improve the functional recovery trajectory for individuals post-stroke.

5.4.2 Outcome Prediction does not Imply a Reduction in Therapy or Worse Patient Outcomes

One of the most common concerns encountered when presenting the objectives of this study to rehabilitation providers was an immediate assumption that prediction of outcomes would be used to limit access to therapy by third party payers. This response may not be surprising as therapists in the US have just been dealt a nine percent reduction in reimbursement from the Centers for Medicare and Medicaid Services (CMS)[178] and insurers are incentivized to limit therapy as a cost containing measure. But the quantification of patient progress and improved clarity in documentation does not have to equate with less therapy for the patient (or a resultant worse outcome).

Poor PUE motor recovery prognosis based upon known physiologic disruption should not prevent a stroke survivor from regaining independence or returning to community participation, nor should it preclude them from receiving quality rehabilitation services. Dedicated training in compensatory techniques, increased use of the unaffected extremity, and education in equipment management may be more effective strategies to employ for those with predicted *Limited* or *Poor* outcomes in order to recover independence earlier, reduce the overall burden of care, and improve the quality of life for stroke survivors and their care partners. This will require a dissemination strategy that identifies the primary knowledge brokers for clinicians (i.e., training program faculty, senior therapists, clinical managers), engages with these key stakeholders to identify effective training opportunities, and ensures clear communication regarding the advantages of clinical precision in maximizing individual patient outcomes.

5.4.3 Predictive Metrics may be Useful in Guiding Care Along the Continuum of Recovery

The potential benefits of harnessing prognostic indicators for motor recovery outcomes are not limited to use in AR settings. Paired with our knowledge of neuroplasticity and motor learning, predictive tools may also improve recommendations for how to structure outpatient therapy in the context of limited insurance coverage. Therapists should weigh the potential benefits of frontloading outpatient therapy and prioritizing maximization of experience-dependent plasticity or recommending a more consistent therapeutic presence throughout the duration of patient need. Both strategies center on the goal to regain

independence and reduce disability, but become more nuanced according to patient need and care requirements.

Additionally, patients and their care partners are increasingly expecting transparency in healthcare. Outcome prediction may enable greater collaboration during the recovery process but thoughtful communication of predictive information will be required to ensure patients have a realistic sense of their recovery potential while maintaining their motivation to engage in rehabilitation post-stroke.[142] Further, neuroplastic change demands a magnitude of repetition which often cannot be fully achieved within the time constraints of therapy.[179–181] As patients and care partners develop greater ownership of the recovery process, it may allow for increased repetition of specific, salient tasks that are appropriate to the individual's probable recovery outcome.

5.5 Driving Value in US Healthcare Delivery

Systemically, the quantification of quality of care and of patient outcomes are not well defined, studied, or reported in stroke rehabilitation, which presents a major barrier to delivery of high-value care in the US. Increasingly, the patient, hospital, and payer are becoming more closely aligned in wanting to maximize efficiency in care while maintaining a high standard of patient outcomes. However, the therapist currently resides in a precarious position where they are financially incentivized to work less efficiently as more therapy equates to additional reimbursement. Thus, aligning reimbursement structure with care quality and patient outcomes may help drive the therapeutic profession toward high-value care delivery.

5.5.1 Reimbursement Structure Will Change the Way we Think About Therapy

It is becoming increasingly more common for physician reimbursement structures to be based on quality of care provided and successful patient outcomes.[182] However, rehabilitation professionals in the US healthcare system are reimbursed in a fee-for-service model based upon units of therapy provided, incentivizing quantity of care over quality and efficiency.[183] Standardized quality indicators such as the IRF-PAI are beginning to emerge in therapeutic practice; recall that the use of the IRF-PAI became mandated by CMS in 2019 as a measure of care quality and to determine service reimbursement in rehabilitation settings.[130] It is likely only a matter of time before value-based payment models become standard for therapeutic reimbursement and when that does happen, we may be left scrambling to define and measure therapeutic value.

If we can tease apart recovery due to intervention that uniquely enhances experience-dependent plasticity from spontaneous biological recovery occurring irrespective of therapy post-stroke, then we may begin to find definitively optimal therapeutic paradigms for our patients post-stroke. As a necessary first step toward the goal of quantifying our contribution in a patient's recovery process, we need to measure long-term outcomes.

5.5.2 Long-term Evaluation of Therapeutic Practice Standards is Needed in the US

In order to measure the current quality of care standards, we must understand the recovery outcome of our patients. Under the current US healthcare system however, early clinical decision makers are unable to evaluate the quality of care allocated or to assess evidenced

best practices in a clinical setting. Follow up of long-term patient outcomes (≥ 90 days) in the context of stroke rehabilitation is virtually nonexistent within the current, fractured US healthcare delivery model. This was highlighted in our cohort as < 3% of patients treated at EUH for acute stroke remained in the Emory system for rehabilitation for at least 90 days post-stroke. If we are to improve practice standards and clinical guidelines in stroke rehabilitation however, we must receive feedback about the long-term patient outcomes and critically assess whether current care strategies are optimal for promoting patient independence and quality of life.

