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RECOVERY AND PREDICTION OF HAND MOTOR FUNCTION AFTER STROKE - A LONGITUDINAL STUDY USING NOVEL METHODS TO QUANTIFY HAND FUNCTION AND CONNECTIVITY IN BRAIN NETWORKS

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Stockholm 2021
RECOVERY AND PREDICTION OF HAND MOTOR FUNCTION AFTER STROKE - A LONGITUDINAL STUDY USING NOVEL METHODS TO QUANTIFY HAND FUNCTION AND CONNECTIVITY IN BRAIN NETWORKS
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at The Lecture Hall at Danderyd Hospital, on September 14, 2021, at 08:00 AM

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To my mother and father, always there, with love.
And to you, Lova, who knows how to lit a fire.
And who brings warmth and light
with your brilliant smile.

The white page milks the pen,
the nib's arrhythmic dance
unravels the ductile darkness of the ink
to a quinkled, esoteric shade of light:
mind-light that the sun
(now drying characters it does not comprehend)
remotely lit.

A drop of midnight, thus unwound to light, embodies
Meaning - the dark heart of the light, its being known,
the inmost gleam of light.

Raymond Tallis
“Let us for moment direct our attention to the seemingly insignificant parts, the arm and the hand, and their capacity for language and signifying ... What rich movements, what expressiveness there is in the hand. The hand over the forehead shows ... pain and worry, deliberation and reflection; it shades the shyness of the eyes; brought to the mouth it signifies silence, to the bosom protestation, proud self-esteem, heartfelt affection. Pleasure and malicious delight clap their hands, desperation wrings them, reverence folds them. Hence, as a famous writer says about the pantomimic expressions of the hands, that by them we can desire, promise, summon, reject, threaten, pray, plead, refuse, ask, admire, confess, fear; by them display shyness, doubt, indignation, flattery, agreement, delight, empathy, wrath, desperation and admiration; in short, all the emotions that spring up in our bosom.”

Johan Ludvig Runeberg¹
Johan Ludvig Runeberg, (1804-77) was Finland's national poet. These lines were originally published in Efterlämnade skrifter I (Posthumous Works I), and are here quoted from ‘The Hand - A Philosophical Inquiry into Human Being’, by Raymond Tallis, Edinburgh University Press, 2003.
ABSTRACT

Background: Stroke is a heterogeneous disease and a leading cause of physical disability among adults, severely affecting people’s health and life worldwide. According to current figures, one in four people risk suffering a stroke during their lifetime. One of the most common and enduring symptoms of stroke is unilateral weakness of the upper extremity. A key challenge in post stroke rehabilitation and research is the highly variable degree of recovery in patients and a remaining incomplete understanding of which factors contribute to this variability. This problem contributes to less effective interventions. Today’s prediction models lack precision on the individual level. Improved prediction models could assist clinicians in giving information on an individual’s expected outcome and recovery potential, and guide selection of interventions matching the specific impairment profile of the patient.

Aim: The overall aim of this longitudinal prospective study was to identify key determinants for recovery of hand function after stroke by combining fine-grained measures of sensorimotor impairment and activity together with commonly used clinical scales and a multimodal neuroimaging protocol.

Method and materials: Patients admitted to a regional in-patient rehabilitation department in Stockholm, Sweden, within 2-6 weeks of onset of a first time ischemic or haemorrhagic stroke and with upper extremity hemiparesis were eligible for inclusion. Exclusion criteria were inability to understand or follow instructions, disorders other than stroke affecting hand function, a cerebellar lesion, or contraindications for Magnetic Resonance Imaging (MRI) examination. Written informed consent was obtained from all participants. The study was approved by the Regional Ethical Review Board. The four Studies of this thesis were based on data collected in a prospective observational study of one study cohort, who underwent repeated assessments at three time points: ~3 weeks, 3 months and 6 months after stroke onset.

Novel sensorimotor methods applied were as follows: Study I) the NeuroFlexor© for quantification of hand spasticity, Study II) the strength dexterity test for quantification of precision grip force control, Study III) the Adult Assisting Hand Assessment Stroke (Ad-AHA Stroke) for detailed characterization of bimanual activity performance and Study IV) a visuomotor grip force task for quantification of grip force modulation and force release. All studies incorporated the common comprehensive clinical assessment protocol and structural MRI, yielding a measure of corticospinal tract (CST) lesion load (wCST-LL) and Voxel based Lesion Symptom Mapping (VLSM). Resting-state functional MRI was included in studies III and IV.

Results: In total n = 89 individuals with stroke were included, of whom n = 61 participated in Study I, n = 80 in Study II and all n = 89 in studies III and IV. In Study II, n = 23 healthy control subjects were included. Specific and nuanced assessments allowed delineation and understanding of the heterogeneous impairment and recovery profiles among stroke survivors, across multiple ICF levels. In Study I, subgroups of patients with divergent
spasticity severity were identified. Severity of spasticity was predictive of poor hand motor recovery and development of secondary complications. In studies II and IV, evidence was found of persisting deficits in the ability to grasp and control finger and power-grip forces after stroke. In particular, force release explained unique variance in recovery of dexterous hand use over time. In studies II-IV, wCST-LL was confirmed to be a strong predictor of voluntary movement function over time, and was found to be a strong predictor of more severe hand spasticity and poorer bimanual activity performance. In Study III, a derived measure of shoulder abduction and finger extension (FMA-SAFE score) was found to be a strong clinical marker of bimanual activity performance over time. Additional predictive factors were sensory and cognitive impairment. Resting state functional connectivity explained some additional variance in distal unimanual hand function and bimanual activity performance.

Conclusions: As a whole, this thesis generated an improved understanding regarding force generation and force control functions of the hand, their interrelationship over time and relation to clinically assessed outcome and recovery after stroke. Moreover, this thesis advances our knowledge regarding longitudinal recovery and prediction of grasp and release capability. Further, this thesis provides the first detailed comparison of unimanual and bimanual recovery and their predictors after stroke. Increased understanding of factors contributing to variability in stroke recovery could contribute to development of new treatment paradigms with more specific targets for evaluation in clinical trials. This cohort represents a younger stroke population and the findings need further external validation in other age groups and in larger cohorts.
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<tr>
<td>Ad-AHA Stroke</td>
<td>Assisting Hand Assessment Stroke</td>
</tr>
<tr>
<td>aIPS</td>
<td>Anterior Intraparietal Sulcus</td>
</tr>
<tr>
<td>BI</td>
<td>Barthel Index</td>
</tr>
<tr>
<td>BBT</td>
<td>Box and Block Test</td>
</tr>
<tr>
<td>BoNT</td>
<td>Botulinum Neurotoxin</td>
</tr>
<tr>
<td>BTT</td>
<td>Baking Tray Task</td>
</tr>
<tr>
<td>CST</td>
<td>Corticospinal Tract</td>
</tr>
<tr>
<td>dPMC</td>
<td>Dorsal Premotor Cortex</td>
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<tr>
<td>EC</td>
<td>Elastic Component</td>
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<tr>
<td>FC</td>
<td>Resting-state Functional Connectivity</td>
</tr>
<tr>
<td>FMA-Hand</td>
<td>Fugl-Meyer Assessment for the Upper Extremity Hand Subscale</td>
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<tr>
<td>FMA/FMA-UE</td>
<td>Fugl-Meyer Assessment for the Upper Extremity</td>
</tr>
<tr>
<td>FMA-SAFE</td>
<td>Fugl-Meyer Assessment Shoulder Abduction Finger Extension</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>ICF</td>
<td>International Classification of Functioning</td>
</tr>
<tr>
<td>M1</td>
<td>Primary Motor Cortex</td>
</tr>
<tr>
<td>MAS</td>
<td>Modified Ashworth Scale</td>
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<tr>
<td>MRC Muscle Scale</td>
<td>Medical Research Council Muscle Scale</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NC</td>
<td>Neural Component</td>
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<tr>
<td>NIHSS</td>
<td>National Institute of Health Stroke Scale</td>
</tr>
<tr>
<td>PCG</td>
<td>Prefrontal Gyrus</td>
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<tr>
<td>RD</td>
<td>Release Duration</td>
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<tr>
<td>RZC</td>
<td>Rostral Cingulate Zone</td>
</tr>
<tr>
<td>SAFE-score</td>
<td>Shoulder Abduction Finger Extension – score</td>
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<tr>
<td>SMA</td>
<td>Supplementary Motor Area</td>
</tr>
<tr>
<td>STN</td>
<td>Subthalamic Nucleus</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>VC</td>
<td>Viscous Component</td>
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<tr>
<td>VLSM</td>
<td>Voxel Based Lesion Symptom Mapping</td>
</tr>
<tr>
<td>vPMC</td>
<td>Ventral Premotor Cortex</td>
</tr>
<tr>
<td>wCST-LL</td>
<td>Weighted Corticospinal Tract Lesion Load</td>
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1 INTRODUCTION

1.1 STROKE – DEFINITION, IMPACT AND GLOBAL TRENDS

Stroke has a major impact on people’s health and life worldwide and constitute a major socioeconomic challenge for society (Avan et al., 2019). Recent international health surveys rank stroke as the third most common cause of death after ischemic heart disease and neonatal disorders (GBD 2017 Causes of Death Collaborators., 2018) and a leading cause of physical disability among adults in the world (Feigin, Norrving, & Mensah, 2017).

Stroke is characterized by the sudden loss of neurological function, most commonly due to intracerebral infarction (84.8%) or haemorrhage (15.2%) (Rathore, Hinn, Cooper, Tyroler, & Rosamond, 2002). The World Health Organization (WHO)’s definition of stroke relies on symptomatic criteria; ‘rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin’ (Aho et al., 1980). An updated definition of stroke has been proposed by the American Heart Association/American Stroke Association (Sacco et al., 2013) which adds radiological criteria (CT scan or MRI verified signs of stroke) in order to facilitate the distinction between silent stroke (the incident passes unnoticed by the patient or observers, but causes actual neural injury which can be detected at later brain imaging examination) from transient ischemic attack (TIA). The updated version also incorporates focal injury within the whole central nervous system (CNS) (including the spinal cord and retina). Most international public health surveys still use the WHO’s definition.

In Sweden, 25,700 incident cases of stroke were registered 2019, among which 21% were recurrent stroke (Riksstroke, 2019). Preliminary data from 2020 are also available, but may however be influenced by the Covid19 pandemic (www.riksstroke.se). The age standardized incidence rate per 100,000 in Sweden in 2017 was 101.7 (95% CI 93.9-110.6), similar to western Europe and other high-income regions (North America, New Zealand, Australia). The highest incidence rates were reported in East Asia, North Africa and the Middle East. The global age-standardized incidence rate of stroke was 150.5 (95% CI 140.3–161.8) in 2017 according to data published by Krishnamurthi, Ikeda, and Feigin (2020). This translates one in four risk for people to suffer a stroke during their lifetime (GBD 2016 Stroke Collaborators, 2019). According to the Global Burden of Disease (GBD) Study 2017, the global incidence of a clinically diagnosed first-ever stroke was 11.9 million (95% CI 11.1–12.8), and 104.2 million (95% CI 98.6–110.2) prevalent cases were reported the same year. Incidence rates were similar for women and men. However, in the age range 55-75 years, the incidence was significantly higher for men. The Swedish National Register Riksstroke for the year 2019, reported a mean age of 75 years for acute stroke (73 years for men and 77 for women). Men were in a majority among younger stroke-survivors, below 65 years, while women dominated stroke-survivors, aged 85 years or above (Riksstroke, 2019).

In most world regions, stroke mortality and incidence rates have declined during the last three decades (1990-2016) (GBD-2016-StrokeCollaborators, 2019). However, the decrease in
incidence has been more modest than the decline in mortality (~8% versus ~36%). There are also important geographical differences. For example, over the period 1990 to 2016, stroke incidence overall has increased by about 5% in East Asia, whilst ischemic stroke specifically increased by 18% in this region, the opposite to global trends. Further, despite the global decline in incidence, the total number of people suffering a stroke and the number of stroke survivors in the world has almost doubled since 1990 (Krishnamurthi et al., 2020). The number of people living with post-stroke physical disability (disability-adjusted life-years, DALYs) has also increased, and further rises are expected due to increased stroke survival, and with a growing population. A trend towards a growing stroke burden specific for the middle-aged (45–59 years old) and the oldest old (80+ years) has also been noted (Krishnamurthi et al., 2020). Together, the global burden of stroke constitutes a growing challenge for clinicians, health-care systems and the research community to provide effective post-stroke rehabilitation interventions to alleviate the impact of stroke on the individuals affected, their next of kin and population and society as a whole.

1.1.1 Neurological impairments after stroke

Unilateral weakness or loss of voluntary movement in the upper extremity, contralateral to the lesion, is one core symptom of stroke, occurring in about 75-80% of persons with stroke (Rathore et al., 2002; Semrau, Herter, Scott, & Dukelow, 2015). Upper limb weakness often occurs in conjunction with paresis of the face (55%) and the lower extremity (69%) (Rathore et al., 2002). Somatosensory deficits and disturbed sensory functions occur in about 50-70% of persons with stroke (Carey & Matyas, 2011; Semrau et al., 2015). Other neurological impairments, such as disordered speech and language (e.g. aphasia) (20–25%), visual disorders (15–20%), attention disorders (25–30%) or other impairments involving higher cognitive functions (15–40%) are also common (Nys et al., 2007; Rathore et al., 2002), although it remains unclear how they co-vary with upper limb impairments (Hybbinette et al., 2021).

1.2 UPPER EXTREMITY SENSORIMOTOR IMPAIRMENTS AND DISABILITY

A complete loss of voluntary movement of the arm, hand and leg contra-laterally to the stroke lesion, is commonly denominated as hemiplegia, a term that find its roots in the Greek plegia (or plēgē meaning ‘blow’ and plēssein ‘to strike’), while partial loss of voluntary movement is referred to as hemiparesis, from Greek parienai (meaning ‘letting go’ or ‘to send’, ‘throw’). Conceptually, ‘arm and hand motor impairment’ or ‘impaired hand motor function’ concerns affected ‘body functions’ as classified by the International Classification of Functioning, Disability and Health (ICF) framework (WHO, 2001) (see APPENDIX A), more specifically ‘neuromusculoskeletal and movement-related body functions’. In his classical paper, Twitchell (1951) considered arm and hand paresis a movement disorder, in the sense that it affects the production of movement together with a range of voluntary and non-voluntary (reflex) movement control functions.
<table>
<thead>
<tr>
<th>Terms</th>
<th>Definitions and source publications*</th>
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<tr>
<td><strong>Prediction</strong></td>
<td>In this thesis, prediction was defined as “the process of determining the magnitude of statistical variates at some future point of time. In statistical contexts the word may also occur in slightly different meanings; e.g. in a regression equation expressing a dependent variate y in terms of dependent x’s, the value given for y by specified values of x’s is called the “predicted” value even when no temporal element is involved”. (Marriott &amp; Kendall, 1990, cited in Statistical Portal, 2005)</td>
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<td><strong>Biomarker</strong></td>
<td>“Biomarkers are indicators of disease state that can be used clinically as a measure reflecting underlying molecular/ cellular processes that may be difficult to measure directly in humans, and could be used to predict recovery/ treatment response” and include “…markers of biology (blood, genetics), imaging (structural, functional, chemical), neurophysiology (patterns of brain excitability or electrical activity), or combinations of such.”(Bernhardt et al., 2016).</td>
</tr>
<tr>
<td><strong>Rehabilitation</strong></td>
<td>“A set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment” (WHO, 2021).</td>
</tr>
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</table>
| **Recovery and Outcome** | In this thesis, recovery was defined as “the extent to which an individual’s body structure and/or functions*, as well as activities*, have returned to their pre-stroke state” (Bernhardt, Hayward, et al., 2017), over a defined time period.  
‘Outcome’ was defined as ‘an individual’s status (e.g. a motor score), at a predefined future time point’.  
*Regarding the International classification of Functioning, Disability and Health (ICF) taxonomy (World Health Organization, 2020), see Appendix A. |
| **Behavioural restitution / ‘true recovery’** | “A return towards more normal patterns of motor control with the impaired effector (a body part such as a hand or foot that interacts with an object or the environment) and reflects the process toward ‘true recovery’. ‘True recovery’ defines the return of some or all of the normal repertoire of behaviours that were available before injury.”(Bernhardt, Hayward, et al., 2017) |
| **Compensation** | In this thesis, compensation was defined as an individual’s new motor behaviour not seen in healthy subjects, developed to accomplish a goal with this person’s post-stroke residual strength and motor control functions.  
Compensation may include all body parts, including both the more and less affected upper extremity. Compensation replaces a normal pre-stroke (motor) behavioural repertoire due to stroke induced arm and hand motor impairment (Bernhardt, Hayward, et al., 2017). |
| **Spasticity** | “Spasticity is a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes, (‘muscle tone’) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as a component of the upper motor neuron syndrome.”(Lance, 1980) |
| **Hand spasticity** | Hand spasticity, was in thesis defined as: ‘A neural component, as quantified with the NeuroFlexor© method (Lindberg et al., 2011), exceeding the threshold of 3.4N, determined in a group of healthy control subjects’ (Pennati, Plantin, Borg, & Lindberg, 2016) and refers to muscle groups acting on wrist and/or fingers. |
| **Time periods of recovery after stroke** | “Hyper-acute: 0-24 hours; Acute: 1-7 days; Early subacute: 7 days-3 months; Late subacute: 3-6 months; Chronic: >6 months”. (Bernhardt, Hayward, et al., 2017). |

*This is the source for the definitions applied in this thesis and presented this list of terms. This may or may not be the original source for the definition.
Results from earlier neuroimaging studies demonstrate divergent lesion characteristics (Burke Quinlan et al., 2015; Siegel et al., 2016; Ward et al., 2007) and resulting heterogeneous sensorimotor impairments after stroke (Grafton, 2010; Lang & Schieber, 2003, 2004; Lang et al., 2005; Nowak, 2008; Wenzelburger et al., 2005). Impairments and disability reported in stroke research is variable and encompass affected force generation and force control, reach and grasp movements, bimanual hand use and non-voluntary movement control function. Below follows a descriptive summary of arm and hand motor impairments following stroke.

1.2.1 Loss of muscle power and the control of movement

Weakness strongly contributes to arm and hand motor impairment after stroke (Kamper, Fischer, Cruz, & Rymer, 2006). A typical distribution of post-stroke unilateral weakness follows a distal to proximal gradient, where muscles acting on the wrist, hand and fingers are more severely affected than muscles of the elbow and shoulder (Colebatch & Gandevia, 1989). However, as commented by Twitchell (1951), the distribution of weakness varies between individuals. For example, voluntary movement of wrist and finger flexors may be partially preserved in patients with profound proximal weakness (Colebatch & Gandevia, 1989; Mercier & Bourbonnais, 2004). An imbalanced distribution of weakness between flexor and extensor muscles of the arm and hand has also been reported, i.e. more pronounced weakness in extensor muscles relative to flexors (Griffin, Hoffman, & Strick, 2015; Hoffmann, Conrad, Qiu, & Kamper, 2016). However, findings are inconclusive in the sense that equally weak or even more weakness in flexor muscles (relative to the less affected arm and hand) have been reported (Colebatch, Gandevia, & Spira, 1986; Mercier & Bourbonnais, 2004). One explanation for the inconsistent findings might be differences between the cohorts studied, regarding for example lesion location and/or severity of hand motor impairment. In a recent study that included a large cohorts of patients with severe arm and hand motor impairments (mean Fugl-Meyer score = 15 of maximum 66 and mean grip strength = 4kg), only 6 out of 95 individuals could produce any voluntary finger extension (assessed as net rotation torque around the metacarpophalangeal [MCP] joint) (Barry, Kamper, Stoykov, Triandafilou, & Roth, 2021). These results are in line with earlier studies suggesting that among patients with severe hand motor impairment, finger extension is particularly affected (Hoffmann et al., 2016; Kamper & Rymer, 2001).

