Dynamics of neurological and behavioural recovery after stroke

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DYNAMICS OF NEUROLOGICAL AND BEHAVIOURAL RECOVERY AFTER STROKE

Mique Saes

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DYNAMICS OF NEUROLOGICAL AND BEHAVIOURAL RECOVERY AFTER STROKE

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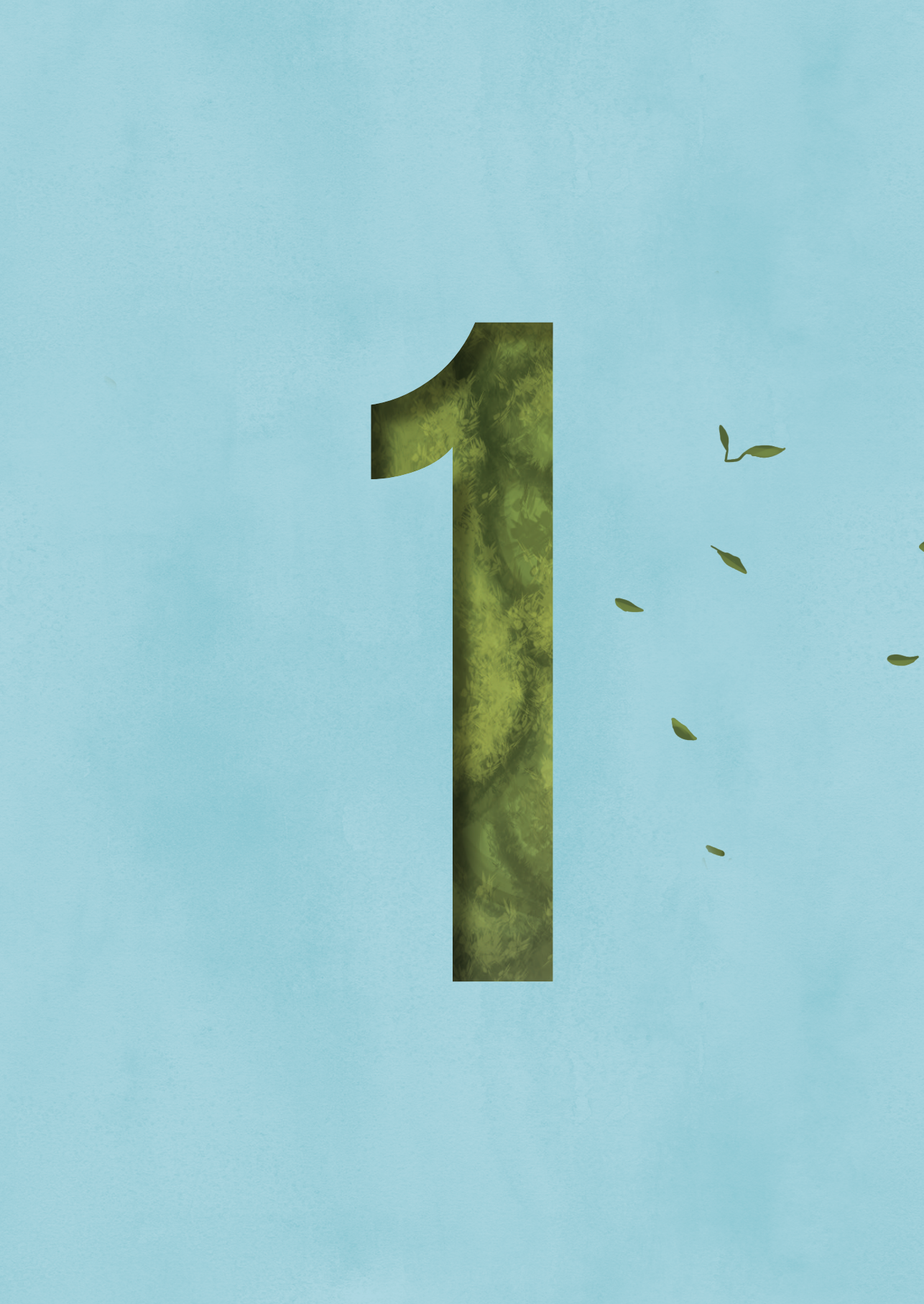

Glossary of terms and general introduction

Glossary of terms

Activity: execution of a task or action by an individual.[1]

Behavioural restitution: a return towards more normal patterns of motor control with the impaired effector (a body part such as the hand or foot that interacts with an object or the environment) and reflects the process towards true recovery.[2]

Behavioural compensation: recovery of the ability to complete a motor task due to the appearance of new motor patterns resulting from the adaptation of remaining motor elements or substitution, meaning that functions are taken over, replaced, or substituted by different end effectors or body segments.[3] Behavioural compensation results in deviating quality of movement compared to healthy individuals.

Biomarker: A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention.[6] See also prognostic biomarker and monitoring biomarker.

Body functions: physiological functions of body systems.[1]

Body structures: anatomical part of the body such as organs, limbs, and their components.[1]

Diaschisis: brain areas distant to the lesion which are affected due to stroke.[4]

Electroencephalography (EEG): a non-invasive electrophysiological technique with high temporal resolution for the recording of electrical activity arising from neurons in the human brain by placing electrodes onto the scalp. Neural activity detected by EEG is a summation of excitatory and inhibitory postsynaptic potentials of relatively large groups of neurons firing synchronously.[5]

Impairments: problems in body function or body structure such as a significant deviation or loss.[1]

International classification of functioning, disability, and health (ICF): multipurpose classification which provides a standard language and framework for the description of health and disability, where disability is an umbrella term for impairments, activity limitations and participation restrictions.[1]

Ischemic stroke: a stroke resulting from an arterial thrombotic blockage leading to oxygen deprivation.

Kinematic metric: a standard of measurement concerning segment movement, without consideration of the forces involved.

Kinetic metric: a standard of measurement regarding forces from or on body segments.

Monitoring biomarker: serially measured characteristics for assessing status of a disease or medical condition, or for evidence of exposure to (or effect of) a medical product or an environmental agent.[6]

Motor control: the process whereby the central nervous system produces purposeful coordinated movements to interact with the rest of the body and the environment.[7]

Motor recovery: reflects the extent to which body structure and functions, as well as activities, have returned to their pre-stroke state.[2]

Neuroimaging: various techniques to either directly or indirectly image the structure, function, or pharmacology of the brain. Examples of neuroimaging techniques are electroencephalography (EEG), magnetoencephalography (MEG), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and computed tomography (CT).

Neuronal oscillations: neurons in the brain can fire synchronously, resulting is oscillatory activity at a variety of frequencies. Also referred to as brain waves. Synchronized activity of a large group of neurons can be detected and recorded using electroencephalography (EEG). See also quantitative EEG parameter.

Neural restitution: when areas affected due to the stroke heal, neural pathways resume activity and the functions associated with the involved neural systems are restored.[8]

Neural substitution: spontaneous restoration of function through substitution and reorganization of neuronal structures.[8] In the chronic phase, neural substitution is assumed to be the predominant mechanism of behavioural recovery.[8]

Performance assays: tasks which isolate core motor execution capacities outside of a motor task context.[9]

Phases of recovery after stroke: a framework of five epochs based on the biology of recovery. Hyper-acute: 0-24 hours post stroke, acute: 1-7days, early subacute: 7 days – 3 months, late subacute: 3-6 months, and the chronic phase: >6 months post stroke.[2]

Prognostic biomarker: characteristics used to identify the likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.[6] See also Biomarker.

Quality of movement (QoM): operationally defined by comparing a patient's motor task execution to a reference population of non-disabled age-matched control subjects. The closer the movement matches those seen in controls, the better the quality of their movement.[9]

Quantitative EEG parameters: also referred to as spectral characteristics. Frequency dependent quantification of the power of detected neuronal oscillations, calculated per frequency band and/or converted to certain ratios.

Reaching: using the upper extremity to extend outwards and touch and/or grasp something, such as when reaching across a table or desk for a book.[10]

Resting-state: relaxed but awake state without performing any task.

Spontaneous neurological recovery: improvements of behaviour in the absence of a specific targeted treatment which is highly determined by time and occurs within a restricted time window (weeks to months for arm function) after stroke.[2]

Stroke: 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.[11]

Upper extremity: region of the upper limb in animals, extending from the deltoid region up to the hand, and including the arm, axilla, and shoulder.[12]

General Introduction

Each year, 1.5 million European people suffer from a stroke, of whom around 3 out of 4 survive. As a result, there are currently 9 million stroke survivors in Europe.[13] With that, stroke is one of the main causes of adult disability. In the near future, costs of stroke will rise substantially, putting a further strain on health and social care budgets.[13] While primary and secondary prevention measures aim to reduce the number of stroke patients and to detect and treat the stroke as soon as possible, investing in tertiary prevention (e.g., neurorehabilitation interventions) is important to accelerate and enhance post-stroke recovery.

Around 80% of stroke survivors suffer from motor impairment, referring to problems in body functions or body structures[1], typically affecting unilateral motor control of the face, arm, and leg[14]. Since motor impairment of the upper extremity greatly affects patient's activities of daily living, recovery of arm function in the activity domain of the International Classification of Functioning, Disability and Health (ICF) is among the top ten research priorities of stroke survivors, caregivers, and health care professionals.[15]

Developing effective interventions requires understanding of motor recovery after stroke. Motor recovery occurs at the level of the brain, referred to as neurological recovery, and can be observed during the performance of motor tasks, referred to as behavioural recovery. Two main issues in stroke recovery research will be discussed in this thesis. First, the inability to monitor neurological recovery after stroke due to the absence of adequate quantification of neurological state. Secondly, the demand for additional prognostic biomarkers of motor recovery in more severely affected stroke patients.

In order to improve our understanding of motor recovery after stroke, we investigate: 1) the association between observed dynamics of neural state of the brain and behavioural recovery reflected by improvement of motor behaviour, 2) the added value of neurophysiological parameters that may serve as biomarkers to predict behavioural recovery, and 3) the determination of which measures of behavioural recovery may indicate neurological recovery. Recently, these topics were prioritized by an international group of neurorehabilitation experts, the Stroke Recovery and Rehabilitation Roundtable task force (SRRR).[16,17] By addressing abovementioned topics, this thesis aims to provide a better understanding of how to quantify neurological recovery after stroke.

1.1. Defining stroke

The World Health Organisation (WHO) defines **stroke** as *"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"*.[11] The diagnosis is based on pathological-, imaging-, or other objective evidence, or based on clinical evidence such as symptoms that remain present more than 24 hours after onset (e.g., paresis of an arm or a leg, or the inability to comprehend and produce speech).[18]

Stroke can be caused by haemorrhage or ischemia, which in turn can be divided into different subcategories, emphasizing its heterogeneity.[18] A cerebral haemorrhagic stroke occurs when a blood vessel bursts within the brain. An ischemic stroke is caused by a blood clot that blocks the blood flow in an artery supplying brain tissue (**Figure 1.1**). In Western countries, ischemic strokes are most common (87%).[19] Ischemic stroke leads to hypo-perfusion, which prevents brain tissue from getting oxygen and nutrients. Depending on the level and duration of hypo-perfusion, stroke will lead to permanent or non-permanent tissue damage.[20] Within minutes post stroke, cells at the ischemic core are irreversibly damaged. It has been estimated that in a typical large vessel acute ischemic stroke 1.9 million neurons are lost per minute.[21] Cerebral tissue surrounding the core (i.e., perilesional region or penumbra) are dysfunctional due to moderate hypo-perfusion and shock. To prevent these cells from dying, reperfusion is required within hours post stroke.[20] This enables penumbral tissue to recover. Besides brain tissue at the core and surroundings of the lesion, also brain areas distant to the lesion are affected after stroke, referred to as neuronal diaschisis or shock[4]. The extent to which neural networks are affected, especially motor and attentional networks, corresponds to clinical findings. Normalization of these networks have been associated with recovery.[22]

1.2. Studying neurological and behavioural recovery after stroke

Figure 1.2 shows a phenomenological model of motor recovery of the upper extremity after stroke, which encompasses two levels: neurological recovery and behavioural recovery. From the perspective of neural networks, recovery can be described in terms of neural networks showing restitution (i.e., recovery to pre-stroke state) or adaptation (i.e., recovery using alternative activation). This can be measured as time-dependent changes that occur at the level of the brain using non-invasive technologies (e.g., functional magnetic resonance imaging (fMRI), electroencephalography (EEG) or magnetoencephalography (MEG)). Another way to investigate motor recovery is by systematically studying the time-dependent changes in behaviour at the different levels of the ICF model (**Figure 1.3**)[1]. With that, behavioural recovery covers improvements

both at the level of *body functions and structures* (e.g., decreasing muscle synergies, increasing muscle strength, and improving quality of movement) and at the level of *activities* (e.g., regaining the ability perform functional tasks with the upper extremity or the ability to walk). These two mentioned sources of information for investigating motor recovery after stroke will be used and discussed in this thesis.

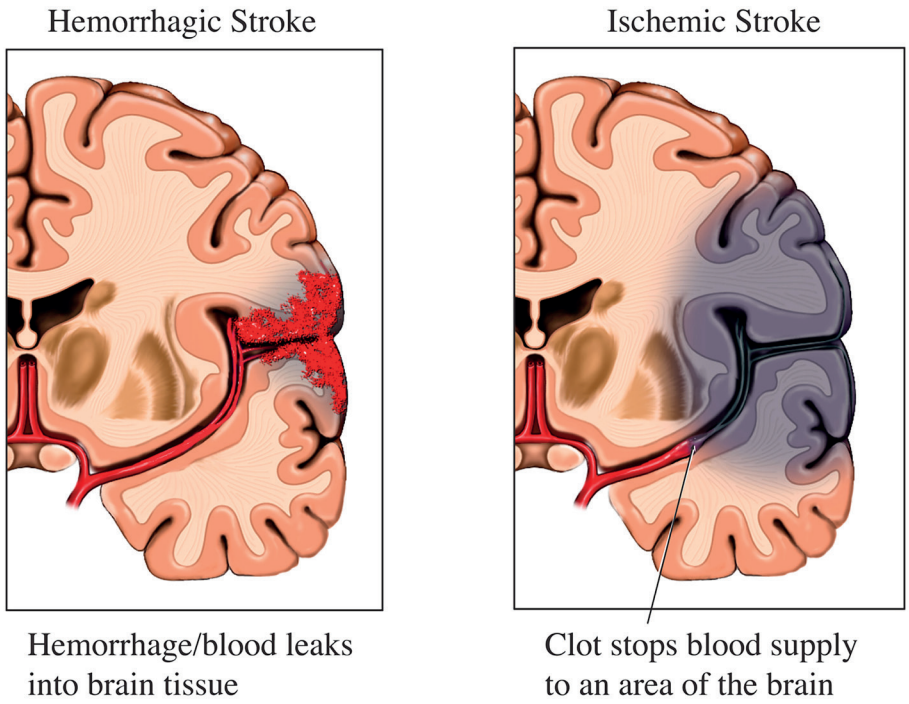

Figure 1.1 *Visualisation of the cause of a stroke. Copyright Nucleus Medical Media, Inc.*

1.2.1. Neurological recovery

Neurological recovery has been argued to be a combination of neural restitution and neural substitution. After stroke, some brain tissue may survive and, with that, neural networks may recover by spontaneous neurological recovery, which may be referred to as **neural restitution**.[8] Definitive evidence of these restorative processes in humans is scarce, but markers that suggest neurogenesis, gliogenesis, and neural sprouting have been found in human post-stroke perilesional brain tissue.[23,24] The time window of neural restitution is unknown, but may range from minutes for those with a transient ischemic attack, to several months post stroke. In addition, new and alternative pathways will be formed by structural plasticity of intact cerebral tissue after stroke.[23] This process is referred to as **neural substitution** for the first time in

the eighties.[8] More recent literature is confirmative to above regenerative processes and suggests that mechanisms of neural restitution and substitution are enhanced in the first weeks after stroke by growth-promoting processes.[25] In contrast to neural restitution, neural substitution is believed to continue in the chronic phase post stroke due to learning-dependent plasticity.

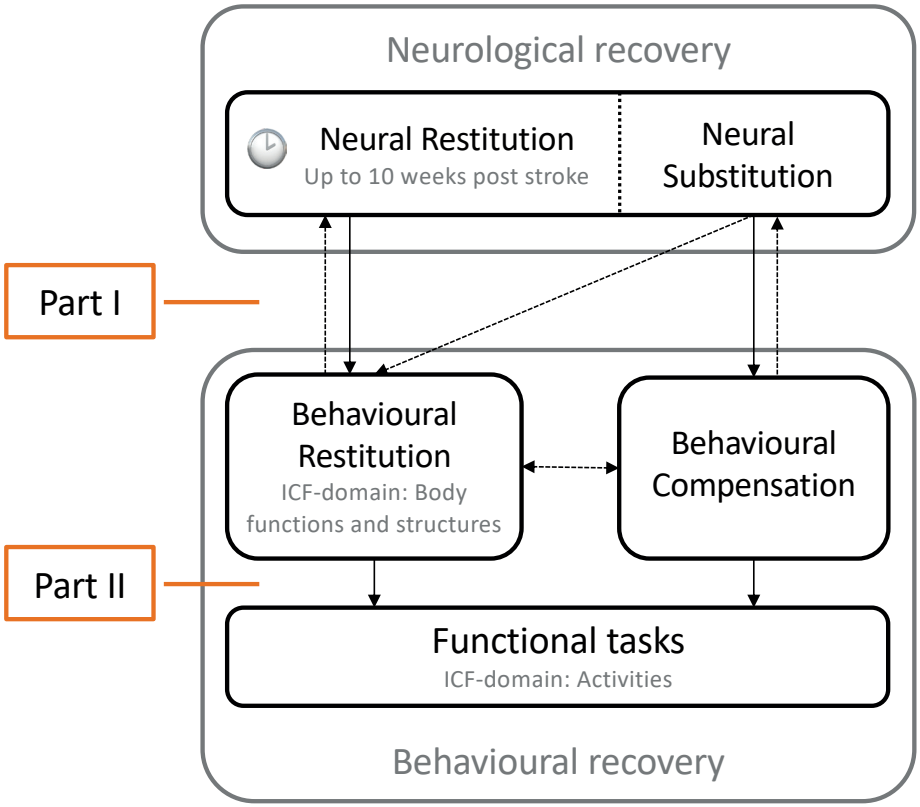

Figure 1.2. *Phenomenological model of upper extremity motor recovery after stroke. A visualisation of the scope of this thesis. In Part I of this thesis the association between neurological and behavioural recovery after stroke will be investigated. In Part II of this thesis the current ability to discern behavioural restitution, as a proxy for neurological recovery, from behavioural compensation will be investigated, focussing on quality of movement. Solid lines represent relations that are consented to exist, whereas dashed lines represent possible relations.*

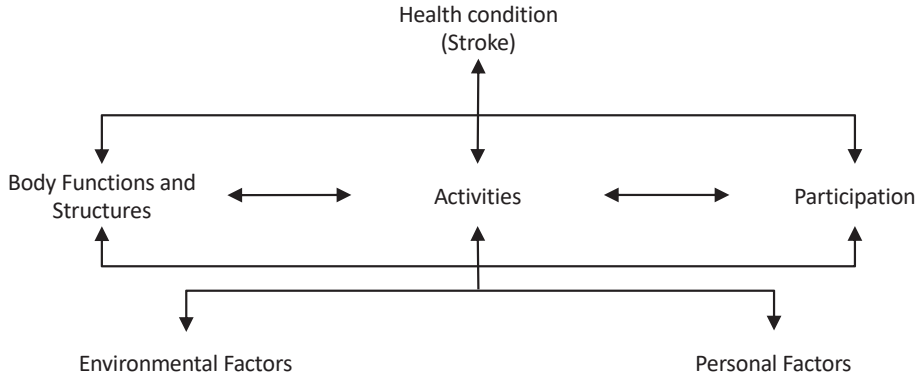

Figure 1.3. *International Classification of Functioning, Disability and Health (ICF) (adapted from: WHO 2001).*

Since it is difficult to measure what is changing at molecular and cellular level in humans in-vivo, non-invasive techniques such as fMRI, EEG, or MEG may be used to quantify brain activity to reflect neuronal processes of recovery early after stroke.

1.2.2. Behavioural recovery

Behavioural recovery refers to regaining the ability to perform a motor task and is assumed to be a combination of behavioural restitution and behavioural compensation. **Behavioural restitution** is defined as a return towards more normal patterns of motor control with the impaired body part[17,26], which results in improving quality of movement (QoM). Behavioural restitution is argued to require neural restitution, which is seen as its main driver.[8] Behavioural recovery can also be achieved by learning new compensating strategies by using intact muscles, joints, and effectors in a different way rather than normal pre-stroke behaviour, referred to as **behavioural compensation**.[3,26] Using these alternative compensatory strategies is believed not to require neural restitution.[3,17,26] Neural substitution is assumed to be the main driver of behavioural compensation.[3,27] Both mechanisms of motor recovery contribute to an improved ability to perform a motor task, but result in different movement executions.