5.6 Future Directions: Strategies to Maximize the Breadth and Depth of Translational Impact

5.6.1 Future Validation Studies

Findings from this in-depth retrospective data analysis will be critically important for future prospective application of valid, predictive tools for post-stroke motor recovery in the US healthcare system. In anticipation of an upcoming multi-center NIH StrokeNet trial (VERIFY) that aims to prospectively validate PREP2 as a prediction tool for upper limb outcomes after stroke, these data may serve to inform trial protocols.

Additionally, I want to emphasize the clear need for future research to include cross discipline collaboration with implementation scientists and experts in behavioral change. Change management in clinical practice may require expertise in navigating organizational

dynamics to ensure clinicians support and adopt evidence-based practices which serve to drive therapeutic professions forward.[174]

5.6.2 There is Still Room to Improve Prediction Accuracy

Though findings from this dissertation have added to our understanding of how to predict post-stroke motor recovery, there is still substantial work to be done in order to comprehensively understand the mechanisms of post-stroke recovery and further, how to harness those mechanisms to meaningfully improve individual patient outcomes.

Recovery of upper extremity motor function post-stroke is a multifaceted and dynamic process influenced by a wide range of physiological and psychological factors. Unsurprisingly, even the most well-evidenced prediction tools are inaccurate for approximately 25% of patients, meaning there are still opportunities to refine and improve these prediction tools with additional information. There remain several factors that may serve to provide a more comprehensive understanding of motor recovery post-stroke which were not investigated as part of this project. The influence of socio-economic status, psychosocial factors, patient comorbidities, genetic factors, impairment to non-motor domains, and disruption to sensorimotor integration networks may all play a role in motor outcomes post-stroke and require future investigation.[18] Further, analysis of factors contributing to lower extremity outcome may deepen our understanding of physiologic mechanisms of post-stroke recovery. Lastly, more expansive exploration and analysis of subcortical motor and sensory network biomarkers may enable increased precision of PUE outcome prediction for those with initially lower levels of PUE strength.

5.6.2.1 Socioeconomic and Psychosocial Factors

This project did not evaluate factors including healthcare access and health insurance status that may play a role in recovery outcomes. Socioeconomic factors as a determinant of health outcomes have been widely reported but outcomes are often defined by mortality, not functional independence or quality of life.[184,185] Psychosocial dynamics such as familial presence or caregiver support may also play a role in therapeutic engagement and post-stroke outcomes.[18,186] In addition, post-stroke depression is reported to affect up to a third of stroke survivors and is known to complicate the recovery process by diminishing quality of life and impeding engagement in rehabilitation.[187] Opportunities to evaluate these socioeconomic and psychosocial influences as potential cofactors for PUE motor outcomes post-stroke will further our understanding of environmental factors that affect recovery.

5.6.2.2 Comorbidities

We attempted to account for the influence of comorbidity load on PUE motor outcomes in our studies by evaluating the predictive utility of comorbidities, including the presence and severity of white matter disease, and through use of the Charlson comorbidity index (ISCCI).[129] Diabetes mellitus, severe periventricular white matter disease, and the ISCCI have all been shown to be negatively associated with post-stroke outcomes.[18,128,188,189] Though many patients in our cohort had complex health histories, all had low ISCCI scores, suggesting that the ISCCI may lack the ability to comprehensively index patient comorbidities relevant to post-stroke outcomes. Our analyses did not identify predictive utility in any comorbidity, though multiple disease processes logically effect recovery

outcomes for patients post-stroke. Therefore, additional studies are needed to evaluate the influence of different comorbidities on post-stroke motor recovery.

5.6.2.3 Genetic Factors

Genetic factors which control neural mechanisms underlying both spontaneous cellular repair and experience-dependent plasticity are likely responsible for some degree of the heterogeneity seen in post-stroke recovery.[190] Individuals with a greater capacity to remodel cortical connectivity may correspondingly have a higher likelihood for functional motor recovery. Biomarkers for variants in genes known to play a role in plasticity, motor learning, and memory retention, such as brain-derived neurotrophic factor (BDNF) and apolipoprotein E (Apo-E), may predict the potential for reparative post-stroke plasticity and influence both the efficacy of rehabilitation and motor outcomes.[18,190] Therefore, future studies should also seek to include genetic factors in predictive models as these endogenous factors may offer additional individual-specific information that can further refine specificity or improve accuracy of motor outcome predictions post-stroke.