Along with a significant reduction of force magnitude, stroke related hand motor impairment is characterized by irregularities in force production and control (Ada, Odwyer, Green, Yeo, & Neilson, 1996; Barry et al., 2021; Blennerhassett, Carey, & Matyas, 2006; Dewald & Beer, 2001; Zackowski, Dromerick, Sahrmann, Thach, & Bastian, 2004). Imbalance between forces produced by the agonist and antagonist muscle groups have been reported, for example during finger extension (Kamper & Rymer, 2001). Co-activated antagonist (e.g. wrist flexor) muscles interrupt the movement or act against the intended direction (e.g. wrist extension). Excessive antagonist co-activation, regardless of intended movement direction (extension or flexion), has been observed around the wrist joint (Chae, Yang, Park, & Labatia, 2002), elbow (Levin, Selles, Verheul, & Meijer, 2000; Vinti et al., 2012) and shoulder (Dewald &
Unintentional co-activation of adjacent digits when intending to perform isolated finger movement is also characteristic for hand motor impairment after stroke (Lang & Schieber, 2003, 2004; Wolbrecht et al., 2018; Zackowski et al., 2004). Irregularities regarding force steadiness and accuracy (Kang & Cauraugh, 2015; Lindberg et al., 2012; Lodha, Naik, Coombes, & Cauraugh, 2010; Naik, Patten, Lodha, Coombes, & Cauraugh, 2011), as well as delayed force initiation and release (Lindberg et al., 2012; Seo, Rymer, & Kamper, 2009) have also been reported.

Weakness of the muscles controlling finger movements (Garcia Alvarez, Roby-Brami, Robertson, & Roche, 2017; Kamper et al., 2006), impaired finger extension (Lang, DeJong, & Beebe, 2009) and impaired finger individuation (Lang & Schieber, 2003) severely affects grasping abilities after stroke. Different hand motor impairments observed among stroke survivors may contribute to development of compensatory grasping strategies, for example, reduced hand aperture (Kamper & Rymer, 2001), abnormal scaling of forces (Eidenmüller, Randerath, Goldenberg, Li, & Hermsdörfer, 2014; Hermsdörfer, Hagl, Nowak, & Marquardt, 2003), reduced work space of hand and fingers (Cruz, Waldinger, & Kamper, 2005; Wolbrecht et al., 2018), slowed movement and reduced flexibility of hand and finger movements (Roby-Brami, Bennis, Mokhtari, & Baraduc, 2000). This results in difficulty in adapting hand and finger configuration to the requirements that come with objects’ size, shape and position and task demands (Michaelsen, Jacobs, Roby-Brami, & Levin, 2004; Parry et al., 2019; Raghavan, Santello, Gordon, & Krakauer, 2010; Touvet, Roby-Brami, Maier, & Eskiziitmirliler, 2014).

Precision grip, used for example in picking up and manipulating small objects (Wenzelburger et al., 2005), is particularly affected by lesions to sensorimotor cortical areas and descending motor pathways due to stroke. Common deficits include unwanted coupling of intrinsic and extrinsic muscles controlling the index finger and thumb, which impair coordination between the fingers (Jones & Kamper, 2018). Wenzelburger et al. (2005) reported exaggerated forces during precision grip and prolonged time for hand configuration while preparing for thumb-index precision grip. A study of isometric precision grip and lift task in patients with late effects of stroke (>6 months from onset), reported impaired force scaling with more irregular and exaggerated forces in stroke patients compared to controls, despite the patient group having relatively preserved pinch grip strength (Nowak et al., 2007). A more recent study found impaired force scaling, coordination and speed of movement related to impaired grasping behaviour among stroke survivors (Allgöwer & Hermsdörfer, 2017).

Reach-to-grasp of objects is a common movement component in the performance of daily activities. A kinematic study showed equally impaired (proximal) arm and (distal) hand movements during reach to grasp, as indicated by movement parameters (for example regarding movement trajectories during arm transport or hand opening and closing to grasp the target item) (Lang et al., 2005). Typically, impaired prehension and reaching are closely interrelated, and involve movements of the trunk and posture (G. M. Johansson, Frykberg, Grip, Broström, & Häger, 2014; Kline, Schmit, & Kamper, 2007; Michaelsen et al., 2004;
Robertson & Roby-Brami, 2011; Roby-Brami et al., 2000; Roby-Brami, Feydy, et al., 2003). Regarding reach-to-grasp movements, significantly reduced peak velocity and reduced arm movement speed and decreased smoothness are reported among stroke survivors as compared to healthy control subjects (Collins, Kennedy, Clark, & Pomeroy, 2018; Kamper, McKenna-Cole, Kahn, & Reinkensmeyer, 2002). Further, impaired elbow extension and shoulder flexion during reach-to-grasp diminish workspace and reach-to-grasp is therefore often accompanied by compensatory trunk displacement, serving to gain extra movement range (Roby-Brami, Feydy, et al., 2003; Roby-Brami, Jacobs, Bennis, & Levin, 2003). Movement quality (e.g. path deviation and poor grasp configuration) has been shown to vary with the distance to the target and the direction of movement, where larger deviations follow movement at larger distances and into the opposite hemispace (Roby-Brami et al., 2000). Compensatory movements during reach-to-grasp as well as related deficits of coordination are primarily observed in patients with moderate to severe overall arm and hand motor impairment (Cirstea & Levin, 2000).

Both post stroke weakness and impaired movement control functions are strongly associated with reduced ability to perform activities of daily living, impacting on participation and quality of life (Mayo, Wood-Dauphinee, Cote, Durcan, & Carlton, 2002). Impaired arm and hand function affects independent completion of activities involving manipulation of objects, e.g. tying a knot, turning a coin with the fingers or lifting and displacing a cup (Wenzelburger et al., 2005), and (based on self-rated performance), the use of the hands together (Basílio et al., 2016).

1.2.2 Bimanual impairment and disability

Few studies have investigated bimanual hand use after stroke. The existing literature has mainly focused on kinetic (the study of forces and/or energy associated with movement) and kinematic (the study of motion, without reference to the masses or forces involved in it) aspects of bimanual motor control, rather than actual hand use during bimanual activity performance (Kantak, Jax, & Wittenberg, 2017; Obhi, 2004). Poor inter-limb coordination has been reported in hemiparetic patients, especially at movement onset (Kantak, Zahedi, & McGrath, 2016; R. K. Kim & Kang, 2020; Wu et al., 2009). Movement time and trajectory of the less affected hand have been reported to be adapted to match the more affected hand at movement endpoint (Obhi, 2004; Wu et al., 2009). Impaired matching of grip force between the hands has also been reported (R. K. Kim & Kang, 2020; Lodha, Coombes, & Cauraugh, 2012). Meyer, De Bruyn, Krumlinde-Sundholm, et al. (2016) used a novel clinical observation based assessment instrument (Krumlinde-Sundholm, Lindkvist, Plantin, & Hoare, 2019), in a large cohort of 122 individuals, 6 months after a first stroke. The authors found overall poor involvement of the more affected hand during bimanual task performance in that cohort (median [IQR] = 51 [14-80] of maximum 100 units). The authors also reported a significant association between less efficient bimanual hand use and more severe somatosensory impairment and spatial neglect.
1.2.3 Sensory and cognitive contributions to upper limb impairments

The significance of somatosensory feedback for dexterous hand movements and efficient handling of objects is well documented (R. S. Johansson & Westling, 1987; Westling & Johansson, 1984). Several somatosensory modalities may be affected by stroke (Carey & Matyas, 2011; Meyer, De Bruyn, Lafosse, et al., 2016; Welmer, von Arbin, Murray, Holmqvist, & Sommerfeld, 2007), for example proprioception (sensing position and movement of the body or body parts), touch and/or tactile discrimination (the ability to distinguish between e.g. materials of different qualities by the sense of touch). Somatosensory impairment has been shown to contribute to grasping deficits (Blennerhassett, Matyas, & Carey, 2007; Nowak & Hermsdorfer, 2003) and to impaired reaching capability (Wagner et al., 2006; Zackowski et al., 2004) after stroke. In a longitudinal study, two-point discrimination and muscle strength, measured at 2 weeks post-stroke, were significantly associated with outcome for dexterous hand function at 6 months (Au-Yeung & Hui-Chan, 2009).

Efficient grasping and fine hand use also require cognitive resources such as attention and executive function (Guillery, Mouraux, & Thonnard, 2013; Mullick, Subramanian, & Levin, 2015). A number of studies indicate that impaired cognitive function may contribute to motor impairment and limited recovery (Chen, Leys, & Esquenazi, 2013). In a meta-analysis, Mullick et al. (2015) found that studies using quantitative measures of arm and hand motor impairment, such as kinematic measures, showed stronger relationships between degree of motor recovery after stroke and early cognitive status. In a recent study including 167 patients, Rinne et al. (2018) found a disassociation between motor function and attention such that severe motor impairment occurred in patients with intact or impaired attention, but normal motor performance did not co-exist with impaired attentional processes. The authors concluded that motor control in the hand requires intact attention control. In another large stroke cohort (N=172), Ramsey et al. reported a correlation between attention and motor impairment (Ramsey et al., 2017). Finally, a recent study on upper limb dual tasking in stroke patients also found a moderate correlation between the decrement in motor performance while performing a simultaneous cognitive task (i.e., dual-task effect) and motor impairment (measured using the Fugl-Meyer assessment) (Bank et al., 2018). Together these studies suggest an important cognitive contribution, especially regarding attention, to performance of hand motor tasks and clinical measures of hand motor impairment in stroke.

1.2.4 Spasticity

It has been postulated that spasticity may contribute to dysfunctional movement of the upper extremity (‘disabling spasticity’) (Lundström, Terent, & Borg, 2008). Spasticity is a multidimensional motor disorder that occurs commonly after stroke with arm and hand paresis (Lundström, Smits, Terent, & Borg, 2010; Opheim, Danielsson, Alt Murphy, Persson, & Sunnerhagen, 2014; Sommerfeld, Eek, Svensson, Holmqvist, & von Arbin, 2004; Urban et al., 2010) A core clinical sign of spasticity is the exaggerated stretch reflex, manifested by an increased resistance to passive muscle stretch (Brown, 1994; Gracies, 2005b; Kamper,
Spasticity is associated with altered passive mechanical properties in the soft tissues surrounding a joint, also manifested by increased joint stiffness (Gracies, 2005a; O'Dwyer & Ada, 1996). Spasticity is often associated with a more severe sensorimotor impairment, reduced passive range of movement and joint pain (Opheim et al., 2014).

The pathogenesis of spasticity and its contribution to impaired motor control is a matter of ongoing discussion (Dietz & Sinkjaer, 2007; Krakauer, 2005; Lackritz et al., 2021; Li & Francisco, 2015). In broad terms, spasticity is considered a motor impairment, and is classified as an impaired muscle tone function within the ICF-framework (WHO, 2001), developing over a period of time after stroke and other lesions within the central nervous system. Alternative definitions and conceptualizations of spasticity have been proposed (Balakrishnan & Ward, 2013; Calota & Levin, 2009; Mirbagheri, Tsao, & Rymer, 2009), the definition by Lance (1980) being the most commonly cited (Malhotra, Pandyan, Day, Jones, & Hermens, 2009): “spasticity is a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes, (´muscle tone´) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as a component of the upper motor neuron syndrome”. Aimed to capture a wider range of clinical presentations of spasticity, the SPASM consortium, suggested the following definition: “disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles” (Pandyan et al., 2005), arguing that spasticity may not be a purely neurophysiological phenomenon and that a more descriptive definition would therefore be more appropriate. However, this definition does not offer a framework to which an appropriate measure could be matched. In contrast, the narrower definition of spasticity, proposed by Lance (1980), enables specific quantification of distinct sources of resistance to passive muscle stretch, i.e. neural (stretch-reflex) related resistance and non-neural biomechanical resistance. Therefore, the definition by Lance seems to date to be the most adequate (Dietz & Sinkjaer, 2007; Gracies, 2005a; Lorentzen et al., 2010; Malhotra et al., 2009).

There remains a gap between the most commonly applied clinical method for assessment of spasticity, i.e. graded resistance to manually imposed muscle stretch (Ashworth, 1964; Bohannon & Smith, 1987), and the definition of spasticity by Lance (Lance, 1980). It is difficult, by manual tests alone, to distinguish between hyper-excitable stretch-reflexes and mechanical resistance originating from altered soft tissue properties in a reliable and valid way (Fleuren et al., 2010; Malhotra et al., 2009). Thus, there remain scientific and clinical challenges to gain a better understanding of how spasticity evolves over time and how spasticity relates to recovery of voluntary hand motor function.
1.3 RECOVERY OF ARM AND HAND SENSORIMOTOR IMPAIRMENT OVER THE FIRST YEAR AFTER STROKE

1.3.1 Spontaneous biological recovery
The highly heterogeneous picture of sensorimotor impairments and disability described above, is largely based on findings in the chronic phase after stroke, i.e. more than 6 months after stroke onset (Bernhardt, Hayward, et al., 2017). During this phase, stroke survivors experience the long term effects of stroke, when the process of recovery is mainly dependent on therapy-induced mechanisms (Cassidy & Cramer, 2017), and improvement of motor impairment as an effect of time alone is minimal (Kwakkel, Kollen, & Twisk, 2006). A major proportion of hand motor recovery occurs during the first weeks and months post stroke (for proposed definitions of recovery phases, see Table 1), (Duncan, Lai, & Keighley, 2000; Kwakkel et al., 2006). This process of change is often referred to as spontaneous recovery or spontaneous biological recovery (Bernhardt, Hayward, et al., 2017; Cassidy & Cramer, 2017; Cramer & Riley, 2008; Dobkin & Carmichael, 2016; Dromerick et al., 2015). In response to the stroke induced neural injury, a series of time dependent biological mechanisms are active. Some of these mechanisms are active, primarily during the first hours and days and may cause further injury (e.g. inflammatory processes), while some significantly facilitate neural reorganization and repair (Bernhardt, Hayward, et al., 2017; Dobkin & Carmichael, 2016). These beneficial endogenous plasticity mechanisms may be enhanced by therapeutic interventions (Cassidy & Cramer, 2017; Dancause & Nudo, 2011).

1.3.2 Longitudinal cohort studies after stroke
A series of longitudinal prospective studies have demonstrated this time dependent pattern of recovery among stroke survivors, often in terms of change as a function of time (Langhorne, Bernhardt, & Kwakkel, 2011). When plotted, the graph takes the shape of a reversed logarithmic curve, with an exponential increase followed by a gradual flattening of the slope (showing a plateau effect) (Biernaskie, Chernenko, & Corbett, 2004; Cortes et al., 2017; Duncan et al., 2000; Kwakkel, Kollen, & Lindeman, 2004). This general pattern has been demonstrated regarding recovery from arm and hand sensorimotor impairment (Beebe & Lang, 2009; Duncan, Goldstein, Matchar, Divine, & Feussner, 1992; Duncan et al., 2000; Kwakkel, Kollen, van der Grond, & Prevo, 2003; Persson, Parziali, Danielsson, & Sunnerhagen, 2012; Semrau et al., 2015; van Kordelaar, van Wegen, & Kwakkel, 2014) and from activity limitations (Beebe & Lang, 2009; Nijland, van Wegen, Harmeling-van der Wel, & Kwakkel, 2010; Semrau et al., 2015) after stroke. However, at an individual level, these studies together have demonstrated highly variable patterns of change and outcome.

There are also reported differences regarding the degree and pace of recovery at group level (Cortes et al., 2017; Duncan et al., 2000; Kwakkel & Kollen, 2007). For example, rate and pace of recovery may differ significantly between subgroups with differing initial impairment severity (Duncan et al., 2000; Kwakkel et al., 2003). Although the extent of recovery may be more limited among individuals with a more severe stroke, recovery may be extended over a longer period of time in this group (Duncan et al., 2000). Importantly, recovery and outcome
in the same group of patients may differ depending on how outcome is defined (dichotomous outcome categories or continuous scales) and depending on the domain assessed (disability versus impairment) (Kwakkel & Kollen, 2007). Common to these reports however, is the illustration of a striking degree of residual impairment and activity limitation for a large proportion of stroke survivors after the first months of recovery have passed.

Another group of studies have suggested that post-stroke recovery not only shows a similar pattern in relation to time, but also suggest that extent of recovery is typically proportional to the initial degree of impairment, reaching on average around 70% of the initial residual impairment (Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; Prabhakaran et al., 2008; Winters, van Wegen, Daffertshofer, & Kwakkel, 2015). It is further implicated that this ‘fixed’ proportion is determined by limited capacity of spontaneous biological recovery processes (Byblow et al., 2015; Winters et al., 2015). For example, if a patient’s hypothetical initial score is 3 out of maximal 10, residual impairment equals 10-3=7 points and estimated proportional recovery 7 * 0.70 = 4.9. A proportional recovery rule has also been suggested for visuospatial neglect and aphasia (Lazar et al., 2010; Winters, van Wegen, Daffertshofer, & Kwakkel, 2017). Further, according to this model, the recovery rule is not applicable across the full range of initial impairment. Typically, plots of individual data-points representing expected recovery versus actual recovery, generate a homogenously distributed straight regression line, plus a cluster of ‘outliers’ or ‘non-fitters’, representing data from a subgroup of patients with severe initial impairment and minimal recovery across time (Winters et al., 2015).

Several recent publications have questioned the proportional recovery rule due to statistical bias related to factors such as mathematical coupling between initial scores and estimates of recovery (Bowman, Bonkhoff, Hope, Grefkes, & Price, 2021; Hawe, Scott, & Dukelow, 2018; Hope et al., 2019), and strongly encourage caution when making choices regarding of methods of analysis, defining outcomes and when drawing conclusions from statistical associations (Lohse, Hawe, Dukelow, & Scott, 2021). Although there may be a risk of overestimating the significance of the fixed recovery rule, these studies are reflective of a considerable residual arm and hand motor impairment in a majority of patients at 3-6 months post stroke. They also point out the need for increased understanding of the underlying biological processes of recovery that may open new opportunities for the development of interventions specific to certain subgroups and may even allow individually tailored therapeutic interventions (Byblow et al., 2015; Prabhakaran et al., 2008; Winters et al., 2015).

A growing area of research concerns the longitudinal development of stereotypical synergistic movement patterns post stroke (Dewald & Beer, 2001; McMorland, Runnalls, & Byblow, 2015; Roh, Rymer, & Beer, 2015), and the role of the integrity and recruitment of residual descending motor pathways for the ability to perform fractionated movements (McMorland et al., 2015; McPherson et al., 2018). It is hypothesized that an upregulation of the contralesional cortico-reticulospinal tract (CRST) contributes to these observed stereotypical movement patterns to the cost of corticospinal tract (CST) dependent,
fractionated and dexterous movements (McPherson et al., 2018). In a recent large retrospective cohort study (n=319), Senesh, Barragan, and Reinkensmeyer (2020) identified a negative correlation between recovery of dexterity (assessed with the Box and Block Test) and performance of ‘in-synergy’ arm movements (according to the Fugl-Meyer Assessment). Concurrently, a strong positive relationship was observed between dexterous ability and performance on ‘out-of-synergy’ movements. These findings are in line with the neuroanatomical hypothesis of an imbalance between the CRST and CST, impeding acquisition of skilled movements after stroke. It is as yet unproven whether the balance between descending motor pathways is modifiable and possible to exploit in post stroke rehabilitation programs, which should encourage combinations of modality specific assessment tools together with neuroimaging examinations should be in future studies of post stroke recovery.