1.2.3. Quantifying behavioural restitution in absence of compensation

Investigating whether therapeutic interventions can influence neurological recovery is necessary to adequately assess the effects of neurorehabilitation interventions. This requires quantification of neural restitution, which is difficult to measure in a direct way. Hypothetically, neural restitution may be reflected by recovery of specific neurological modalities at the level of the ICF domain *body functions and structures*, such as strength, ability to dissociate movements, and somatosensory deficits. In this

domain, observed recovery is assumed to reflect behavioural restitution, which is established by neural restitution rather than by neural substitution. However, clinical assessments able to quantify behavioural restitution in absence of compensation strategies are lacking. Therefore, there is a need to investigate and achieve consensus on a set of performance assays which are able to quantify behavioural restitution in the purest way, without being influenced by behavioural compensation.

Stroke patients often suffer from abnormal muscle synergies, a systematic coupling or co-articulation across different joints or a fixed pattern of co-activation of muscles.[28,29] Muscle synergies are believed to have the purpose to simplify motor control to reduce computational burden of the brain.[30,31] During recovery, patients go through different stages of typical muscle synergy dependent motor control. The Fugl-Meyer motor assessment of the upper extremity (FM-UE) is a further refinement of the stages of motor recovery described by Signe Brunnström in the sixties who classified the longitudinal observations of Thomas Twitchell after stroke in the fifties[32]. The FM-UE is frequently used in stroke recovery and rehabilitation studies and has been argued as the clinical test which fits best in the *body functions and structures domain*[33] and thereby most closely reflects behavioural restitution. However, it should be noted that muscle synergies are influenced by strength deficits[34].

In contrast to clinical scales, kinematic measurements have potential to provide objective high-resolution metrics of particular aspects of motor control, such as QoM, which closer relate to underlying neurological deficits. QoM is operationally defined by comparing a patient's motor task execution to a reference population of non-disabled age-matched control subjects. The closer a patients' movement matches that of age-matched healthy control subjects, the better the QoM.[17] The process of normalization of QoM may be seen as a more accurate quantification of the degree of motor control, and may thereby serve as a better proxy of behavioural restitution compared to clinical measures[17]. This will be further discussed in **chapter 5-7**.

1.2.4. Spontaneous neurological recovery after stroke

It is assumed that neurological recovery after stroke is highly determined by time and therefore reflects a process called *spontaneous neurological recovery*.[35–37] Most behavioural recovery is observed in the first 10 weeks post stroke[38], after which gradually a plateau is reached, as visualized in **Figure 1.4**. In the previous decade, several longitudinal studies have shown that a variety of neurological modalities show a similar time-dependent pattern of recovery, suggestive for spontaneous neurological recovery[39–41]. In this thesis, we will mainly focus on motor recovery after stroke.

Behavioural recovery shows a logarithmic time course. This emphasizes the importance of applying frequently repeated measurements in the first few weeks post stroke, if the aim is to properly report the progress of recovery. To enable comparison of outcomes between studies, recently, a framework of five epochs was defined based on current knowledge about the biology of recovery: hyper-acute (first 24 hours post stroke), acute (1-7days), early subacute (7 days – 3 months), late subacute (3-6 months) and the chronic phase (>6 months) (**Figure 1.5**).[26]

1.2.5. Biomarkers

In vivo it is challenging to accurately quantify the neurological state or ongoing neurological recovery by identifying underlying molecular or cellular processes. **Biomarkers** are referred to as indicators of disease state that can be used clinically as a substitute measure of such underlying processes.[26] Definitions of context specific biomarkers were proposed by the U.S. Food and Drug Administration and the National Institutes of Health to improve appropriate application.[6] Biomarker subtypes that will be discussed in this thesis are *monitoring biomarkers* and *prognostic biomarkers*. Monitoring biomarkers may allow for identification of underlying processes of neurological recovery; prognostic biomarkers may offer insight into the intactness or state of the brain to predict motor recovery after stroke.

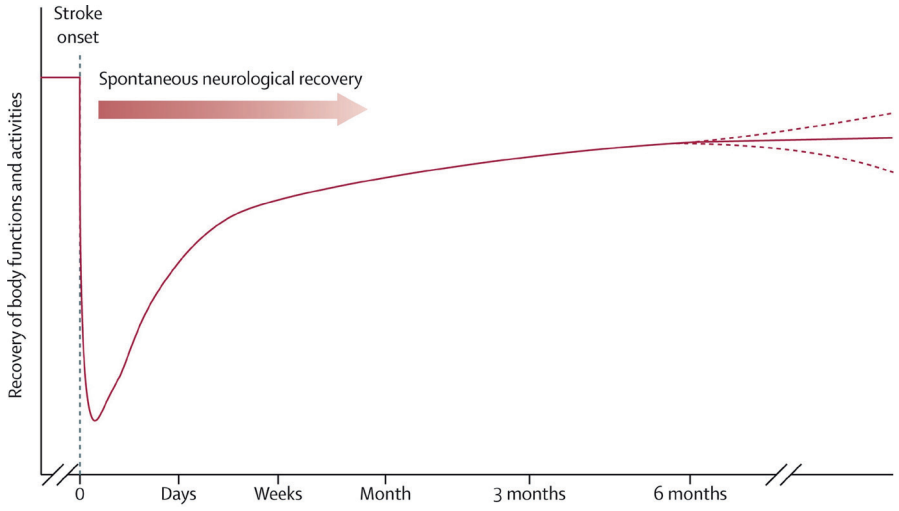

Figure 1.4. *Time window of spontaneous neurological recovery of body functions and activities after stroke. (Adjusted from Langhorne et al., 2011)*

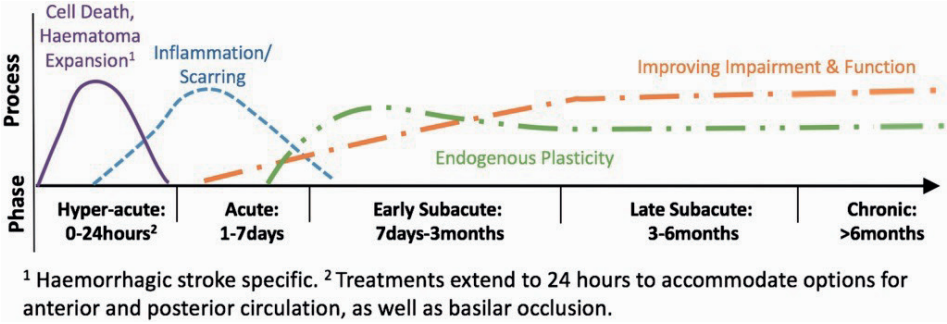

Figure 1.5. *Definitions of critical time points post stroke that link to the currently known biology of recovery (Figure from Bernhardt et al., 2017).*[26,42]

Monitoring biomarkers
Serially measured characteristics for assessing status of a disease or medical condition, or for evidence of exposure to (or effect of) a medical product or an environmental agent.[6]

Prognostic biomarkers
Characteristics used to identify the likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.[6]

1.2.6. Prediction of motor impairment after stroke

Prediction of recovery from motor impairments after stroke is important for patients and care providers and helps to choose the most optimal type of therapeutic intervention. An important issue in stroke recovery research is the lack of understanding why some patients show spontaneous neurological recovery and others do not. Early performed clinical motor assessments explain a large portion of the variance in presence of motor impairments in a late stage after stroke.[39,40,43] However, professionals still have difficulties in predicting the time course of recovery of individuals with upper limb motor impairment.[38] Recently, the large heterogeneity between patients regarding the rate and degree of motor recovery was studied, whereafter five subgroups were identified based on their magnitude and rate of motor recovery quantified by FM-UE.[38] Despite this further sub-specification, predicting the time course of recovery based on clinical baseline scores of motor impairment often remains uncertain.

Therefore, it is urgently needed to identify additional prognostic biomarkers beyond previously identified clinical biomarkers.[44] Such biomarkers may elucidate prospective behavioural recovery before it can be observed by clinical assessments.[23] In **chapter 4** we investigate whether neurophysiological information obtained using EEG may serve as a prognostic biomarker, and whether these prognostic biomarkers have added value beyond clinical assessments early post stroke.

1.3. Scope of this thesis

Figure 1.2 provides a visualisation of the scope of this thesis. In **Part I** of this thesis recovery is investigated based on brain activity. It focuses on the association between neurological recovery and behavioural restitution by determining the potential of quantitative EEG parameters measured during rest to serve as monitoring or prognostic biomarkers. Therefore, we investigate the time course of EEG parameters and their longitudinal association with improvements on clinical assessment scales at the level of body functions and structures of the ICF. Furthermore, we investigate the prognostic value of quantitative EEG parameters derived early post stroke regarding prediction of motor impairment of the upper extremity at six months. Moreover, we investigate whether these EEG parameters have added prognostic value beyond clinical scores of motor impairment early post stroke. In **Part II** of this thesis, recovery is investigated based on behavioural recovery. It focuses on recovery of quality of movement after stroke quantified using kinematics, and the current ability to distinguish behavioural restitution and behavioural compensation.

1.4. Part I. The association between neurological recovery and behavioural restitution after stroke

1.4.1. Neuro-imaging techniques

Various non-invasive neuroimaging techniques are available to obtain neurophysiological information from the brain to reflect its neural state. Structural information can for example be obtained using magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) or transcranial magnetic stimulation (TMS) combined with neuronavigational systems. Brain activity can be measured based on blood-oxygenation levels by performing functional MRI (fMRI), or based on neuronal oscillations by performing magnetoencephalography (MEG) or electroencephalography (EEG). MEG and EEG have a high temporal resolution and reflect brain activity in the most direct way. The recorded signal is a summation of cortical pyramidal cell activity.[45] Moreover, modifications of the frequency content of neuronal oscillations after stroke are associated with stroke severity.[46] It has been suggested that neuronal oscillations may elucidate the neural state of the brain which determines whether a patient will show recovery or not, and may therefore predict motor recovery before

this behaviour is observed.[23] While **neuronal oscillations** have been mentioned as one of the promising sources of monitoring and prognostic biomarkers[23,44,46,47], MEG and EEG are hardly investigated till so far[23].

Neuro-imaging techniques can help to quantify neurological recovery after stroke. This requires frequently repeated measurements of neural activity during the early phase post stroke. In order to limit burden of patients and concomitant drop-outs in longitudinal studies early after stroke, portable measurement systems are preferred. Although MEG shows higher signal-to-noise ratios and a higher spatial resolution compared to EEG, EEG is more feasible since it is suitable for use in a portable system which enables to perform measurements at the location of the participating patient.

1.4.2. Measurement of brain activity using EEG

EEG is a non-invasive technique to record activity from the brain using electrodes on the skull. These electrodes record voltage fluctuations caused by ionic currents within brain neurons relative to a ground electrode. During the recordings presented in this thesis 64 electrodes were attached to a tight-fitting cap, and systematically and symmetrically distributed over the skull (**Figure 1.6**). Impedances between electrodes and the skin were reduced using saline gel.

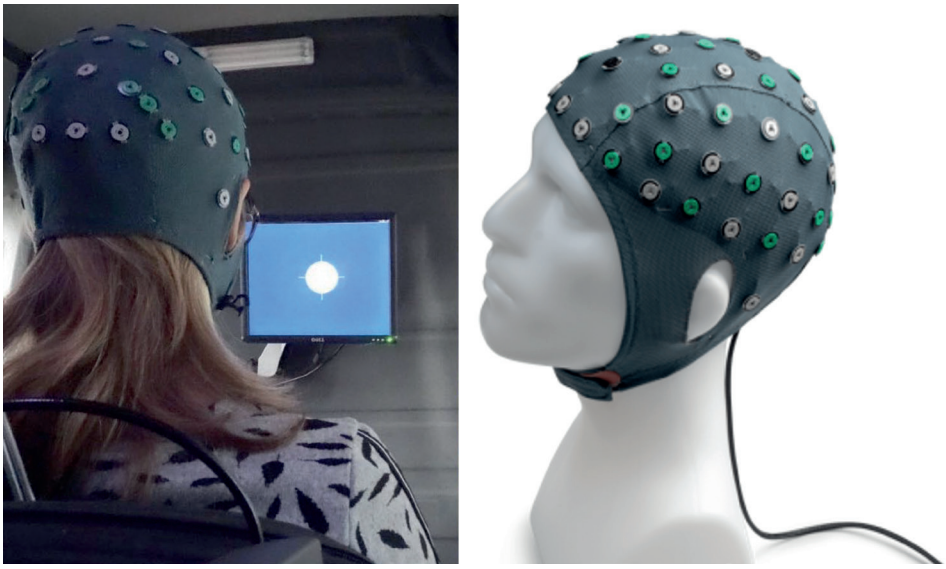

Figure 1.6 *EEG measurement set-up (BrainWave EEG head cap, TMSi)*

Stroke patients participate in observational scientific studies alongside their rehabilitation program. To make it feasible to perform repeated recordings of neuronal oscillations at fixed moments between stroke onset and six months post stroke, a specially equipped van was developed to perform EEG recordings at the place of residence of the participant (**Figure 1.7**).

1.4.3. Recovery of brain activity in resting-state

In this thesis, resting-state brain activity refers to spontaneous cortical activity of the brain over a period of time during awake state, while the subject is sitting and doing nothing. Cortical resting-state activity is a potential source for monitoring biomarkers of neurological recovery and prognostic biomarkers of behavioural recovery. Early after stroke, cortical resting-state activity has prognostic value regarding global neurological deficits quantified using the NIHSS and degree of dependency assessed with the modified Rankin Scale (mRS).[48–52] Brain activation patterns during rest are also related to motor deficits.[53] Since lesions cause changes in structural and functional neuronal networks in the brain, deviations in cortical activation patterns may reflect the level of brain damage caused by stroke. Moreover, in contrast to motor tasks, resting-state assessment is an experimental condition which is also feasible for more severely affected patients early post stroke, which restricts selection bias.

Figure 1.7 *EEG measurement van to enable brain activity recordings at the place of residence of the participant. (photo: Anita Edridge)*

1.4.4. Abnormalities and changes in resting-state EEG observed after stroke

Part I of this thesis focuses on quantitative resting-state EEG parameters which reflect the frequency content of the recorded signal. Although the function of the different frequencies of neuronal oscillations is not fully understood, the frequency content in healthy individuals is rather stable over repeated measurements.[54] Changes in the frequency content of the recorded signal in adults have been associated with pathological phenomena in the brain.[46,55] Hemispheric stroke has been associated with increased low-frequency oscillations in the delta (1-4 Hz) and theta (4-8 Hz) band.[5,50,56,57] This is in line with the finding that in stroke survivors increased low-frequency activity is indicative of a localized structural lesion.[58] Activity in the alpha frequency band is often decreased after stroke[55], and patients with unaltered activity in the alpha frequency band show to be less affected by stroke.[59] A combination of the commonly observed increased delta power and decreased alpha power is reflected by the quantitative EEG parameter delta-alpha ratio (DAR), which showed increased values early after stroke.[60] Unilateral lesions also result in an asymmetrical power distribution over the hemispheres, which can be quantified by the pairwise-derived brain symmetry index (BSI).[61] Early after stroke, patients show an increased power asymmetry compared to healthy individuals.[61,62] Whether and how these parameters change over time after stroke within patients is currently unclear. Moreover, hypotheses concerning development of these EEG parameters after stroke cannot be made since information on DAR and BSI values in the chronic phase post stroke is lacking. Such information will be obtained in **chapter 2**.

Although the cause of changed frequency content of neuronal oscillations after stroke is largely unknown, several potential explanations have been mentioned in literature. Animal studies indicate that abnormalities in delta activity are caused by partial cortical deafferentation[63,64], since delta activity was found in the cortex overlying white matter lesions in cats[63]. Others speculate that low-frequency brain activity may drive reorganisation or recovery with axonal sprouting, since these phenomena were strongly correlated in the adult brain of rats.[65,66] Furthermore, neuronal oscillations are influenced by GABAergic signalling, especially in the low-frequency bands.[23] Therefore neuronal oscillations show potential to serve as biomarkers of cortical excitatory-inhibitory balance, which may influence neurological recovery after stroke[23]. Increased amplitudes of slow waves were observed in different neurological disorders and are not restricted to stroke. Therefore, the presence of increased low-frequency oscillations has been linked to general cerebral dysfunction of the brain.[57]

1.4.5. Resting-state EEG based biomarkers

Chapter 3 of this thesis identifies a number of quantitative resting-state EEG parameters that may serve as monitoring biomarker to assess the status of the brain post stroke. We investigate how these EEG parameters change over time, reflecting neurological recovery, and whether they are longitudinally associated with clinical assessments in the *body function and structure* domain of the ICF as reflection of behavioural restitution.

Quantitative resting-state EEG parameters derived early post stroke have shown prognostic value regarding global neurological deficits quantified using the NIHSS and degree of dependency assessed with the modified Rankin Scale (mRS) in a later phase after stroke.[48–52] However, the potential of quantitative resting-state EEG parameters measured early post stroke to serve as prognostic biomarkers to predict motor impairment of the upper extremity six months after stroke is unclear. Moreover, the prognostic value of EEG based parameters beyond clinical assessments is important, but hardly considered.[52] Both aspects will be investigated in **chapter 4** of this thesis.

1.4.6. Clinical assessments approaching behavioural restitution

Clinical assessments at the level of *body functions and structures* approach the quantification of behavioural restitution. In this thesis, two clinical assessments are used: the NIHSS and FM-UE. The NIHSS quantifies global neurological deficits, whereas the FM-UE is focused on motor recovery. The FM-UE is based on the stages of recovery a patient goes through after stroke regarding the ability to move outside pathological muscle synergies. With this, most of the observed behavioural recovery reflected by FM-UE scores is assumed to originate from neurological restitution. Although the FM-UE cannot be used to measure pure behavioural restitution, the FM-UE is argued to be the clinical assessment which most closely approaches behavioural restitution.

1.5. Part II. Measuring behavioural recovery using kinematics

Clinical assessments are commonly performed to determine behavioural recovery after stroke, whereas kinematics and kinetics may provide more objective information on neurological recovery underlying behavioural recovery. Kinematic metrics are metrics of segment movement, without consideration of the forces involved. Kinetic metrics are metrics of forces from or on body segments. As argued by the SRRR, kinematic and kinetic metrics are the only way to quantify QoM.[17] QoM can reflect the ability of the central nervous systems to regulate motor executions, and may thereby reflect underlying neurological recovery. Kinematic and kinetic metrics may be useful as reflection of behavioural restitution and thereby as a proxy (i.e., monitoring biomarker) of neural restitution post stroke. In **Part II** we will investigate which metrics are used to quantify QoM and how quality of a reaching movement develops early post stroke.

1.5.1. Reaching task

Reaching movements are an important component of many daily activities and are therefore commonly included in exercise therapy post stroke. Reaching requires simultaneous coordination of movements around the elbow and shoulder, which are often limited post stroke as a result of abnormal muscle synergies.[67,68] In this thesis we focus on kinematics and kinetics obtained during *reaching* to quantify QoM. Quality of reaching movements will improve during recovery when patients improve their motor control and become able to perform movements outside abnormal synergies. Furthermore, a reaching task is feasible to study over time since this task is easy to explain and suitable to perform in a standardized way. This, in turn, enables comparing performance of stroke patients and non-disabled individuals, but also enables to investigate behavioural recovery within stroke patients over time.

1.5.2. Metrics investigated in stroke literature

Kinematic and kinetic metrics have been argued to enable to discern behavioural restitution, as a proxy for neural restitution, from behavioural compensation.[17] This requires to investigate such metrics longitudinally after stroke. Recently, the SRRR provided recommendations of corresponding study designs.[17] An overview of what has been done so far to distinguish behavioural restitution and compensation is lacking. **Chapter 5** provides an overview of longitudinal studies which used kinematic and/or kinetic metrics to quantify recovery of quality of reaching movements post stroke and what metrics were obtained. Moreover, this systematic review elucidates whether in these studies it was tried to distinguish behavioural restitution and compensation, and whether these studies were performed in line with recent recommendations provided by the SRRR.

1.5.3. Smoothness

A kinematic metric often argued to reflect quality of movement is movement smoothness.[69–72] Although a uniform definition for movement smoothness was lacking for a long period of time, to date, movement smoothness has been defined as the continuality or non-intermittency of a movement, independent of its amplitude and duration.[73] Optimizing movement smoothness has been suggested as a cost-effective motor control strategy.[74–76] The increased predictability of smoother movements[77–79] reduces the computational burden of motor control.[30]

Deficits in movement smoothness are commonly observed after stroke. Several possible causes have been suggested for smoothness deficits. A lack of smoothness could for example be caused by the inability to synchronize motor units or control agonist and antagonist muscles in their right proportions[80,81], but it could also be a

reflection of enhanced segmentation in multi-joint movements[31,81–83]. To date, the neurophysiological mechanisms of smoothness deficits after stroke remain unclear. A prerequisite for investigating the cause of diminished smoothness after stroke, is the availability of an adequate metric to quantify smoothness. Unfortunately, there is currently no consensus on a standardized metric to quantify movement smoothness of the upper extremity.[73] Many different metrics have been used in literature for investigating smoothness of multi-joint reaching movements post stroke without underpinning of the chosen metric.[73] In **chapter 6**, we provide a systematic overview of smoothness metrics investigated during a reaching task in stroke research. Moreover, we investigate which of these metrics are adequate to quantify smoothness. Subsequently, in **chapter 7**, the most appropriate smoothness metric was used to reflect smoothness and investigate whether recovery of smoothness is longitudinally associated with recovery from motor impairment post stroke.