5.6.2.4 Non-Motor Domains

It is understood that sensory, perceptual, and cognitive processes contribute to motor control and recovery but clinical measurements of these processes in clinical practice lack sensitivity and specificity. Though we evaluated documented impairment to the somatosensory, coordination, visual, language, and cognitive systems, we did so in a binary manner (impaired/not impaired). This was done out of necessity as documentation of impairment in these domains was often imprecise however, our binary coding sacrificed clear understanding of the nuanced impact that impairment to other, non-motor systems

might have on motor recovery. Therefore, future studies are needed to more comprehensively investigate the trajectory of non-motor system recovery post-stroke and the effects of sensory, perceptual, cognitive, or language impairment on post-stroke motor outcomes.

5.6.2.5 Influences of Sensorimotor Integration on Motor Outcomes

Successful, voluntary, functional movements, such as reach and grasp actions, necessitate the integration of motor and sensory information to plan, execute, and adjust motion during object manipulation. This requires the generation of an internal model of the body in space and an external model of the object and surrounding environment, both of which require tactile, proprioceptive, and visual sensory input to inform successful task execution.[191]

Deficits in tactile sensation, proprioception, or stereognosis are common after stroke and have important implications on the recovery of motor function.[192] As was mentioned above, the presence or absence of sensory and coordination deficits were evaluated in this dissertation but our data did not yield an association between deficits to these systems and post-stroke motor outcomes however, impairment to proprioception and tactile sensation have previously been found to be inversely associated with recovery of arm and hand function post-stroke.[193] Further, we did not assess clinical MRI biomarkers for disruption to sensorimotor networks.

Several regions contribute to sensorimotor integration including S1, the basal ganglia, cerebellum, thalamus, posterior parietal cortex (PPC), and ascending networks which transmit sensory information to the CNS.[23] As was discussed briefly in Chapter 1, signals from S1 allow for refinement of motor commands to ensure successful task

completion.[191,194] The cerebellum receives descending cortical signals and afferent sensory input from the SC, influencing movement through projections to motor cortex through the thalamus and to the SC through the red nucleus.[23,191] The thalamus enables complex encoding and gating of sensory information prior to relaying those signals to cortical motor regions and to S1.[23,191,195] Similarly, the PPC amalgamates several sensory modalities prior to projecting to M1 and premotor cortices and, in primate literature, the PPC has been shown to have disynaptic connections with the α motoneurons supplying muscles of the hand, implicating more direct control of distal upper extremity movement.[23,196–198]

In this dissertation, patients with cerebellar stroke were excluded from the study in keeping with previously established inclusion and exclusion criteria.[100] Patients with damage within the thalamus or structures of the basal ganglia did not demonstrate a trend in PUE outcomes, however, we did not analyze the extent of lesion overlap in these areas nor did we investigate projections to motor areas from the thalamus, PPC, basal ganglia, or cerebellum. In humans, strokes within the PPC have been found to correlate with diminished coordination of finger movements necessary for grasping tasks.[199] In primate literature, even lesions restricted to M1 (i.e., lesions not specifically in sensory areas or tracts) were found to have a significant effect on proprioception during the execution of reach and grasp tasks.[200] Therefore, more precise accounting for damage to the network including cortical and subcortical sensory areas, ascending sensorimotor projections, and the cortical motor regions on which these projections synapse may improve our understanding of certain aspects of upper extremity control. This, in turn, may enable better prediction of PUE motor outcomes post-stroke.

5.6.2.6 Predicting Lower Limb Functional Outcome Post-Stroke

As was mentioned above, we found no significant association between upper and lower extremity impairment nor did we find correlations between early measures of lower extremity function and MRI metrics. Regarding this lack of association between early measures of mobility (IRF-PAI sit-to-stand and ambulation), measures of PUE strength at the same time points (E-SAFE), and measurement of PUE functional outcome (E-ARAT), it is important to note the differences in measurement tools used. The IRF-PAI solely measures level of assistance necessary when transitioning from sit-to-stand or ambulation over a 10-foot distance, rather than impairment in strength, coordination, movement quality, or function in the lower extremities.[130] However, this lack of association may also be reflective of the physiologic differences in upper and lower extremity control and recovery mechanisms or of the redundancy in descending pathways that control the trunk and lower extremities.[146]

Previous work has shown that, similar to the PUE, initial impairment of the PLE is a clear predictor of PLE functional recovery outcome.[145] Interestingly, early trunk control has also shown strong utility as a predictor for both the likelihood and timing of regaining independent walking post-stroke.[146,201–203] In contrast, biomarkers of CST integrity, using either TMS or MRI, have shown less definitive predictive value for PLE recovery than when used to predict PUE functional outcome.[46,145–147,204] These differences in CST metric utility may be indicative of differences between the upper and lower extremities in neuroanatomical motor control mechanisms as subcortical descending motor networks, particularly those of the reticulospinal and vestibulospinal pathways, may offer alternative physiologic routes for the restoration of walking function.[146]