The studies mentioned above underline the need for the development of new effective rehabilitation interventions and suggest possible targets. A large number of pre-clinical (Biernaskie et al., 2004; Sugiyama et al., 2013) and clinical trials (Corbetta, Sirtori, Castellini, Moja, & Gatti, 2015a; Pollock et al., 2014; Veerbeek et al., 2014) have addressed this problem. Interventions evaluated in animal models during the early period of high neuroplasticity include early initiated therapy (Biernaskie et al., 2004), exposure to increased positive social and environmental stimulation (Biernaskie & Corbett, 2001; B. B. Johansson & Ohlsson, 1996) and intensified skilled movement-practice (Adkins, Boychuk, Remple, & Kleim, 2006; Nudo, Milliken, Jenkins, & Merzenich, 1996) but these findings have not yet resulted in successful human applications (Birkenmeier, Prager, & Lang, 2010; Dromerick et al., 2009).

1.3.3 Intervention induced recovery in the chronic phase after stroke

Clinically meaningful recovery has been achieved by the use of high therapy dosage, although sufficiently large numbers of therapy hours and repetitions may not be tolerated by all patients (Kwakkel, van Peppen, et al., 2004; Schneider, Lannin, Ada, & Schmidt, 2016). A well-studied therapeutic intervention targeting arm and hand motor impairment and activity limitation after stroke is constrained induced movement therapy, CIMT. This concept, originally developed in animal-models (Taub, 2012), supports high-intensity and gradually increased demands on the skilled use of the more affected hand while restraining use of the less affected hand. Today, many national guidelines and best practice recommendation include CIMT as a post-stroke intervention for patients with mild to moderate hemiparesis after stroke (Hebert et al., 2016; Winstein, Stein, et al., 2016). Accumulated data in meta-analyses support high-intensity and repetitive task-specific practice such as CIMT (Veerbeek et al., 2014). However, other studies have reported only modest treatment induced improvement (Corbetta, Sirtori, Castellini, Moja, & Gatti, 2015b; Kitago et al., 2013; Langhorne, Coupar, & Pollock, 2009; Schneider et al., 2016; Veerbeek et al., 2014; Winstein, Wolf, et al., 2016). Further, questions remain regarding the optimal timing of interventions, the interaction between timing and intensity (Dromerick et al., 2009), and the choice of
therapeutic approaches that may optimize the inherent potential for recovery in an individual, given that individuals have specific health profile and unique stroke lesion characteristics (Hunter et al., 2017; Kwakkel et al., 2016).

The findings from the clinical trials mentioned above, show that upper limb motor recovery is (i) sub-optimal in the first months after stroke for many patients and (ii) efficient interventions in the chronic phase are lacking. This argues for the need for more personalized interventions. Rehabilitation approaches that are targeted to the individual patient’s needs and specific arm and hand motor impairment profile would likely be more effective (Cassidy & Cramer, 2017; Hummel & Cohen, 2006; Plow, Cunningham, Varnerin, & Machado, 2015), which would likely reduce long-term negative effects of stroke on activity and participation in everyday life (Ytterberg, Dybäck, Bergström, Guidetti, & Eriksson, 2017). An important first step in the development of targeted rehabilitation approaches is to be able to measure individual motor impairments in a more nuanced way.

In the next section, some work on upper limb motor impairment assessment using kinematic and kinetic approaches is summarized. Some of the assessment methods applied may potentially contribute to future development of targeted upper limb interventions post stroke. A brief summary of what we know today regarding prediction of arm and hand sensorimotor recovery is also provided.

1.3.4 Kinematic studies after stroke

Kinematics is the study of body movement through measurement of joint angles or displacement of body parts. Findings from kinematic studies show that patients gradually improve in smoothness of reaching and grasping during the first approximately 8 weeks after stroke onset, thus following a similar recovery pattern as previously found with clinical assessment (van Kordelaar et al., 2014). Assessment of movement quality has also been studied in combination with functional MRI (Hidler, Hodics, Xu, Dobkin, & Cohen, 2006). For example, in a longitudinal study including recovering patients with stroke (n=17), Buma et al. (2016) assessed smoothness of grasp aperture using 3D kinematics while the patient was in the scanner. The authors found a significant association between improved movement quality and increased recruitment of secondary sensorimotor areas in both hemispheres. Moreover, kinematic measures have been shown to provide valuable information about the coupling between elbow and shoulder movements during reaching. Thereby, new knowledge has been gained regarding illustrating how patient’s movement patterns tend either to normalize or to develop compensatory and less beneficial strategies during the course of time post stroke. For example, Roby-Brami, Feydy, et al. (2003) showed that kinematic measures of hand movement during reaching and grasping measured longitudinally differed significantly between patients with ‘good’ and ‘poor’ recovery. Patients with more severe hemiparesis used less fractionated movements, such as elbow extension and elbow flexion, and more compensatory movements, like trunk displacement, during reaching. There is a knowledge gap remaining regarding the relation between type of impairments, spatial and temporal movement characteristics, and neural correlates after stroke. In addition, a limitation
of kinematic studies is related to potential floor effects, as the patient needs to have some residual voluntary movement control for kinematic measurements to be possible.

1.3.5 Kinetic studies after stroke
Kinetics, the study of forces, has been applied to the upper limb after stroke, in particular to the study of grip force control (Nowak, 2008). Cross-sectional reports in the chronic phase after stroke (>6 months) show impaired grip and lift movements and force scaling during grasping (Eidenmüller et al., 2014; Hermsdorfer, Hagl, Nowak, & Marquardt, 2003). Grip force has been shown to be possible to assess in patients with limited residual hand function (Lindberg et al., 2012). Studies on kinetic control of grip forces have been performed in stroke patients at different time points during recovery (Nowak, Hermsdorfer, & Topka, 2003). Individuated finger movements and force control are especially dependent on the integrity of the motor cortex or descending corticofugal pathways (e.g. the cortico reticulospinal tract), and are potentially important for the identification of unwanted compensatory movements (Lang & Schieber, 2004). However, the study of kinetics has not yet been fully exploited in movement research and clinical context and longitudinal studies using kinetic outcome variables are lacking.

1.4 PREDICTION OF OUTCOME AND RECOVERY AFTER STROKE
1.4.1 Clinical markers of recovery
Prediction is commonly applied in different medical disciplines and in research, and with varying purpose and method, depending on the specific context (Rosso & Lamy, 2020). For example, at an acute stroke unit, reliable prediction is vital for informing the patient and the patients family on the expected outcome and long-term consequences of the patient’s condition, and to guide short term and long term planning of treatment. In the context of a clinical trial, prediction may be aimed at stratifying patients to different treatment arms, based on the individual’s predicted recovery potential, and thereby facilitate interpretation of treatment results. Prediction of arm and hand sensorimotor recovery after stroke is difficult, much depending on the heterogeneous characteristics of neurological impairments and highly variable recovery trajectories (Horn, Grothe, & Lotze, 2016; Stinear & Byblow, 2014). In this section, some key work on early post-stroke determinants of arm and hand motor outcome and recovery are presented.

Sunderland, Tinson, Bradley, and Hewer (1989) studied the predictive value of grip strength in a cohort of 38 patients with hand motor impairment. Assessments of grip strength were performed at 4 time points, from 3 weeks to 6 months after stroke, in combination with 5 other clinical tests. A beneficial outcome was defined as having a score above zero on the Frenchay Arm test (Heller et al., 1987), an activity measure of functional tasks. The authors found that the patients with no measurable grip strength at 1 month did not improve in grip force at 6 months and had no return of activity performance in all but one case. The patients
in this study had similar average recovery pattern in relation to time, regardless of test used. Moreover, this study suggests that poor initial motor function is indicative of limited recovery, but does not inform about individual variations, nor the underlying process of recovery.

Further, in a prospective study (n=48), Smania et al. (2007) showed that simple bedside tests, especially finger extension and shoulder movement, assessed at one week after stroke onset, may be predictive of voluntary movement outcome (at three and six months after the stroke injury). In a later prospective study, with 188 patients with hemiparesis, the predictive value of voluntary finger extension and shoulder abduction was investigated (Nijland et al., 2010). Beneficial recovery was defined as having ≥10 points (out of maximum 57 points) on the Action Research Arm Test (ARAT) (Lyle, 1981). The authors found that the patients who could perform the finger extension and shoulder abduction test within 72 hours after stroke onset, had a probability of 98 % for regaining some dexterity by six months, compared to 25 % in the group that could not perform the test. However, the definition of beneficial recovery used in this study (ARAT ≥10) provides limited information about the final activity capacity. In addition, the same group recently showed that some recovery occurs also in the group of patients with no initial hand function (Houwink, Nijland, Geurts, & Kwakkel, 2013; Winters, Kwakkel, Nijland, van Wegen, & consortium, 2016).

Another prediction study combined rapid clinical testing of upper limb movements with neurophysiological measurement of corticospinal excitability (presence or absence of motor evoked potential using TMS) and MRI evaluation of integrity of corticospinal tract structure (the Predicting Recovery Potential, PREP algorithm) (Stinear, 2010). Motor outcome was defined as ARAT-based recovery categories (limited, notable, near complete, complete). Assessments made within 72 hours from stroke onset were used to predict outcome at 3 months. In the PREP algorithm, the first stratification step is determined by adding the Medical Research Council grades for the selected movements (the SAFE-score) ranging from 0-10. Patients with a score ≥8 within 72 hours after stroke onset are predicted to have a complete or near complete recovery. The next level of predicted recovery; notable outcome, is determined by the presence or absence a motor evoked potential (MEP+/−) in a selected muscle of the affected hand, during TMS over the motor cortex of the lesioned hemisphere. In case of no identified motor evoked potential (MEP−), a diffusion-weighted MRI examination is performed providing more detailed information on the degree of damage to descending white matter pathways of the motor system. A cut-off value has been identified for the stratification of patients with potential of limited recovery versus “a point of no return” meaning that no potential recovery is expected. This prediction model has been validated and further refined in a cohort with 40 patients (Stinear, Barber, Petoe, Anwar, & Byblow, 2012) in which the model explained 80% of the variance (partial η2=0.811) in this specific sample.

These studies represent improvements in the precision of prediction of motor outcome. However, models like the PREP algorithm, do not provide information about changes that occur during recovery, in e.g. motor performance measures or in the respective neural
correlates, nor regarding potential targets for interventions. Combining clinical and neurophysiological measures seems to be promising, however studies exploring how neuronal and behavioural factors change and interplay over time after stroke may improve prediction of long-term outcome and support the development of individualized interventions.

### 1.4.2 Magnetic Resonance Imaging – role in prediction of hand motor recovery

A number of neuroimaging studies have demonstrated the predictive value of structural integrity of the corticospinal tract for hand motor function after stroke. These findings concern prediction of level of hand motor function in the chronic phase (Lindenberg et al., 2010; Lo, Gitelman, Levy, Hulvershorn, & Parrish, 2010; Stinear et al., 2007; Wolbrecht et al., 2018), as well as prediction of long-term outcome (Groisser, Copen, Singhal, Hirai, & Schaechter, 2014) and recovery (Doughty et al., 2016; Feng et al., 2015) in acute stroke patients.

In order to address shortcomings in rehabilitation efficacy and to guide the design and stratification of patients in new clinical trials, a better understanding of the underlying mechanisms that drive recovery of motor function after stroke is needed (Corbetta et al., 2015b).

It is still unclear how brain activation patterns are related to specific aspects of motor impairments and recovery of function after stroke (Baldassarre, Ramsey, Siegel, Shulman, & Corbetta, 2016). The high anatomical resolution of MRI techniques allows for detailed non-invasive three dimensional mapping of the brain. In the study of motor recovery, several imaging techniques have been applied to map lesion location and volume, changes in brain structure and function and may potentially contribute to the understanding of recovery trajectories and neural correlates of motor behaviour after stroke (Stinear & Ward, 2013).

Functional MRI (fMRI) makes use of the variability of the Blood Oxygen Level Dependent (BOLD) signal a sensitive measure of cortical activity. Resting state fMRI, a development of this technique, measures spontaneous fluctuations in the BOLD signal in distributed areas of the brain that are functionally linked while the patient is awake and completely at rest, and can thus inform about changes in brain connectivity in specific areas of interest, also in patients that have no voluntary motor function. Using resting state fMRI in a longitudinal study with 31 patients with motor impairment following stroke, Golestani, Tymchuk, Demchuk, Goodyear, and Group (2013) showed that connectivity in key motor networks correlated significantly with measures of upper extremity motor impairments over time.

Similar results were found in a longitudinal study by Rosso et al. (2013). Forty patients with ischemic stroke and impaired motor function, and 28 healthy subjects were enrolled. Functional connectivity between ´regions of interest´, correlated significantly with NIHSS motor sub-scores for arm and hand. The strongest determinant of recovery of upper limb motor function however, was degree of integrity of the corticospinal tract (CST), previously
shown to be a potential marker for motor recovery (Lindenberg et al., 2010). The structural axonal connectivity of the CST was quantified with fractional anisotropy values from diffusion tensor imaging (DTI) which provides sensitive quantification of white matter microstructure.

Another method to quantify CST integrity has been presented by Zhu, Lindenberg, Alexander, and Schlaug (2010). This group developed an alternative method to investigate stroke lesion engagement of the CST by overlaying the respective image of the patient’s lesions by manually drawing the patient’s lesion on each slice of the normalized T1-weighted anatomical image, with a probabilistic map based on images from a group of healthy controls. Thereby an estimated measure of lesion overlap on the CST can be calculated. This method also takes into account (weights) the anatomical structure of descending pathway, given that specific levels of the CST is especially vulnerable to injury (thus weighted CST lesion load/ wCST-LL).

To evaluate the relationship between motor impairment according to the FMA-UE and wCST-LL this group performed a study in which 50 patients with chronic stroke and moderate to severe motor impairment were enrolled (Zhu et al., 2010). Regression analysis of the behavioural data and wCST-LL measures showed highly significant association between lesion load and degree of motor impairment, also when taking the total lesion volume into account. Together, these MRI studies are promising for improving prediction of recovery. However, studies linking anatomical and functional neural integrity measures to quantitative behavioural measures are lacking (Boyd et al., 2017).

Altogether, these studies illustrate the unsatisfying results found in rehabilitation intervention studies and discrepancies regarding therapeutic approaches and methods of evaluation, as well as in timing of intervention and sample characteristics. This complicates interpretation and generalization of results which is a problem for matching interventions to the individual needs. Stratification of patients in clinical trials is also an important matter in this context, since differences in outcome that are attributed to different therapies, could in part also be explained by for example a patient’s specific impairment profile, type of lesion or age.

### 1.5 RATIONAL OF THIS THESIS

In studies of hand function recovery, the most commonly applied outcome measure is the Fugl-Meyer Assessment that provides information about basic components of voluntary movement control functions. In this and other commonly applied outcome measures, two subjects with identical initial scores may have divergent recovery profiles. This constitutes an important clinical problem, since these patients may need different types of intervention at different time, and may respond differently when participating in clinical trials for evaluation of novel therapies. This matter has been addressed in research aimed at developing prediction models for guidance of clinical management in the acute phase after stroke (Stinear, 2010) and for individualized rehabilitation intervention and stratification of patients in clinical trials (Kwakkel et al., 2003). However, further study is needed to understand the underlying
mechanisms explaining interindividual variation in hand function recovery, at the different levels of the ICF, i.e. to identify key determinants for recovery of hand motor function after stroke. In this thesis project, a comprehensive protocol was applied to address this challenge. This protocol comprised quantification of brain lesion characteristics and structural and functional connectivity over time, longitudinal changes in global and dexterous voluntary movement control, assessed by clinical and novel instrumented methods, quantification of hand spasticity by the differentiation between neural and biomechanical components of passive movement resistance, as well as actual hand use during the performance of bimanual activities.

The fundamental problem addressed in this thesis concerns the question why some patients recover better than others. The overall aim is to improve understanding of the variable motor recovery profiles of stroke patients.

This thesis thus addresses some key challenges in post stroke rehabilitation and research, namely i) the large portion of patients undergoing incomplete recovery, ii) that the degree of change and long term outcome is difficult to predict, iii) the modest of post stroke rehabilitation as well as negative results in recent clinical trials (Carey et al., 2015; Dromerick et al., 2009; FOCUS Trial Collaboration, 2019; Hunter et al., 2017; Langhorne, Wu, Rodgers, Ashburn, & Bernhardt, 2017; AFFINITY Trial Collaboration, 2020; EFFECTS Trial Collaboration, 2020; Winstein, Wolf, et al., 2016), iv) lack of evidence to guide clinicians in tailoring individualized treatment programs and v) lack of approaches for efficient stratification of patients in clinical trials. Addressing these problems may elucidate underlying mechanisms of interindividual variability in hand motor recovery and how to optimize and facilitate motor recovery, how to obtain more precise prediction models and more efficient clinical trials by improved stratification of patients.
2  RESEARCH AIMS

The overall aim of this work was to identify key determinants for recovery of hand motor function after stroke by applying novel quantitative and fine-grained assessments together with conventional clinical scales and MRI measures of Structural and functional connectivity of sensorimotor brain networks. In particular, this thesis examined four main research questions addressed in four studies:

Table 2. Specification of research questions and novel assessments in the four included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Research questions</th>
<th>Novel sensorimotor assessment instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>How does neural stretch-resistance in wrist and finger flexors develop over time and relate to hand motor recovery, secondary complications and lesion location</td>
<td>NeuroFlexor© for quantification of spasticity</td>
</tr>
<tr>
<td>Study II</td>
<td>How does dynamic precision grip recover over time and relate to clinical and imaging markers of recovery</td>
<td>Strength-dexterity test for measurement of dynamic precision grip force control</td>
</tr>
<tr>
<td>Study III</td>
<td>How does bimanual activity performance recover over time and relate to unimanual motor impairment and to clinical and to imaging biomarkers of recovery</td>
<td>Ad-AHA Stroke for measurement of how effectively the more affected hand contributes to bimanual activity performance</td>
</tr>
<tr>
<td>Study IV</td>
<td>How does grip force generation, modulation and release recover over time and a) contribute to recovery of functional hand use and b) relate to clinical markers and imaging biomarkers of recovery</td>
<td>Visuomotor grip force tracking task for measurement of force control</td>
</tr>
</tbody>
</table>
3 MATERIALS AND METHODS

3.1.1 Study design
The four Studies included in this thesis are all based on one prospective observational study of one study cohort who underwent repeated assessments at three time points.

3.1.2 Setting
Recruitment took place between March 2013 and September 2019 at an in-patient clinic at the Department of Rehabilitation Medicine Stockholm, at Danderyd Hospital, Sweden. The clinic mainly provides sub-acute rehabilitation (varying between 1 to ~12 weeks) for persons of working age (18-70 years) with acquired brain injury.

3.1.3 Inclusion and exclusion criteria
Patients with a first time ischemic or haemorrhagic stroke, within 2-6 weeks from onset, with upper extremity hemiparesis were eligible for inclusion. Arm and hand motor impairment was verified by the admitting physician, using the MRC Manual Muscle Test (≤4/5) and the upper extremity items of the National Institute of Health Stroke Scale (NIHSS), (≥0/4). Exclusion criteria were inability to comply with or understand instructions, disorders other than stroke affecting hand function, a cerebellar lesion, or contraindications for MRI examination. Written informed consent was obtained from all participants. Speech and language therapists were consulted in the recruitment process of patients with aphasia, to ensure the patients’ ability to provide an informed consent. The study was approved by the Regional Ethical Review Board in Stockholm (DNR: 2011/1510-31/3).

3.1.4 Study sample
In total n = 89 individuals with stroke were included, of whom n = 61 participated in study I, n = 80 in Study II and all n = 89 in Study III and IV. In Study II, n = 23 healthy control subjects were included.

3.1.5 Assessments
The first assessment was performed at study inclusion, i.e. at 2-6 weeks post stroke. The relatively wide time window permitted inclusion also of patients with severe stroke, that would otherwise not have been available due to longer stay at the acute stroke units. When possible, the first assessment was performed between week 3 and 4 after stroke onset. Follow up assessments were performed at three and six months respectively. A summary of assessment instruments used in study I-IV is given in Table 3 and listed below.
Table 3 Assessment methods used in Study I-IV.