1.6. Outline of this thesis

The first aim of this thesis is to determine whether EEG measures of brain activity can serve as biomarker of neurological recovery underlying behavioural recovery of the upper extremity. Therefore, quantitative EEG parameters are computed based on resting-state EEG recordings as reflection of neural state. Behavioural restitution is reflected by FM-UE scores. In **chapter 2**, we study chronic stroke patients to determine which quantitative EEG parameters show deviations from healthy individuals, and whether these EEG parameters are associated with upper extremity motor impairments. Based on these finding, hypotheses can be prepared concerning brain activity changes over time and longitudinal associations with recovery from the early sub-acute phase until the chronic phase post stroke. In **chapter 3**, we determine the time course of EEG parameters within the first six months post stroke, together with their longitudinal association with global neurological deficits and motor impairments. In **chapter 4**, we investigate whether quantitative resting-state EEG parameters measured early post stroke show potential to serve as predictors (i.e., prognostic biomarkers) of motor impairment in the chronic phase. Moreover, we study whether these biomarkers can explain motor impairment in the chronic phase beyond what could already be explained by clinical outcome measures.

The second aim of this thesis is to determine how QoM of the upper extremity is measured using kinematics and kinetics to quantify behavioural restitution. **Chapter 5** provides a systematic overview of longitudinal studies in which kinematic and/or kinetic metrics are used to quantify recovery of quality of reaching movements post stroke and what metrics were obtained. Moreover, this systematic review elucidates to which level these studies tried to distinguish behavioural restitution and compensation,

and whether they were performed in line with recent recommendations provided by the SRRR. A kinematic metric which is often argued to reflect QoM during a reaching task is smoothness of the hand trajectory. In **chapter 6**, we first provide an overview of kinematic metrics which have been used to reflect smoothness of reaching movements after stroke. Subsequently, by use of simulation analyses, the validity and robustness of these smoothness metrics are studied, in order to determine which smoothness metrics are valid and can properly be used in stroke studies. In **chapter 7**, we investigate whether recovery of smoothness deficits is longitudinally associated with recovery from motor impairment reflected by the FM-UE score, and whether their time courses are congruent within the first six months post stroke.

Chapter 8 provides an overview and further discusses the interpretation of our findings in the chapters as well as the methodological considerations and consequences of this thesis for future research after stroke.

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PART I

The association between neurological recovery and behavioural restitution after stroke


2

How does upper extremity Fugl-Meyer motor score relate to resting-state EEG in chronic stroke?

A power spectral density analysis.

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Abstract

Objective: We investigated the potential added value of high-density resting-state EEG by addressing differences with healthy individuals and associations with Fugl-Meyer motor assessment of the upper extremity (FM-UE) scores in chronic stroke.

Methods: Twenty-one chronic stroke survivors with initial upper limb paresis and eleven matched controls were included. Group differences regarding resting-state EEG parameters (Delta/Alpha ratio (DAR) and pairwise-derived Brain Symmetry Index (BSI)) and associations with FM-UE were investigated, as well as lateralization of BSI and the value of different frequency bands.

Results: Chronic stroke survivors showed higher BSI compared to controls ($p<0.001$), most pronounced in delta and theta frequency bands ($p<0.0001$; $p<0.001$). In the delta and theta band, BSI was significantly negatively associated with FM-UE (*both* $p=0.008$) corrected for confounding factors. DAR showed no differences between groups nor association with FM-UE. Directional BSI showed increased power in the affected versus the unaffected hemisphere.

Conclusions: Asymmetry in spectral power between hemispheres was present in chronic stroke, most pronounced in low frequencies and related to upper extremity motor function deficit.

Significance: BSI is related to motor impairment and higher in chronic stroke patients compared to healthy controls, suggesting that BSI may be a marker of selective motor control.

Introduction

Stroke is one of the main causes of serious disability in adults nowadays.[1] 80% of acute stroke survivors suffer from paresis of the upper extremity.[2] The Fugl-Meyer motor assessment of the upper extremity (FM-UE) often serves as the primary outcome measure for quantifying behavioural restitution in clinical trials, in particular in the field of upper limb robotics.[3] FM-UE is considered reliable and valid for measuring motor function.[4–6] It assesses the patient's ability of moving outside the abnormal synergistic dependent motor patterns and reflects patient's control of selective and isolated joint movements.[7–9] However, the FM-UE is an indirect measure of neural deficits, and its relation with direct biomarkers of cortical state is still underexplored. Knowledge about the association between severity of upper limb motor impairment and cortical activity, measured with non-invasive techniques such as EEG, can be of value to provide more insight into the cortical reorganization accompanied with stroke recovery.

Presence of low frequency oscillations in the EEG signal have been associated with cerebral dysfunction[10] including neural deficits post stroke[11,12]. The Delta/Alpha ratio (DAR) and the pairwise-derived Brain Symmetry Index (BSI) are resting-state EEG parameters which are potentially valuable early predictors of neurological function in stroke survivors.[13] DAR is the ratio between the spectral power in the delta and alpha frequency band. For adults in awake state, increased low-frequency components like delta and theta oscillations reflect cerebral dysfunction[14], while preserved activity in the alpha frequency band represents general well-functioning[15]. The pairwise-derived BSI, which is a variation on the original BSI[11], reflects the amount of asymmetry in spectral power of the EEG signal between homologous channels forming pairs over the affected and unaffected hemisphere[16].

Both DAR and BSI are increased in the (sub) acute phase post stroke.[13,16,17] However, it is still unknown whether these power spectral density measures differ between chronic stroke survivors when compared to healthy individuals and whether they are related to motor impairment reflected by the FM-UE. Moreover, BSI analysis might be improved by considering the value of frequency bands and directionality of asymmetry.

The aim of the current study was to address the potential added value of resting-state EEG as a biomarker for neurological recovery post stroke. Therefore, we investigated whether chronic stroke survivors deviate from healthy individuals regarding their resting-state power spectral densities, in particular the resulting measures DAR and BSI. In addition, we studied the association between DAR/BSI and FM-UE scores in

chronic stroke. We hypothesized that DAR and BSI of chronic stroke survivors are increased compared to healthy subjects and negatively associated with FM-UE scores. For the BSI, this was expected to be specifically the case in the lower frequency bands (delta and theta) since these are most affected in stroke.[14]

Methods

The study was approved by the Medical Ethical Reviewing Committee of the VU University Medical Center Amsterdam (registration number 2014.140) and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Subjects

Twenty-one chronic stroke survivors were included in this study (15 males; mean age, 60.6; range, 48-77). Patient characteristics can be found in Table 1. The inclusion criteria were: 1) a first-ever cerebral stroke; 2) ≥6 months post stroke; 3) initial upper limb paresis in the acute phase; 4) ≥18 years of age; 5) Mini Mental State Examination score ≥20 and 6) written informed consent. Exclusion criteria were: 1) a pacemaker or other metallic implants; 2) upper extremity orthopaedic limitations present before stroke onset; 3) recurrent stroke. Furthermore, eleven healthy age- and gender- matched controls without a history of neurologic disorders were recruited (7 males; mean age, 58.5; range, 42-75).

Procedure

All participants provided written informed consent. Clinical tests were performed by the chronic stroke group. Resting-state EEG was measured in a specially equipped van, which allowed for visiting participants at their current residence. Five consecutive trials of one minute each were recorded. Participants were measured while seated in a wheelchair with eyes opened. Participants were asked to focus on a dot that was presented on a computer screen just below eye level to prevent drowsiness and artefacts due to eye movements. One hospital visit was required for a structural MRI measurement of the brain.

Data acquisition

Electroencephalography

A high-density 64-channel EEG recording was performed using an EEG cap with Ag/AgCl electrodes ordered according to the international 10–20 system and a multichannel amplifier (Refa, TMSi, Oldenzaal, the Netherlands). Electrodes located at the mastoids (m1, m2) were not used, resulting in a 62-channel recording. Recordings were performed at a rate of 2048 Hz using ASA software (ANT software BV, The Netherlands). The ground electrode was placed on the mastoid process. Signals were recorded to average reference. Electrode impedances were kept below 20 kΩ.

Clinical tests

A sensitive, valid and reliable clinical test to measure the motor function of the upper limb at the impairment level is the upper extremity domain of the Fugl-Meyer motor assessment, (FM-UE)[4–6]. The FM-UE is an impairment scale specific for stroke survivors and determines the ability to execute dissociated movements with the upper paretic limb[8]. It is a valid predictor of upper extremity motor recovery and is suggested to reflect most appropriately 'true' neurological motor recovery[18], in the body structure and function domain of the International Classification of Functioning, Disability and Health (ICF) model. A higher score corresponds to better motor function, with a maximum score of 66. The National Institutes of Health Stroke Scale (NIHSS) served to quantify stroke severity. Lower NIHSS scores correspond to less neurological impairments; the maximum score of this test is 42. Motricity Index of the upper (MI-UE) and lower extremity (MI-LE) was performed in order to provide information on the level of paresis. The maximum score is 100 for each extremity separately.

Lesion localization

Structural magnetic resonance images of each participant were obtained at the VU Medical Center, Amsterdam. T1-weighted volumes were acquired with a Discovery MR750 3 Tesla scanner (GE, Waukesha, WI, USA) running a 3D fast spoiled gradient-recalled-echo sequence. The volume consisted of 172 sagittal slices (256 × 256). The scans were reviewed by a certified radiologist, where after lesions were rated as cortical, subcortical or cortical-subcortical, in line with the Automated Anatomical Labelling atlas. Furthermore, the clinically obtained information on the side of the affected hemisphere (left/right) was checked based on the MRI data, which did not show discrepancies.

Data analysis

Pre-processing

Offline analysis was realized using Matlab (R2012a, The Mathworks, Natwick, MA) using the FieldTrip toolbox for EEG/MEG-analysis[19]. EEG data were filtered with a 4th order high-pass Butterworth filter (cut-off at 0.5 Hz). Power-line artefacts were reduced using notch filters around 50, 100, and 150 Hz (4th-order bidirectional Butterworth, bandwidth 1 Hz). Further artefact rejection consisted of the exclusion of eye-blinks and -movements using independent component analysis (ICA) based on visual inspection of the components' waveforms and topographic distributions. Noisy channels were removed followed by re-referencing to the remaining average. Subsequently, EEG signals were divided into non-overlapping contiguous epochs of 2s for further analyses. Spectral power was estimated after correction with a Hanning taper of window size equal to epoch length.

Outcome variables

Delta/Alpha Ratio (DAR)

The DAR was defined as the ratio of the delta power to the alpha power. For every channel *c* the power of the delta (alpha) frequency band *f*=1,...,4 Hz (8,...,12 Hz) was determined as the mean of the spectral power $P_c(f)$. With these mean values, the delta/alpha ratio was computed as

$$\mathrm{DAR_c} = \frac{\langle P_c(f)\rangle_{f=1,\ldots,4\ \mathrm{Hz}}}{\langle P_c(f)\rangle_{f=8,\ldots,12\ \mathrm{Hz}}} \tag{1}$$

Subsequently, we averaged the ratios over all *N* EEG channels yielding the global DAR:

$$\mathrm{DAR} = \frac{1}{N}\sum_{c=1}^{N} \mathrm{DAR_c} \tag{2}$$

Pairwise-derived Brain Symmetry Index (BSI)

The BSI was defined as the absolute pairwise normalized difference in spectral power between the homologous channels c_L and c_R for left and right, respectively. The difference was averaged over a range from 1 to 25 Hz (adapted from Sheorajpanday et al., 2009[16]) according to

$$\mathrm{BSI_{cp}} = \left\langle \left| \frac{P_{c_R}(f) - P_{c_L}(f)}{P_{c_R}(f) + P_{c_L}(f)} \right| \right\rangle_{f=1,\ldots,25\ \mathrm{Hz}} \tag{3}$$

These values were averaged over all channel pairs *cp*:

$$\mathrm{BSI} = \frac{2}{N}\sum_{cp=1}^{N/2} \mathrm{BSI_{cp}} \tag{4}$$

BSI has an upper bound of one, reflecting maximal asymmetry for all channel pairs; the lower bound is zero, representing perfect symmetry. In (3) and (4), electrodes of the mid-line were excluded since they do not form channel pairs. Whenever one of the electrodes of a channel pair was considered a bad channel, the corresponding channel pair was excluded. Next to the assessment over the range of 1-25Hz, BSI was determined separately for the delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz) and beta (12-30Hz) frequency band.

Directional Brain Symmetry Index

The BSI provides information on the asymmetry between the spectral powers obtained from the hemispheres. However, it does not take the direction of this asymmetry into account. For the latter, we omitted the modulus computation in (3). The resulting directional BSI ($\mathrm{BSI_{dir}}$) indicates whether the power is higher in the left or right hemisphere.

$$\mathrm{BSI}_{\mathrm{dir}_{\mathrm{cp}}} = \langle \frac{P_{c_R}(f) - P_{c_L}(f)}{P_{c_R}(f) + P_{c_L}(f)} \rangle_{f=1,\ldots,25\ \mathrm{Hz}} \quad (5)$$

Values were averaged over all channel pairs:

$$\mathrm{BSI}_{\mathrm{dir}} = \frac{2}{N} \sum_{cp=1}^{N/2} \mathrm{BSI}_{\mathrm{dir}_{\mathrm{cp}}} \quad (6)$$

BSI_{dir} ranges from -1 to +1 with BSI_{dir} = 0 representing perfect symmetry. Positive values represent higher power in the right hemisphere compared to the left hemisphere, vice versa for negative values. For left side lesions, BSI_{dir} was multiplied by -1. Therefore, for stroke survivors a positive value always corresponds to higher power in the affected hemisphere compared to the unaffected hemisphere and vice versa for negative values.

Statistics

It was verified whether the EEG based parameters followed a normal distribution by visual inspection of the histogram and probability distribution (q-q plot) and by the Kolmogorov-Smirnov test. Resting-state EEG parameter differences between chronic stroke survivors and healthy individuals were investigated using independent-samples t-tests. If assumptions of normality were not met, a log transformation was applied, after which the distribution was checked again. After Bonferroni correction, the critical α-level for significance was set to 0.008 (0.05/6). Effect-sizes were estimated via Hedges' G in view of the sample sizes.

We used linear regression analysis to investigate the association between resting-state EEG parameters and motor function. Associations were tested for possible confounding factors: age, gender, affected hemisphere, lesion location, time post stroke and other neurological deficits (i.e., the sum of the affected non-motor items of the NIHSS: visual impairment, facial palsy, ataxia, sensory, aphasia, dysarthria, and extinction/inattention). If the regression coefficient changed more than 10% after adding the covariate, it was considered a confounder. Subsequently, a correction was applied for the strongest confounder.

Results

Comparisons between chronic stroke survivors and healthy individuals

Table 2.1 summarizes the characteristics of the participating stroke survivors. Descriptive statistics and results of the independent-samples t-tests can be found in **Table 2.2**. DAR was log transformed in order to attain normal distributed data before an independent t-test was performed. No significant differences were found between chronic stroke survivors compared to healthy individuals regarding DAR (*p=0.15*). Chronic stroke survivors showed higher BSI values (M=0.180, SD=0.044) compared to healthy individuals (M=0.125, SD=0.026, t(30)=4.4, *p<0.001, g=1.38*). This difference was most pronounced in the delta (Stroke: M=0.216, SD=0.088; Controls: M=0.112, SD=0.020, t(30)=5.2, *p<0.0001, g=1.39*) and theta band (Stroke: M=0.198, SD=0.086; Controls: M=0.116, SD=0.031, t(30)=3.9, *p<0.001, g=1.10*). No significant differences were found between the groups in BSI calculated over the alpha (*p=0.06*) or beta frequency band (*p=0.085*).

Association between EEG parameters and motor impairment

Associations were tested for possible confounding factors; age, gender, affected hemisphere, lesion location (based on MRI), time post stroke and other neurological deficits. In case of confounding, *other neurological deficits* emerged as most powerful, for which a correction was applied.

Raw and corrected regression coefficients of the associations between EEG parameters and FM-UE based on linear regression analyses are shown in **Table 2.3**. No significant association was found between the DAR and FM-UE (*p=0.211*). Significant negative associations with FM-UE were confirmed for the BSI calculated over the delta and theta frequency band when corrected for other neurological deficits (delta: *b=-130, 95%CI=-222 to -37, p=0.008;* theta: *b=-119, 95%CI=-202 to -35, p=.008*). No significant associations were found in the alpha or beta band (*p=0.29; p=0.67*).

Figure 2.1 shows the uncorrected association between BSI_{dir} in the delta and theta frequency band and FM-UE. Increased BSI_{dir} towards the affected hemisphere in the delta and theta frequency band was associated with lower FM-UE scores corrected for other neurological deficits (delta: *b=-95, 95%CI=-152 to -38, p=0.003;* theta: *b=-99, 95%CI=-153 to -44, p=.001*). Also in the alpha band a negative association between BSI_{dir} and FM-UE post stroke was found when corrected for other neurological deficits (*b=-103, 95%CI=-188 to -19, p=0.020*, but not in the beta band (*p=0.45*). Healthy individuals showed BSI_{dir} values around zero (**Figure 2.1**).

Table 2.1. Patient characteristics.

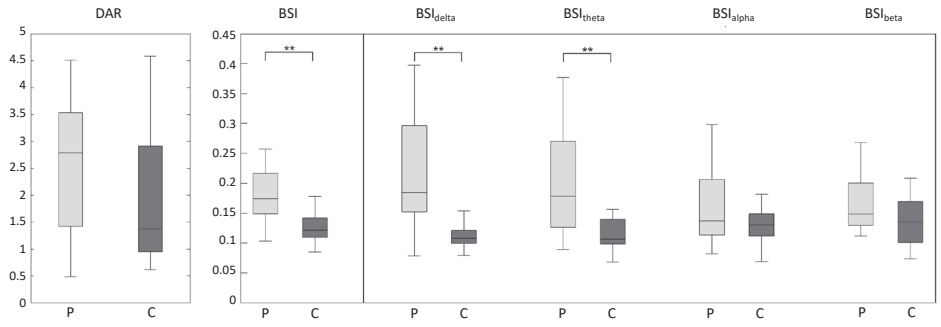
ID	Age	Gender	Time PS	Affected hemisphere	Lesion location	FM UE	NIHSS
1	64	M	82	R	C-SC	13	3
2	62	M	49	L	C	39	3
3	77	M	7	R	C-SC	62	0
4	66	F	212	L	C-SC	9	9
5	76	F	35	R	C	63	2
6	54	M	21	R	C-SC	8	7
7	67	M	26	L	C-SC	54	1
8	55	M	75	R	C-SC	58	0
9	59	M	70	R	C-SC	9	4
10	68	F	67	L	C	66	0
11	49	F	40	R	C	59	1
12	57	M	10	R	C	66	0
13	48	M	80	R	C-SC	10	5
14	65	M	22	R	C	64	2
15	50	F	53	L	C-SC	59	1
16	50	M	34	L	C-SC	48	1
17	56	M	10	R	C-SC	56	0
18	48	M	88	L	C	66	0
19	61	F	10	L	C-SC	60	3
20	72	M	15	R	C-SC	26	4
21	68	M	142	R	C-SC	20	5

ID: Subject number; Age (years); Gender (M: male, F: female); Time PS: Time post stroke (months); Affected hemisphere (L: left, R: right); Lesion location (C: cortical, C-SC: cortical-subcortical); FM-UE: Fugl-Meyer motor assessment score of the upper extremity [0-66]; NIHSS: National Institutes of Health Stroke Scale [0-42]; MI UE/LE: Motricity Index Upper Extremity / Lower Extremity [0-100]; DAR: Delta Alpha power Ratio; BSI: pairwise derived Brain Symmetry Index; $BSI_{delta/theta/alpha/beta}$: BSI over a specific frequency band.

MI UE	MI LE	DAR	BSI	BSI_{delta}	BSI_{theta}	BSI_{alpha}	BSI_{beta}
28	72	4.40	0.215	0.356	0.319	0.141	0.183
70	77	2.17	0.242	0.174	0.117	0.187	0.342
83	91	3.62	0.150	0.184	0.192	0.217	0.115
23	48	1.50	0.201	0.296	0.253	0.167	0.171
76	72	1.14	0.147	0.171	0.145	0.097	0.166
39	64	13.57	0.240	0.297	0.178	0.114	0.268
76	75	1.15	0.163	0.236	0.285	0.112	0.127
91	100	2.52	0.174	0.313	0.229	0.128	0.132
28	64	1.20	0.194	0.217	0.274	0.298	0.139
84	100	1.57	0.118	0.081	0.090	0.105	0.163
72	91	0.88	0.150	0.129	0.163	0.205	0.148
100	100	7.39	0.257	0.139	0.131	0.249	0.340
23	28	2.87	0.173	0.265	0.269	0.119	0.146
100	91	0.49	0.166	0.156	0.102	0.082	0.236
100	80	2.79	0.103	0.078	0.098	0.117	0.119
65	53	2.94	0.137	0.173	0.130	0.160	0.116
76	83	2.98	0.194	0.252	0.324	0.241	0.112
100	100	3.38	0.117	0.140	0.101	0.098	0.130
76	91	3.50	0.190	0.177	0.170	0.213	0.194
54	72	2.12	0.221	0.300	0.207	0.137	0.220
39	72	4.51	0.225	0.397	0.377	0.136	0.143

Table 2.2. Descriptive statistics and outcomes of independent-samples t-tests.