As was discussed briefly in Chapter 1, both the reticulo- and vestibulospinal pathways project, primarily ipsilaterally, to medial motoneuronal pools in cervical, thoracic and lumbar SC segments and are thought to control axial musculature to facilitate preparation and coordination of movements and to maintain upright body position, respectively.[23,38,41] Though these subcortical pathways may be less likely to mediate restoration of dexterous, distal movement of the upper extremity, their termination sites in the SC suggest they may play a role in trunk and/or lower extremity functional recovery through upregulation of previously redundant pathways.[21] Clinical evidence in individuals in the chronic phase of stroke with complete injury to the affected CST supports this notion; patients who regained independent walking showed greater fiber volume in the reticulospinal pathway of the unaffected hemisphere over both those who did not regain independent walking and healthy controls.[47] These findings suggest that recovery of repetitive, functional, PLE activities such as walking may be less reliant on the CST and may explain why early measures of trunk control are better predictors of PLE outcome than biomarkers of CST integrity. It may also explain why results in this dissertation showed no association between early measures of lower extremity function and MRI metrics which quantify CST integrity in the affected hemisphere. Future investigation which identifies post-stroke neuroimaging biomarkers associated with the return of function in the trunk and paretic lower extremity may contribute to more generalized understanding of physiologic mechanisms of motor control and recovery in humans.

5.6.3 Investigation of Additional Neuroanatomic Networks May Improve Post-Stroke Motor Outcome Prediction

While keeping in mind the feasibility constraints associated with post-stroke clinical practice and the necessity for streamlined clinical assessments with high prognostic utility, expanded investigation of clinical neuroimaging biomarkers may be the research avenue with the highest potential to improve prediction accuracy for PUE motor outcomes and to enable prognosis of more generalized post-stroke motor recovery. By applying methodologies similar to those used in Aim 3, future research may investigate associations between post-stroke motor outcomes and clinical MRI-based metrics of damage to CST, subcortical motor pathways, corticobulbar projections, and sensorimotor integration networks to improve and refine recovery predictions, particularly for those with initially lower PUE strength (i.e., those in *Limited* or *Poor* outcome groups). Expanding the use of a more comprehensive set of available neuroimaging biomarkers may also enable the creation of clinical assessment tools which better identify unique elements of post-stroke motor dysfunction (i.e., weakness, spasticity, or abnormal synergies) in addition to precision-based treatment paradigms to improve individual motor outcomes.

5.7 Conclusions

This dissertation described the validation feasibility of the PREP2 prediction tool[100] in US healthcare systems and the utility of readily implementable clinical measures and structural CST biomarkers to predict PUE functional outcomes in individuals post-stroke. In an era of precision medicine, the early and intentional use of validated predictive algorithms may allow for improved care plan development and optimized allocation of rehabilitation resources. In order to meet the long-term objective of enabling optimally accurate prediction of recovery potential for patients post-stroke, results indicate that validation of PREP2 in a US setting is warranted but that a principled implementation strategy will be needed to support SAFE score and CST functional integrity evaluation for the use of PREP2 in routine clinical care.[122] Further, our results indicate that prospective evaluation of predictive models using SAFE measured at admission to AR and of clinical MRI-based CST metrics is useful in determining if lesion involvement in M1 and/or non-M1 corticospinal projections is predictive of PUE recovery. If optimized, evidence-based outcome prediction tools have the potential to inform and improve the delivery of therapeutic interventions post-stroke, to improve the trajectory of upper extremity motor recovery, and to maximize independence for individual stroke survivors.

APPENDIX A. SAFE ESTIMATION METHODOLOGY

A.1 Methods

Shoulder abduction (SA) and finger extension (FE) manual muscle tests were summed to calculate the SAFE score (/10). When SA and FE manual muscle tests were not documented, alternate tests were utilized for E-SAFE scoring purposes. Abbreviations used allowed analysis of manual muscle testing frequency within current care standards. See **Table A.1** below.

When manual muscle tests were not documented but an entire upper extremity or joint was described in a single value or phrase, strength was noted as "grossly" and assigned a numeric value if possible. Examples include: "grip strength," "proximal weakness," "proximal," or "distal." Strength score assignments were then given if any reference was available to do so. Examples: "proximal 2/5" was assigned as 2/5 for shoulder abduction; "no movement observed" was assigned 0/5; "no antigravity" was assigned 2/5; "much weaker than" was assigned a numeric value if a reference value was present, if not, they were omitted. The general terms "within functional limits" (WFL) and "within normal limits" (WNL) are commonly used in therapy documentation and were found in a large number of patient charts. WFL was interpreted as 3/5 with the rationale that to be considered "functional" the patient likely exhibited full active range of motion against gravity. WNL was interpreted as 4/5 as it is deemed to signify more than functional ability, though the patient's toleration of manual resistance cannot be assumed to be strong. With consideration of the cutoff score of SAFE $\geq$ 5/10, when deciding if a patient needs further assessment of corticospinal tract integrity, the investigative team also notes that strength

of neither WFL nor WNL would likely imply that TMS testing would be necessary. Documentation with only "impaired," was noted as such, but no numeric value was assigned as it was regarded as too broad a term to infer an exact muscle test score, though it can be assumed to be less than 5/5. See **Table A.1** for a SAFE score estimation key used during data extraction.