<table>
<thead>
<tr>
<th>Assessment methods</th>
<th>ICF-domain*</th>
<th>Assessment time-points</th>
<th>Study</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 weeks (T1) 3 months (T2) 6 months (T3)</td>
<td>I</td>
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<tr>
<td>Clinical scales and instruments</td>
<td></td>
<td></td>
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<tr>
<td>NIH Stroke Scale (NIHSS)</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
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<tr>
<td>BNI Screen for Higher Cognitive Function (BNIS)</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hospital anxiety and depression scale (HADS)</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>A-NING Neurolinguistic Aphasia Examination</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Baking Tray Task (BTT)</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Barthel Index (BI)</td>
<td>Activity Performance</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Modified Ashworth Scale (MAS)</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Maximum key pinch force</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Maximum power grip force</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Fugl-Meyer Assessment for the Upper Extremity (FMA-UE) - motor domain section A-D</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Multimodal somatosensory examination</td>
<td></td>
<td>Two-point discrimination – DiscCriminator</td>
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<td></td>
<td></td>
<td>Touch – Monofilament</td>
<td>x</td>
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<tr>
<td></td>
<td></td>
<td>Proprioception – FMA, section H</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vibration – Tuning fork</td>
<td>x</td>
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<tr>
<td>Pain – FMA, section J</td>
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<tr>
<td>Box &amp; Block Test (BBT)</td>
<td>Activity Capacity</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Novel scales and instruments</td>
<td></td>
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<tr>
<td>NeuroFlexor©</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Strength Dexterity Test</td>
<td>Body Function</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

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### Novel Assessment Instruments

#### 3.1.6.1 NeuroFlexor© hand module

Hand spasticity and none-neural resistance to passive wrist and finger extension was examined with the NeuroFlexor© devise (www.aggeromedtech.com) (Figure 1). The NeuroFlexor method was developed to quantify three force components of distinct origin (neural [NC], elastic [EC], and viscous [VC]) in response to passive stretch resistance at slow (5°/s) and fast (236°/s) constant velocities (Lindberg et al., 2011). The force components are derived according to a biomechanical model. The NeuroFlexor method has been developed considering velocity dependence in tonic stretch reflexes as a core sign of spasticity, as proposed by Lance (Lance, 1980). In accordance with this definition, data demonstrating a velocity-dependent increase of the neural force component (NC) and the corresponding EMG response in the flexor carpi radialis muscle in patients with upper limb spasticity after stroke—but not in controls has been reported (Lindberg et al., 2011). The NeuroFlexor method was further validated by showing a reduction of the stretch reflex response and NC after an ischemic nerve block (Lindberg et al., 2011). NeuroFlexor measurements have exhibited good reliability and sensitivity to change (Gäverth et al., 2014; Gäverth, Sandgren, Lindberg, Forssberg, & Eliasson, 2013). The assessment followed a standardized procedure (Gäverth et al., 2013). The bodyweight of the patient was recorded as well as the passive range of movement of the wrists’ flexion and extension, while keeping the fingers in an extended position. All participants were familiarized with the assessment before initiating the assessment, including a slow and a fast run with the moving platform. During the assessment, the patient was seated with full back support with the shoulder in a slightly abducted position and the forearm pronated, resting on the device and fixated by three straps (Figure). A slow and fast test run was performed after the patient was positioned. The less affected hand was examined first followed by the more affected hand, with five slow runs followed by 10 fast runs with each hand. Two extra slow and fast runs without the hand were performed at the end of the examination, for the biomechanical calculation.
Normative data for each force component have been established in a previous study including n = 107 healthy subjects (Pennati et al., 2016). Based on the results of this study, hand spasticity was defined as having a NC value above 3.4N cut-off level, corresponding to the mean+3SD of the healthy subjects.

3.1.6.2 Strength Dexterity Test

To quantify fine regulation of fingertip forces while performing a dynamic precision grip, the Strength-Dexterity test was used (Figure 2). This test has been used previously in children hemiparetic cerebral palsy (Duff, Aaron, Gogola, & Valero-Cuevas, 2015; Vollmer et al., 2010) and in patients with stroke (Pavlova & Borg, 2018). The method is described in detail in Study II (with supplement) and is here briefly summarized. The test comprises n=8 springs of varying free length, from 1.80 cm (spring 8) to 4.60 cm (spring 1). The stiffness is the same across springs (0.8581 N/cm). However, with increasing length, the pinch force required for a full compression also increases (up to maximum 3.95N). The springs’ instability also increases with higher length. Thus, the longer the spring, the more prone it is to buckling, and the higher the demands on both precision grip strength and dexterity. The Strength Dexterity test protocol consists of two tasks. First, the springs were presented in order starting with the shortest and easiest, until the longest spring that the patient was able to compress successfully was identified, (for example spring 4), and the following (slightly longer) spring in line (spring 3 in the example) was selected as the “test spring”. Secondly, the patient was instructed to compress the test spring as far as possible and maintain the
compression during 5 seconds and thereafter release the compression. This procedure was repeated ten times. The healthy control subjects performed the test with their dominant hand while the patients with stroke performed the test first with their less affected hand followed by the more affected hand.

Force data was recorded using 2 force sensors (unit: gram-force) (Duff et al., 2015) attached to each end of the “test spring”, and analysed off-line using Matlab R2017B (MathWorks, Natick, MA). Three metrics of dynamic precision grip was extracted. 1) “CorrForce” which corresponds to the degree of synchronization between the index finger and thumb forces, 2) “Repeatability-score” which corresponds to the reproducibility of the mean force produced in each of the ten trials and 3) “Dexterity-score” which corresponds to a combination of maximum precision grip force and instability that the patients could successfully control during the task. The 3 respective strength dexterity test scores have a range from 0-1 and a higher value equals a better performance plus 3SD of the healthy subjects.

3.1.6.3 Adult Assisting Hand Assessment Stroke (Ad-AHA Stroke)

Bimanual activity performance was assessed by use of the newly developed adult version of the Assisting Hand Assessment Stroke (for brevity hereafter referred to as Ad-AHA) (Figure 3). The performance of one out of two bimanual activities is evaluated, or preparing a sandwich or wrapping a present. Both activities are outlined to challenge the patients’ spontaneous use of the hands together in a naturalistic environment. Examples of task components included in both activities are opening/closing containers, cutting, applying adhesive tape, folding, stabilizing and using different grips. In each assessment, one of the tasks was selected according to the study protocol, to be carried out by the patient.

After providing informed consent, the patients’ performance was video-recorded. The scoring was performed after task completion by a certified assessor. The scale is composed of 19 items, each rated on a four-level ordinal scale. The summary score is transformed to a logit-
based Ad-AHA-unit scale, ranging from 0–100. A higher Ad-AHA-unit indicates better performance.

Ad-AHA has shown good to excellent interrater and intrarater reliability for patients with subacute stroke (Van Gils et al., 2018) and provides a valid measure of bimanual performance (Krumlinde-Sundholm et al., 2019).

3.1.6.4 Visuomotor Grip Force Tracking

To assess force control with the power grip, a visuomotor force tracking task was undertaken (Lindberg et al., 2012) (Figure 4). During this task, the patient was seated in a chair with full back support and the forearm resting in the lap in a mid-prone position, supported by a cushion. A grip force sensor with the size of x by x (www.sensix.fr) (resembling a mobile phone), consisting of two levers, acting on a force transducer, was positioned in the palm of the hand. The patient exerted isometric grip force displayed in real-time by a cursor on a (12 inch) computer screen. On the screen, a target trajectory with a ramp – hold – and release configuration was displayed. One session had a duration of 8 minutes, and comprised n=47 ramp-hold-and-release blocks with a target force alternating between 10% of each individuals’ maximum voluntary compression and an absolute force level of 5N. The patient was instructed to, as precisely as possible follow the target trajectory with the cursor. Before start, a test-trial of a few blocks were performed to assure that the patient was familiar with and understood the task instruction. Both hands were tested, the less affected hand first, followed by the more affected hand. Force output was amplified and then sampled at 1 kHz.
Two specific measures of force control using the poser grip were derived from the visuomotor force tracking task. “Tracking Error” quantifies the difficulty to modulate grip force with precision using the power grip by calculating the area (or sum over each bin) of the absolute difference between the actual force and the target force (Lindberg et al., 2012). Tracking error was recorded during the (2-second long) ramp phase of each block, during which the patient scales up from baseline (zero force) to the target force to reach the hold phase. To specifically address the control of small forces, force data generated during the 5N target level only, was extracted and averaged. Tracking error provides an inverse measure of force control accuracy, thus, a lower score equals a better performance (with fewer errors). “Release Duration” quantifies the difficulty to abruptly release the power grip by calculating the duration of force reduction from 75% of the target force to 25% at the end of each hold phase. The onset of force release was defined as the time when the slope (dF/dt) first crossed a negative threshold (Lindberg et al., 2012).

**Figure 4** Visuomotor grip Force Tracking task (left) and the force manipulandum (right) used in study IV. Two grip force metrics were derived from the Visuomotor grip force tracking task. Tracking error and Release duration. A manipulandum consisting of two levers, acting on a force transducer, was positioned in the palm of the patients’ hand. The patient exerted isometric grip force displayed in real-time by a cursor on a computer screen. All patients were instructed to, as precisely as possible, follow a target ramp-hold-and-release force trajectory with the cursor. Tracking error quantifies errors in isometric power grip force modulation. Release duration was computed as the time taken to abruptly reduce the grip force from 75% to 25% of the target force. (This figure is a modified version of an original figure published by Carment et al. in Brain. 2019 Jul 1;142(7):2149-2164. doi: 10.1093/brain/awz127. Courtesy to L. Carment.)
3.1.7 Clinical assessment scales

3.1.7.1 Fugl-Meyer Assessment for the Upper Extremity

Unimanual arm and hand motor impairment was assessed with Fugl-Meyer Assessment for the Upper Extremity (FMA-UE) (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975; Gladstone, Danells, & Black, 2002). This scale corresponds to control of voluntary movement functions incorporated in movement related functions in the body function domain of the ICF. (In this thesis, equated to and referred to as motor function/motor impairment). The FMA-UE comprises 33 motor function items that are scored on a three level ordinal scale (none/partial/full or marked/slight/none) yielding a total score of 66. The items are divided into four sections, A) upper extremity (0-36 points), B) wrist (0-10 points), C) hand (0-14 points) and D) coordination/speed (0-6 points). One exception from the otherwise uniform scale focusing on voluntary movements, are the three reflex items incorporated in section A. These three items instead reflect involuntary motor functions and have been found to deviate from the otherwise unidimensional structure of the scale (Woodbury et al., 2007). Accordingly, in the sub-studies included in this thesis, the three reflex-items were omitted, yielding maximum FMA-UE score of 60 points. Severity of initial arm and hand motor impairment was categorized based on FMA-UE scores into severe (0-19), moderate (20-47) and mild (47-60) (Woodbury, Velozo, Richards, & Duncan, 2013).

To specifically address distal motor impairment, the FMA-Hand subscale (section C, 0-14 points) was used in isolation (Page, Hade, & Persch, 2015).

Further, the sum of graded shoulder abduction and finger extension force according to the MRC scale (SAFE-score, scale range 0-10) has been proposed an important predictor of arm and hand motor recovery. The original SAFE-score could not be used here since it was not included in the study protocol. To specifically address these functions, an alternative SAFE-score was derived by adding the FMA-UE items for shoulder abduction and finger extension, yielding a 5-level ordinal scale (range = 0-4).

Pain during passive movement was assessed by use of the FMA subdomain for pain (Gladstone et al., 2002). Twelve upper extremity joint movements are rated as pronounced/some/no pain, yielding a maximum score of 24 points, where a higher score represents less pain. In this work, the scale was dichotomized, so that a score of ≤23 (of 24) indicated pain.

3.1.7.2 Maximum key pinch

Maximum key pinch grip force was assessed using an analogue Jamar pinch gauge (Pinch Gauge; B&L Engineering).

3.1.7.3 Maximum power grip strength

Maximum power grip force was assessed using a digital hand held dynamometer (Saehan, South Korea).
3.1.7.4 Examination of somatosensory impairments

All somatosensory assessments started with testing the ipsilateral (less affected) hand. A screen was placed on the surface of a table to prevent the patient from view during the assessment.

Assessment of discriminative sensation of the index finger and thumb was performed with a Disc-Criminator (Dellon-McKinnon) for two-point discrimination (2pD). Three mm, 7mm and 12mm distances were assessed starting with 7mm and then moving up or down depending on if 7mm could be detected or not. A minimum of five continued correct answers (yes/no) for the respective finger was required to pass each level.

Touch of the index finger and thumb was assessed with a 5 item-kit of Monofilaments (North Coast Medical). The 5 monofilaments’ number/pressure in grams were as follows: 1) 2.83/0.07g, 2) 3.61/0.2g, 3) 4.31/2.0g, 4) 4.56/4.0g, 5) 6.65/279g. As for 2pD, a minimum of five continued correct answers (yes/no) was required to pass each level. The assessment started with the second finest monofilament, if yes, the finest level was tested, and if no, the next thicker monofilament was tested and so forth.

Vibration sense was assessed by use of a tuning fork, applied to the 1st MCP bone on the dorsal surface of the hand. Intact vibration sense required the ability to 1) distinguish vibration from no vibration and 2) to indicate the moment at which the vibration was stopped by the assessor.

Assessment of proprioception was performed using the Fugl-Meyer subdomain for position sense of the shoulder, elbow, wrist and thumb (Duncan, Propst, & Nelson, 1983). Proprioceptive dysfunction is rated on a 3-level scale from 0 – 2, corresponding to anaesthesia, hypoesthesia or dysesthesia and normal with a maximum score =8.

3.1.7.5 Modified Ashworth Scale

Resistance to manually imposed muscle stretch was graded according to the modified Ashworth Scale (Bohannon & Smith, 1987), a commonly used clinical method for assessment of spasticity. The scale ranges from zero (0) “no increase in muscle tone” to four (4) “affected part(s) rigid in flexion or extension”. The modified version differs from the original by the addition of an extra scale step, (1+) “slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension”. Thus, in total the modified version comprises six rating levels (0-5). The scale has received mixed reviews for its measurement properties (Malhotra et al., 2009; Min et al., 2012). Specifically, non-neural resistance, not directly related to hyper excitable stretch reflexes may influence the response to passive stretch (Kamper et al., 2001; Pandyan et al., 1999). In this thesis, the modified Ashworth scale was included for the purpose of comparison with the instrumented assessment with the NeuroFlexor© device.
3.1.7.6 Box & Block Test

Gross unimanual dexterity was quantified with the Box and Block Test (BBT). The BBT comprises 150 wooden cubes (2.5x2.5cm) contained in rectangular box, divided into two compartments by a partition. The subject is instructed to move as many blocks as possible, one at a time, from one container to the other, during one minute. The score corresponds to the number of blocks successfully carried over the partition during one trial.

Normative values for the adult stroke population for the corresponding age group (23-69 years) are n=72 to 86 blocks per minute for females and n=68 to 85 for males. A minimum detectable change has been estimated to n=5.5 blocks per minute.

3.1.7.7 Barthel Index

Self-care and mobility abilities were assessed using the Barthel Index of activities of daily living (ADL) (score range 0-100), (Collin, Wade, Davies, & Horne, 1988; Mahoney & Barthel, 1965). A higher score indicates a higher degree of independence.

3.1.7.8 Baking Tray Task

For assessment of unilateral spatial neglect (Heilman, Valenstein, & Watson, 2000), a behavioural test, the Baking Tray Task (BTT) (Tham, 1996) was applied. The task entails to spread out 16 wooden cubes evenly across a 75*100cm board. A unilateral bias of cube placement is indicative of unilateral neglect (Appelros, Karlsson, Thorwalls, Tham, & Nydevik, 2004). The result of the BTT was compared to the performance on the Albert’s line cancellation test (Fullerton, McSherry, & Stout, 1986) since it has been suggested that the detection rate of unilateral spatial neglect may be improved by a multi-dimensional assessment approach (Appelros et al., 2004).

3.1.7.9 The National Institute of Health Stroke Scale

A comprehensive screening of neurological impairment was performed using the National Institute of Health Stroke Scale (NIHSS). The NIHSS comprises key assessments of a standard neurological examination, such as level of consciousness, extraocular movements, visual fields, muscle function/strength, somatosensory function, coordination/ataxia, language/aphasia, speech/dysarthria, and hemispatial attention/spatial neglect (Appelros & Terént, 2004; Brott et al., 1989).

3.1.7.10 The Barrow Neurological Institute screen for higher cerebral functions

An examination of cognitive impairment was performed using the Barrow Neurological Institute screen for higher cerebral functions (BNIS). The BNIS is a comprehensive cognitive screening instrument for cognitive dysfunction after stroke (Prigatano 1991, Denvall, Elmstahl et al. 2002). The instrument includes an initial examination of arousal and alertness, basic communication skills and level of cooperation. Seven additional domains are examined: language, orientation, attention, visuospatial and visual problem-solving, memory, affect and awareness. The scale ranges from 0-50 and a score ≤47 indicates cognitive impairment. The
scale has demonstrated Valid and sensitive (Redfors 2014, Hofgren J Rehab Med 2007;39: 547-553.)

3.1.7.11 Assessment of mood disorder
For assessment of mood status, the Hospital Anxiety and Depression Scale (HADS-A/HADS-D) was used. The scale range of the respective domain is 0-21.

3.1.7.12 A-NING Neurolinguistic Aphasia Examination
Speech and language impairments were assessed using the A-NING Neurolinguistic Aphasia Examination (Lindström & Werner, 1995, 2000). This examination covers a broad range of language domains, such as informative speech, repetition, auditory comprehension, reading comprehension, overt reading dictation and writing. The A-NING summary score range is 0-200 and the A-NING index 0-5. An A-NING index <4.7 indicated aphasia.

Demographic variables (age, educational level) were obtained from the patient's medical records.

3.1.8 Magnetic resonance imaging
A multimodal brain imaging protocol was developed in order to quantify the anatomical characteristics of the stroke lesion, impact of the stroke lesion to white matter pathways of the motor system and functional connectivity within resting-state brain networks. Brain imaging was performed with an Ingenia 3.0T MR system (www.usa.philips.com) with an 8HR head coil.

Three structural imaging sequences were included: 1) T1-weighted anatomical images using a 3-dimensional gradient echo-based sequence (field of view 250x250x181 mm; matrix 228x227; slice thickness 1.2 mm; slice spacing 0.6 mm; and number of slices 301 (echo time [TE] = 3.456 milliseconds; repetition time [TR] = 7.464 ms). This sequence provides high-resolution anatomical images contrasting white and grey matter in the brain. 2) T2 fluid attenuated inversion recovery images (FLAIR), (field of view 250x250x157 mm; matrix 224x224; slice thickness 2.5 mm; TR 4800 ms; TE 30 ms). This sequence provides high contrast between uninjured and injured tissue (hyper-intense lesions). 3) T2-weighted fast field echo (FFE) images (field of view 230x183x149 mm; matrix 256x163; slice thickness 4 mm; TR 500 ms; TE 16 ms). This sequence also highlights hyper-intense lesions, e.g. areas containing oedema, infarction and subacute haemorrhage (containing extracellular meta-haemoglobin and hemosiderin that are breakdown products from haemorrhage strokes).