	Age	DAR*	BSI	BSI_{delta}	BSI_{theta}	BSI_{alpha}	BSI_{beta}
Stroke (N=21)							
Mean	60.6	2.79	0.180	0.216	0.198	0.158	0.177
SD	9.0	2.21	0.044	0.088	0.086	0.059	0.069
Controls (N=11)							
Mean	58.5	1.37	0.125	0.112	0.116	0.128	0.136
SD	9.9	2.07	0.026	0.020	0.031	0.030	0.044
t (df = 30)	0.61	1.5	4.4	5.2	3.9	1.9	1.8
p-value	0.55	0.15	<0.001	<0.001	<0.001	0.06	0.09
Effect size	0.22	0.54	1.38	1.39	1.10	0.57	0.65



Differences between chronic stroke patients and healthy controls concerning power spectral density measures. N = number of participants; P = stroke patients; C = controls; SD: standard deviation; t = t-statistic; df = degrees of freedom; Effect size: reflected by Hedges' g (unbiased); DAR: Delta Alpha Ratio; BSI: pairwise-derived Brain Symmetry Index; $BSI_{delta/theta/alpha/beta}$: BSI over a specific frequency band. *Median and IQR are provided of non-transformed data instead of mean and SD, Independent samples t-test was performed on log-transformed data; ** p<0.001, Bonferroni corrected α-level = 0.008. Error bars indicate standard deviation, horizontal lines indicate means.

Table 2.3. Associations between EEG parameters and Fugl-Meyer motor assessment of the upper extremity based on linear regression analyses.

Independent variable	Uncorrected				Corrected*		
	B	[95% CI]	p-value	R^2	B	[95% CI]	p-value
DAR	-2.3	[-6.0 1.4]	0.21	0.08			
BSI	-275	[-489 -61]	0.01	0.276	-145	[-350 60]	0.16
δ	-185	[-273 -97]	<0.01	0.505	-130	[-222 -37]	**<0.01**
θ	-158	[-261 -54]	<0.01	0.347	-119	[-202 -35]	**<0.01**
α	-29	[-214 157]	0.75	0.005	-73	[-214 67]	0.29
β	-29	[-189 130]	0.71	0.008	26	[-100 152]	0.67
Directional BSI	-86	[-238 66]	0.25	0.069	-142	[-244 -40]	**<0.01**
δ	-130	[-187 -73]	<0.01	0.542	-95	[-152 -38]	**<0.01**
θ	-124	[-195 -54]	<0.01	0.417	-99	[-153 -44]	**<0.01**
α	-21	[-139 97]	0.71	0.007	-103	[-188 -19]	**0.02**
β	23	[-68 114]	0.61	0.014	-27	[-102 47]	0.45

DAR: Delta Alpha power Ratio; BSI: Brain Symmetry Index; δ/θ/α/β: delta/theta/alpha/beta frequency band; B: regression coefficient; CI: confidence interval; R2: R-squared; *Corrected for confounding factor: other neurological deficits (defined as the sum of the affected non-motor items of the NIHSS: visual impairment, facial palsy, ataxia, sensory, aphasia, dysarthria, and extinction/inattention).

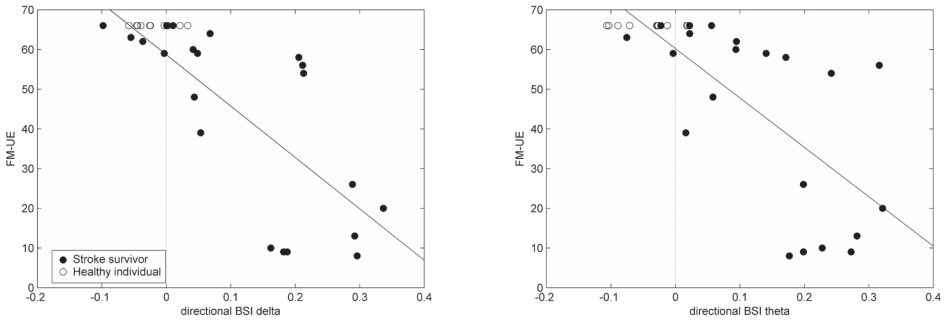


Figure 2.1. *Visualisation of the uncorrected association between directional Brain Symmetry Index (BSIdir) of the delta or theta frequency band as independent variable and Fugl-Meyer motor assessment of the upper extremity (FM-UE) as dependent variable. Circles reflect data of healthy individuals. Filled dots reflect data of chronic stroke survivors. The gray line reflects pure symmetry. For chronic stroke survivors a positive BSIdir value refers to higher power in the affected hemisphere compared to the unaffected hemisphere, vice versa for negative values.*

Discussion

We studied the potential added value of resting-state EEG as biomarker for neurological recovery post stroke. Therefore, resting-state spectral density measures as DAR and BSI were compared between chronic stroke survivors and gender- and age-matched healthy individuals. Moreover, the association between these EEG parameters and the FM-UE in chronic stroke survivors was investigated. Significant differences between chronic stroke survivors and age- and gender-matched healthy individuals were found regarding BSI, but not for DAR. The asymmetry differences were most pronounced in the delta and theta frequency bands. In these frequency ranges significant negative associations were found between BSI and FM-UE.

DAR

In contrast to our hypothesis, DAR in chronic stroke survivors did not differ significantly from healthy individuals. This finding is incongruent with data from (sub) acute stroke survivors showing increased DAR values compared to healthy individuals.[13,16] However, Poryazova et al. (2015)[20] showed an increased delta activity in early sub-acute stroke patients compared to matched controls, while this difference was no longer present in the late sub-acute phase. Therefore, we suggest that the discrepancies concerning the DAR may be caused by a difference in the time window of assessment post stroke, i.e., (sub) acute or chronic. In previous studies in (sub) acute stroke, DAR was shown predictive regarding recovery reflected by NIHSS.[12,21] However, in the current study conducted in the chronic phase, we did not find any association between DAR and FM-UE.

BSI

Our results support the hypothesis that chronic stroke survivors have a higher pairwise-derived BSI compared to healthy individuals. This asymmetry of brain activity power between hemispheres is more pronounced in chronic stroke survivors when compared to age- and gender-matched healthy controls. While existing literature particularly focuses on the (sub) acute phase, our study showed that this asymmetry may persist even in the chronic phase after stroke. This study shows no significant association of BSI with FM-UE when calculated over a range of 1-25 Hz when corrected for other neurological deficits.

BSI per frequency band

Brain lesions located in the cortex, white matter, or both, have been shown to result in slower background rhythms. In awake adults increased slow wave activity in the delta and theta frequency band indicate cortical brain damage due to for example ischemia resulting from stroke, brain haemorrhage, tumours, or traumatic injury.[14] With

increased severity of cortical brain damage the slowing becomes more pronounced.[14] Analysing the BSI per frequency band revealed that the asymmetry is significantly more pronounced in chronic stroke survivors in the delta and theta band when compared to controls. However, this was not the case in the alpha or in the beta band. Moreover, the BSI in the delta and theta bands showed significant negative associations with FM-UE confirming that stroke survivors who show more asymmetry at the lower frequency bands are also more severely affected regarding the FM-UE. Our results suggest that parameters based on power spectral densities are of value in understanding impaired motor control in chronic stroke and emphasize the value of taking into account the frequency bands when calculating parameters based on power spectral densities.

Directional BSI

BSI_{dir} provides information on the directionality of asymmetry. In more severely affected stroke survivors, the lesioned hemisphere generated more power compared to the non-lesioned hemisphere, especially in the delta and theta frequency band. To the best of our knowledge, this is the first study using this specific parameter, which renders comparing the results with other studies difficult. Moreover, due to inter individual differences and the cross-sectional design of the study, we were not able to investigate whether the non-lesioned hemisphere was truly unaffected in patients with chronic stroke.

Presence of slow activity

Cortical deafferentation, which leads to loss of neuronal input, might be the cause of increased presence of low frequency oscillations.[22] Slow waves, like activity in the delta and theta frequency bands, can be observed in different neurological disorders. Since there is no specific cause of these low frequency oscillations, its presence has been considered to reflect general cerebral dysfunction of the brain.[10] In stroke survivors, it has been shown to be indicative of a localized structural lesion.[22] Several studies showed that this low frequency content is of significant value regarding prognosis of functioning in this population (e.g., Finnigan and Van Putten, 2013[12]). The current study shows that low frequency content is of significant value in the chronic phase as well.

Selective motor control

During resting-state the brain shows active networks in which both hemispheres interact. Reorganization after stroke can result in frequency shifts and shifts in neural activity of anatomically related cortical areas. Therefore, resting state activity might become more lateralized due to stroke. In this way, altered connectivity in the cortex due to stroke may result in an EEG power asymmetry between the affected

and unaffected hemisphere. It has been shown that changed cortical resting state activity is related to motor dysfunction during movements.[23] Moreover, activity in the sensorimotor areas facilitates selective motor control via the corticospinal tract.[24] Disorganization of these sensorimotor areas has been shown to be involved in impairments of selective motor control.[25] Therefore, although speculative, this may be a possible way in which cortical damage, expressed by power spectral density-based EEG parameters, causes deficits in selective motor control.

Limitations and further directions

In this cross-sectional study, a comparatively small number of chronic stroke survivors was investigated. Besides, MRI data was only used to obtain lesion location, lesion volume was not calculated. Current prediction models of motor function recovery post stroke are typically based on clinical measures like FM-UE. They do not predict the outcome properly in all cases and the underlying mechanisms of recovery are still poorly understood. Biomarkers that reflect underlying mechanisms are currently lacking, but can be particularly useful to determine which patients should receive an intervention at what moment in time.[26] Therefore, we recommend to investigate the longitudinal dynamics between power spectral density-based EEG parameters and upper limb recovery, since this may provide insight in the time-course of underlying processes of recovery and may improve prediction models.[27] Based on the findings of the current study, we recommend considering DAR, low frequency asymmetry measures and directional asymmetry measures. Acknowledging that spontaneous neurological recovery mainly defines the pattern of FM-UE improvements in the first eight weeks post stroke[28–30], we further recommend to perform intensive repeated measurement designs with clinical and EEG measurements at fixed moments early post stroke.[31]

Conclusions

Cortical asymmetry in resting-state EEG, expressed by the pairwise-derived BSI, is increased in chronic stroke survivors especially in the lower frequency bands. Higher asymmetry in the delta and theta band is associated with poorer motor function. This implies that asymmetry in the delta and theta frequency band may be a useful biomarker for the neural state after stroke. We conclude that assessing the asymmetry in future stroke-related recovery studies, specifically in delta and theta power distributions, may provide more insight in the relation between reorganization of the cortex and motor recovery.

Declarations of interest

None of the authors have potential conflicts of interest to be disclosed.

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3

Is resting-state EEG longitudinally associated with recovery of clinical neurological impairments early post stroke? A prospective cohort study.

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Abstract

Background: The time course of cortical activation and its relation with clinical measures may elucidate mechanisms underlying spontaneous neurobiological recovery after stroke.

Objective: We aimed to investigate (1) the time course of cortical activation as revealed by EEG-based spectral characteristics during awake rest and (2) the development of these spectral characteristics in relation to global neurological and upper-limb motor recovery in the first six months post stroke.

Methods: Resting-state EEG was measured serially in 41 patients after a first-ever ischemic stroke, within 3 and at 5, 12, and 26 weeks post stroke. We computed the brain symmetry index (BSI) and directional BSI (BSIdir) over different frequency bands (1-25Hz, delta, theta) and delta/alpha ratio (DAR). The National Institutes of Health Stroke Scale (NIHSS) and Fugl-Meyer motor assessment of the upper extremity (FM-UE) were determined as clinical reflections of spontaneous neurobiological recovery. Longitudinal changes in spectral characteristics and within- and between-subject associations with NIHSS and FM-UE were analyzed with linear mixed models.

Results: Spectral characteristics showed a gradual normalization over time, within and beyond 12 weeks post stroke. Significant within- and between-subject associations with NIHSS were found for DAR of the affected hemisphere (DAR_{AH}) and $BSIdir_{delta}$. $BSIdir_{delta}$ also demonstrated significant within- and between-subject associations with FM-UE.

Conclusions: Changes in spectral characteristics are not restricted to the time window of recovery of clinical neurological impairments. The present study suggests that decreasing DAR_{AH} and $BSIdir_{delta}$ reflect improvement of global neurological impairments, whereas $BSIdir_{delta}$ was also specifically associated with upper-limb motor recovery early post stroke.

Introduction

Most stroke survivors suffer from upper limb paresis in the acute phase after stroke.[1] About 70–80% of them will show some level of spontaneous neurobiological recovery (i.e. 'recoverers'), whereas 20–30% of patients do not recover at all (i.e. 'non-recoverers').[2] Spontaneous motor recovery takes place predominantly within the first three months post stroke, after which most patients reach a plateau.[3] The mechanisms that drive spontaneous neurobiological recovery are mainly the salvation of penumbral tissue[4] and spontaneous regenerative processes enhanced by an upregulation of growth-promoting factors, angiogenesis and resolution of diaschisis.[4,5]

The main improvements in terms of the National Institutes of Health Stroke Scale (NIHSS) and Fugl-Meyer motor assessment of the upper extremity (FM-UE) take place in the time window of spontaneous neurobiological recovery, which may extend up to ten weeks after stroke onset.[6] A return of brain function towards its normal neural state is associated with better behavioural outcomes after stroke.[7–9] The longitudinal association between clinical improvements and changes in cortical activation, and whether these changes occur within the time window of spontaneous neurobiological recovery, have hardly been investigated so far.[10,11]

Neuronal oscillations, measured with magneto- or electro-encephalography (MEG/EEG), have been suggested to serve as a measurement tool for potential biomarkers that can be used to study the association with behavioural recovery.[11] In particular, stroke is associated with increased low-frequency brain oscillations in the delta (0.5-4 Hz) and theta bands (4-8 Hz),[12–14] as well as decreased alpha (8-12 Hz) activity.[15,16] A spectral characteristic quantifying this phenomenon is the delta/alpha ratio (DAR). Since stroke may lead to increased delta activity with or without decreased alpha activity, a ratio between these components may be more sensitive compared to the individual components for reflecting severity of neurological deficit, and normalization of the underlying neurological deficits due to spontaneous neurological recovery after stroke. DAR appears to correlate with the severity of global neurological impairments measured with the NIHSS[17] in the acute phase (<1week) post stroke. However, in a recent study performed in the chronic post-stroke phase (>6 months), we could not find significant differences in DAR between patients and age- and gender-matched healthy individuals, nor did we find a significant association between DAR and motor impairment as measured with the FM-UE.[14] The above results suggest a decrease in DAR over time across stroke patients towards normal values, regardless of global neurological impairment or motor impairment.

The pairwise derived brain symmetry index (BSI) captures brain activity lateralization, and seems to be associated with stroke severity.[13,17,18] Several studies have shown that BSI is increased in the early sub-acute phase (between 1 week and 3 months)[17,19] and in the chronic phase[14] post stroke, when compared to healthy individuals. The extended directional version of the BSI showed that increased low-frequency power in the affected hemisphere relative to the unaffected hemisphere (i.e., asymmetry towards the affected side), is highly associated with decreased motor function of the upper extremity in patients with chronic stroke.[14] We argue that directional asymmetry measures based on low-frequency oscillations can be useful in the assessment of the asymmetry of hemispheric activity early post stroke, whose normalization is associated with neurological recovery.

In the present observational cohort study with repeated measurements performed at fixed times post stroke, we investigated the time course of EEG-based spectral characteristics during awake rest as a representation of neuronal deficits. We simultaneously measured the time course of global neurological recovery and upper limb motor function early post stroke, enabling us to investigate the longitudinal associations.

We addressed the following research questions:

1) What is the time course of the spectral characteristics DAR, BSI and BSIdir within the first six months post stroke?
2) Are DAR, BSI and BSIdir longitudinally associated with clinically observed improvements of the NIHSS and FM-UE?

As regards (1), we hypothesized that the spectral characteristics would change in the direction of values seen in healthy individuals.[14] These changes might be caused by decreasing delta activity in the affected hemisphere, and hence might be mainly reflected by the DAR_{AH}, and the BSI and BSIdir when estimated over the delta band. In addition, we hypothesized that changes would occur within the time window of spontaneous neurobiological recovery (i.e., three months post stroke).

We previously found a significant association for FM-UE with BSI and BSIdir but not for DAR in the chronic phase post stroke.[14] Regarding the NIHSS, literature showed a significant association in the acute phase with BSI and DAR.[17] Therefore, as regards (2), we hypothesized that recovery of global neurological impairment as measured with NIHSS would be positively associated with a gradual decrement (i.e., normalization) in DAR. In addition, we hypothesized that a decrease in BSI (i.e., normalization) would be associated with improvement of NIHSS and FM-UE scores within the first three months post stroke.

Methods

Participants

In our multicentre longitudinal cohort study, patients admitted to the stroke units of six participating hospitals from June 2015 till June 2017 were eligible for participation. Fifty-five patients were included within three weeks post stroke. The inclusion criteria were: 1) first-ever ischemic stroke according to CT or MRI scan; 2) <3 weeks post stroke; 3) upper limb paresis (NIHSS 5a/b > 0); 4) ≥18 years of age; and 5) providing written informed consent. Exclusion criteria were: 1) upper extremity orthopaedic limitations present prior to stroke onset; 2) recurrent stroke; and 3) severe cognitive problems, i.e. Mini Mental State Examination score <18[20]. The present study (registered at the Netherlands Trial Register as NTR4221) was approved by the Medical Ethics Committee of the VU University medical centre, Amsterdam, The Netherlands (protocol number 2014.140) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2013).[21]

Procedures

High-density EEG measurements and clinical assessments were performed within the first 3 weeks and at weeks five, 12 and 26 post stroke. The first measurement was conducted as soon as feasible. To optimize the feasibility of assessing early sub-acute patients at fixed times post stroke, a specially equipped van (**Figure 3.1**) was used to perform clinical and EEG measurements, irrespective of the patient's place of residence, such as a hospital, rehabilitation center, nursing home or their own home. With that, the burden of traveling for the patients was reduced. The measurement van was customized to allow EEG acquisition of the same quality as in our hospital setting.[22] The resting-state EEG measurement analyzed in the current study was part of a larger study protocol. The duration of the full EEG protocol was dependent on patient's ability to perform tasks. Including preparation of the patient this took between 45 minutes, in case only resting-state EEG was measured, and two hours, in case all tasks were performed.

Electroencephalography

During the EEG measurement, patients were seated in a wheelchair and were asked to focus their eyes on a dot displayed on a flat screen. Five consecutive trials of one-minute resting-state EEG data were collected. High-density 62-channel EEG was recorded using an actively shielded EEG cap with electrode placement according to the international 10-20 system (Ag/AgCl electrodes and REFA multichannel amplifier, TMSi, Oldenzaal, The Netherlands, with ASA acquisition software, ANT software BV, The Netherlands). Electrode impedances were kept below 20 kΩ. EEG signals were online

referenced to average. In addition, bipolar Ag/AgCl electrodes served to monitor the muscle activity of the m. extensor carpi radialis and m. flexor carpi radialis of both arms. All signals were sampled at a rate of 2048 Hz.

Figure 3.1 *Measurement set-up in a specially equipped van.*

Clinical assessments

Clinical assessments encompassed the NIHSS [0-42] and FM-UE [0-66]. NIHSS is a measure of the severity of global neurological impairment to classify stroke severity.[23] FM-UE measures the synergy-dependent motor recovery of the upper limb. Both are recommended as outcome measure in stroke research,[23–25] and the time window of their change is assumed to reflect the period of spontaneous neurobiological recovery.

Data analysis

Pre-processing

Offline analysis was conducted using Matlab (R2012a, The Mathworks, Natwick, MA) with the FieldTrip toolbox for EEG/MEG analysis.[26] EEG data were filtered with a 4th-order bi-directional high-pass Butterworth filter (cut-off at 0.5 Hz). Power-line artifacts were reduced using notch filters around 50, 100, and 150 Hz (4th-order bi-directional Butterworth, bandwidth 1 Hz). Channels without data or very poor data quality were interpolated as the weighted average of the surrounding electrodes, followed by re-referencing to the remaining average. For each measurement, an average of 0.17 electrodes were interpolated. Further artifact removal consisted of the exclusion of eye-blinks and muscle activity using independent component analysis based on visual inspection of the components' waveforms, power spectrum and topographic distributions. For each measurement, an average of 2.9 components were removed. The resulting signals were again visually inspected and segments of the data which showed remaining artifacts were removed. Analyzed epochs were as large as possible, with a maximum of one minute. Modified periodograms with a Hanning window with size equal to the epoch length served as proxies of the spectral power density per channel.

Spectral characteristics

Delta/alpha ratio

DAR was defined as the ratio of the delta power to the alpha power. For every channel *c* the power of the delta and alpha frequency bands (f = 1,...,4 Hz and 8,...,12 Hz, respectively) was determined as the mean of the spectral power $P_c(f)$ over this range. The delta/alpha ratio was computed as

$$\mathrm{DAR_c} = \frac{\langle P_c(f)\rangle_{f=1,\ldots,4\ \mathrm{Hz}}}{\langle P_c(f)\rangle_{f=8,\ldots,12\ \mathrm{Hz}}} \quad (1)$$

The ratios were averaged over all N EEG channels yielding the global DAR as:

$$\mathrm{DAR} = \frac{1}{N}\sum_{c=1}^{N}\mathrm{DAR_c} \quad (2)$$

In addition to the assessment over all available channels, the DAR was also calculated over the affected (DAR_{AH}) and unaffected hemisphere (DAR_{UH}), in which the electrodes covering the midline were not included.