Table A.1 – SAFE estimation key

Abbreviation	Meaning	Numeric Value Assigned
NT	Not tested. May also be used when note is so vague an estimation cannot be made.	Nothing (leave blank)
WFL	Within functional limits	3
WNL	Within normal limits	4
IMP	Impaired	Nothing (leave blank)
Grossly	Used when an entire UE or joint is described in a single value or phrase. "grip strength" "proximal weakness" "proximal" "distal" "deltoid"	Examples: "no movement observed" = 0 "no antigravity" = 2 "much weaker than" = assigned # if reference value is present
SA	Shoulder abduction	value from chart
SF	Shoulder flexion	value from chart
SE	Scapular elevation	value from chart
EF	Elbow flexion	value from chart
EE	Elbow extension	value from chart
WE	Wrist extension	value from chart
WF	Wrist flexion	value from chart
FE	Finger extension	value from chart
FF	Finger flexion	value from chart

APPENDIX B. ARAT ESTIMATION METHODOLOGY

B.1 Methods

Action Research Arm Test (ARAT) scores were estimated from therapy documentation at approximately 90 days post-stroke in accordance with the grading criteria for each test. Estimated ARAT (E-ARAT) scoring was conducted by two licensed, clinical neurologic therapists who were otherwise blinded to study findings. Rehabilitation provider notes were evaluated in detail to extract the following measures, where available, for each patient: clinical assessments of PUE muscle and grip strength, coordination, active and passive range of motion, observational movement analysis, therapeutic activity, exercises performed, rehabilitation goals, Nine-Hole Peg Test (9HPT) and Box and Block Test (BBT) scores as compared to matched, normative values.[133–137]

The test is composed of 4 sub-tests with 19-items in total and is conducted using the affected upper extremity; each item is scored on a 4-point ordinal, 0-3 scale.[113] A score of 3 indicates that an individual performed the task with "normal" motion, completing it within 5 seconds.[113] A score of 2 indicates an individual was able to complete the task but either 1) had difficulty with task completion, requiring compensatory motion or 2) the time to completion was longer than normal (5 - 60 seconds).[113] A score of 1 indicates only partial performance of the task within 60 seconds, and a score of 0 indicates the individual could not initiate any part of the task within 60 seconds.[113] The first item in each subtest is the most challenging and is followed by the least challenging task, enabling streamlined testing (if the individual scores a 3 on the first item, a full score for that sub-test is recorded or; if the individual scores a 0 on the first two items, the entirety of the sub-test is graded as a

0).[113] All items and sub-tests are listed in the ARAT scoring sheet (**Figure B.1**). The test is conducted with the individual seated at a desk in a neutral position.[113] Grasp subscale tests require the individual to grasp objects of varying sizes and place them on a shelf 37-cm above the desktop.[113] Grip subscale items are all performed at table-level, again with differently sized and shaped items.[113] Pinch subscale tasks require the individual to pinch either a ball-bearing or marble, lifting it from the top of the shelf to place it on the desktop; tests are conducted using specified digits testing thumb opposition motion with index, middle, and ring fingers.[113]

Test Number	Item	Score
	Grasp Subscale	
1	Block, 10 cm	0 1 2 3
2	Block, 2.5 cm	0 1 2 3
3	Block, 5 cm	0 1 2 3
4	Block 7.5 cm	0 1 2 3
5	Cricket ball	0 1 2 3
6	Sharpening stone	0 1 2 3
		Subtotal ___/18
	Grip Subscale	
7	Pour water from one glass to another	0 1 2 3
8	Displace 2.25-cm alloy tube from one side of table to the other	0 1 2 3
9	Displace 1-cm alloy tube from one side of table to the other	0 1 2 3
10	Put washer over bolt	0 1 2 3
		Subtotal ___/12
	Pinch Subscale	
11	Ball bearing, held between ring finger and thumb	0 1 2 3
12	Marble, held between index finger and thumb	0 1 2 3
13	Ball bearing, held between middle finger and thumb	0 1 2 3
14	Ball bearing, held between index finger and thumb	0 1 2 3
15	Marble, held between ring finger and thumb	0 1 2 3
16	Marble, held between middle finger and thumb	0 1 2 3
		Subtotal ___/18
	Gross Movement Subscale	
17	Hand to behind the head	0 1 2 3
18	Hand to top of head	0 1 2 3
19	Hand to mouth	0 1 2 3

Figure B.1 – ARAT Scoring Sheet. From Yozbatiran et. al., 2008.