The resting-state functional MRI protocol consisted of a gradient echo-planar sequence (echo time [TE] = 35 milliseconds, flip angle = 90°, voxel size of 1.8 x 1.8 x 4 mm, repetition time [TR] = 3000 ms) sensitive to Blood Oxygen-Level Dependent (BOLD) contrast. The acquisition time was 6 minutes and the total number of volumes acquired were 160. Patients were instructed to keep the eyes closed, to think about nothing in particular and not to fall asleep.
3.1.8.1 Lesion segmentation

Three-dimensional binary lesion maps (Figure 5) were segmented to enable calculation of degree of overlap between the stroke injury and the corticospinal tract (CST) and to perform Voxel-based Lesion Symptom Mapping (VLSM) (see below). The lesion maps were also used as masks to optimize the normalization of images from native to stereotactic space. Lesions were manually drawn on each axial slice of the T1-weighted images, using the software MRICron (www.nitrc.org/projects/mricron). The T1-images were selected since these had the highest spatial resolution and the highest contrast between lesioned and non-lesioned tissue. The delineation procedure was performed in accordance with a standardized protocol developed by our group in cooperation with neurologist J-CB. The delineation of each lesion was continuously guided by the individuals’ lesion distribution in all spatial dimensions (axial, sagittal and coronal view). For the same purpose, FLAIR and T2-weighted images, co-registered to the T1-weighted image, were also used. Lesion delineation was performed by the author JP, and verified by J-CB.

3.1.8.2 Weighted CST Lesion Load (wCST-LL)

Degree of overlap between the stroke lesion and the corticospinal tract (CST) has been proposed an imaging biomarker of motor outcome (Feng et al., 2015). Here, a weighted measure of CST lesion load (wCST-LL) was calculated as detailed by Birchenall et al. (2019). Two sources of information are used in the calculation, 1) a probabilistic template of the CST, derived from diffusion weighted images obtained from a group of n=18 healthy control subjects (Birchenall et al., 2019), and 2) each patient’s binarized and normalized lesion mask (Figure 5). The volume of the overlapping area between the CST template and
the lesion masks was then calculated. The wCST-LL is expressed as a weighted volume (cubic centimetres, cc) of lesion-CST overlap, which means that the CST circumference at the site of the lesion has been taken into account in the calculation. Subsequently, a lesion close to the (relatively narrow) internal capsule will be weighted higher than a lesion within the (wider) corona radiate.

3.1.8.3 Voxel Based Lesion Symptom Mapping (VLSM)

Voxel-based lesion symptom mapping is a method applied to brain imaging and behavioural data that enables the calculation of lesion site-behaviour relationships. To facilitate group analysis, all lesion masks were flipped to the same (left) hemisphere. Statistical analyses were performed using Matlab scripts compiled in the NiiStat toolbox (https://www.nitrc.org/projects/niistat/) (Rorden, Karnath, & Bonilha, 2007). Voxel overlapped by lesion masks in ≤6 individuals were selected for analysis, i.e. a whole-brain general linear model (linear regression) with 5000 permutations for each behavioural variable tested. Multivariable analyses were corrected for multiple comparisons (FDR corrected p<0.05) (Freedman & Lane, 1983).

3.2 ASSESSMENT PROCEDURES

Two experienced and trained clinicians (physiotherapists) performed baseline and follow-up assessment (Table 3) of arm and hand motor impairment using novel quantitative assessment instruments (NeuroFlexor and Visuomotor force tracking) and part of the clinical assessment protocol (FMA-UE, maximum key pinch and power grip force, somatosensory examination, MAS). A trained medical doctor (GVP) performed all assessments with the Strength dexterity test. A trained group of four occupational therapists rated bimanual performance data (Ad-AHA) based on the video-recorded assessments, and performed part of the follow-up assessments (Ad-AHA, BBT and BI). A comprehensive baseline examination of neurological impairments and activity limitations (NIHSS, BNIS, HADS, A-NING, Ad-AHA, BTT, BBT, BI) was performed by members of the patients’ medical team at inclusion.

The baseline assessments were distributed over two to three days. The follow-up assessments were distributed over one day (generally from 9AM to 14PM) with one longer lunch break and additional periods of rest when needed. At the 6-month follow-up, the MRI and clinical examinations were performed on two separate days, if the patient had not specifically requested to perform all tests on the same day.

All MRI examinations were performed at the Division of Radiology at Danderyd Hospital by a dedicated team of nurses with specialization in radiology. The MRI examinations lasted about 35 minutes and a total time in the scanner of approximately 40 minutes.

3.3 STATISTICAL CONSIDERATIONS

In this thesis, missing data-points were treated differently in the respective sub-study partly due to different sources of missing data and partly depending on differing main outcomes of each study. In Study I, there were two main sources of missing data, first a few cases of loss
to follow-up and a few cases unable to perform a key assessment due to pain in the arm or hand. These data-points could be addressed by adopting a statistical approach that could account for these missing data-points (Linear mixed effects model) without excluding these cases. In Study III the cases that were lost to follow-up at the six-month assessment were imputed with a last observation carried forward approach since the research question concerned the six-month outcome. In Study IV missing data-points occurred due to inability to perform a key assessment (the visuomotor force tracking task). These were treated as ‘not missing at random’ since the main reason for not performing the test was severe paresis in the arm and hand. Here, the data-points of the cases with a complete paresis were imputed with the ‘worst-case’ observation. In addition, data-points missing at random (e.g. technical errors) at the 3-month or six-month time-point were predicted using linear regression with existing data as input variables to the regression equation.

In Study I-IV, behavioural data was first visualised by use of graphs (scatterplots, box-plots, individual line-plots etc.). Besides checking assumptions required for statistical modelling, and investigating data distribution patterns (severely skewed variables were categorized), the aim with this approach was also to detect unexpected patterns in data, of relevance for the defined aims and outcomes of each study. To exemplify, the ROC-curve analysis in sub-Study III and the subsequent additional multivariable regression analysis in a subgroup of patients in this study was a result of this approach.


3.4 ETHICAL CONSIDERATIONS

A large part of the patients treated at the clinic had suffered a moderate to severe stroke with varying degree of neurological impairments and activity limitations. The weekly schedule set up for each patient’s rehabilitation program often leave limited time for rest and leisure. Therefore, several considerations and measures were taken to ensure the safety and best interest of each patient that was approached for inclusion as well as of those that also entered the study after inclusion.

One matter of specific concern was the patients’ ability understand and process information, oral and written, regarding informed consent or other study-related information. Before approaching a patient that had been considered eligible by the admitting physician, the patient’s medical doctor was consulted by the researcher to ensure that all criteria for inclusion were met. Speech and language therapist and psychologist of the patients’ medical team were consulted in the recruitment process in case of severe aphasia or cognitive impairment. This enabled patients with poor communication skills to enter the study. Information regarding the patients’ right to exit the study at any time as well as the purpose of the study was repeated at the follow-up assessments. The potential vulnerability of the patients due to the effects of the stroke and the fact that the recruitment took place in a
hospital and not in the home environment, was a matter of specific concern throughout the study.

One risk was the time consuming assessment protocol that could potentially be tiresome for the patient and absorb time and effort needed for other interventions. To prevent this, the research assessments were scheduled taking the rehabilitation activities, including time for rest into account and if motivated, assessment planning was performed in cooperation with a member of the patient’s medical team.

Another potential risk was that the radiological examination, with a duration of about 30 minutes, could provoke uneasiness or claustrophobia. To ensure that the patients were aware of why the examination was done and that they could stop their participation at any time, in most cases they were accompanied by a member of the research team or a member of the medical team. The health professionals performing the radiological examinations were also fully informed about the study.

This research involves potentially identifiable human material and data. Data was therefore stored and treated in accordance with standard ethical rules and protocols.

This project was undertaken with the overall aim to improve the understanding of key factors regarding the recovery of hand motor function after stroke. By means of this research, clinicians meeting patients living with the effects of stroke, and researchers, could be given access to improved prognostic tools and an improved understanding of the underlying mechanisms of recovery, which could contribute to the development of improved and more effective rehabilitation interventions. With the means taken to protect the interests of the participating patients in this research, the potential benefits could be considered to outweigh the potential risks.
4 RESULTS

Patient characteristics and demographical data at baseline (Study I-IV) are presented in Table 4. A flowchart of the recruitment process is shown in Figure 6. Recruitment was initiated in March 2013 and ended in September 2019.

The study cohort was relatively young, had a mean age of 52 years and a majority, three out of four were male. The overall neurological impairment level at study onset was moderate to moderate-severe, one out of three had aphasia and four out of five had cognitive impairment. A majority of the total cohort (n = 89) had severe arm and hand motor impairment at study onset, and although a significant reduction of impairment over time (see below), the overall arm and hand motor impairment remained low (mean [95%CI] FMA-UE and FMA-Hand at T1 = 24[19-29] and 6[4-7], at T2 = 32[27-37] and 8[6-9], at T3 = 34[30-39] and 8[7-10]).

Acute NIHSS data was obtained from patient records in n=80 patients (missing in n = 9 persons). Acute neurological impairment, according to the NIHSS, was mild (<5 points) in 17% of patients, moderate (6-15 points) in 43%, moderate to severe (16-20 points) in 28% and severe (20-25 points) in 2% of patients with a total mean [SD] = 11 [6] and median [IQR] = [6-16]. At study onset, the severity level was lower, with 39% mild, 51% moderate, 6% moderate-severe and 1% severe overall neurological impairment with a total mean [SD] = 8 [5] and median [IQR] = 7[3-12]. A majority (87.6%) had cognitive impairment according to the BNIS (≤47/50) and 34% had aphasia according to the neuro-linguistic instrument ANING.

Figure 6 Flowchart of the recruitment process.
4.1 DEVELOPMENT OF HAND SPASTICITY AFTER STROKE IN RELATION TO MOTOR RECOVERY, SECONDARY COMPLICATIONS, AND LESION LOCATION (STUDY I)

4.1.1 Occurrence and longitudinal changes of hand spasticity

Neural resistance (NC), quantified by use of the NeuroFlexor method showed high interindividual variability at each time-point (Figure 3A, Study I). At group level, NC (4.38±6.39 [mean±SD]), exceeded the cut-off level for hand spasticity (3.4N, established in Pennati et al 2016), already at T1, and continued to increase over time (NC = 5.7± 8.4 at T2 and 7.66± 9.53 [mean±SD] at T3, F2,54 = 8.12, p = 0.001). Among the n = 61 patients included in study I, 33% had hand spasticity at T1, 46% at T2 and 51% at T3.

Four subgroups with differing initial spasticity severity were identified through qualitative inspection of the distribution of individual NC levels at T1: No spasticity [NC<3.4N], Moderate spasticity [3.4-8N] and Severe spasticity [>8N]). A fourth subgroup of patients developed hand spasticity (NC>3.4N) at T2 and/or T3 and was classified as Late spasticity group. A hypothesis free cluster analysis confirming the patterns observed. Estimated marginal means (EM means) for each spasticity group is presented in Figure 3B, Study I.

4.1.2 Quantitative spasticity measurement and clinical assessment mismatch

The instrumented (NeuroFlexor©, Figure 1) and clinical (MAS) diagnostic methods generated discordant results. The proportion of patients classified as having spasticity was 20% higher according to MAS, at all three assessment time-points. Notably, there was also a mismatch between the two methods regarding the classification of individual patients, e.g. among n = 21 individuals classified as having hand spasticity at T1 according to MAS (MAS≥1), n = 10 individuals (48%) had a NC comparable to healthy controls (NC<3.4N) and thus no hand spasticity according to the NeuroFlexor assessment (Table 2 in Study I). In the same patients, the NeuroFlexor method enabled the detection of abnormal NC in the ipsilateral (less affected) hand in n = 9 patients at T1 and continuously in n = 9 at T2 and n = 5 at T3.

4.1.3 Hand spasticity severity in relation to motor recovery, contracture and pain

Hand spasticity subgroups showed differing levels of active and passive hand functions (FMA-UE, FMA-Hand, BBT and passive ROM) across time-points, and differing degree of change over time (Figure 3 in study I). Notably, the severe spasticity subgroup (NC >8 at T1) had the highest degree of hand motor impairment and activity limitation according to the FMA-UE, FMA-C, Maximal grip force and BBT. The severe spasticity group showed no significant change in FMA-Hand. In contrast, the moderate spasticity group showed a statistically significant improvement in FMA-Hand between each time-point. Regarding BBT, neither the severe nor the late spasticity groups increased significantly over time. The severe spasticity group was the only group with a significant loss of passive ROM across the
### Table 4  Patient characteristics and demographical data at baseline (mean 3 weeks from stroke onset)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III and IV</th>
<th>Group difference (sig.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=61</td>
<td>n=80</td>
<td>Total n=89</td>
<td></td>
</tr>
<tr>
<td>Days from stroke onset to inclusion</td>
<td>24 (8)</td>
<td>25 (7)</td>
<td>25 (7)</td>
<td>23 (7)</td>
</tr>
<tr>
<td>Age</td>
<td>53.0 (10)</td>
<td>47 (13)</td>
<td>53 (9)</td>
<td>52 (9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>20 (30)</td>
<td>12 (52)</td>
<td>23 (29)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>Males</td>
<td>41 (70)</td>
<td>11 (48)</td>
<td>57 (71)</td>
<td>66 (74)</td>
</tr>
<tr>
<td>Higher education *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 (41)</td>
<td>37 (46)</td>
<td>40 (45)</td>
<td>14 (61)</td>
</tr>
<tr>
<td>Lesion side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>24 (39)</td>
<td>33 (41)</td>
<td>40 (44.9)</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>Right</td>
<td>37 (61)</td>
<td>47 (59)</td>
<td>49 (55.1)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>41 (67)</td>
<td>55 (69)</td>
<td>61 (68.5)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>20 (33)</td>
<td>25 (31)</td>
<td>28 (31.4)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>NIH Stroke scale ^</td>
<td>6 (3-11)</td>
<td>7 (3-12)</td>
<td>7 (3-12)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Neglect ^</td>
<td>16 (26)</td>
<td>19 (24)</td>
<td>21 (24)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Aphasia ^</td>
<td>22 (36)</td>
<td>26 (32)</td>
<td>30 (34)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Cognitive impairment ^</td>
<td>41 (11-</td>
<td>38 (30-</td>
<td>38 (31-44)</td>
<td>40 (37-46)</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>60 (30-97)</td>
<td>60 (40-100)</td>
<td>60 (43-100)</td>
<td>100 (95-100)</td>
</tr>
<tr>
<td>Dominant hand affected</td>
<td>24 (39)</td>
<td>33 (41)</td>
<td>41 (41)</td>
<td>14 (34)</td>
</tr>
</tbody>
</table>

Numbers are Mean (SD), n (%) or Median (IQR). **Abbreviations**: NIH Stroke Scale – National Institute of Health Stroke Scale (NIHSS), a) Post-secondary education/degree (yes/no). b) According to the Baking Tray Task (BBT) and verified with the Albert’s line cancellation test. c) Aphasia was indicated by an index ≤4.7p on the Swedish Neurolinguistic Instrument A-NING. d) Cognitive status according to the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS). A score ≤47p indicates impairment, e) Severity of arm and hand motor impairment was categorized based on initial Fugl-Meyer Assessment scores (total range = 0-60, mild ≥ 47, moderate = 20-46, severe ≤ 19 [Woodbury et al., se below]) f) P-values for Kruskal-Wallis or Pearson Chi-square tests. ^ For comparison, for all registered cases of acute stroke in Sweden 2019, median NIHSS was 3 points and mean 6 points, 2/3 of all registered cases were <5 points, i.e. mild stroke severity (Riksstroke, 2019).
whole study period (T3 vs T1) and a continued loss of passive ROM from three to six months.

The proportion of patients reporting pain at 6 months was highest in the severe spasticity group (Fischer exact: p = 0.028, Table e-2, Study I), and the odds of having pain at T3 was 9.1 (95%CI: 1.05–78.54) times higher for the severe spasticity group compared to no spasticity patients.

4.1.4 Hand spasticity - lesion site relationship

Higher neural resistance (NC) correlated with larger degree of lesion to the CST (wCST-LL) (R2 = 0.37, p<0.001 at T3) and this association remained also when including volitional hand function (FMA-Hand) and lesion volume covariates (Table 5).

VLSM analysis identified voxels within the white matter underneath the cortical hand area that were significantly associated with higher neural resistance (NC). A cluster of 54 voxels, located within the CST, remained significant also when including FMA-Hand at T3 as a nuisance variable (Figure 7, left panel), thus confirming the association found between NC and wCST-LL. A lesion in this area explained unique variance in NC since high FMA-Hand values were equally distributed in patients with or without lesions in this area (Figure 7, right panel).
4.2 RECOVERY OF PRECISION GRIP FORCE CONTROL (STUDY II)

4.2.1 Force generation during dynamic precision grip

In patients, the averaged precision grip force generated by the thumb and index finger while performing the Strength dexterity test differed significantly between the more affected (contralateral) and less affected (ipsilateral) hand (mean 43.7 gf versus 109.5 gf at T1) and this difference remained over time. The force produced with the less affected hand differed significantly from healthy controls (mean 146.6 gf), and this difference also remained at later time-points. No significant force increase between time-points was detected in either the more affected or less affected hand. Three force control measures, the Dexterity-score, CorrForce and Repeatability-score were derived from precision grip force profiles exemplified in Figure 8.

4.2.2 Force modulation during dynamic precision grip

The patient’s performance with the less affected hand did not differ significantly from the control group in none of the 3 force control measures (Dexterity-score, CorrForce, Repeatability-score). However, at each time-point, the patient group produced significantly lower values with their more affected hand as compared to the less affected hand, and as compared to the control group (p <0.001, results, Study II). An additional analysis was performed (for this thesis only, and not included in Study 2) aimed at facilitating comparisons between the patients’ performance and the performance. This was done by calculating unitless z-scores, (absolute values are given, meaning that the larger the SD, the poorer performance as compared to controls). and not included in Study II), At 3 weeks, the patient group’s Dexterity-score differed on average 6.5SD from the mean of the control group and 4.6SD at 6 months. The CorrForce performance differed on average with 3.3SD at 3 weeks and 2.0SD at 6 months and the repeatability-score differed with 8.5SD at 3 weeks and 4.8SD at 6 months. Reference values based on the performance of the control group (mean -2SD) were also calculated (included in Study II) to enable the distinction between residual impairment and performance at the level of healthy controls (Dexterity-score = 0.602; CorrForce = 0.541; Repeatability score = 0.881; Maximal grip force = 20.3 and Maximal key pinch force = 5.93).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictors</th>
<th>Unstandardized Coefficients</th>
<th>95% Confidence Intervals</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>lower</td>
<td>upper</td>
</tr>
<tr>
<td>Neural</td>
<td>(Constant)</td>
<td>5.06</td>
<td>2.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component at</td>
<td>FMA-Hand</td>
<td>-0.31</td>
<td>0.21</td>
<td>-0.56</td>
<td>0.08</td>
</tr>
<tr>
<td>T3</td>
<td>wCST-LL</td>
<td>2.08</td>
<td>0.70</td>
<td>0.16</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Lesion Volume</td>
<td>-0.01</td>
<td>0.02</td>
<td>-0.36</td>
<td>0.22</td>
</tr>
</tbody>
</table>
At 6 months, remaining precision grip force control impairment as quantified with the Dexterity-score was observed in 73% of the whole patient group (n = 80, Study II). Notably, among the n = 32 patients with a complete FMA-Hand score (14/14 points), 32% (n = 10) still had remaining impairment according to the Dexterity-score.