Brain symmetry index

The BSI was defined as the absolute pairwise normalized difference in spectral power between the homologous channels C_L and C_R for left and right, respectively. The difference was averaged over a range from 1 to 25 Hz (adapted from [13,17]) according to

$$\mathrm{BSI_{cp}} = \left\langle \left| \frac{P_{c_R}(f) - P_{c_L}(f)}{P_{c_R}(f) + P_{c_L}(f)} \right| \right\rangle_{f=1,\ldots,25\ \mathrm{Hz}} \quad (3)$$

These values were averaged over all channel pairs *cp*:

$$\mathrm{BSI} = \frac{2}{N} \sum_{cp=1}^{N/2} \mathrm{BSI_{cp}} \quad (4)$$

BSI values range from zero to one, indicating maximal symmetry and asymmetry, respectively. In our earlier cross-sectional study performed in the chronic phase post stroke (N=21), we showed the importance of the lower frequency bands.[14] Therefore, next to the assessment over the 1-25 Hz range, BSI was also determined separately for the delta (1-4 Hz) and theta (4-8 Hz) frequency bands.

We supplemented the BSI by a directed version (BSIdir) to account for the direction of the asymmetry.[14] The computation of the BSIdir omitted the absolute value of the numerator of Eq. (3). The sign of BSIdir was chosen such that values between 0 and 1 reflected greater cortical power in the affected hemisphere compared to the unaffected hemisphere, and vice versa for values between -1 and 0.

Statistical analysis

The change in spectral characteristics during the first six months post stroke was investigated with linear mixed models analyses with the factor time (of measurement) as the main fixed effect. A random intercept per individual was used to correct for dependency between measurements. Separate models were used for each dependent outcome parameter (DAR, BSI, BSIdir).

The longitudinal association between spectral characteristics and clinical measures was investigated with longitudinal linear mixed model analyses using two different models. In the first model we investigated the main effects of FM-UE and NIHSS on spectral characteristics using a linear mixed model, for each individual clinical measure. For this model we used a random intercept for each individual, whereas time was added to the model as a potential confounder and effect modifier. Second, we applied a hybrid model[27] for the spectral characteristics which revealed a trend or a significant longitudinal association with clinical scores measured during the first six months post stroke. This model made it possible to distinguish between the between- and within-subject effects of the longitudinal relationship. The between-subject covariate was determined as the individual average value over time of the independent variable, which reveals the association regardless the development over time. The within-subject covariate was calculated as the observed value minus

the individual average, which reveals whether development of the dependent and independent covariates over time within a subject are associated. Subsequently, the associations between clinical measures and spectral characteristics were analysed, resulting in two separate regression coefficients reflecting the within- and between-subject components of the longitudinal relationship.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Multiple testing was accounted for using the Holm-Bonferroni method. For each model, the distribution of residuals was tested for normality by inspecting histograms and Q-Q plots.

Results

Participants

A flowchart of the screening, inclusion and follow-up procedure, and an overview of missing data, are depicted in **Figure 3.2**. Forty-one out of 55 patients completed the four repeated measurements until 26 weeks post stroke and were included in the analyses. Baseline measurements took place at 13±5days (mean±SD) post stroke and were repeated at w5 (32±3 days), w12 (82±4 days) and w26 (185±20 days) post stroke. Patient characteristics at baseline and w26 are presented in **Table 3.1.**

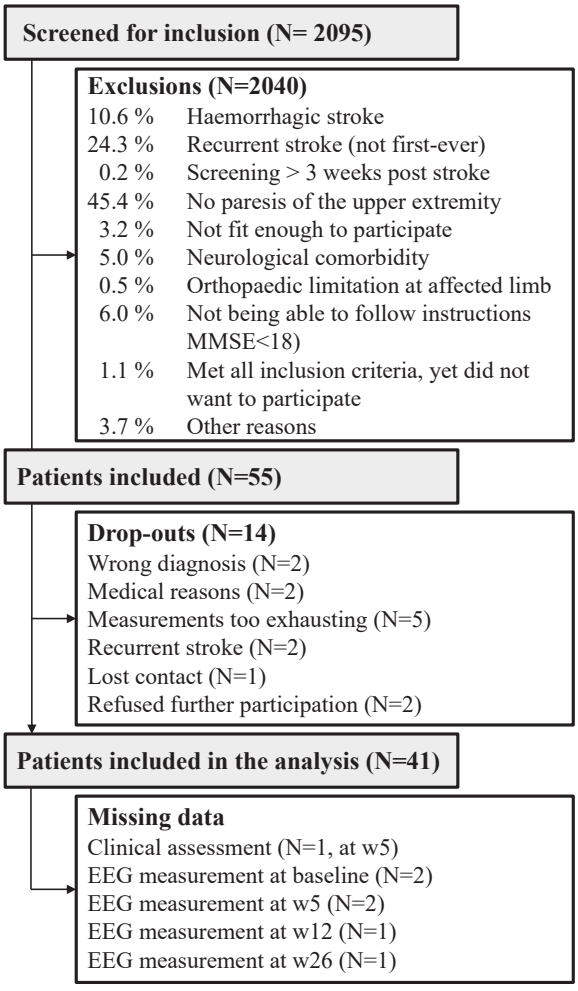


Figure 3.2 *Flowchart of patient screening, inclusion, and follow-up. Abbreviations: N, number; MMSE, mini mental state examination.*

Table 3.1. Patient demographics at baseline and 26 weeks post stroke

	All (N = 41)
Demographics	**Mean (SD) or N**
Time PS (days)	13 (5)
Age (years)	67 (11)
Gender (male/female)	24/17
Affected hemisphere (left/right)	20/21
Bamford classification (LACI/PACI/TACI)	20/16/5
Clinical scores at baseline	**Median (IQR)**
NIHSS	5 (3.5-7.5)
FM-UE	21 (7-45.5)
ARAT	4 (0-32.5)
EmNSA	37 (34.5-40)
MI-UE	50 (21-72)
MI-LE	53 (32.5-75)
Clinical scores at 26 weeks post stroke	**Median (IQR)**
NIHSS	2 (0-3.5)
FM-UE	58.5 (24-63)
ARAT	50 (3-57)
EmNSA	40 (38-40)
MI-UE	76 (47-84)
MI-LE	77.5 (58-100)

Demographics and clinical scores at baseline and 26 weeks post stroke of all patients included in the analysis. Time PS: time post stroke, i.e. time elapsed between stroke onset and baseline measurement. N: number of participants; SD: standard deviation; IQR: interquartile range; LACI: Lacunar Anterior Circular Infarct; PACI: Partial Anterior Circular Infarct; TACI: Total Anterior Circular Infarct; NIHSS: National Institutes of Health Stroke Scale; FM-UE: Fugl-Meyer motor assessment of the upper extremity; ARAT: action research arm test; EmNSA: Erasmus modification of the Nottingham Sensory Assessment of the upper extremity; MI-UE/LE: Motricity Index of the upper/lower extremity.

Changes in spectral characteristics over time

Figure 3.3A-B depicts the individual and averaged time courses of the NIHSS and FM-UE scores. Visual inspection of the NIHSS and FM-UE confirms our assumption that a plateau was reached at 12 weeks post stroke. **Figure 3.3D** depicts the averaged time courses of the investigated spectral characteristics. The corresponding coefficient estimates (*ß*), 95% confidence intervals (CI) and probability estimates (*P*) are summarized in **Table 3.2**. Individual time courses of the spectral characteristics are presented in the supplementary materials (**Figure 3.4**).

DAR showed a significant decrease over time between baseline and w26 (*ß*= -0.69, *P*<0.001), and from w5 to w26 (*ß*= -0.46, *P*=0.03). The largest decrease was found in the affected hemisphere, while only a trend was found for the unaffected hemisphere (Figure 3.3; **Table 3.2**). No decrease over time was observed between baseline and w26 regarding BSI and BSI_{theta}, although a decrease was observed between w12 and w26. BSI_{delta} showed to be decreased at w26 when compared to baseline (*ß*= -0.02, *P*=0.01), w5 (*ß*= -0.02, *P*=0.01) and w12 (*ß*= -0.03, *P*<0.001). A statistically non-significant decrease over time was found for BSIdir and $BSIdir_{theta}$ (**Table 3.2**), while a significant decrease was found for $BSIdir_{delta}$ from baseline to w26 (*ß*= -0.04, *P*=0.003), and from w5 to w26 (*ß*= -0.03, *P*=0.01). This indicates that the power over the hemispheres became less lateralized especially in the lower frequency band.

Association between spectral characteristics and NIHSS

Tables 3.3A-D present the longitudinal associations between spectral characteristics and NIHSS scores. A lower DAR or DAR_{AH} was longitudinally associated with a lower NIHSS score (*ß*=0.12, *P*<0.001; *ß*=0.19, *P*<0.001; **Table 3.3A**). These relations concerned significant positive within- and between-subject effects (**Table 3.3D**). DAR and DAR_{AH} were significantly positively associated with NIHSS at baseline (*ß*=0.12, *P*=0.04; *ß*=0.21, *P*=0.01; **Table 3.3B**), while significance was not reached at other measurement moments. Regarding the DAR_{UH} no significant longitudinal association was found with NIHSS.

BSI was positively associated with the NIHSS score (*ß*=$2.51{\cdot}10^{-3}$, *P*=0.01; **Table 3.3A**). After correction for time, the association with NIHSS became stronger (*ß*=$4.52{\cdot}10^{-3}$, *P*<0.0 01), which suggests an association between the dependent and independent covariates irrespective of the time-dependent changes of the covariates. The longitudinal relation mainly concerned a positive between-subject effect (**Table 3.3D**). The interaction term between NIHSS and time did not reach significance, suggesting that the association between BSI and the NIHSS did not change over time. The BSI_{delta} and BSI_{theta} showed results similar to those for the BSI, yet remained borderline significant (**Table 3.3A, 3.3D**).

$BSIdir_{delta}$ showed a significant positive relation with NIHSS (β=0.84·10^{-2}, P<0.001; **Table 3.3A**), where time was not a confounder. This relation consisted of significant positive within- and between-subject effects (**Table 3.3D**). The relation between $BSIdir_{delta}$ and NIHSS was significant across measurement moments (**Table 3.3B**).

Association between spectral characteristics and FM-UE

Tables 3.3A-D show the longitudinal associations between spectral characteristics and FM-UE. No significant longitudinal association was found between DAR or DAR_{UH} and FM-UE (**Table 3.3A**), neither when corrected for time nor at any specific moment in time (**Table 3.3C**). For DAR_{AH} a trend towards a negative association with FM-UE was found, which was no longer present after correction for time. This agrees with the outcome of the hybrid model, which revealed that this association was primarily caused by a within-subject effect (**Table 3.3D**).

BSI, BSI_{delta} as well as BSI_{theta} did not show significant longitudinal associations with FM-UE (**Table 3.3A**), neither when corrected for time, nor at any moment in time (**Table 3.3C**).

BSIdir showed a trend towards a negative association with FM-UE (β= -0.72·10^{-3}, P=0.02; **Table 3.3A**), but after correction for time this trend was no longer present. In line with this finding, the hybrid model showed only a significant negative within-subject effect (**Table 3.3D**). $BSIdir_{delta}$ was negatively associated with FM-UE (β= -0.14·10^{-2}, P<0.001; **Table 3.3A**), which was borderline significant after correction for time. This relation concerned significant negative within- and between-subject effects (**Table 3.3D**). Further analyses revealed that the interaction term (FM-UE*time) was significant, indicating that the relation varied over time.

Table 3.2. Association models of power spectral density measures and time

	Baseline to W5			Baseline to W12			Baseline to W26		
	ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
DAR	-0.24	[-0.65 – 0.18]	0.26	-0.30	[-0.72 – 0.12]	0.16	-0.70	[-1.11 – -0.27]	**<0.001**
DAR_{AH}	-0.26	[-0.85 – 0.32]	0.37	-0.52	[-1.10 – 0.06]	0.08	-1.00	[-1.58 - -0.42]	**<0.001**
DAR_{UH}	-0.19	[-0.51 – 0.12]	0.23	-0.08	[-0.39 – 0.24]	0.63	-0.39	[-0.70 - -0.07]	**0.02**
BSI	-0.00	[-0.02 – 0.01]	0.64	0.01	[-0.00 – 0.02]	0.17	-0.01	[-0.02 – 0.01]	0.06
BSI_{delta}	-0.00	[-0.02 – 0.02]	0.93	0.01	[-0.01 – 0.03]	0.22	-0.02	[-0.04 - -0.01]	**0.01**
BSI_{theta}	-0.00	[-0.02 – 0.01]	0.67	0.01	[-0.01 – 0.02]	0.27	-0.01	[-0.03 – 0.00]	0.12
BSIdir	-0.01	[-0.03 – 0.02]	0.67	-0.02	[-0.04 – 0.00]	0.07	-0.02	[-0.04 – 0.00]	0.05
$BSIdir_{delta}$	-0.01	[-0.03 – 0.02]	0.69	-0.02	[-0.05 – 0.00]	0.10	-0.04	[-0.06 - -0.01]	**0.003**
$BSIdir_{theta}$	-0.01	[-0.03 – 0.01]	0.42	-0.03	[-0.05 - -0.00]	**0.02**	-0.03	[-0.05 - -0.00]	**0.02**

ß: regression coefficient; 95%-CI: 95% confidence interval; *P*: p-value, Holm-Bonferroni corrected significance level: $P<(0.05/ N_s)$; DAR: delta/alpha ratio; AH: affected hemisphere; UH: unaffected hemisphere;

W5 to W12			W5 to W26			W12 to W26		
ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
-0.06	[-0.48 – 0.35]	0.76	-0.46	[-0.87 – -0.04]	**0.03**	-0.39	[-0.81 – 0.02]	0.06
-0.25	[-0.84 – 0.33]	0.39	-0.74	[-1.32 – -0.15]	**0.01**	-0.48	[-1.06 – 0.09]	0.10
0.11	[-0.20 – 0.43]	0.48	-0.19	[-0.51 – 0.12]	0.23	-0.31	[-0.62 – 0.01]	0.06
0.01	[-0.00 – 0.02]	0.06	-0.01	[-0.02 – 0.003]	0.15	-0.02	[-0.03 – -0.01]	**<0.001**
0.01	[-0.01 – 0.03]	0.19	-0.02	[-0.04 – -0.00]	**0.01**	-0.03	[-0.05 – -0.02]	**<0.001**
0.01	[-0.00 – 0.03]	0.13	-0.01	[-0.02 – 0.01]	0.27	-0.02	[-0.03 – -0.01]	**0.008**
-0.02	[-0.04 – 0.01]	0.17	-0.02	[-0.04 – 0.01]	0.13	-0.00	[-0.02 – 0.02]	0.91
-0.02	[-0.04 – 0.01]	0.21	-0.03	[-0.06 – -0.01]	**0.01**	-0.02	[-0.04 – 0.01]	0.17
-0.02	[-0.04 – 0.00]	0.12	-0.03	[-0.05 – -0.00]	**0.02**	0.00	[-0.02 – 0.02]	0.97

BSI: brain symmetry index; Delta: calculated over the delta band; Theta: calculated over the theta band; BSIdir: directional BSI. P-values <0.05 are shown in bold. Grey-filled boxes indicate significant values.

Table 3.3A Association between clinical and spectral characteristics over all measurement moments corrected and uncorrected for (confounding) factor time

	NIHSS					
	Uncorrected			Corrected for time		
	ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
DAR	0.12	[0.05 – 0.19]	**<0.001**	0.11	[-0.001 – 0.21]	**0.05**
DAR $_{AH}$	0.19	[0.10 – 0.28]	**<0.001**	0.18	[0.04 – 0.32]	**0.01**
DAR $_{UH}$	0.05	[0.00 – 0.11]	**0.04**	0.04	[-0.04 – 0.12]	0.31
BSI	0.25E-2	[0.05E-2 – 0.45E-2]	**0.01**	0.45E-2	[0.17E-2 – 0.74E-2]	**<0.001**
BSI $_{delta}$	3.23E-3	[0.47E-3 – 5.99E-3]	**0.02**	0.44E-2	[0.05E-2 – 0.83E-2]	**0.03**
BSI $_{theta}$	1.94E-3	[-0.41E-3 – 4.28E-3]	0.11	3.41E-3	[-0.03E-3 – 6.85E-3]	**0.05**
BSIdir	0.32E-2	[-0.03E-3 – 0.64E-2]	**0.05**	0.13E-2	[-0.33E-2 – 0.59E-2]	0.57
BSIdir $_{delta}$	0.84E-2	[0.44E-2 – 1.23E-2]	**<0.001**	0.93E-2	[0.33E-2 – 1.53E-2]	**0.003**
BSIdir $_{theta}$	5.37E-3	[1.82E-3 – 8.93E-3]	**0.003**	0.39E-2	[-0.17E-2 – 0.95E-2]	0.17

ß: regression coefficient; 95%-CI: 95% confidence interval; *P*: p-value, Holm-Bonferroni corrected significance level: $P<(0.05/\ N_s)$; DAR: delta/alpha ratio; BSI: brain symmetry index; BSIdir: directional BSI;

Table 3.3B Association between NIHSS and spectral characteristics per measurement moment.

	At baseline			At week 5		
	ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
DAR	0.12	[0.28E-2 – 0.24]	**0.05**	0.11	[-0.02 – 0.24]	0.11
DAR $_{AH}$	0.21	[0.05 – 0.37]	**0.01**	0.17	[-0.01 – 0.34]	0.07
DAR $_{UH}$	0.03	[-0.06 – 0.12]	0.48	0.07	[-0.03 – 0.17]	0.14
BSI	0.48E-2	[0.14E-2 – 0.81E-2]	**<0.01**	0.36E-2	[-0.01E-2 – 0.72E-2]	0.06
BSI $_{delta}$	0.49E-2	[0.04E-2 – 0.94E-2]	**0.03**	0.34E-2	[-0.16E-2 0.84E-2]	0.18
BSI $_{theta}$	0.34E-2	[-0.05E-2 – 0.74E-2]	0.09	0.25E-2	[-0.18E-2 – 0.68E-2]	0.26
BSIdir	-0.18E-2	[-0.71E-2 – 0.36E-2]	0.52	0.03	[-0.43E-2 – 0.01]	0.25
BSIdir $_{delta}$	0.82E-2	[0.14E-2 – 1.51E-2]	**0.02**	0.01	[0.27E-2 – 0.02]	**0.008**
BSIdir $_{theta}$	0.27E-2	[-0.35E-2 – 0.89E-2]	0.39	0.47E-2	[-0.21E-2 – 1.15E-2]	0.18

ß: regression coefficient; 95%-CI: 95% confidence interval; *P*: p-value, Holm-Bonferroni corrected significance level: $P<(0.05/\ N_s)$; DAR: delta/alpha ratio; BSI: brain symmetry index; BSIdir: directional BSI;

FM-UE					
Uncorrected			Corrected for time		
ß	95%-CI	P	ß	95%-CI	P
-0.01	[-0.03 – 0.001]	0.07	0.20E-2	[-0.02 – 0.02]	0.83
-0.02	[-0.04 – -0.13E-2]	**0.04**	-0.12E-3	[-0.02 – 0.02]	0.99
0.01	[-0.02 – 0.01]	0.32	0.29E-2	[-0.01 – 0.02]	0.68
-0.30E-3	[-0.69E-3 – 0.09E-3]	0.13	-0.32E-3	[-0.81E-3 - 0.17E-3]	0.20
-0.37E-3	[-0.89E-3 - -0.16E-3]	0.17	-0.20E-3	[-0.85E-3 – 0.46E-3]	0.55
-0.27E-3	[-0.72E-3 - 0.19E-3]	0.25	-0.27E-3	[-0.84E-3 - 0.30E-3]	0.36
-0.72E-3	[-1.21E-3 – -0.12E-3]	**0.02**	-0.49E-3	[-1.21E-3 – 0.24E-3]	0.19
-0.14E-2	[-0.22E-2 - -0.06E-2]	**<0.001**	-0.11E-2	[-0.21E-2 - -0.01E-2]	**0.04**
-0.90E-3	[-1.61E-3 – 0.19E-3]	**0.01**	-0.46E-3	[-1.40E-3 – 0.49E-3]	0.34

P-values <0.05 are shown in bold. Grey-filled boxes indicate significant associations.

At week 12			At week 26		
ß	95%-CI	P	ß	95%-CI	P
-0.01	[-0.17 – 0.15]	0.86	0.06	[-0.12 – 0.23]	0.52
0.03	[-0.19 – 0.25]	0.78	0.09	[-0.15 – 0.33]	0.46
-0.05	[-0.17 – 0.07]	0.41	0.03	[-0.11 – 0.16]	0.70
0.63E-2	[0.18E-2 – 0.01]	**0.006**	0.52E-2	[0.03E-2 – 0.01E-2]	**0.04**
0.57E-2	[-0.04E-2 – 0.01]	0.07	0.47E-2	[-0.21E-2 – 0.01]	0.17
0.61E-2	[0.07E-2 – 1.14E-2]	**0.03**	0.48E-2	[-0.10E-2 – 1.07E-2]	0.11
0.698E-2	[-0.03E-2 – 0.01]	0.06	0.25E-2	[-0.55E-2 – 0.01]	0.54
0.01	[0.29E-2 – 0.02]	**0.01**	0.01	[0.33E-3 – 0.02]	**0.04**
0.76E-2	[-0.09E-2 – 1.60E-2]	0.08	0.01	[0.22E-2 – 0.02]	**0.02**

NIHSS: National Institutes of Health Stroke Scale; FM-UE: Fugl-Meyer motor assessment of the upper extremity. P-values <0.05 are shown in bold. Grey-filled boxes indicate significant associations.