As scores for each item were estimated, all medical records taken at and around day-90 post-stroke were utilized to aid in estimation. Each ARAT estimator independently reviewed the electronic medical record (EMR) and determined maximal and minimal scores for each ARAT test item, creating a score range for every patient. E-ARAT for every patient was calculated by taking each estimator's median score and averaging the two values. Scoring for two patients from our cohort are described below.

B.1.1 ARAT Estimation - Patient Example 1

The occupational therapy treatment note states that the patient demonstrates full active range of motion (AROM) of the affected upper extremity. The patient performs the 9HPT in 25 seconds (normative value for the patient's sex and age is 22.29 seconds).[133] Patient's grip strength measured via hand-held dynamometer is 66.3 lbs, and the normative value for hand, sex, and age is 76.8 lbs.[137] The patient performed tasks including "sustained overhead activity placing nuts and bolts together on board on middle shelf," "1# wrist weight to L UE to complete overhead placement of 1" cubes on shelf," and "fine motor coordination task placing clothespins and pennies in ruler with minimal difficulty." The occupational therapist documented assessments such as, "patient making good progress towards goals. Continues to have mild decrease in LUE strength and coordination," and "patient with good participation, fatigue noted with increased weight, but good form."

Considering the therapist-chosen treatment interventions and demonstration of full AROM on assessment, the member of the research team estimating the ARAT score could reasonably assume the patient possessed sufficient anti-gravity shoulder strength and range

of motion to perform items on the gross movement subscale within 5 seconds and without compensation, scoring 9/9 points. The patient's participation in advanced activities including overhead reaching, object manipulation, and grasping indicate they would likely score 3/3 on some of the grasping and griping subtests. The patient does have decreased grip strength when compared to age- and sex-matched norms, however, grip strength of 66.3 lbs would be sufficient to complete grip and grasp tasks without difficulty. The occupational therapist does note coordination deficits throughout interventions and outcome assessments, suggesting the patient may use minor compensatory movements or require increased time to complete the initial, more challenging items. As a result, the patient was scored within a minimum of 15/18 and a maximum of 18/18 on the grasp subscale and a similar 10-12/12 range on the grip subscale. Finally, the patient was engaged in tasks involving pinching and manipulating small objects with "minimal difficulty" and performed the 9HPT marginally slower than normative values. Therefore, the patient would likely have scored a 2/3 on the more challenging pinch subtests but 3/3 on the less challenging items, resulting 15-18/18 range on the pinch subscale. Summing the minimum and maximum potential scores yields an E-ARAT score range of 49-57/57. The median of this range is 53 which would be the E-ARAT score attributed to this patient for one of the examiners. The same scoring was independently conducted by a second examiner; 53 would then be averaged with the median score of the second examiner to yield the E-ARAT score for this patient.

B.1.2 ARAT Estimation - Patient Example 2

For another patient in our cohort, the occupational therapist set goals primarily related to proper positioning of the impaired arm, increasing grip strength to 10 pounds, increasing active shoulder flexion 10 degrees, the ability to manipulate 12 blocks on the Box and Blocks Test,[134] and using the unimpaired arm in techniques to care for and facilitate function in the impaired arm. Therapeutic exercises and activities were performed in gravity-minimized positions with therapist or patient self-assistance using the unimpaired arm. One treatment session was focused on "bringing object to [the] mouth and then reaching forward with R UE." The grip strength goal was not met by 90-days post-stroke (patient achieved a maximum of 7 pounds of grip strength). The patient did achieve 10 degrees of active shoulder flexion but was not able to complete the Box and Blocks Test.[134] The occupational therapist notes that the "hand continues to be extremely limited by decreased shoulder strength."

Using this information, the member of the research team estimating the ARAT score could assume that the patient had sufficient isolated shoulder and finger muscle activation to initiate all of the items on each subscale, thus achieving a minimal score of 1/3 on each item. The patient was also able to perform the "hand to mouth" item of the gross movement scale, as this was specifically indicated within one of the treatment interventions. Given the gross shoulder weakness however, it is likely the patient would rely on extensive compensation to perform any actions within the gross movement subscale, resulting in a score range 3-5/9. As the patient demonstrates considerable proximal weakness with some preservation of hand and finger dexterity, it is possible they would perform best on the grip subscale, as it does not require movement of the object from desk-height to shelf-height,

as the grasp and pinch subscales do. Though the patient would not be able to perform any of the grip subscale tasks within the 5-second requirement and without motor compensation, it is possible the patient would achieve a 2/3 on the easier items, thus completing the task with increased time and/or some compensatory motion. This would result in a score range of 5-7/12 for the grip subscale. As stated previously, the grasp and pinch subscales both involve moving the object from the desk-to-shelf or shelf-to-desk, requiring anti-gravity shoulder strength this patient was not documented to have. Therefore, the patient would be likely to score a 1/3 for initiation of many of the grasp and pinch subscales while successfully completing a few of the easier subtests (2/3). This would result in a score range of 6-10/18 on the grasp and a 6-8/18 on the pinch subscales, for a total score range of 18-30/57. The median of this range is 24 which would then be averaged with the other ARAT examiner to yield the E-ARAT score for this patient.