Among the n = 32 patients with full FMA-Hand recovery, the proportions of patients with and without remaining Dexterity-score impairment did not differ significantly (32% vs 68%, binomial test, p = 0.071) (Figure 9A box III and IV). Similarly, remaining impairment according to the Dexterity-score was observed also among patients that could produce Maximal grip forces within norm al range (Figure 9B-C). Among the n = 27 patients with full Maximal grip force at 6 months, 26% (n = 7) had remaining Dexterity-score impairment (Figure 8B, box IV), a significantly lower proportion than those with normal Dexterity-score performance (73%, binomial test, p = 0.19) (Figure 9B, box III). However, among the n = 33 patients with full Maximal key pinch grip force at 6 months, the proportion of patients with and without remaining Dexterity-score impairment, did not differ significantly (31% versus 69%, binomial test, p = 0.296) (Figure 8C, box III and IV). Only one case was observed with Maximal grip force below the reference value and with a Dexterity-score within the range of the control group. This was also true for Maximal key pinch grip force (see Figure 8B-C, box I). The relationship between CorrForce and clinical scores showed a different pattern (Figure 8D-E, below). At 6 months, 51% of the patients had a CorrForce above the reference value and this group was distributed across the whole range of FMA-Hand and grip force measures (box I and II Figure 8D-F, below). Among the patients a full FMA-Hand score at 6 months, a majority also had a CorrForce within normal range (87%). This was also true for Maximal grip force (85%) and Maximal key pinch force (82%) (box II and IV, Figure 8E-F, below). Repeatability-score resembled CorrForce in its relation to clinical scores (Figure 8G-I, below).
Figure 8 Precision grip force profiles from which three force control measures, the Dexterity-score, the CorrForce and the Repeatability-score were derived. These dynamic precision grip force profiles were generated by one patient with the less-affected hand (left column) and the more affected hand (right column) at 3 weeks, 3 months, and 6 months after stroke onset. Line depicted in red is force data from the thumb sensor, depicted in yellow is force data from the sensor of the index finger, and in blue the averaged compression force. A lower force amplitude is notable for the more affected hand at each time-point (right column). Forces produced with the more affected hand were lower and more irregular, as compared to the less affected hand. (This figure is a reproduction of Figure 1, Study II, first published by Pennati et al. in Stroke. 2020 Mar;51(3):944-951. doi: 10.1161/STROKEAHA.119.026205. Courtesy to G.V. Pennati and L. Carment.)
Figure 9 Scatterplots of individual Dynamic Precision Grip force data against clinical hand motor impairment, assessed at 6 months (T3). Higher values on both axes correspond to better performance. Colors represent initial impairment severity categories determined by Fugl-Meyer Assessment for the Upper Extremity (FMA-UE) scores; severe (0-19) depicted in red, moderate (20-47) in blue, and mild (48-60) in green (Woodbury et al. 2013). Dotted line and numbers in gray are reference values (mean ±2SD) based on the performance of healthy control subjects. A Dexterity-score against FMA-Hand. Note occurrence of incomplete recovery (in n=10) according to the Dexterity-score in patients with full FMA-Hand score (14 points). B-C. Similarly, patients with Maximal grip force and key pinch force within normal range had incomplete recovery according to Dexterity-score (see box IV in the respective graphs). D-F. In contrast, CorrForce, representing coordination of forces between the fingertips, within normal range, was observed across high (box II) to low (box I). Patients with low clinical scores could To note, both good and poor performance on the CorrForce measure (box I and III respectively) was observed also in patient with poor clinical scores.
Dynamic change over time was observed regarding Dexterity-score and CorrForce performance but not the Repeatability score (results and Figure 2, Study II).

### 4.2.3 Prediction of precision grip force control at 6 months (Study II)

Hierarchical linear regression analysis confirmed wCST-LL as a strong predictor of precision grip force control outcome at 6 months (50% variance explained for Dexterity-score and 34% for CorrForce). Continued multivariable analyses showed that two-point discrimination and FMA-Hand contributed with additional substantial variance (18% and 20% respectively for Dexterity-score and 17% and 5% for CorrForce). Weighted CST-LL was also the strongest predictor of the probability to recover (dichotomous outcomes) in precision grip force control (Dexterity-score \( \chi^2=11.31, p=0.001 \) and CorrForce \( \chi^2=6.53, p=0.011 \)), i.e. a larger wCST-LL was associated with a reduced likelihood of recovering Dexterity-score and CorrForce above the reference value determined in healthy controls (odds ratio 0.72 [95% CI: 0.59–0.89], \( p = 0.002 \) for Dexterity-score and 0.79 [95% CI: 0.66–0.96], \( p=0.017 \) for CorrForce respectively). The predictive model of Dexterity-score recovery explained 25% of the variance with a correct prediction rate of 79%. For CorrForce the model explained 14% of the variance and correctly classified 61% of the cases (online-only Data Supplement of Study II). Thus, every 1-cc increase in wCST-LL decreased the odds of having positive recovery in Dexterity-score by about 28% and in CorrForce by about 21%. Logistic regression analysis was used to identify a critical level of wCST-LL, above which no or limited positive recovery was observed. For Dexterity-score the critical wCST-LL identified was 6.14cc (0.77 specificity) and for CorrForce 4.42cc (0.60 specificity).

### 4.2.4 The contribution of force generation, force modulation and release to recovery of dexterous hand use after stroke (Study IV)

In Study IV, including a total of 89 patients, recovery patterns of force generation (Maximal grip force) and precision grip force control/modulation (Dexterity-score) was studied further and set in relation to other aspects of grip force control, namely, power grip force modulation (Tracking error) and motor inhibition (Release duration). The significance of these motor control functions for the recovery of dexterous hand use, as assessed with the Box and Block Test (BBT) was then evaluated, as well as neural correlates of the respective force control function.

#### 4.2.4.1 Interrelationship and recovery of grip force control functions

A high inter-individual variability was observed in each of the 4 grip force control measures at each time-point. Degree of recovery also varied widely (Figure 1 A-D, Study IV), although at group level, each force control measure increased across time (Maximal grip force [F2,88 = 21.8, \( p<0.001 \)], Dexterity-score [F2,86 =20.2, \( p<0.001 \)], Tracking error [F2,88 =11.6, \( p<0.001 \)] and Release duration [F2,88 =16.5, \( p<0.001 \)]. Non-unit specific extent of recovery (effect size) ranged between 0.26 to 0.39 (Table 2 and Figure 2 in Study IV). Residual impairment in the more affected hand was quantified by taking the mean minus 2SD of the scores produced with the less affected hand. A comparison regarding the proportion of patients...
with residual impairment at six months revealed large differences between measures (range 17.2-70.4%, Table 3 and Figure 1 A-D in Study IV). Still, grip force control measures were interrelated, both regarding status at each timepoint and degree of change. However, change in Dexterity-score correlated with change in Maximal grip force only ($r = 0.520, p<0.001$) and change in Tracking error correlated with change in Release duration only ($r = 0.355, p<0.001$) (eTable 1, Study IV).

4.2.4.2  **Significance of grip force control for recovery of dexterous hand use**

At each time-point, BBT scores correlated significantly with each of the 4 grip force control measures, and the strongest univariate association at T1 was with Maximal grip force ($r = 0.906, p < 0.0001$) at T2 and T3 with Dexterity-score ($r = 0.037, p<0.0001$ and $r = 0.037, p<0.0001$) while the lowest association was found Tracking error ($r_{abs} range = 0.424-0.550, p < 0.001$) across all time-points (eTable 1, supplement of Study IV). Correlations between BBT at T3 and initial grip force control measures at T1 was strongest for Release duration ($r = -0.837, p<0.001$) and lowest for Tracking error ($r = -0.597, p<0.001$) (Table 6). Univariate correlations between BBT change scores and initial force control measures were however strongest for Tracking error ($r = -0.478, p<0.001$), followed by Release duration ($r = -0.404, p<0.001$) while associations with Maximal grip force and Dexterity-score were non-significant (Table 6).

When including initial BBT as a control variable, initial Maximal grip force did no longer correlate with BBT outcome. Instead, BBT at 6 months was best explained by initial Release duration (partial $R = -0.592, p<0.001$), followed by Tracking error and Dexterity-score (Table 6).

A multivariable linear regression analysis was performed to predict BBT score at 6 months while controlling for initial BBT (Table 7). Release duration emerged as the strongest predictor. This effect remained when i) including initial two-point discrimination, wCST-LL, hand spasticity and cognitive impairment as covariates and ii) when including Maximal grip force and Release duration in the same model, which cancelled the effect of Maximal grip force, but not Release duration (model 1 and 2, eTable 2, Study IV). These two examples illustrate that Release duration captures unique variance in BBT recovery. Step-wise multivariable linear regression was undertaken to identify a best fitting model of BBT outcome while considering all predictor candidates. The best fitting model included SAFE-score, BBT (initial) and Release duration and these predictors together explained 91% of the variance in BBT at 6 months (Table 7). However, in this model, Release duration accounted only for a small (but significant) part of the variance (2%, last line Table 7).
Figure 10 Similar to Figure 9, these scatterplots illustrate individual data derived from the Visuomotor grip force tracking task against clinically assessed hand motor impairment at 6 months. To note, a lower Tracking error (Root mean square error RMSe, N) and Release duration (ms) value correspond to better performance. A. Tracking error values across the whole range of performance were observed in low-range Maximal grip force, while higher Maximal grip force was associated with better Tracking error performance. B. In contrast, Tracking error values across the whole range of performance were observed in both high and low range of the Fugl-Meyer Assessment Hand subscale (FMA-Hand). C. The association between Release duration and Maximal grip force resembled that of Tracking error. D. Release duration was captured relatively well by Fugl-Meyer Hand, i.e. longer Release duration was associated with the lowers range of the FMA-Hand, while batter/shorter Release Duration was associated with FMA-Hand in the higher range.
### Table 6 Interrelationship between grip force control measures and Box and Block Test scores.

<table>
<thead>
<tr>
<th></th>
<th>Max. grip force</th>
<th>Dexterity score</th>
<th>Tracking error</th>
<th>Release duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T1</td>
<td>T1</td>
<td>T1</td>
</tr>
<tr>
<td>Box and Block Test (BBT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0.906*</td>
<td>0.841*</td>
<td>-0.424*</td>
<td>-0.751*</td>
</tr>
<tr>
<td>T2</td>
<td>0.871*</td>
<td>0.845*</td>
<td>-0.536*</td>
<td>-0.837*</td>
</tr>
<tr>
<td>T3</td>
<td>0.815*</td>
<td>0.825*</td>
<td>-0.597*</td>
<td>-0.837*</td>
</tr>
<tr>
<td>Δ</td>
<td>0.140</td>
<td>0.259</td>
<td>-0.478*</td>
<td>-0.404*</td>
</tr>
</tbody>
</table>

**Partial correlations**

|                                      |                 |                 |                |                 |
|--------------------------------------|-----------------|-----------------|                |                 |
| Box and Block Test (BBT)             |                 |                 |                |                 |
| (Control variable: BBT at T1)        |                 |                 |                |                 |
| T3                                   | 0.318           | 0.445*          | -0.494*        | -0.592*         |

**Abbreviations:** BBT – Box and Block Test. Numbers are Pearson correlation coefficients, * indicate statistical significance after correction for multiple comparisons (p ≤0.001). Δ = change scores. A Partial correlation was calculated including BBT at T1 as a control variable. Note: negative correlations for Tracking error and Release duration, for which smaller values indicate better performance. This Table correspond to Table 4 in Study IV.

### Table 7 Multivariable Linear Regression models predicting dexterous hand use (BBT score) at 6 months

<table>
<thead>
<tr>
<th>Model</th>
<th>Independent variables (at T1)</th>
<th>Unstandardized B</th>
<th>Coefficient Std. Error</th>
<th>R2 change</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Constant)</td>
<td>9.70</td>
<td>1.93</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>BBT</td>
<td>0.53</td>
<td>0.16</td>
<td>0.67</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>&amp; Maximal grip force</td>
<td>27.32</td>
<td>9.47</td>
<td>0.03</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>(Constant)</td>
<td>8.69</td>
<td>1.85</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>BBT</td>
<td>0.49</td>
<td>0.12</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>&amp; Dexterity score</td>
<td>41.92</td>
<td>9.26</td>
<td>0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(Constant)</td>
<td>24.79</td>
<td>3.13</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>BBT</td>
<td>0.81</td>
<td>0.07</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>&amp; Tracking error</td>
<td>-5.45</td>
<td>1.05</td>
<td>0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(Constant)</td>
<td>38.93</td>
<td>4.45</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>BBT</td>
<td>0.51</td>
<td>0.09</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>&amp; Release duration</td>
<td>-0.05</td>
<td>0.01</td>
<td>0.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Best fitted model:**

|       | (Constant)                     | 12.99            | 5.02                   | 0.011     |       |
|       | SAFE score                     | 6.01             | 1.31                   | 0.73      | <0.001|
| 5     | & BBT                          | 0.47             | 0.07                   | 0.09      | <0.001|
| 6     | & Release Duration             | -0.02            | 0.01                   | 0.02      | 0.002 |

**Abbreviations:** BBT – Box and Block Test. Numbers are Pearson correlation coefficients, * indicate statistical significance after correction for multiple comparisons (p ≤0.001). Δ = change scores. A Partial correlation was calculated including BBT at T1 as a control variable. Note: negative correlations for Tracking error and Release duration, for which smaller values indicate better performance. This Table correspond to Table 4 in Study IV.
4.3 NEURAL CORRELATES OF GRIP FORCE CONTROL

Lesion distribution of the complete sample (n = 87) is displayed in Figure 11A. Each of the 4 grip force control measures at 6 months correlated strongly with Weighted CST lesion load (wCST-LL) (Table e-3). Notably, the reverse correlations between wCST-LL and Maximal grip force and Dexterity-score indicate that a higher wCST-LL, the lower performance in the respective test. Subsequently, the positive correlations between wCST-LL and the force tracking variables, indicate that a higher CST lesion load corresponds to larger Tracking error and longer Release duration. Weighted CST-LL correlated strongest with Dexterity-score at T3 (r = -0.673, p<0.001). The associations were slightly lower for Release duration (r = 0.647, p<0.001), Maximal grip force (-0.644, p <0.001) and Tracking error (r = 0.614, p<0.001) (Table e-3). The only measure of behavioural change (improvement from T1 to T3) that correlated with wCST-LL was the Dexterity-score (r = -0.326, p=0.003).

The association between larger degree of force control impairment and extent of lesion to the CST was confirmed by Voxel based lesion symptom mapping (VLSM). Larger degree of force control impairment according to the respective variable, correlated with CST lesion (voxels) involving corona radiata and the internal capsule as well as the striato-capsular region (Figure 11B). Weak Maximal grip force was specifically associated with lesion to the internal capsule (Figure 11B, in violet). Poor Dexterity-score was associated with lesion to similar areas as Maximal grip force (not shown). In contrast, larger Tracking error and longer Release duration were associated with lesions incorporating a more extended cluster of voxels, including insular cortex, parietal operculum (including SII, the secondary somatosensory area), external capsule and putamen (Figure 11B in orange). Complementary VLSM analysis with Maximal grip force added as a nuisance regressor, revealed that increased Tracking error and longer Release duration was specifically associated with lesion to fronto-striatal pathways (Figure 11C).

Functional connectivity (FC) at T1 did not correlate with any of the force control measures at T3, when corrected for multiple comparisons, (Table e-3, Study IV). We noted a tendency for association between interhemispheric M1 FC at T1 and a decrease in Release duration over time (r = -0.258, p = 0.052). However, weak ipsilesional intrahemispheric M1-SMA FC at T3 correlated with larger Tracking error at 6 months (r = -0.435, p = 0.001) and an uncorrected association was found with longer Release duration at T3 (r = -0.363, p = 0.008) (significance level after BH correction: p≤0.001).
Figure 11 (A) Overlapping lesion maps of the cohort. The most common lesion site was the striato-capsular region including the internal capsule, followed by cortical areas including (but not limited to) the primary motor and somatosensory cortex (hand-knob indicated by blue arrows). Color code: degree of lesion overlap in 0-41 patients (yellow indicates high overlap). (B) Voxel based lesion symptom mapping (VLSM) showing lesioned voxels relating to force control variables. Blue=Maximal grip force; Red=Tracking error; Yellow=Release duration; Orange=common to Tracking error and Release duration; Violet=common to Maximal grip force, Tracking error and Release duration. Extent of lesion to the corticospinal tract (CST; violet voxels in internal capsule) predicted performance in each variable of force control (Dexterity-score not shown). No unique voxels were found for Maximal grip force. Tracking error (red) showed some unique voxels in insular cortex and parietal opercular (PO) region. Release duration (yellow) showed some unique voxels in white matter extending more anteriorly to CST. Note the common extended pattern of voxels relating to both Tracking error and Release duration (orange) including insular cortex, parietal operculum, external capsule, fronto-parietal white matter and putamen. (C) VLSM analysis including Maximal grip force as a nuisance regressor revealed significant voxels within the fronto-parietal white matter that specifically predicted increased force tracking error and longer release duration. Inset: Normalized Release duration (at T3) as a function of absence or presence of lesions to fronto-parietal white matter shown to the left in (C). Higher normalized Release duration (RD) reflects longer release duration.
4.4 RECOVERY AND PREDICTION OF BIMANUAL ACTIVITY PERFORMANCE AND UNIMANUAL MOTOR FUNCTION (STUDY III)

4.4.1 Bimanual and unimanual recovery across time

Ad-AHA and FMA-UE/FMA-Hand showed high inter-individual variability both regarding status at each time-point and recovery (Figure 12A-C). Bimanual and unimanual measures correlated strongly at each time-point (Ad-AHA with FMA-UE r range = 0.877-0.938, p < 0.001 and with FMA-Hand r range = 0.886-0.923, p < 0.001), example visualized in Figure 13A. Change scores also correlated strongly (Ad-AHA with FMA-UE r = 0.839, p < 0.001 and FMA-Hand r = 0.824, p < 0.001, Figure 13B-C). In patients with mild unimanual impairment, Ad-AHA and FMA-UE/FMA-Hand correlations were low or non-significant (r range = 0.188-0.322, p > 0.05 and r range = 0.367-0.469, p ≥ 0.027 respectively) while patients with moderate and severe impairment showed significant positive correlations (r range = 0.564-0.826, p < 0.015).

Linear mixed effects model analyses showed a main effect of time on both bimanual and unimanual measures (Ad-AHA F2, 87 = 30.0, p < 0.001, FMA-UE F2, 87 = 40.5, p < 0.001 and FMA-Hand F2, 87 = 24.3, p < 0.001) (Figure 12D-F). All three impairment subgroups underwent significant change across time in Ad-AHA, while the mild impairment group showed no significant change in FMA-UE (Figure 2D-F in study IV).

4.4.2 Prediction of unimanual and bimanual outcome and recovery

The prediction analyses were based on a subsample of n = 66 with moderate-severe initial impairment. The mildly impaired patient group (n = 23, initial FMA-UE = 56±3.6 points [mean±SD]) was excluded due to known ceiling effects of the FMA. Univariate associations are shown in Supplementary Materials eTable 1 in Study III. Scatterplots of individual data (Ad-AHA vs FMA-SAFE and FMA-UE/FMA-Hand vs FMA-SAFE) are shown in Figure 14A-D. Results from Multivariable linear regression are presented in Table 2 and 3 in Study III.
Figure 12 Individual case profiles (raw values) of A. Adult Assisting Hand Assessment Stroke (Ad-AHA), B. Fugl-Meyer Assessment for the upper extremity (FMA-UE), and C. Fugl-Meyer Assessment hand (FMA-Hand) subscale. Colors illustrate initial motor impairment sub-groups according to the FMA-UE score (mild >47 points [green], moderate 20–47 points [blue], and severe ≤19 points [red]). Dark bars represent whole group absolute mean. D–F. Linear mixed effects model showing degree of change to the respective time-point (fixed effects). Each marker represents whole group estimated marginal means. Vertical bars are 95% confidence intervals.

Figure 13 Bimanual activity performance (Adult Assisting Hand Assessment Stroke [Ad-AHA]) was positively associated with arm and hand motor impairment (Fugl-Meyer Assessment for the upper extremity [FMA-UE]) (A). Extent of recovery was similar between both Ad-AHA and FMA-UE scores at 6 months (A) and degree of change (B). To note in C, a complete recovery in Fugl-Meyer Assessment Hand subscale (recovery ratio = 1), did not equal a correspondingly full recovery in Ad-AHA score. This figure is a reproduction of Figure 3, paper III, by Plantin et al., published in Neurology. 2021 Aug 17;97(7):e706-e719.
A strong positive linear association was found between bimanual activity performance (Adult Assisting Hand Assessment Stroke [Ad-AHA]) and the clinical scale derived from the Fugl-Meyer Assessment (FMA-UE) items for shoulder abduction and finger extension, i.e. FMA-SAFE score. Colors represent subgroups with different severity of initial arm and hand motor impairment according to the FMA-UE (Woodbury et al 2013).