Table 3.3C Association between FM-UE and spectral characteristics per measurement moment.

	At baseline			At week 5		
	ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
DAR	0.17E-2	[-0.02 – 0.03]	0.89	0.38E-2	[-0.02 – 0.03]	0.72
DAR_{AH}	-0.29E-2	[-0.04 – 0.03]	0.86	-0.29E-2	[-0.03 – 0.03]	0.79
DAR_{UH}	0.01	[-0.01 – 0.03]	0.50	0.18E-2	[-0.01 – 0.02]	0.83
BSI	-0.57E-3	[-1.25 E-3 - -0.11 E-3]	0.10	-0.12E-3	[-0.71E-3 – 0.47E-3]	0.68
BSI_{delta}	-0.24E-3	[-1.17E-3 – 0.68E-3]	0.60	-0.09E-3	[-0.89E-3 – 0.01E-3]	0.81
BSI_{theta}	-0.54E-3	[-1.34E-3 - 0.25E-3]	0.18	-0.01E-3	[-0.67E-3 – 0.67E-3]	0.97
BSIdir	-0.36E-3	[-1.43E-3 – 0.71E-3]	0.51	-0.55E-3	[-1.46E-3 – 0.37E-3]	0.24
$BSIdir_{delta}$	-0.11E-2	[-0.26E-2 – 0.03E-2]	0.11	-0.88E-3	[-2.09E-3 – 0.33E-3]	0.15
$BSIdir_{theta}$	-0.53E-3	[-1.81E-3– 0.75E-3]	0.42	-0.17E-3	[-1.27E-3 – 0.94E-3]	0.77

ß: regression coefficient; 95%-CI: 95% confidence interval; *P*: p-value, Holm-Bonferroni corrected significance level: $P<(0.05/ N_s)$; DAR: delta/alpha ratio; BSI: brain symmetry index; BSIdir: directional BSI;

Table 3.3D Within- and between-subject associations between clinical and spectral characteristics

	NIHSS between-subject effects			NIHSS within-subject effects		
	ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
DAR	0.23	[0.05 – 0.42]	**0.02**	0.10	[0.03 – 0.18]	**0.007**
DAR_{AH}	0.36	[0.13 – 0.60]	**0.003**	0.16	[0.06 – 0.26]	**0.003**
BSI	0.74E-2	[032E-2 – 0.01]	**<0.001**	0.12E-2	[-0.11E-2 – 0.34E-2]	0.31
BSI_{delta}	0.99E-2	[0.44E-2 – 0.02]	**<0.001**	0.12E-2	[-0.19E-2 – 0.44E-2]	0.44
BSI_{theta}	0.78E-2	[0.27E-2 – 0.01]	**0.004**	0.05E-2	[-0.21E-2 – 0.31E-2]	0.70
BSIdir	0.02	[-0.41E-2 – 0.88E-2]	0.46	0.34E-2	[0.03E-2 – 0.72E-2]	0.07
$BSIdir_{delta}$	0.02	[0.01 – 0.03]	**<0.001**	0.67E-2	[0.23E-2 – 0.01]	**0.003**
$BSIdir_{theta}$	0.01	[0.11E-2 – 0.02]	**0.03**	0.45E-2	[0.07E-2 – 0.84E-2]	**0.02**

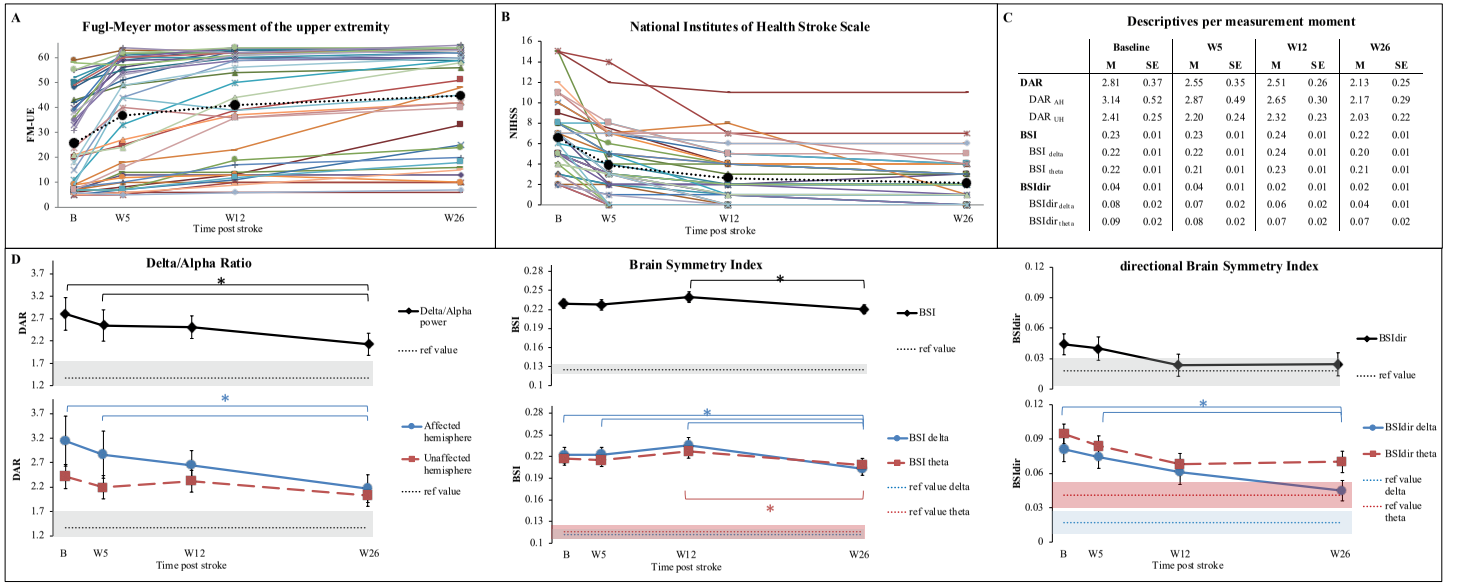
ß: regression coefficient; 95%-CI: 95% confidence interval; *P*: p-value, Holm-Bonferroni corrected significance level: $P<(0.05/ N_s)$; DAR: delta/alpha ratio; BSI: brain symmetry index; BSIdir: directional BSI;

At week 12			At week 26		
ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
0.46E-2	[-0.02 – 0.03]	0.68	-0.32E-2	[-0.03 – 0.02]	0.77
0.17E-2	[-0.03 – 0.03]	0.73	-0.57E-2	[-0.04 – 0.02]	0.71
0.58E-2	[-0.01 – 0.02]	0.48	-0.43E-3	[-0.02– 0.02]	0.96
-0.40E-3	[-1.00E-3 – 0.19E-3]	0.18	-0.34E-3	[-0.94E-3 – 0.27E-3]	0.27
-0.41E-3	[-1.21E-3 – 0.39E-3]	0.31	-0.08E-3	[-0.90E-3 – 0.74E-3]	0.85
-0.49E-3	[-1.19E-3 – 0.20E-3]	0.16	-0.19E-3	[-0.90E-3 – 0.52E-3]	0.59
-0.85E-3	[-1.78E-3 – 0.07E-3]	0.07	-0.09E-3	[-1.03E-3 – 0.86E-3]	0.86
-0.13E-2	[-0.25E-2 - -0.04E-3]	**0.04**	-0.11E-2	[-0.24E-2 – 0.01E-2]	0.08
-0.73E-3	[-1.85E-3 – 0.40E-3]	0.20	-0.49E-3	[-1.6E-3 – 0.65E-3]	0.39

NIHSS: National Institutes of Health Stroke Scale; FM-UE: Fugl-Meyer motor assessment of the upper extremity. P-values <0.05 are shown in bold. Grey-filled boxes indicate significant associations.

FM-UE between-subject effects			FM-UE within-subject effects		
ß	**95%-CI**	***P***	***ß***	**95%-CI**	***P***
-0.01	[-0.04 – 0.02]	0.46	-0.01	[-0.03 – 0.24E-2]	0.10
-0.02	[-0.05 – 0.02]	0.31	-0.02	[-0.04 – 0.15E-2]	0.07
-0.04E-2	[-0.11E-2 – 0.03E-2]	0.22	-0.02E-2	[-0.07E2 – 0.03E-2]	0.33
-0.06E-2	[-0.15E-2 – 0.02E-2]	0.15	-0.02E-2	[-0.09E2 – 0.05E-2]	0.57
-0.05E-2	[-0.13E-2 – 0.03E-2]	0.23	-0.02E-2	[-0.07E2 – 0.04E-2]	0.59
-0.02E-2	[-0.11E-2 – 0.07E-2]	0.63	-0.11E-2	[-0.19E-2 – -0.03E-2]	**0.006**
-0.18E-2	[-0.32E-2 – -0.04E-2]	**0.01**	-0.12E-2	[-0.22E-2 – -0.03E-2]	**0.01**
-0.09E-2	[-0.23E-2 – 0.05E-2]	0.21	-0.09E-2	[-0.17E-2 – -0.77E-4]	**0.03**

NIHSS: National Institutes of Health Stroke Scale; FM-UE: Fugl-Meyer motor assessment of the upper extremity. P-values <0.05 are shown in bold. Grey-filled boxes indicate significant associations.



	Baseline		W5		W12		W26	
	M	SE	M	SE	M	SE	M	SE
DAR	2.81	0.37	2.55	0.35	2.51	0.26	2.13	0.25
DAR $_{AH}$	3.14	0.52	2.87	0.49	2.65	0.30	2.17	0.29
DAR $_{UH}$	2.41	0.25	2.20	0.24	2.32	0.23	2.03	0.22
BSI	0.23	0.01	0.23	0.01	0.24	0.01	0.22	0.01
BSI $_{delta}$	0.22	0.01	0.22	0.01	0.24	0.01	0.20	0.01
BSI $_{theta}$	0.22	0.01	0.21	0.01	0.23	0.01	0.21	0.01
BSIdir	0.04	0.01	0.04	0.01	0.02	0.01	0.02	0.01
BSIdir $_{delta}$	0.08	0.02	0.07	0.02	0.06	0.02	0.04	0.01
BSIdir $_{theta}$	0.09	0.02	0.08	0.02	0.07	0.02	0.07	0.02

Figure 3.3 Panel A: Development of the Fugl-Meyer motor assessment of the upper extremity over time (max=66), N=41. Panel B: Development of the National Institutes of Health Stroke Scale over time (max=42), N=41. Panel C: mean and standard error of the mean, per measurement moment, for the different spectral characteristics. Panel D: Development of the spectral characteristics over time; mean and standard errors of the mean are displayed. The blue and red dashed lines and surrounding colored area indicate the mean values of 11 healthy subjects and their standard error of the mean, as taken from Saes et al.[14] *indicates a significant mean difference between moments, after Holm-Bonferroni corrections ($P<0.05/N_5$). Delta band: 1-4 Hz, theta band:4-8 Hz. Abbreviations: B: baseline measurement within three weeks post-stroke; W: measurement week post stroke; DAR: delta/alpha ratio; BSI: brain symmetry index; BSIdir: directional BSI; FM-UE: Fugl-Meyer motor assessment of the upper extremity; NIHSS: National Institutes of Health Stroke Scale.

Discussion

Current literature argues the importance of knowledge concerning the association between clinical improvements and changes in the brain after stroke.[28] Studies focused on brain activity related to impairments after stroke mainly have a cross-sectional design. In the current study resting-state EEG and clinical data were measured repeatedly at recommended fixed moments in the first six months post stroke.[28] The aim was to investigate longitudinal changes in the EEG-derived spectral characteristics DAR, BSI and BSIdir, as well as their changes over time in relation to improvements of NIHSS and FM-UE scores within and beyond the window of spontaneous neurobiological recovery.

We hypothesized that DAR, BSI and BSIdir would decrease mainly within the time window of spontaneous neurobiological recovery after stroke as reflected by changing neurological impairments such as FM-UE and NIHSS. However, our findings revealed that this time window did not fully match with the time window of changes in spectral characteristics, which were found to normalize within and beyond the first three months. In line with our second hypothesis, the time course of DAR_{AH} and $BSIdir_{delta}$ within subjects was significantly positively associated with the severity of global neurological impairments as reflected by the NIHSS score. Moreover, $BSIdir_{delta}$ showed a clear negative within-subject association with recovery of motor impairments of the upper extremity as reflected by FM-UE scores. This means that a decreasing asymmetry in the delta band within a patient was related with recovery of motor function of the upper extremity.

Time course of spectral characteristics differs from spontaneous neurobiological recovery

Most of the spectral characteristics we investigated showed normalization over time to a certain extent, in line with what has been reported in the literature.[12,14,29] More specifically, DAR_{AH} and BSIdir approached values found in healthy subjects,[14] whereas lateralization as reflected by the BSI persisted. The seemingly inconsistent results for BSI and BSIdir might be the result of reciprocal asymmetries over the channel pairs, which accumulate in BSI while cancelling out in BSIdir. Nonetheless, our results show decreasing lateralization in the delta band for both asymmetry measures. Comparable with our results, a previous longitudinal MEG study reported delta activity to be increased in the affected hemisphere in the acute phase and to decrease over time during the early sub-acute phase post stroke.[29]

The time course of the investigated spectral characteristics did not plateau at the same moment as spontaneous neurobiological recovery reflected by the NIHSS and FM-UE scores. This continuing normalization of EEG parameters suggests that not all changes measured with EEG reflect neurological improvements reflected by a global neurological deficits assessment as the NIHSS or motor function assessment as the FM-UE. Although speculative, the continuing normalization observed in EEG parameters may parallel more refined neurological improvements, which are not detectable with NIHSS and FM-UE due to their ceiling effect. Obviously, molecular and cellular processes related to post-stroke recovery (i.e. upregulated growth factors, angiogenesis and synaptogenesis)[7,30,31] affect synaptic connections and network integrity, and lead to remapping,[5] which - in turn - may alter brain oscillations.[32] The underlying relationship between these processes remains to be investigated.

Spectral characteristics as monitoring biomarkers of recovery

The positive within-subject effects found for DAR and DAR_{AH} reveal decreasing values within patients as NIHSS scores improved. This is in line with the findings of the aforementioned longitudinal MEG study, which revealed that patients with persistent low-frequency activity also had lower NIHSS scores than patients without such persistent low-frequency activity.[29]

The increased DAR values in both the affected and unaffected hemispheres, compared to healthy values, confirm the current literature reports suggesting that the unaffected hemisphere is also affected early after stroke.[33,34] Therefore, our asymmetry measure may have underestimated the neurological deficits early post stroke. Since the unaffected hemisphere is less affected than the affected hemisphere, DAR_{AH} might be more appropriate to capture the relevant signals than DAR calculated over both hemispheres.

Our BSI results agree with those presented by Agius Anastasi and co-workers.[19] They reported a trend towards a decrease in BSI over time, and the absence of a significant correlation with FM-UE. We only showed a significant positive between-subject effect between NIHSS and BSI. This suggests that a lower NIHSS score in patient A compared to patient B, is related to a decreased BSI value in patient A compared to patient B.

The longitudinal associations between $BSIdir_{delta}$, stroke severity, and motor function as reported here emphasize the validity of this specification favoring the use of frequency bands and directionality. The within- and between-subject effects reveal that a lower degree of asymmetry in the delta band compared to another patient, or a decreasing degree of asymmetry in the delta band over time within a patient, were associated with decreased stroke severity and improved motor function of the

upper extremity. This suggests that the development of $BSIdir_{delta}$ and clinical scores over time within individuals are related. $BSIdir_{delta}$ therefore shows potential as a monitoring biomarker of spontaneous neurobiological recovery.

In congruence with our data, which suggests increased activity towards the affected hemisphere in the delta frequency band (increased $BSIdir_{delta}$), Fanciullacci and co-workers (2017)[35] showed delta power to be increased in the affected compared to the unaffected hemisphere in stroke patients with subcortical lesions. Nonetheless, in the same sample they showed a negative correlation between pdBSI and NIHSS, which is different from our findings. This discrepancy may result from methodological issues such as small sample sizes in combination with the lack of correction for multiple testing. Hence, the influence of lesion location on these results has yet to be investigated. Other techniques and imaging methods (e.g., MRI or DTI) are necessary to better understand the impact of anatomical integrity on the time course of spectral characteristics early post stroke.

Limitations and future directions

Several limitations of the study should be taken into consideration. Additional analyses were performed in which the time courses of the spectral characteristics were compared between three patient groups classified based on their FM-UE recovery pattern (See supplementary materials). Unfortunately, due to small subgroups this analysis was underpowered. Furthermore, since in the current study MRI data was unavailable for a large proportion of the patients, we were not able to correct for lesion size or location, while we acknowledge that this might influence the observed resting-state oscillations and motor recovery post stroke.[35,36] In previous work, DAR was found to be only increased in patients with a cortico-subcortical lesion, while BSI was only increased in patients with a subcortical lesion when compared to healthy individuals.[35] Future studies are needed to further investigate the influence of lesion location on the time course of DAR and BSI. Additionally, we restricted the present study to spectral characteristics representing low-frequency activity. Whether alpha, beta and gamma frequencies may also be sensitive neurophysiological biomarkers of recovery early post stroke needs to be investigated. Finally, due to the limited capacity of patients in the acute phase post stroke, the baseline measurement took place at an average of 12 days post stroke, which means that a substantial amount of recovery might already have occurred.[37] Hence, we may have missed some of the early changes in spectral characteristics over time.

In future research we suggest to investigate the contribution of low-frequency oscillations during upper limb movements. Previous work in rodents suggest that low-frequency oscillations are a possible target for neuromodulation to improve motor function recovery post stroke.[38]

Conclusion

In the current study, it was concluded that normalization of resting-state EEG asymmetry measures was not restricted to the time window of recovery of clinical neurological impairments measured with NIHSS and FM-UE. This might reflect an ongoing neural recovery beyond three months, which is not detectable by these impairment-focused outcome measures. In addition, global neurological recovery and recovery of motor function of the upper extremity are associated with normalization of their spectral characteristics in the low frequency bands in patients who suffered from ischemic stroke. Future research should investigate the influence of lesion location on this relationship as well as and the potential role of spectral characteristics as a prognostic biomarker of recovery.

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Declaration of Conflicting Interests
The authors declare that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Are early measured resting-state EEG parameters predictive for upper limb motor impairment six months poststroke?

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Abstract

Objectives: Investigate whether resting-state EEG parameters recorded early poststroke can predict upper extremity motor impairment reflected by the Fugl-Meyer motor score (FM-UE) after six months, and whether they have prognostic value in addition to FM-UE at baseline.

Methods: Quantitative EEG parameters delta/alpha ratio (DAR), brain symmetry index (BSI) and directional BSI (BSIdir) were derived from 62-channel resting-state EEG recordings in 39 adults within three weeks after a first-ever ischemic hemispheric stroke. FM-UE scores were acquired within three weeks ($FM\text{-}UE_{baseline}$) and at 26 weeks poststroke ($FM\text{-}UE_{w26}$). Linear regression analyses were performed using a forward selection procedure to predict $FM\text{-}UE_{w26}$.

Results: BSI calculated over the theta band (BSI_{theta}) (β=-0.40; p=0.013) was the strongest EEG-based predictor regarding $FM\text{-}UE_{w26}$. BSI_{theta} (β=-0.27; p=0.006) remained a significant predictor when added to a regression model including $FM\text{-}UE_{baseline}$, increasing explained variance from 61.5% to 68.1%.

Conclusion: Higher BSI_{theta} values, reflecting more power asymmetry over the hemispheres, predict more upper limb motor impairment six months after stroke. Moreover, BSI_{theta} shows additive prognostic value regarding $FM\text{-}UE_{w26}$ next to $FM\text{-}UE_{baseline}$ scores, and thereby contains unique information regarding upper extremity motor recovery.

Significance: To our knowledge, this is the first time to show that resting-state EEG parameters can serve as prognostic biomarkers of stroke recovery, in addition to $FM\text{-}UE_{baseline}$ scores.