APPENDIX C. IMAGE PROCESSING PIPELINE

C.1 Image Identification, Image Processing, and Lesion Mapping

1. Obtain clinical scans from the Department of Radiology at EUH. When multiple MRI sequences were acquired during the acute inpatient stay, identify scans performed closest to the date of admission to EUH.

2. Visualize lesion topography using ITK-SNAP version 3.8.0[154] (image viewing software) and T2 images:

    a. Diffusion weighted images (DWI) for ischemic strokes

    b. Gradient echo images (GRE) for hemorrhagic strokes

3. Confirm current lesion location using neuroradiology documentation, noting any previous/chronic stroke locations using same methodology.

    a. If lesion location is unclear, Dr. Samir Belagaje, a board-certified neurologist, is available for additional consultation to ensure accuracy of lesion masks.

4. Lesion tracing is conducted in ITK-SNAP version 3.8.0[154] in a slice-by-slice manner in the axial plane using the built-in, semi-automated segmentation process.

    a. Create a speed image to delineate between structures of interest (cortical boundaries, subcortical structures, lesion boundaries, etc.)

    b. Manually place initialization seeds in multiple slices. Note: you may adjust seed size as is necessary/appropriate for lesion size and boundary shape.

c. Run active contour segmentation.

d. Manually adjust lesion masks as necessary in either the sagittal and/or coronal planes to ensure accurate segmentation in three-dimensions.

5. Note: lesion mask location and extent must be independently verified visually by another member of the study team.

6. Once the lesion mask is verified, extract lesion volume calculated using ITK-SNAP software.

7. Spatially normalize the lesion masks into standard Montreal Neurological Institute (MNI) space using the combined normalization-segmentation process in Statistical Parametric Mapping software (SPM12) [156,157] and the associated clinical toolbox using the following parameters:[156–158]

   a. Anatomical Scans = T1-weighted image

   b. Lesion Map = Lesion mask drawn in ITK-SNAP

   c. Pathological Scans = T2-weighted image (DWI or GRE)

   d. Template = 2mm T1-weighted MNI152 template (“T1 younger”)

   e. Bounding Box = [−90 −126 −72; 90 90 108]

   f. Voxel Size = $2mm^3$

8. Validation of normalization in standard stereotaxic space must then be visually confirmed by an additional member of the study team to ensure proper alignment of

cortical boundaries, subcortical anatomical landmarks, and drawn lesions. The following coregistration fidelity inspections are conducted using MRIcron© (NeuroImaging Tools & Resources Collaboratory).[205]

a. Coregistered T1-image overlaid on the "T1 younger" template to ensure boundaries and anatomical landmarks are well-aligned.[156,206]

b. Coregistered lesion file ("ws____lesion") overlaid on coregistered 152T1-image to ensure boundaries and anatomical landmarks are well-aligned.

9. Convert lesion mask file to img/hdr file type. See **Figure C.1** for a visualization of the image processing pipeline.

C.2 CST Lesion Overlap Calculation

10. Process the spatially normalized lesion mask (img/hdr file) for each participant in the MNI ROI overlap calculator software to obtain CST tract overlap values using two atlases, SMATT and JHU. [159,161]

11. Data analysis output includes voxel sizes for each tract, the number of voxels disrupted by the lesion, and percent tract lesion overlap. For SMATT atlas results are individuated by seed region (M1, PMv, PMd, SMA, preSMA, and S1).[159]

12. Calculate a whole CST lesion overlap percentage (CST overlap) using individual SMATT atlas tracts

a. Sum the number of voxels overlapped by the lesion.

b. Sum the number of voxels in each tract to obtain a whole CST voxel number.

c. Divide A/B

d. Note: This calculation is conducted using tract voxel numbers for the **affected hemisphere**.