**A-B.** Associations with FMA-SAFE was slightly stronger for Ad-AHA-outcome at 6 months than for Ad-AHA recovery. **C-D.** FMA-UE and FMA-SAFE associations resembled those between Ad-AHA and FMA-SAFE. This figure is a reproduction of Figure 3, paper III, by Plantin et al., published in Neurology. 2021 Aug 17;97(7):e706-e719.
4.4.2.1 Prediction of outcome

The multivariable linear regression analysis showed that Ad-AHA outcome was best predicted by FMA-SAFE and 2pD, together explaining 86% of the variance, 2pD contributing with 5% (Table 2 in study III). When repeating the analysis without FMA-SAFE, alternative independent predictors were wCST-LL (44%), 2pD (15%), BNIS (7%) and pain (3%), which together explained 70% of the variance.

In comparison, FMA-UE outcome was best predicted by FMA-SAFE and interhemispheric FCPCG, together explaining 87% of the variance, of which FCPCG accounted for 3%. The best fitted model without FMA-SAFE included wCST-LL (49%), 2pD (7%) and BNIS (6%), together explaining 62% of the variance. Results for FMA-Hand were almost identical (Table 2 in study III).

4.4.2.2 Prediction of recovery

Ad-AHA recovery was best predicted by FMA-SAFE as a single predictor, explaining 64% of the variance. Without FMA-SAFE, the best model included wCST-LL (31%) combined with 2pD (9%), together explaining 40% of the variance (Table 2 in study III).

In comparison, FMA-UE recovery was also best predicted by FMA-SAFE as a single predictor, explaining 72% of the variance. Without FMA-SAFE, the best prediction model included wCST-LL (36%) and 2pd (5%), together explaining 41% of the variance. Results for FMA-Hand were similar to FMA-UE but more variance was explained by interhemispheric FCPCG (Table 2 in study III).

4.4.3 ROC analysis of CST integrity

4.4.3.1 Sensitivity and specificity of CST lesion load

The ROC analysis on wCST-LL data for the moderate and severe impairment groups revealed a predictive threshold of 5.5cc, separating patients who showed a clinically meaningful increase in FMA-UE, ≥10 points, from those who did not (Figure 4A-B in study III). The sensitivity of this predictive threshold was 0.73 and specificity was 0.91 (AOC=0.889, SE=0.043, p<0.001, 95%CI: 0.802-0.971). Two patients only out of n=28 with wCST-LL >5.5cc recovered ≥10 points in FMA-UE (Figure 4B in study III). The variability of actual change in FMA-UE was high among individuals with wCST-LL < 5.5cc (summary score = 19.4±10.6 [mean ±SD], range 0-37, corresponding to recovery ratio of 0.54±0.30, range 0-1; Figure 4 in study III).

Figure 4C in study III illustrates changes in Ad-AHA between 3 weeks and 6 months in relation to the same wCST-LL cut-off. Ad-AHA recovery was poor in patients with wCST-LL >5.5cc and more variable in patients with wCST-LL<5.5cc, with no patient with wCST-LL >5.5cc having Ad-AHA increase above ~20. Conversely, Ad-AHA recovery was highly variable in patients with wCST-LL<5.5cc (Figure 4C in study III). Given this high variability in unimanual and bimanual recovery, multivariable linear regression was therefore
implemented in the subsample of n=38 patients with wCST-LL <5.5cc (Figure 4B in study III).

4.4.3.2 Outcome and recovery in patients with CST lesion load <5.5cc

Multivariable regression identified FMA-SAFE, 2pD and BNIS as the main predictors of Ad-AHA outcome as well as recovery in this subgroup. Hemorrhagic stroke was also identified as favorable for outcome and recovery (Table 3 in study III).

The main predictors of FMA-UE and FMA-Hand outcome and recovery were FMA-SAFE, 2pD, FCPCG and BNIS, with lower total amount of variance explained, compared to the previous models (Table 2 in study III).
5 SUMMARY OF FINDINGS

Study I
Severe hand spasticity early after stroke was common, with increasing occurrence and severity over time. Severe hand spasticity was negatively associated with hand motor recovery and positively associated with the development of secondary complications. Corticospinal tract damage predicted the development of hand spasticity.

Study II
Evidence was found of persisting deficits in the ability to grasp and control finger forces after stroke, which was noted even when impairment severity was relatively mild. Weighted CST lesion load was the strongest predictor of performance at 6 months, but early two-point discrimination and Fugl-Meyer score had substantial additional predictive value.

Study III
FMA-SAFE, a simple clinical measure of shoulder abduction and finger extension, strongly predicted bimanual recovery. Sensory function explained additional variance in bimanual recovery, and interhemispheric motor cortex functional connectivity explained additional variance in unimanual outcome and recovery. Cognitive function and CST integrity were other important predictors for both bimanual and unimanual outcome and recovery. A CST lesion load >5.5 cc was associated with poor bimanual and unimanual outcome and recovery.

Study IV
This study revealed persistent impairment of grip force generation, modulation and release at 6 months after stroke, and detected preserved force control abilities in patients with severe hand motor impairment. Degree of CST integrity was one major determinant of recovery of grip force generation and force control. Lesion to pathways specifically involved in motor inhibition explained additional variance in recovery of force modulation and force release. Poor initial force control capacity predicted limited dexterous hand use at 6 months. This association was particularly strong for force release, a probe of motor inhibition and a less studied aspect of force control.
6 DISCUSSION

This longitudinal prospective study contributes novel findings regarding recovery of sensorimotor function and activity during the subacute phase after stroke, and on prediction of outcome and recovery. The combined application of novel fine-grained sensorimotor assessment methods and traditional clinical scales, together with a multimodal neuroimaging protocol provided new insights into the heterogeneous recovery process in stroke survivors. Below some findings and some key lessons learned regarding recovery trajectories of specific hand motor control functions and actual hand use, their interplay, their neural correlates and prediction are discussed.

6.1.1 The contribution of novel sensitive measures of hand motor function and activity to the understanding of hand motor recovery after stroke

The resistance to passive muscle stretch, a core sign of spasticity, has its origins in several contributing components (Dietz & Sinkjaer, 2007; Lindberg et al., 2011), which typically makes manually assessed resistance difficult to interpret (Malhotra et al., 2009).

Quantification of neural resistance by use of the NeuroFlexor© device (Gäverth et al., 2013; Lindberg et al., 2011) (Study I, III and IV), enabled assessment of the distinct force components contributing to resistance to imposed muscle stretch. Moreover, longitudinal assessment of neural resistance (Lindberg et al., 2011), enabled early detection of hand spasticity, characterization of its development over time and identification of spasticity subgroups, and revealed different profiles of hand motor recovery and secondary complications (Study I). Early severe hand spasticity was found to be a negative predictor of hand motor function and dexterous hand use over time, and indicated an increased risk for development of secondary complications.

At the same time, a comparison between numbers of patients diagnosed with hand spasticity based on sensitive quantitative measurements (Gäverth et al., 2014), and clinically assessed hand spasticity using the Ashworth scale, revealed a considerable disagreement between measures. This disagreement implies that decisions taken in the clinic, for example regarding selection of patients for a specific treatment, or in a scientific context such as stratification of patients in clinical trials, could give different results, depending on the assessment method used.

Intramuscular injection of Botulinum neurotoxin (BoNT), which blocks neuromuscular transmission, is currently a recommended pharmacological therapy for focal spasticity after stroke. It is considered safe and efficacious for treatment of upper extremity spasticity, also contributing to pain reduction and improved limb positioning (Sheean, Lannin, Turner-Stokes, Rawicki, & Snow, 2010; Simpson et al., 2008). However, BoNT has not been consistently shown to improve hand motor function (Gracies et al., 2015; Kwakkel & Meskers, 2015). This has been attributed to the lack of specific assessments that can be used in the clinic to capture the critical target for a pharmacological agent, i.e. the hyper-excitabile stretch reflex (Dobkin et al., 2009). The findings in Study I may aid developing more
efficient targeting of BoNT treatments to patients in whom increased resistance to passive stretch is due to spasticity rather than to other factors. It could be possible to target treatment to individuals with early signs of severe spasticity, and thus support the development of precision medicine in this area. Future studies are required to evaluate such targeted treatments in recovering stroke patients.

The use of fine-grained measures of force generation and force control provided new insights regarding recovery from hand motor impairments (Study II and IV). Substantial residual impairment at six months was identified (Study IV). The degree of residual impairment also differed significantly between measures. Moreover, different force generation and force control measures were incompletely related to impairment as assessed clinically. For example, in Study II, impaired dynamic precision grip was detected in one third of patients, who were fully recovered according to FMA-Hand (Figure 9A). This was not the case regarding coordination of forces between fingertips (CorrForce, Figure 9D). Normalized performance of force modulation at six months (Tracking error, Study IV) was observed across the whole range of upper limb motor impairment (both mild and severe) (Study IV, Figure 10). These findings suggest that fine-grained assessment enabled important discrimination between different aspects of motor impairment, of relevance for specific subgroups of patients. One aspect was the detection of residual impairment (here, the control of small forces between the finger tips) that would have remained undetected if clinical assessments had been used in isolation, especially in the subgroup of initially mild impairment severity. Another was the detection of residual functional capacity (force control using the power grip) that also would have remained undetected, especially in the subgroup with severe initial impairment.

Generation and control of forces is important for manipulation of small objects (Nowak, 2008) and flexible hand positioning during grasping (Roby-Brami, Jarrassé, & Parry, 2021) and is therefore an important target for post stroke rehabilitation interventions. Specific assessment of force generation and control in the clinic could facilitate individually tailored therapies, by enabling focus on distinct force control abilities during task practice. Differing recovery profiles of force generation and force control have been observed, with longer recovery periods for force control (Xu et al., 2017). Divergent recovery profiles imply differing underlying recovery mechanisms which may require distinct interventions at different time-points during post stroke recovery for different individuals.

The findings reported in Study IV showed that force release is a motor control function of specific importance for the capability to grip and release objects. Force release was more similar to force modulation ability than to force generation and precision grip, likely due to a shared higher dependence on motor inhibition (Buccolieri, Abbruzzese, & Rothwell, 2004). Partly differing neural correlates (see further below) and underlying mechanisms, may explain the negative, slightly non-linear relationship between the Release duration and Maximal grip force (see Figure 10, presented in this thesis only). Both Release duration and Maximal grip force correlated strongly with the activity measure BBT, however, Release
duration also explained some unique variance in BBT recovery. The unique variance explained by force release, as compared to force generation, implies that two patients with similar maximal grip force may have different grasp and release capability. The measurement of force release may thus represent a clinically useful assessment that could guide clinicians to train this specific motor control function.

The use of a novel assessment instrument for detailed evaluation of bimanual activity performance (Study III), revealed a broad range of bimanual performance levels over time, and a considerable amount of residual bimanual disability at six months. It was also shown that outcome and recovery of bimanual activity performance overall was highly comparable to outcome and recovery from arm and hand motor impairment. However, bimanual activity performance correlated differently with the overall FMA-UE impairment scale and the FMA hand subscale. More specifically, incomplete recovery was observed among a group of patients with normalized distal hand motor function according to the FMA hand subscale. No such subgroup was observed among patients fully recovered according to the total FMA-UE scale. The necessity of both proximal and distal voluntary movement function for efficient bimanual hand use was further indicated by the strong association between Ad-AHA and FMA-SAFE score, a scale that specifically represent degree of voluntary movement function at the shoulder and extension of the fingers (Nijland et al., 2010; Stinear et al., 2012). To note, statistical associations alone are no proof of causality. Therefore, these associations require further evaluation and external validation. Subsequently, the strong linear relationship between the full FMA-UE scale and the Ad-AHA, is not a proof of causal relationship between arm and hand motor impairment and improved bimanual hand use. The linear relationship between the two scales is however, interesting. One interpretation may be that the Fugl-Meyer scale captures several key movement functions that enable efficient bimanual hand use.

6.1.2 What has been learned regarding prediction

6.1.2.1 Clinical predictors of recovery

The FMA-SAFE (derived from the FMA-UE items), performed at 3 weeks after stroke, was found to be a strong clinical marker of future unimanual motor function and bimanual activity performance (Study III). The FMA-SAFE items, finger extension and shoulder abduction, together constitute an easy-to-perform bed-side test, and is therefore easily implemented in clinical practice. As a single predictor, the FMA-SAFE captured about 80% of the variance in unimanual and bimanual outcome. In addition, FMA-SAFE provided clinically valuable information regarding degree of change over time (60% of variance explained). Thus, The FMA-SAFE can be used to inform about both expected level of outcome, but also expected potential for change.

Previous prediction studies using the SAFE-score, have most often used a categorization of upper limb motor outcome, as opposed to evaluating continuous measures of outcome (Nijland et al., 2010; Stinear, 2010; Stinear et al., 2017). This implies that although a strong
association between SAFE-score (based on the MRC muscle test), and outcome category is obtained, the predicted degree of outcome cannot be more precise than the resolution of defined outcome categories (e.g. ‘some functional level’ versus ‘no functional level’).

Findings in Study III, showed that the FMA-SAFE was highly predictive of outcome according to the fine-grained Ad-AHA scale (range 0-100) and the multi-level ordinal FMA-UE (ranged 0-60) (Figure 14), forming a strong linear relationship with these variables. This suggests that the FMA-SAFE may provide predictive information across a wider range of functioning.

Other important predictors were revealed when the FMA-SAFE was excluded from the statistical model. For example, sensory and cognitive impairment were two additional clinical predictors that contributed significantly to explain unimanual and bimanual outcome and recovery (Table 3, Study III). Cognitive function was particularly important for recovery of distal hand function and bimanual activity performance. Further, degree of somatosensory impairment was one important predictor of dynamic precision grip (Study II). The wide range of motor functions and abilities captured by these factors point to a close integration of these domains from a biological perspective. A large body of literature has demonstrated the interdependence between the sensory, motor and cognitive domains for skilled goal-directed motor behaviour (Carey, Lamp, & Turville, 2016; Mullick et al., 2015; Rinne et al., 2018; Welmer, Holmqvist, & Sommerfeld, 2008). Together the findings in Study II and III, suggest a significant interdependence between these domains also during the process of recovery. In light of the clear need for the development of more precise prediction models and for the identification of markers of recovery (Boyd et al., 2017) and new effective rehabilitation interventions (Bernhardt, Godecke, Johnson, & Langhorne, 2017), these findings are of particular clinical and scientific interest. Their contribution to multiple aspects of voluntary movement functions, widens the opportunity for potential applications, for example as targets for rehabilitation interventions aimed at enhancing hand motor outcome and recovery.

Multiple deficits within the same behavioural domain (e.g. grasping) may be present at the same time and may require selective measurement to be detected and managed. Clinical assessment scales alone may not provide sufficient detail and precision regarding different aspects of motor control that may be affected by the stroke lesion, leading to residual impairment and inherent (subclinical) capacity for recovery may thus remain undetected.

6.1.3 Neural correlates of hand motor recovery and bimanual hand use after stroke

The combination of novel sensorimotor assessments and a detailed neuroimaging protocol in this thesis was based on the assumption that sensorimotor networks that serve hand movement are likely differentially damaged in individuals with varying recovery and are best evaluated with a complimentary imaging analysis approach (combining both structural and functional connectivity analysis). Combining imaging with novel functional assessments provided insights on lesion-motor behaviour relationships. The major findings are discussed below.
6.1.3.1 Structural connectivity

Results from the four studies included in this thesis corroborate a key role of the degree of CST integrity for prediction of hand motor outcome and recovery over the first six months after stroke (Boyd et al., 2017). Further, these findings extend previous knowledge regarding the importance of CST integrity for a number of voluntary movement functions assessed using both commonly applied clinical scales and novel fine-grained sensorimotor measures (Study II-IV). The CST lesion load strongly predicted dynamic precision grip force control at six months after stroke (45-50% of variance, Study II and IV). Only slightly lower amount of variance was explained for force generation, modulation and release using the power grip (38-42%, Study IV). A higher predictive strength of CST lesion load for dynamic precision grip is expected, given the well-established role of the CST for dexterous finger movements (Lemon, 2008; Lemon, Johansson, & Westling, 1995) which was not required for force generation, modulation and release. In addition, CST lesion load correlated with neural resistance to passive muscle stretch at six months (37% variance explained, Study I), and was highly predictive of outcome of bimanual activity performance and unimanual hand motor impairment (50% and 56% of variance explained respectively, Study III).

The association of CST integrity and to different aspects of motor control, might be viewed to reflect the complex nature of the corticospinal system. Beside the unique role of the CST for human dexterity (Lemon, 2008), the CST is critical for the mediation and control of high level coordination of whole body movements and adjustments based on sensory feedback. As a unifying link, the fiber bundles of the CST communicate outgoing (efferent) neural code for goal-directed motor behaviour and transmits back (afferent) perceptual information from the body and the periphery. The CST originates in multiple cortical regions beside the primary motor cortex (Dum & Strick, 1991; Newton et al., 2006; Zaaimi, Dean, & Baker, 2018). Further, as it descends, the CST send out divergent collateral axons which terminate on their target neurons within nuclei in the brainstem and at multiple segmental levels in the spinal cord (Schulz et al., 2012). Somatosensory and motor processing is also highly integrated at the cortical level, in the descending motor pathways and in spinal circuitry (Dubbioso, Raffin, Karabanov, Thielerscher, & Siebner, 2017; Moreno-Lopez, Olivares-Moreno, Cordero-Erausquin, & Rojas-Piloni, 2016; Paixão et al., 2019).

A key role of the CST for arm and hand sensorimotor recovery after stroke does not exclude important contributions of other descending motor pathways (Honeycutt, Kharouta, & Perreault, 2013; Rimmmele et al., 2018). These other motor pathways, for example the corticoreticulospinal pathway (Baker, 2011), include pathways ipsilateral and contralateral to the lesion (i.e. descending from the non-lesioned hemisphere) and mediate communication with spinal circuits (Aguiar & Baker, 2018). Other cortico-cortical pathways, such as the frontoparietal pathways may also contribute to recovery (Schulz et al., 2015). Structural connectivity analyses (VLSM) in Study IV, suggest a key role of cortico-striatal pathways for motor inhibition processes (Forstmann et al., 2012; Toxopeus et al., 2007), for post stroke abilities regarding timely up and down regulation of grip force (force modulation and release) and dexterous hand use (BBT).
6.1.3.2 Resting-state functional connectivity

Measures of resting-state functional Connectivity (FC) yielded few significant associations with sensorimotor measures of outcome and recovery (Study III and IV). Findings from Study III and IV still suggest potential of FC as a predictor of hand motor outcome and recovery, especially regarding distal voluntary movement function of the hand. Functional connectivity explained additional variance FMA-hand and further more in the subgroup of patients with relatively preserved CST.

Both large and small focal lesions of brain structures may influence how multiple cortical and subcortical regions, distant from the lesion, interconnect and cooperate (Carrera & Tononi, 2014; Siegel et al., 2016). Therefore, a combined study of structural and functional connectivity may be particularly important for improved understanding of how the brain reorganizes after a stroke injury. Moreover, increased knowledge regarding how the structural and functional reorganization following a stroke lesion relate to individual motor impairment and recovery potential (Carter et al., 2012; Siegel et al., 2016) could be particularly valuable from a clinical standpoint. As compared to task based functional MRI, FC has specific advantages regarding the assessment of brain function in patients with severe arm and hand motor impairment, since it allows measurement of the whole brain, while the patient is at rest. Future research will be required to fully evaluate how to best use FC in prediction of hand motor outcome and recovery. Further research is ongoing (Smith et al., 2013; Thompson et al., 2020), for further development of consensus based analysis approaches.