Introduction

Stroke is a major cause of adult disability worldwide.[1] In the early phase, about 80% of stroke survivors suffer from motor impairments of the upper extremity.[2] Recently, five subgroups of stroke patients were identified, based on their highly heterogeneous patterns of motor recovery within a time window of ten weeks poststroke[3]. Motor recovery is largely independent of the type of therapeutic intervention and is referred to as spontaneous neurological recovery.[4,5] Motor impairment, measured by the Fugl-Meyer motor assessment of the upper extremity (FM-UE), includes patients' stereotypical co-articulation of multiple joints[6]. This so-called synergy dependency in motor control appears to be a major limitation when performing selective, dissociated movements.[7] Several studies showed that one of the best early phase predictors of chronic motor impairment, reflected by the FM-UE six months after stroke, is the FM-UE scores at baseline.[8,9] However, recent studies showed that the variation in degree of recovery between subjects may range from non-recoverers to excellent recoverers, suggesting that FM-UE measured at baseline ($FM\text{-}UE_{baseline}$) in itself may not be an optimal predictor.[3,8,9] As noted by the Stroke Recovery and Rehabilitation Roundtable (SRRR) task force, there is an urgent need for complementary prognostic biomarkers in addition to clinical assessments to optimize the accuracy of current prediction models for spontaneous motor recovery.[10,11] This is particularly important as early poststroke clinical assessments may not be able to distinguish patients who will show spontaneous upper limb motor recovery from those who will not.[3]

Parameters derived using structural imaging techniques showed that corticospinal tract (CST) integrity has predictive value for motor recovery.[12–14] The predictive value of motor evoked potentials and asymmetry in fractional anisotropy of the posterior limbs of the internal capsules also indicates a role for the CST regarding motor recovery.[15] Next to these structural imaging characteristics, potential biomarkers that might be associated with motor outcome include derivatives of cortical activity in the brain, which can be recorded using electroencephalography (EEG).[10] The level of cortical deficits after stroke may be quantified by resting-state EEG, as altered resting-state cortical activity has been associated with motor dysfunction.[16,17] Resting-state EEG recording is specifically suitable for the stroke population early after onset, since it is portable, non-invasive and does not require voluntary motor performance with the paretic upper limb.

Hemispheric stroke has been associated with altered low-frequency oscillations in the delta and theta bands[18–21], whereas unaltered alpha activity seems to be associated with healthy brain activity.[22] A combination of these spectral characteristics can be expressed by the delta/alpha ratio (DAR). This ratio may more sensitively reflect the

severity of neurological deficits compared to the individual spectral components, as, for instance, delta activity may increase with or without decreased alpha activity. Unilateral stroke may also affect the activity of the cortical areas involved through modified spectral power distributions over the hemispheres. This power asymmetry can be quantified via the pairwise-derived brain symmetry index (BSI)[23] and directional BSI (BSIdir)[24].

Quantitative resting-state EEG parameters such as DAR and BSI, measured early poststroke, are predictors of future global neurological deficits reflected by the National Institutes of Health Stroke Scale (NIHSS) and degree of dependency assessed with the modified Rankin Scale (mRS).[20,25–28] Furthermore, recent analyses showed that BSI calculated over the delta frequency band (BSI_{delta}) was longitudinally associated with FM-UE, whereas DAR, DAR of the affected hemisphere (DAR_{AH}), BSI, BSIdir over the delta ($BSIdir_{delta}$) and theta band ($BSIdir_{theta}$), were longitudinally associated with NIHSS.[29] However, the potential of EEG parameters to serve as additional prognostic biomarker when combined with clinical scores regarding upper limb motor recovery poststroke remains unclear.[28]

The first objective of the current analysis of the prospective cohort study named 4D-EEG was to investigate whether early measured resting-state EEG parameters have predictive value regarding motor impairment of the paretic upper limb, as reflected by FM-UE, six months after a first-ever ischemic stroke. We expected this to be true, especially for the BSI and BSIdir over the low frequency bands which were previously found to be longitudinally associated with FM-UE.[29] Our second aim was to investigate whether these resting-state EEG parameters have prognostic value in addition to FM-UE measured at baseline.

Methods

Participants

All patients who were admitted to the stroke units of six participating hospitals between June 2015 and June 2017 were potentially eligible for participation. The inclusion criteria were: (1) first-ever ischemic stroke according to CT or MRI scan; (2) less than three weeks poststroke; (3) upper limb paresis (NIHSS 5a/b>0); (4) ≥18 years of age; and (5) having provided written informed consent. Exclusion criteria were: (1) upper extremity orthopedic limitations prior to stroke onset; (2) recurrent stroke; (3) severe cognitive problems, i.e. Mini Mental State Examination score <18; (4) other neurological deceases; and (5) using medication which is likely to affect neuronal oscillations. The study was registered at the Netherlands Trial Register (NTR4221), approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands (4D-EEG: NL47079.029.14) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2013).[30] Analyses were performed on longitudinal data of 39 participants, which belong to the same dataset as used for analyses in Saes et al (2020). There was no overlap regarding participants included in Saes et al (2019). All participants received usual care according to the Dutch stroke guidelines for physical therapy.[31]

Procedures

The baseline measurement involved an EEG recording and a clinical assessment performed on consecutive days, as soon after stroke onset as feasible, but at least within the first three weeks. EEG recordings were performed in a specially equipped van.[29] This provided the opportunity to visit patients at their place of residence, to limit their burden and ensure standardization. FM-UE was performed as part of the baseline clinical assessment ($FM\text{-}UE_{baseline}$) and repeated at 26 weeks poststroke ($FM\text{-}UE_{w26}$).

Electroencephalography

High-density 62-channel EEG was recorded using an actively shielded EEG cap with electrode placement according to the international 10-20 system at a sampling rate of 2048 Hz (Ag/AgCl electrodes and REFA multichannel amplifier, TMSi, Oldenzaal, The Netherlands, with ASA acquisition software, ANT software BV, The Netherlands). Resting-state EEG with eyes open was acquired while subjects were seated and focused their eyes on a dot displayed on a screen for one minute. Five 1-minute trials were recorded, with sufficient rest in between. Electrode impedances were kept below 20 kΩ. EEG signals were online referenced to average. During the EEG recording, muscle relaxation of the arms was monitored using bipolar Ag/AgCl electrodes to detect muscle activity of the m. extensor carpi radialis and m. flexor carpi radialis of both arms.

Pre-processing

Offline analysis was conducted using Matlab (R2012a, The Mathworks, Natick, MA, USA) in combination with the FieldTrip toolbox for EEG/MEG analysis[32]. EEG signals were filtered using a 4th-order bi-directional high-pass Butterworth filter with a cut-off at 0.5 Hz. A notch filter around 50, 100 and 150 Hz with a bandwidth of 1 Hz was used to reduce power-line artefacts, followed by a low-pass filter at 130 Hz. Channels which showed no data or very poor data quality were rejected and interpolated as the weighted average of the surrounding electrodes, followed by re-referencing to the remaining average. On average, 0.17 electrodes were interpolated per measurement. Eye-blinks and muscle activity artefacts were removed using independent component analysis based on visual inspection of the components' waveforms, power spectrum and topographic distributions. On average 2.9 components were removed per measurement. Remaining artefacts were removed during a second round of visual inspection. Modified periodograms with a Hanning window with size equal to the epoch length served as proxies of the spectral power density per channel.

Quantitative resting-state EEG parameters

Delta/alpha ratio

Hemispheric stroke has been associated with increased low frequency oscillations in the delta and theta band.[18–21] On the other hand, unaltered alpha activity has been associated with healthy brain activity.[22] The delta/alpha ratio (DAR) combines these spectral characteristics and was defined as the ratio between the mean delta power (1-4 Hz) and the mean alpha power (8-12 Hz). For every channel *c* the power of the delta and alpha frequency bands (f=1,...,4 Hz and f = 8,...,12 Hz, respectively) was determined as the mean of the spectral power $P_c(f)$ over this range. The DAR was computed as

$$\mathrm{DAR_c} = \frac{\langle P_c(f)\rangle_{f=1,\ldots,4\ \mathrm{Hz}}}{\langle P_c(f)\rangle_{f=8,\ldots,12\ \mathrm{Hz}}} \quad (1)$$

Subsequently, we averaged the ratios over all *N* EEG channels yielding the global DAR:

$$\mathrm{DAR} = \frac{1}{N}\sum_{c=1}^{N} \mathrm{DAR_c} \quad (2)$$

In addition to the assessment over the whole brain, DAR was also determined over the affected (DAR_{AH}) and unaffected hemisphere (DAR_{UH}).

Brain symmetry index

The BSI represents the spectral power distribution asymmetry over the hemispheres, which may be affected due to unilateral stroke altering cortical activity. BSI was defined as the absolute pairwise normalized difference in spectral power between

the homologous channels over the left C_L and right C_R hemisphere. The difference was averaged over a range from 1 to 25 Hz (adapted from Sheorajpanday et al., 2009) according to

$$\mathrm{BSI_{cp}} = \left\langle \left| \frac{P_{c_R}(f) - P_{c_L}(f)}{P_{c_R}(f) + P_{c_L}(f)} \right| \right\rangle_{f=1,\ldots,25\ \mathrm{Hz}} \quad (3)$$

These values were averaged over all channel pairs *cp*:

$$\mathrm{BSI} = \frac{2}{N} \sum_{cp=1}^{N/2} \mathrm{BSI_{cp}} \quad (4)$$

BSI values theoretically range from 0 to 1, indicating maximal symmetry and maximal asymmetry, respectively. In (3) and (4), electrodes of the mid-line were excluded since they do not form channel-pairs. In our earlier study, we showed the relevance of the lower frequency bands for the stroke population.[24] Therefore, in addition to the estimates over the entire 1-25 Hz range, BSI was also determined separately for the delta (1-4 Hz) and theta (4-8 Hz) frequency bands (BSI_{delta} and BSI_{theta}).

To account for the direction of the asymmetry, we also computed the directional BSI (BSIdir).[24] The BSIdir disregards the absolute value of the numerator of the BSI calculation shown in (3). The sign of BSIdir was chosen such that values between 0 and 1 reflected greater cortical power in the affected hemisphere compared to the unaffected hemisphere, and vice versa for values between -1 and 0. Also BSIdir was determined separately for the delta ($BSIdir_{delta}$) and theta ($BSIdir_{theta}$) frequency band.

Clinical measures

FM-UE (range [0-66]) is a valid and reliable clinical test reflecting motor impairment after stroke.[33] Additional clinical assessments for subject characterization included NIHSS, Action Research Arm Test (ARAT), Erasmus MC modification of the Nottingham Sensory Assessment of the upper extremity (EmNSA), Motricity Index of the Upper/Lower Extremity (MI-UE/MI-LE), Edinburgh Handedness Inventory and Bamford classification.

Statistics

A forward selection procedure was used to identify the strongest predictor of $FM\text{-}UE_{w26}$ based on quantitative resting-state EEG. Investigated EEG parameters concerned: DAR, DAR_{UH}, DAR_{AH}, BSI, BSI_{delta}, BSI_{theta}, BSIdir, $BSIdir_{delta}$, and $BSIdir_{theta}$.

Subsequently, a stepwise forward selection procedure with FM-$UE_{baseline}$ as base model, was used to find the EEG parameter which has the most added value. The F-test was used to check whether adding a quantitative resting-state EEG parameter significantly increased the explained variance.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). For each model, the distribution of residuals was tested for normality by inspecting histograms and Q-Q plots. As is common in prediction models, the significance level of covariates was set to $\alpha < 0.05$.

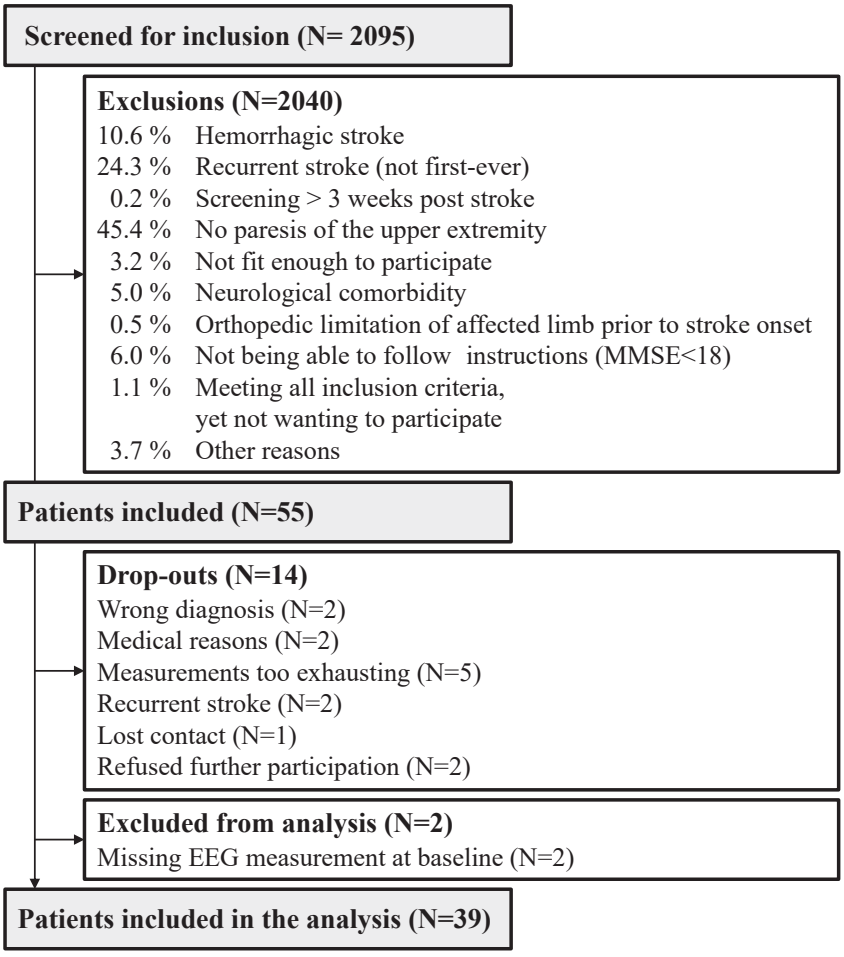

Figure 4.1. *Flowchart of screening, inclusion, and drop-outs.*

Abbreviations: N, number; MMSE, mini mental state examination.

Results

Participants

A total of 2095 patients were screened, 55 of whom were eligible and willing to participate in this longitudinal observational cohort study. Thirty-nine patients completed the EEG recording at baseline and the clinical assessments at baseline and 26 weeks poststroke, and were included in the analyses. A flowchart of screening, inclusion and drop-outs is depicted in **Figure 4.1**. The EEG recording was performed at 12.3 ± 5.8 days (mean ± SD) poststroke. Clinical assessments were performed at 11.6 ± 5.3 and 185.2 ± 20.0 days poststroke, referred to as *baseline* and *w26*, respectively. In the present study, the number of days between stroke onset and the baseline clinical measurement or EEG recording was not significantly correlated with FM-$UE_{baseline}$ ($r(37) = -0.206$, $p = 0.21$ and $r(37) = -0.273$, $p = 0.09$; respectively). Patient characteristics are summarized in **Table 4.1**. A complete overview of the data can be found in Supplementary Table S1.

EEG-derived predictors of FM-UE_{w26}

The forward selection procedure revealed that BSI_{theta} is the strongest predictor of the investigated EEG parameters with respect to FM-UE_{w26} scores (B = -156.81, 95%-CI = [-277.93 - -35.70], $p = 0.013$, $\beta = -0.40$, $R^2 = 0.16$) (**Table 4.2**). Hereby, a higher BSI_{theta} predicts a lower FM-UE_{w26}.

EEG parameters with additive prognostic value in addition to FM-$UE_{baseline}$

The forward selection procedure revealed that BSI_{theta} was the EEG parameter with most predictive value in addition to FM-$UE_{baseline}$ (B = -108.09, 95%-CI = [-182.74 - -33.44], $p = 0.006$, $\beta = -0.27$, $R^2_{adj} = 0.68$), where a higher BSI_{theta} value predicts a lower FM-UE_{w26} (**Table 4.3**). FM-$UE_{baseline}$ remained significant ($p < 0.001$; **Table 4.3**). FM-$UE_{baseline}$ alone explained 61.5% of the variance ($R^2_{adj} = 0.615$, $F(1,37) = 61.7$, $p < 0.001$; **Table 4.3**). Adding BSI_{theta} increased the explained variance of the prediction model significantly to 68.1% ($R^2_{adj} = 0.681$, F-change(1,36) = 8.6, $p = 0.006$; **Table 4.3**).

Table 4.1. Patient characteristics

Demographics and clinical scores	Baseline Mean (SD) or N		26 weeks post stroke	
Time post stroke (days), clinical assessment	11.6 (5.3)		185.2 (20.0)	
Time post stroke (days), EEG recording	12.3 (5.8)			
Age (years)	67.3 (11.4)			
Gender (male/female)	23/16			
Affected hemisphere (left/right)	18/21			
Hand dominance (left/right)	5/34			
Bamford classification (LACI/PACI/TACI)	20/14/5			
FM-UE*	21	(7 – 42)	59	(20 – 63)
NIHSS*	5	(4 – 8)	1	(0 – 3.5)
EmNSA*	38	(34.5– 40)	40	(39 – 40)
MI-UE*	39	(12.5 – 71)	76	(43 – 87.5)
MI-LE*	53	(28 – 73.5)	77.5	(58 – 100)
ARAT*	3.5	(0 – 32)	50	(3 – 57)

*Demographics and clinical scores of all patients included in the analysis (N=39) at baseline and 26 weeks poststroke. *Median (interquartile range). Abbreviations: Time post stroke: days elapsed between stroke onset and baseline measurement. N: number of participants; SD: standard deviation; IQR: interquartile range; LACI: lacunar anterior circular infarct; PACI: partial anterior circular infarct; TACI: total anterior circular infarct; FM-UE: Fugl-Meyer motor assessment of the upper extremity; NIHSS: National Institutes of Health Stroke Scale; EmNSA: Erasmus modification of the Nottingham Sensory Assessment of the upper extremity; MI-UE/LE: Motricity Index of the Upper/Lower Extremity; ARAT: Action Research Arm Test.*

Table 4.2. Regression coefficients of early measured resting-state EEG parameters to predict FM-UE score at six months poststroke.

	EEG parameters as predictors of FM-UE$_{w26}$				
	B	**95%-CI**	***p***	**β**	**R^2**
DAR	-0.63	[-3.76 – 2.50]	0.685	-0.07	0.00
DAR $_{AH}$	-0.90	[-3.11 – 1.32]	0.418	-0.13	0.02
DAR $_{UH}$	1.08	[-3.51 – 5.68]	0.636	0.08	0.01
BSI	-183.88	[-332.90 – -34.87]	**0.017**	-0.38	0.15
BSI $_{delta}$	-98.19	[-198.43 – 2.05]	0.055	-0.31	0.10
BSI $_{theta}$	-156.81	[-277.93 – -35.70]	**0.013**	-0.40	0.16
BSIdir	27.44	[-83.00 – 137.88]	0.618	0.08	0.01
BSIdir $_{delta}$	-58.09	[-116.87 – 0.70]	0.053	-0.31	0.10
BSIdir $_{theta}$	-53.33	[-122.22 – 15.56]	0.125	-0.25	0.06

Dependent variable: FM-UE$_{w26}$. *Abbreviations: FM-UE$_{w26}$, Fugl-Meyer motor assessment of the upper extremity at 26 weeks poststroke; DAR, delta/alpha ratio; AH/UH, affected/unaffected hemisphere; BSI, brain symmetry index; BSIdir, directional BSI; delta/theta, calculated over the delta (1-4Hz) or theta (4-8Hz) frequency band; B, regression coefficient; 95%-CI, 95% confidence interval; p, probability value; significance level was set to α<0.05, significant p-values are displayed in Bold font; β, standardized beta; R^2, explained variance.*

Table 4.3. Regression coefficients of early measured EEG parameters in addition to FM-UE baseline scores to predict FM-UE score at six months poststroke.

	Covariate estimates of early EEG parameters and FM-UE$_{baseline}$ to predict FM-UE$_{w26}$										
	EEG parameter				**FM-UE$_{baseline}$**				**total**		
	B	**95%-CI**	***p***	**β**	**B**	**95%-CI**	***p***	**β**	**R^2_{adj}**	**F_{change}**	**$p_{Fchange}$**
	-	-	-	-	0.89	[0.67 – 1.11]	**<0.001**	0.79	0.615	-	-
DAR	-0.01	[-1.97 – 1.95]	0.991	-0.00	0.90	[0.67 – 1.14]	**<0.001**	0.79	0.604	0.00	0.991
DAR $_{AH}$	-0.38	[-1.77 – 1.01]	0.584	-0.06	0.90	[0.66 – 1.13]	**<0.001**	0.79	0.607	0.31	0.584
DAR $_{UH}$	1.41	[-1.42 – 4.23]	0.320	0.10	0.91	[0.67 – 1.14]	**<0.001**	0.79	0.615	1.02	0.320
BSI	-104.22	[-200.67 - -7.77]	**0.035**	-0.21	0.85	[0.62- 1.08]	**<0.001**	0.74	0.651	4.80	**0.035**
BSI $_{delta}$	-76.63	[-137.10 - -16.16]	**0.014**	-0.24	0.88	[0.66 – 1.10]	**<0.001**	0.77	0.665	6.61	**0.014**
BSI $_{theta}$	-108.09	[-182.7 - -33.44]	**0.006**	-0.27	0.85	[0.64 – 1.07]	**<0.001**	0.75	0.681	8.62	**0.006**
BSIdir	36.05	[-31.77 – 103.87]	0.288	0.11	0.91	[0.67 – 1.14]	**<0.001**	0.79	0.616	1.16	0.288
BSIdir $_{delta}$	-24.35	[-63.09 – 14.40]	0.211	-0.13	0.87	[0.63 – 1.11]	**<0.001**	0.76	0.621	1.63	0.211
BSIdir $_{theta}$	-33.41	[-76.49 – 9.68]	0.125	-0.16	0.88	[0.65 – 1.11]	**<0.001**	0.77	0.630	2.47	0.125

Dependent variable: FM-UE$_{w26}$. *Abbreviations: FM-UE$_{baseline}$, Fugl-Meyer motor assessment of the upper extremity measured within three weeks poststroke; FM-UE$_{w26}$, FM-UE at 26 weeks poststroke; DAR, delta/alpha ratio; AH/UH, affected/unaffected hemisphere; BSI, brain symmetry index; BSIdir, directional BSI; delta/theta: calculated over the delta (1-4Hz) or theta (4-8Hz) frequency band; B, regression coefficient; 95%-CI, 95%-confidence interval; p, probability value; significance level was set to α<0.05, significant p-values are displayed in Bold font; β, standardized beta of the particular covariate; R^2_{adj}, adjusted R-squared, variance explained by the model; F_{change}, change of F-statistic relative to the prediction model based on FM-UE$_{baseline}$ only; $p_{Fchange}$, probability value of F-change.*

Discussion

We investigated whether early measured resting-state EEG parameters have prognostic value regarding upper extremity motor impairment at six months poststroke in 39 patients. From the investigated quantitative resting-state EEG parameters, hemispheric power asymmetry in the theta band (BSI_{theta}) was the strongest prognostic biomarker of $FM\text{-}UE_{w26}$. A higher BSI_{theta}, reflecting more asymmetry between hemispheres in the theta band, predicts a lower $FM\text{-}UE_{w26}$. Moreover, BSI_{theta} showed prognostic value in addition to baseline FM-UE alone and increased the explained variance from 61.5% to 68.1%. This reveals that BSI_{theta} contains unique information compared to upper extremity motor scores at baseline regarding upper extremity motor impairment at six months, and therefore has potential to serve as additive prognostic biomarker of stroke recovery.