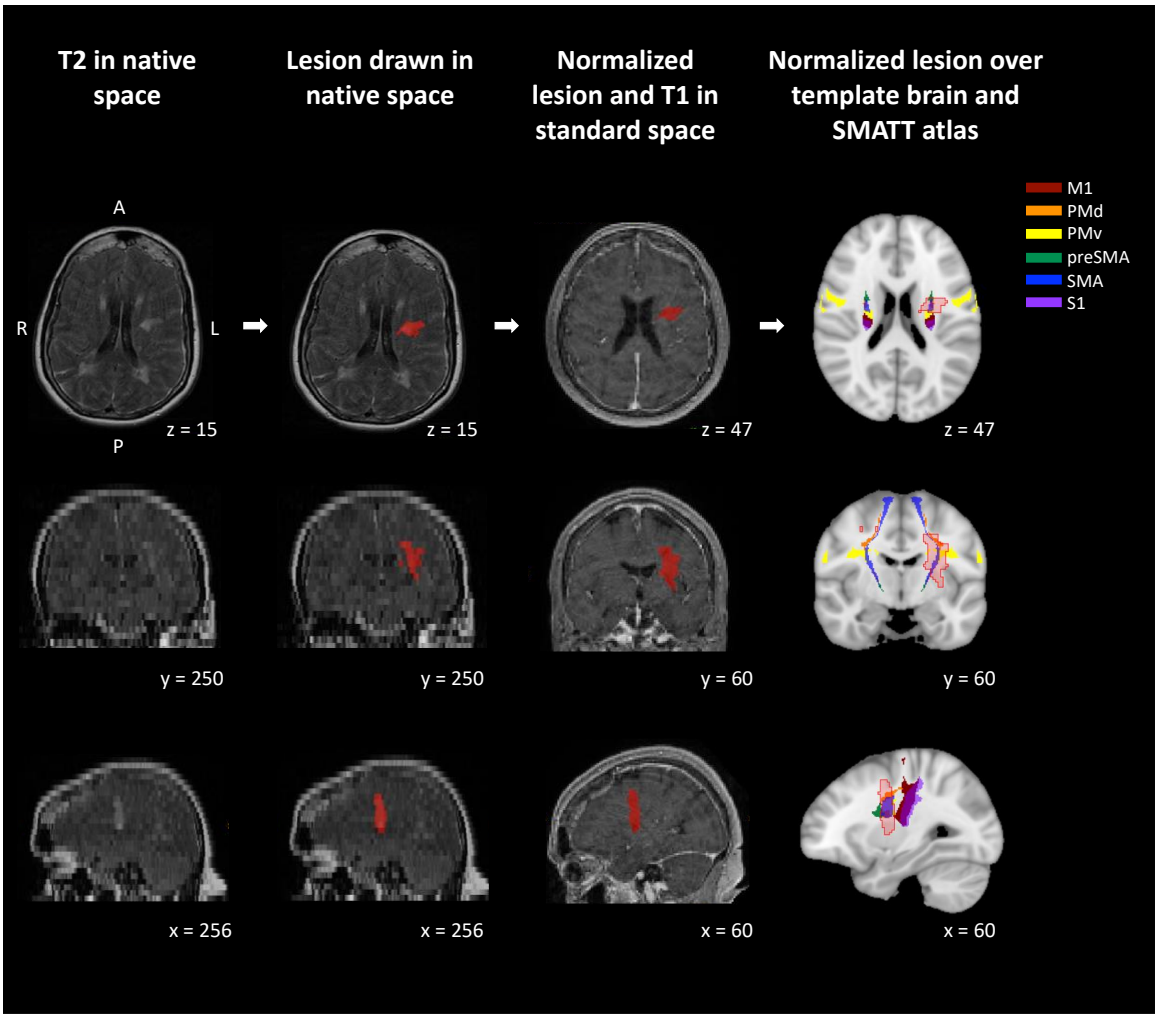

Figure C.1 - Representative example of lesion processing in ITK-SNAP as drawn using a T2-weighted MRI. Lesion was visualized in native space using T2-weighted images in the axial, sagittal, and coronal planes (first column). Lesions were drawn in the axial plane in native space a using semi-automatic segmentation workflow (second column). Coregistration into standard space was conducted in SPM using the 2mm T1-weighted MNI152 template, a standard template bounding box ([−90 −126 −72; 90 90 108]), and $2mm^3$ voxel size. Normalization into standard stereotaxic space allows lesions to be visualized over the normalized T1-image (td hird column) or the MNI152 template and SMATT atlas (fourth column).

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VITA

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Mary Alice Saltão da Silva was born in Los Angeles, California. She attended the University of California, Berkeley for her undergraduate degree, where she received a B.A. in Dance and Performance Studies in 2004. After graduation, Mary Alice moved to New York City to pursue a career in the performing arts. She worked as a professional dancer for 8 years, performing with numerous companies both nationally and internationally. After retiring from her first career as a professional dancer, Mary Alice returned to school, driven by a curiosity to understand the biological underpinnings for how and why we move the way we do. She began by completing a postbaccalaureate in premedical sciences from Columbia University where her passion for neuroscience and physiology sparked her interest in research. Mary Alice went on to graduate from the Doctor of Physical Therapy (DPT) program at Emory University School of Medicine in 2018, the first student to enroll in a new dual-institution DPT/PhD program in conjunction with Georgia Institute of Technology. She began her PhD in Applied Physiology at Georgia Tech in 2018, working in the Neural Plasticity Research Laboratory. Dr. Saltão da Silva's passion lies in translating scientific innovation from bench to bedside, specifically implementing evidence-based technologies to enhance healthcare delivery and improve patient outcomes. When she is not working in the lab or hospital, Dr. Saltão da Silva enjoys spending time with her husband and her dogs, practicing yoga, taking dance class, painting, and cooking.