Together, the four studies suggest a critical importance of the CST for hand motor outcome and degree of recovery over the first six months after stroke, as previously demonstrated for voluntary movement function and activity capacity after stroke (Boyd et al., 2017). The findings of this thesis further support the importance of the CST for hand motor recovery. Firstly, the strong association found between CST integrity and non-voluntary movement functions, indicating a key role for the development of hand spasticity. Secondly, the strong association found between CST integrity and recovery of bimanual hand use, indicate a key role of the CST for coordinated use of the hands in daily task performance.

6.2 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

A longitudinal prospective research design applied in this project was motivated by the specific focus on post stroke recovery, i.e. the study of change over time. This design enabled the evaluation of how the implemented novel measures related to i) time and to ii) clinically assessed motor impairments at baseline and iii) imaging measures of stroke lesion characteristics. This design also enabled the evaluation of predictive strength of selected factors of interest and the study of their interrelationships in motor control functions.

This thesis involved novel measures across impairment and activity levels of ICF. However, we did not use kinematic measures of arm movements in this project that may have revealed
knowledge on control of upper limb movements (Kwakkel et al., 2019). Kinematic measures have been proposed to evaluate movement quality and would have contributed additional understanding of reaching and grasping (Kwakkel et al., 2017). However, including kinematic measures was not possible in this project since the test battery was already comprehensive and additional time for further assessments was not possible. We also chose measures easy to implement early after stroke in patients with severe motor impairment. In hindsight a more detailed measurement of cognitive domains such as attention and working memory would also have been of interest (Mullick et al., 2015).

The study of neural correlates incorporated distinct structural and functional MRI techniques. Integrity of the CST was assessed using the weighted CST lesion load (wCST-LL) metric, representing the volume of overlap between the patient’s lesion map and a probabilistic CST template (wCST-LL), derived from diffusion tensor images of healthy control subjects (Birchenall et al., 2019; Zhu et al., 2010). We also used VLSM to correlate lesion location with motor control impairments. Other measures of CST integrity are also available such as TMS for the assessment of motor evoked potentials (MEPs) and DTI measures of fractional anisotropy ratio (Bigourdan et al., 2016; Jin, Guo, Zhang, & Chen, 2017; K. H. Kim et al., 2015). To date, there is a lack of evidence supporting superiority of one method over another (Hoonhorst et al., 2018). The methods selected proved feasible in all patients and corroborated each other (VLSM confirming findings regarding CST integrity based on CST lesion load calculations). However, neuroimaging derived measures require technical and analytical resources that are not yet generally implemented clinically in post stroke rehabilitation services. Automatized MRI processing steps could be of benefit requiring minimal input from a radiologist. Further standardization of the analysis procedure could represent a quick and ready manner to obtain a measure of CST injury, easier to obtain than TMS and with fewer processing steps than DTI. However, which neuroimaging and or neurophysiological method that can offer the most feasible and reliable estimate of CST integrity remains to be determined (Boyd et al., 2017).

Another study limitation was the sample size in this project. A total of 89 patients were followed-up longitudinally (61 in Study I, 80 in Study II). A larger sample would have increased power and may have improved the capacity to detect additional predictors and perform extended multivariable prediction models with improved precision of estimates. This would have aided study of sub-groups with impairment specific profiles. However, the present sample size still enabled small but significant contribution to multivariable prediction models, such as the categorical two-point discrimination variable explaining a few additional percent of variance. Despite comprehensive and time consuming assessment protocol, including MRI examination, there were few cases lost to follow up for known reasons. Data was incomplete in some cases, due to inherent properties of the assessment scales (e.g. floor effects in kinetic measures) and also due to excluded imaging data due to for example movement artefacts. In addition, the studied cohort was relatively young, as compared to the overall stroke population and epidemiological trends point to increasing future demands on post stroke care and rehabilitation in adult stroke patients below ~70 years of age. Whilst
study of a younger cohort has some advantages in terms of likely lower likelihood that co-
morbidity impacts on findings, it does limit generalization of the finding; before the findings
based on this young cohort may be translated to other age groups, further validation is
required.

Previous prediction models, such as the PREP2 algorithm, have primarily been aimed at
quick and feasible prediction of three or six month outcome based on factors obtained during
the first hours or first week, i.e. in the acute phase after stroke (Bernhardt et al., 2016; Rosso
& Lamy, 2020). The overall aim of this thesis was to identify key determinants for hand
motor outcome and recovery up to six month post stroke, based on data obtained in the early
subacute phase, i.e. 2-6 weeks after stroke onset. At this time point the purpose of prediction
and the medical context for implementation differ from the acute phase, when high numbers
of patients pass through a stroke unit and time for qualified decision making is limited, and
course outcome predictions are often quite appropriate as a basis for the clinical decisions to
be made at that time point. However, on the in-patient rehabilitation unit, prediction would
ideally aid decisions regarding individualized rehabilitation planning and interventions, and
as such requires a deepened understanding of factors critical for successful recovery and
optimized outcome. Ideally, initial predictions would be successively refined by measurement
across time. Findings from this thesis are a stepping stone towards the development of
individualized predictions and therapies of the future. Findings will also support the
necessary stratification in clinical trials that will be needed to evaluate rehabilitation
interventions. A summary of key findings and conclusion is given below.
7 CONCLUSIONS

In this longitudinal prospective research project of arm and hand motor recovery after stroke, a combination of fine-grained measures of sensorimotor impairment and activity performance were applied in combination with commonly used clinical scales and a multimodal neuroimaging protocol. These specific and nuanced assessments allowed for further delineation and understanding of the heterogeneous impairment and recovery profiles among stroke survivors, across multiple ICF levels.

Identified key predictors:

i) hand spasticity severity, with potential to predict limitations in hand motor recovery and secondary complications over time,

ii) the clinically assessed FMA-SAFE score and measures of sensory and cognitive impairment, were highly predictive of unimanual sensorimotor function and bimanual activity performance,

iii) force release was highly predictive of grip and release capability,

iv) the MRI derived measure of CST integrity (wCST-LL) was highly predictive of arm and hand sensorimotor recovery across all ICF levels, including detailed measures of force control

v) other cortico-striatal motor pathways were specifically predictive of force release,

vi) resting state functional connectivity, which contributed with some additional predictive information in addition to other factors.

Altogether, this thesis generated an improved understanding regarding force generation and force control functions of the hand, their interrelationship over time and coherence with clinically assessed outcome and recovery after stroke. Moreover, this thesis advances our knowledge regarding longitudinal recovery and prediction of grasp and release capability. Further, this thesis provides the first detailed comparison of unimanual and bimanual recovery and their predictors after stroke. Increased understanding of factors contributing to variability in stroke recovery could contribute to development of new treatment paradigms with more specific targets for evaluation in clinical trials. This cohort represents a younger stroke population and the findings need further external validation in other age groups and in larger cohorts.
8 ACKNOWLEDGEMENTS

This thesis is the sum of effort, dedication and commitment by many, over several years. To all of you, I am forever grateful.

To the patients who participated in the studies of this thesis, and to your family members who also contributed in many ways, I would like to express my sincere gratitude. For your effort and hard work, for your courage and for sharing your knowledge and experience and for sharing your valuable time, you have my deepest thanks.

My profound thanks to all members of the control group in study II. Your readiness to volunteer and to share your time is greatly appreciated.

To the members of the data-collection team, Birgitta Johansson, Gaia Valentina Pennati, Sahil Bhaskar, Mia Reistedt, and Karin Weber for hard work and invaluable support, especially at times I’ve lost my way, and you’ve guided me back on track as true friends, thank you from the bottom of my heart.

Through the years, the Division of Rehabilitation Medicine at Danderyd Hospital has embraced this project and carried it forward with incessant support. For this I want to say my deepest thanks. At the very beginning of this project, when the challenges were many, invaluable contributions and support were given by many, that saw to that research and clinical activities could work together, and enrich one another. For this I want to express my gratitude to Jörgen Borg, Marie-Louise Schult, Jean-Luc af Geierstam, Christian Andersen, Kristian Borg, Vera Häglund, Charikleia Pappas, Eva Kedvik and Carin Persson. A special thanks also to Karola Ollas, Anne Åvall and Agneta Tamwelius.

To the Division of Radiology at Danderyd Hospital, for continued support for this project, I would like to say my deepest thanks. Evaldas Laurencikas, thank you for always being there with help and support. This work could not have been done without you. Lars Nilsson and Patrick Beijner, thank you for always finding solutions, for taking such good care of our patients at the MRI examination, and simply always doing your best. Thank you!

As a doctoral student, you must seek knowledge and advice. So you go to the library. And there you find it. Because at the library, you also find the most helpful, knowledgeable and service-minded people. Then, the struggle of learning turns into a pleasure and for this I am forever grateful. At the University Library of Karolinska Institutet and the Medical Library at Danderyd Hospital, there is where it happens.

It has been such a fortune to find you, fellow doctoral students at The Rehabilitation Medicine clinic. Thank you Ann-Christine Persson, Gabriella Markovic, Christian Oldenburg, Giedrė Matusevičienė, Christina Sargėnienė Landahl, Märta Berthold and Gaia Pennati. With all my affection, Anneli Wall and Helena Hybbinette, for all good times, thank you. You made all the difference to me and I couldn’t have done this without you. I would
also like to thank Marika Möller and Monika Löfgren for inviting room and spirit for fruitful discussions and learning.

I would like to give my sincere gratitude to all the members of the medical teams, at the in-patient and out-patient clinics, for investing your time and knowledge into this project. Your expertise and high standards have made all the difference for this research and encouraged and inspired me. A special thanks to Isa Gustin, for your invaluable investment of time and knowledge. Hanna Bergling, you´re missed! At numerous times, you´ve been a life-saver. Thank you! A special thanks to all nurses and assistant nurses for always being there for the patients, for helping out with endless practical things that made this research possible, for your interest in this work and for your willingness to contribute, I want to say my sincere gratitude.

Johan Gäverth, thank you for being too good to be true, for your readiness to help out and for your kind patience when you´ve spotted that question mark on my forehead! A special thanks also to Anders Fagergren, for finding the time when there is no time, it has been incredibly valuable.

For you, the best physios and colleagues one can wish for, I am immensely grateful. You´ve been my safe place, where I always long to go. Your trust and faith in me and in this work have been so valuable to me. Thank you! Maria Sandgren, my sincere thanks for your faith in me.

I want to say my sincere thanks to my home department KIDS. For your assistance and advise whatever the question, Åsa Misic, Malin Wirf, Håkan Wallén, Siw Svensson, Thomas Pettersson, Nina Ringart, and not least, Erik Näslund, thank you!

To the research team in Paris, for your welcoming ways, for generously sharing your knowledge and expertise, for all good times on travel, exploring science as well as good food and drink, for all good memories, thank you!

The four papers included in this thesis did not come to life without you. Cherished co-authors, I am immensely proud and thankful for sharing authorship with you. I have learnt so much and I´ve appreciated every part of our correspondence over refinement of message and meaning. Thank you! A special thanks to Lena Krumlinde Sundholm, for bringing your valuable knowledge and expertise into this project, and to all of us in the clinic.

Sverker Johansson, thank you for your mentorship and incredible generosity and for believing in me. For always inviting courage and inspiration, I am forever grateful.

Kenth Malmström and Elisabeth Ginsburg, your shared values are my compass still. To all colleagues at Erstagårdskliniken, not least Birgitta Olsson, Karin Broms and Kristina Westman, for all you´ve taught me, for love and friendship, thank you.

I would like to express my gratitude to Stroke-Riksförbundet, NEURO, Lars Hedlund for generous financial support to this research. And not least, my sincere gratitude to Promobilia
Foundation, for important financial support to this research, and for an assigned research grant, that enabled the completion of this thesis. I cannot say how proud I am.

Special thanks to Tony and Erik Iivonen, for opening a new world of music to me, for sharing your affection for music and for guidance in the art of playing the accordion (bimanually!). You’ve helped me find new inspiration and a key to creativity good energy and peace of mind.

To all members of our research-group at Danderyd, Jörgen Borg, Gaia Pennati, Anna Creamux, Hanna Bergling, Anneli Wall, Beatrice Felixon, Disa Sommerfelt, Påvel Lindberg and Susanne Palmcrantz. Exploring the paths of literature and science, collecting and discussing data, your willingness to helping out when technology crash, thank you for sharing your knowledge and expertise, for all the joy of working together.

To my supervisors Jörgen Borg, Alison Godbolt and Påvel Lindberg, how can I express my gratitude. Your guidance and support has been immensely valuable to me. The opportunity to learn from you, has been so gratifying. Thank you for being so generous, for your patience and for always bringing hope and inspiration.

It came to be so that the last months of my doctoral studies coincided with deep sorrow due to the sudden loss of by beloved farther. To all of you who has been there for me, and especially you Påvel, thank you for helping me through.

My singing, creative, dancing, mountain tracking, extended family, you are my water, nourishment and sunshine, thanks to you I will grow back as a stronger plant. And all my love to you LisaLotta, my very own life gardener!

Käraste Tyresö-töser, thank you for lifelong support and friendship. Thank you PO, for always being there and for always believing in me. To my affectionate First Aid Kit, Lovisa-Lo och Lu, Elin, Ghina and Elis, how proud I am of you, and happy I am for you. Erikssou for being such a good friend. Kaoken Körm Cerenius, I am forever grateful for our friendship, I have learnt so much from you, about life and also how to be the very best physiotherapist I can ever be.

Sist men inte minst vill jag tacka dig min älskade mamma, och mina syskon Joakim och Helena med familjer, och dig min allra käraste Lova för att ni finns, och dig min älskade pappa, för att du alltid funnits.
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10 SVENSK ÖVERSÅTTNING


Det övergripande målet för denna avhandling var att identifiera nyckelfaktorer för armens och handens motoriska återhämtning efter stroke, genom att tillämpa en kombination av väl etablerade kliniska undersökningsmetoder och nya känsliga och specifika mätmetoder samt en kartläggning av hjärnans strukturella och funktionella nätverk.


Sammantaget inkluderades 89 personer med stroke, av vilka 61 deltog i studie I, 80 i studie II och 89 personer i studie III och IV. I studie II deltog också 23 friska kontrollpersoner. Tillsammans genererade delstudierna en detaljerad kartläggning av armens och handens motoriska återhämtning omfattande specifika motoriska funktioner, viljemässig
rörelsekontroll, förmågan att gripa och släppa föremål samt att använda händerna tillsammans i en bimanuell aktivitet.

Studie I visade tidig förekomst av spasticitet av varierande svårhetsgrad vilken ökade över tid. Tidig svår spasticitet var relaterad till minskad motorisk återhämtning och ökad risk för utveckling av smärta och kontraktur över tid. Grad av skada på kortikospinala banan predicerade ökad grad av spasticitet över tid.

Studie II visade kvarvarande funktionsnedsättning gällande kraftreglering under utförande av pincettgreppet, vid 6 månader efter stroke, också hos personer med relativt mild motorisk påverkan enligt sedvanlig klinisk undersökning. Förmågan att använda och reglera pincettgreppet predicerades av grad av skada på kortikospinala banan och grad av viljemässig rörelsekontroll i handen enligt klinisk skattningsskala samt grad av sensorisk funktionsnedsättning (tvåpunkts-diskrimination).

Studie III visade på stora individuella variationer gällande bimanuell aktivitetsförmåga över tid och stora likheter med unimanuell motorisk förmåga vid respektive mättillfälle. Bimanuell återhämtning förklarades till över 80 % av initial viljemässig skulder-abduktion och finger-extension, mätt med hjälp av ett enkelt kliniskt skattningsmått (FMA-SAFE). Andra betydelsefulla prediktorer var initial sensorisk och kognitiv funktionsnedsättning samt av kortikospinala banans integritet. Interhemisfärisk funktionell konnektivitet mätt med MRI förklarade ytterligare en liten andel varians i återhämtningsgrad. En uppmätt stroke-inducerad skadevolym, som överlappade med kortikospinala banan (wCST-LL) med >5.5cm³, indikerade minimal bimanuell och unimanuell återhämtning över tid.


Sammanfattningsvis har delstudierna i denna avhandling bidragit till en ökad förståelse och kunskap om hur olika både specifika och sammansatta motoriska funktioner och aktivitetsförmågor återhämtas över tid efter stroke, och hur dessa samverkar och är relaterade till vanliga kliniska mått på viljemässig motorisk handfunktion. Därutöver har ökat kunskap erhållits, gällande hur variationer i motorisk funktion och aktivitetsförmåga över tid kan förklaras och predicas. Denna kunskap kan bidra till att förbättra klinisk handläggning och att identifiera specifika områden, som kan utgöra mål för individuellt riktad behandling samt
mål för utveckling av nya behandlingsmetoder. Denna kohort representerar en yngre andel av strokepopulationen (18-67 år), varför dessa resultat behöver valideras i andra åldersgrupper och i större kohorter.
## 11 APPENDIX A

### 11.1 A BRIEF GLOSSARY OF THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH (ICF) TAXONOMY

(World Health Organization, 2020)

<table>
<thead>
<tr>
<th>The ICF biopsychosocial model of functioning and disability</th>
<th>A model which describes the interaction between health, functioning (body function and structure, activities and participation) and contextual factors (environmental and personal). As such it recognizes a wider perspective to the consequences of a health condition that includes functioning and contextual factors.</th>
</tr>
</thead>
</table>
| Health condition | Refers to disease, disorder, injury or trauma. It may also include conditions such as pregnancy, stress or ageing. Health conditions are coded with the ICD-10 classification system. Stroke is in this context a health condition, specified within ICD-10.  
  E.g. ‘Stroke, not specified as haemorrhage or infarction’ (ICD-10: I64). |
| Body function | The physiological functions of a body system, including psychological and motor functions. “Body” refers to the human organism as a whole, thus including the brain.  
  E.g. ‘Control of voluntary movement functions’. |
| Body structure | The anatomical parts of the body such as organs, limbs and their components.  
  E.g. ‘Structure of brain’. |
| Impairment | A loss or abnormality in body structure or physiological function (including mental functions).  
  E.g. ‘Voluntary movement control problems’ or ‘coordination problems’ |
| Activity / activity limitation | Refers to an individual’s action or execution of a task. / Difficulties of an individual to execute activities (qualitatively and/or quantitatively).  
  E.g. ‘Fine hand use (picking up, grasping, manipulation and releasing)’ / ’Fine hand use problems’. |
| Participation / Participation restriction | Refers to an individual’s involvement in a life situation. As such representing the societal perspective of functioning.  
  E.g. ‘Preparing meals’ / ‘Problems preparing meals’.
| **Capacity** | Relates to what an individual *can* do in a standardised environment, i.e. the environmentally adjusted ability of an individual to execute a task or an action (i.e. an activity).

For example, may Indicate e.g. a person’s ability to ‘maintain a sitting position’, in a test situation and without personal assistance or assistance devices. |
| **Performance** | Refers to what an individual does or is able to do in the current (usual) environment. Represents aspects of a person’s involvement in life situations or ‘lived experiences’.

Indicates e.g. a person’s ability to ‘maintain a sitting position’, in the home environment, with possible personal assistance and assistance devices. |
| **Functioning** | Incorporates body functions, body structures, activities and participation. Refers to positive aspects of individual’s body function and structure, activity and participation and contextual factors (environmental and personal).

In the context of stroke, an individual’s functioning describes the level of integrity of body structures and functions, activity capacity and performance as well as supporting environmental and personal factors in daily life situations. |
| **Disability** | Incorporates impairments, activity limitations and participation restrictions, and refers to negative aspects of an individual’s contextual factors (environmental and personal)

In the context of stroke, a description of an individual’s disability includes injury to and loss of body structures and functions, activity limitations and participation restrictions. It would also include negative aspects regarding how these limitations and restrictions relate to the individual’s environment and personal factors in daily life situations. |