The present study is the first to investigate the prognostic value of quantitative resting-state EEG parameters (DAR and BSI, and variations thereof) measured early poststroke regarding upper extremity motor impairment after six months, as reflected by FM-UE. Earlier studies showed that these EEG parameters could serve as predictors of global neurological impairment (NIHSS) and degree of dependency regarding daily activities (mRS) poststroke.[26–28,34]

In contrast to BSI, DAR was not a predictor of the motor function of the upper extremity at 26 weeks poststroke, although earlier studies did show prognostic value of DAR regarding global neurological impairments reflected by NIHSS at 30 days poststroke[20,25] or negative functional outcome reflected by mRS≥3 at 12 months poststroke[27]. The absence of predictive value of DAR regarding FM-UE is in line with our earlier analyses, in which we showed a longitudinal association of DAR with NIHSS, but not with FM-UE.[29] Furthermore, Butz and colleagues (2004) showed no relation between clinical symptoms and increased delta activity near the lesion measured between one and fourteen days post stroke.[35] DAR was previously found to be a predictor of NIHSS when assessed within 48 hours after stroke onset, and DAR_{AH} was shown to be a predictor of negative functional outcome (mRS≥3) when assessed within 72 hours, while the mean poststroke measurement time in the current study was 12.3 days.[25,27] It has been suggested that DAR decreases (i.e. normalizes) between 24 and 48 hours poststroke.[25,36] Therefore, although speculative, when DAR may serve as prognostic biomarker, this may be restricted to the very early stage poststroke.

The present results show that BSI_{theta} has added value in predicting upper extremity motor impairment at six months post stroke compared to the $FM\text{-}UE_{baseline}$ score alone. Previously, BSI was shown to be a predictor of negative functional outcome (mRS≥3), but not when corrected for other clinical scores.[27] However, the BSI over the low frequency bands was not investigated. BSI_{theta} may have the potential to serve as additive prognostic biomarker of motor recovery in addition to clinical measures. Our findings suggest that EEG data contains unique information regarding stroke severity, possibly as a reflection of cortical network integrity, which is required for behavioural recovery. The fact that this added value originates especially from low-frequency oscillations, is in line with the suggestion that such activity is related with reorganization. Low-frequency cortical activity may be the result of partial deafferentation of the cortex caused by a lesion which damaged cortico-cortical connections.[35,37] Furthermore, synchronous neuronal activity in the low-frequency range has been related with axonal sprouting after ischemic lesions in rats.[38] Therefore, it has been suggested that increased low-frequency activity may be related with reorganization after stroke.[35]

BSI_{theta} showed to have prognostic value in contrast to $BSIdir_{theta}$. This suggests that not just the affected hemisphere shows increased theta power compared to the less-affected hemisphere but also vice-versa. Therefore, compared to $BSIdir_{theta}$, BSI_{theta} might be a better reflection of neuronal damage with predictive value.

Limitations

Despite using a specially equipped van that allowed to visit patients at their place of residence to limit their burden[29], a number of patients (14 out of 55) dropped out during this longitudinal observational study. The measurement protocol presented here was part of a larger serially conducted protocol of the 4D-EEG study, and the resting-state condition recording took only a few minutes of the quite extensive EEG recording protocol. The protocol as actually performed was adjusted for each patient to ensure feasibility and prevent overloading. However, five patients experienced the measurements as too exhausting, especially regarding the combination of their usual care and participating in research. Generalizability was analysed by performing a cross-validation using a leave-one-out procedure, which showed that the standard error of the estimate increased by only 3.4% compared to the model based on all data. External cross-validation using an independent dataset should be performed to confirm presented findings. The maximum NIHSS score observed at inclusion was 15, indicating that our sample does not contain severely affected patients and may suffer from sampling bias. Nevertheless, we see a large variety in upper extremity motor deficits reflected by FM-UE, which was the focus of our study. Inclusion of severely

affected stroke patients would most likely have increased the number of patients with low FM-UE scores. Since in those patients $FM\text{-}UE_{baseline}$ may be limitedly informative regarding the prediction of their recovery[3], we expect the additive predictive value of EEG to increase. This requires further investigation. Methodological procedures resulted in a time delay of about twelve days between stroke onset and the first measurement. Therefore, we could not quantify possible changes regarding neurological deficits in the first days after stroke onset. In addition, the present study focused on DAR and BSI (and variations thereof), while other quantitative EEG parameters, such as delta-theta/alpha-beta ratio or relative powers per frequency band, might have prognostic value as well.[27] Furthermore, in the current study MRI data was unavailable for a large proportion of the patients. Finally, the present study was focused on FM-UE, which is the clinical assessment closest related with neurological impairment. However, BSI_{theta} also showed potential for prediction of upper limb capacity reflected by ARAT as outcome measure, emphasizing its robustness (Supplementary Tables S2 and S3).

Future directions

Prediction modelling for the identification of patients who show recovery poststroke is of high interest in the current literature. A recently proposed mixture model classifies stroke patients into five recovery groups based on initial FM-UE scores and their recovery pattern.[3] Moderately and severely affected patients in particular were shown to be often misclassified and may benefit from additional prognostic biomarkers.[3,8] It remains to be investigated whether quantitative resting-state EEG parameters improve the accuracy of the mixture model, and thereby improve the identification of severely affected patients who will show recovery. Allowing to take early changes into account, the first EEG recording should preferably be performed within the first days after stroke and repeated more frequently within the first weeks.

Second, the current study only concerned the recovery of FM-UE scores, which is assumed to be a clinical measure most closely related to behavioural restitution. However, it is known that FM-UE scores suffer from ceiling effects after three months poststroke.[33] Kinematic or kinetic performance assays, such as selective elbow extension during restrained reaching, finger individuation or pinch and grip strength, may be more fine-grained and responsive to behavioural restitution as a reflection of true neurological repair.[39]

Furthermore, the additive prognostic value of very early derived EEG parameters (< 72 hours poststroke) above clinical measures has still to be established. Limiting the number of electrodes lowers the burden of patients and increases feasibility of performing EEG recordings in the acute phase. For example, a previous study showed that quantitative EEG parameters derived from only four electrodes have prognostic value regarding cognitive functioning.[40] The minimum number and exact location of the EEG electrodes to obtain data with added value regarding motor recovery in the very early phase has yet to be investigated.

Finally, besides quantitative resting-state EEG parameters, several other parameters can be derived from EEG data, which should be considered. An example is the dynamic signal propagation between active cortical sources during a sensory stimulation task, derived from a combination of EEG, MRI and diffusion MRI data.[41] This technique enables the association between the quality of task-specific signal propagation and functional recovery to be investigated serially during motor recovery after stroke. Furthermore, a MEG study in stroke patients showed that reduced movement-related beta desynchronization is related to the level of motor impairment.[42] Also EEG parameters reflecting the quality of functional network organization within and between hemispheres might be of interest for understanding which patients show recovery after stroke and which do not.[17,43] For example, inter-regional synchronization of neural oscillations in the first weeks after stroke has been associated with improvement of motor function.[43] It remains to be investigated how these parameters develop longitudinally within the different subgroups of proportional recovery[3] and whether they may serve as prognostic biomarkers for the outcome at six months poststroke.

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Declaration of Conflicting Interests

The authors declare that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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PART II

Measuring behavioural recovery using kinematics


5

Quantifying quality of movement longitudinally post stroke a systematic review.

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Abstract

Background: Disambiguation of behavioural restitution from compensation is important to better understand recovery of upper limb motor control post-stroke and subsequently design better interventions. Measuring quality of movement (QoM) during standardized performance assays and functional tasks using kinematic and kinetic metrics potentially allows for this disambiguation.

Objectives: To identify longitudinal studies that used kinematic and/or kinetic metrics to investigate post-stroke recovery of reaching; and assess whether these studies distinguish behavioural restitution from compensation.

Methods: A systematic literature search was conducted using the databases PubMed, Embase, Scopus and Wiley/Cochrane Library up to July 1st, 2020. Studies were identified if they performed longitudinal kinematic and/or kinetic measurements during reaching, starting within the first six months post stroke.

Results: Thirty-two longitudinal studies were identified, which reported a total of forty-six different kinematic metrics. Although the majority investigated improvements in kinetics or kinematics to quantify recovery of QoM, none of these studies explicitly addressed the distinction between behavioural restitution and compensation. One study obtained kinematic metrics for both performance assays and a functional task.

Conclusions: Despite the growing number of kinematic and kinetic studies on post-stroke recovery, longitudinal studies that explicitly seek to delineate between behavioural restitution and compensation are still lacking in the literature. To rectify this situation, future studies should measure kinematics and/or kinetics during performance assays to isolate restitution, and during a standardized functional task to determine the contributions of restitution and compensation.

Introduction

About 80% of stroke survivors suffer from upper extremity motor impairment[1] which affects activities of daily living[2]. Therefore, being able to use the arm to complete functional tasks is among the top ten priorities for stroke survivors, caregivers and health care professionals.[3] Upper extremity motor impairment after stroke is comprised of weakness, diminished dexterity and abnormal muscle synergies.[4]

Most patients exhibit some degree of spontaneous recovery of upper extremity motor impairment, with 80-90% of clinical improvements occurring within the first 8-10 weeks post stroke.[5–7] Studies suggest that reaching movements tend to converge toward healthy patterns, without necessarily returning fully to pre-stroke patterns (i.e. partial behavioural restitution).[8–10] The ability to use the upper limb during functional tasks may further improve through the use of compensatory strategies; in which patients accomplish a functional goal in a different way then pre-stroke (i.e. behavioural compensation).[11] The ability to distinguish between behavioural restitution and compensation would help to better identify interventions that can influence true neurological recovery.

Quality of movement (QoM) reflects the degree of motor control.[12] Despite consensus on a standardized set of clinical measures in stroke studies[13], these clinical measures lack the ability to capture small changes in QoM[12,14] and cannot distinguish behavioural restitution from compensation. Longitudinal kinematic studies early after stroke are needed to investigate the time course of QoM of the upper limb. Recommendations on suitable study designs were provided by the Stroke Recovery and Rehabilitation Roundtable task force (SRRR).[12] The arguments in the body of the paper of the SRRR, which are implicit in the recommendations, suggest kinematic and/or kinetic measurements during four standardized performance assays for quantifying behavioural restitution in addition to a functional task to distinguish true recovery from compensation strategies.[12] Performance assays are needed to quantify the different components of motor impairment: weakness, diminished finger individuation and abnormal muscle synergies. Thereby, performance assays were suggested to serve as a proxy for behavioural restitution.[12] To capture these components of impairment, the SRRR defined the following performance assays: grip strength[15,16], precision grip[16], finger individuation[17,18] and 2D planar reaching[19,20]. It was recommended to perform these measurements repeatedly in the first six months post stroke. Moreover, given the non-linear time course of recovery, these measurements should be repeated more frequently in the first months post stroke, preferably at fixed times.[13] Investigating these performance assays is not only important to quantify behavioural restitution

the in absence of compensation, the association between performance assays and clinical assessments may also elucidate which motor impairment component is most strongly represented by a clinical assessment score. This may make clear whether, for example, the Fugl-Meyer motor assessment of the upper extremity (FM-UE), a clinical assessment commonly used in stroke rehabilitation, truly captures synergy-driven intra-limb coupling or to which degree it is contaminated by other motor impairment components such as strength.[21,22] Furthermore, to determine the degree to which recovery has converged on normal movement, the SRRR recommended that a healthy control group should be included.[13] A recent review showed that the number of studies that use kinematics and kinetics to investigate reaching performance is growing exponentially.[23] However, the focus of that particular review was not on longitudinal studies, nor on the metrics that distinguish between behavioural restitution and compensation.

Our objective was to review the literature on the use of kinematic and/or kinetic metrics to measure recovery of QoM after stroke. We focused on upper limb reaching and pointing tasks, as they require coordination of the elbow and shoulder, which is an important component of many daily activities and is often limited post-stroke as a result of weakness, loss of motor control and the intrusion of abnormal muscle synergies.[19,24] We aimed to:

(1) Identify longitudinal studies that used kinematic and/or kinetic metrics reflecting QoM to investigate post-stroke recovery of reaching, to show the reported responsiveness of these metrics over time, and their longitudinal association with clinical measures; and

(2) Assess whether these studies have addressed or provided suggestions on how to best capture behavioural restitution and distinguish it from compensation during a reaching task.

Methods

Search strategy

A systematic literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement[25] and registered in PROSPERO (number CRD42018100648). To identify all relevant publications, systematic searches were conducted (by MS, MIMR and EJ) in the databases PubMed, EMBASE.com, Scopus (Elsevier) and the Cochrane Library (Wiley) from inception to July 1st, 2020. Search terms included controlled terms from MeSH in PubMed and EMtree in EMBASE.com as well as free text terms. Free text terms only were used in Scopus and the Cochrane Library. Search terms expressing 'stroke' were used in combination with search terms comprising 'reach and grasp activity' and 'kinematics and kinetics'. Search filters for human studies and English language were used. Reference tracking was performed to identify other relevant publications. Finally, duplicate articles were removed. The full search strategies for all databases can be found in Appendix A.

Study selection

After the initial literature search, the titles and abstracts of all papers found were screened independently by two researchers (MS, MIMR). Differences of opinion were discussed, and if no consensus was reached a third reviewer (EW) was approached. Criteria for inclusion were: (1) adult participants who suffered from a stroke; (2) use of a repeated measures study design with at least two serial within-subject measurements starting before the chronic phase (< 6 months)[11] post stroke; (3) at least one kinetic or kinematic outcome metric, measured with any device that does not interfere (i.e., disturb/restrict) with the specific movements assayed during an active goal-oriented reaching or pointing task. A study was excluded when: (1) it was a review or conference proceeding; or (2) the investigated population consisted of fewer than ten subjects; or (3) it was not written in English. Investigated cohorts were allowed to be part of an intervention study. A full-text version of all remaining studies was obtained for thorough reviewing by the researchers (IR, MS) to establish the definitive inclusion.

Data analysis

Definitions

Behavioural restitution was defined as changes of movement execution patterns that made them more similar to those observed in healthy subjects.[11] Behavioural compensation was defined as regaining the ability to accomplish a goal through substitution with a new movement approach that differs from pre-stroke behavior.[11] Performance assays were defined as tests that quantify aspects of affected motor control performance in the absence of compensatory movements and outside the

context of a functional task.[12] Quality of movement was defined as a measure of patient's motor task execution in comparison with age-matched normative values of healthy individuals.[12] An extensive list of definitions of other terms can be found in Appendix B.

Data extraction

The following data were extracted (when applicable): (1) authors and date of publication; (2) sample size; (3) characteristics of included participants; (4) assessment moments; (5) authors' description of the investigated reaching task; (6) the performed clinical sensory and motor assessments; (7) measurement setup (equipment, segments, sample frequency, dimensions, number of repetitions); (8) definitions of the investigated kinematic and kinetic metrics; (9) the change of the outcome metrics over time; (10) association of metrics with clinical assessments; (11) psychometric properties (validity, reliability, and responsiveness) of these metrics; and (12) investigated performance assays.

Data interpretation

First, an overview is provided regarding the reported metrics, how they are used to quantify movement trajectories, their responsiveness (i.e., change over time) and longitudinal association with clinical measures.

Thereafter, we describe any suggestions made by the authors of the studies on how to track behavioural restitution or distinguish restitution from compensation. We discussed what the reviewed studies reported about kinematics in association with behavioural restitution and/or compensation. We also assessed whether the study design of the articles is compatible with recent recommendations of the SRRR for studying QoM post-stroke using kinematics and/or kinetics.[12,13] This was only meant as a retrospective review, as most of the studies included in this review were conducted before the taskforce's recommendations were published. The SRRR recommendations concern measurement time points and measurement methods, such as: (1) performing the first measurement within or before the early sub-acute phase (≤ 3 months) post stroke, when changes in QoM are still to be expected due to spontaneous neurobiological recovery; (2) inclusion ≤ 1 week post stroke, pursuing an inception cohort; (3) perform measurements at fixed time points post-stroke[5,6]; (4) repeat measurements at least in weeks 1, 12 and 26 post stroke; (5) presence of reference data of age-matched non-disabled subjects; (6) use high-resolution digital optoelectronic systems to capture movements; (7) use a sample frequency ≥ 60Hz; (8) ≥ 15 movement repetitions; and (9) investigate performance assays related to motor impairments[12] in addition to the reaching task.

Results

Study identification

The PRISMA flow diagram of the search and selection process is presented in **Figure 5.1**. The literature search generated a total of 17943 references: 6063 in PubMed, 6678 in EMBASE, 1839 in Scopus and 3363 in The Cochrane Library. After removing duplicates, 10712 references remained. Of these articles 10538 were discarded after reviewing title and abstract. The full-text of the remaining 174 articles was assessed for eligibility.[26] Thirty-two articles, involving a total of 1259 unique patients with a hemorrhagic or ischemic stroke, met all criteria and were included in the current systematic review[8–10,27–55]. **Table 5.1** shows detailed characteristics of the included studies.

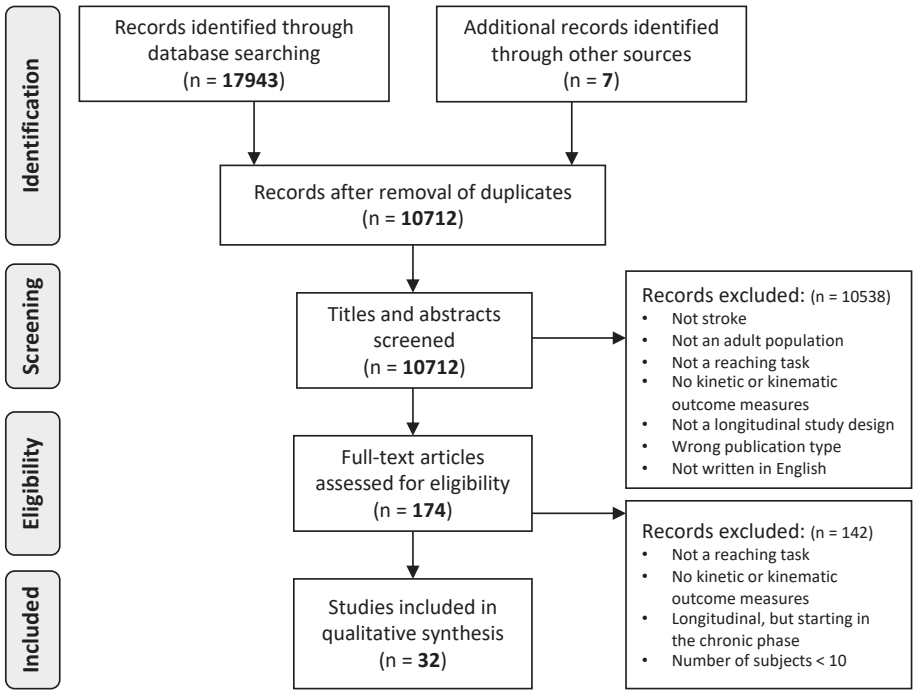

Figure 5.1 *PRISMA flow diagram of included studies.*

Longitudinally investigated kinematic and kinetic metrics

Kinematic metrics to quantify quality of movement

Spontaneous neurological recovery leads to improved QoM. In healthy individuals the movement trajectory during a standardized reaching task is close to a straight line between the starting position and the target.[19,56] The velocity profiles of healthy individuals are

smooth and bell-shaped curves with one clear velocity peak.[19,56] A pre-planned and well-controlled movement results in a smooth increase of velocity whereby an adequate peak velocity is reached.[45] **Figure 5.2** shows 2D movement trajectories during a standardized reaching task and typical velocity profiles at different time points post-stroke.[8,57] Through visual inspection, one can clearly conclude that QoM is affected early after stroke and improves over time, especially in the first weeks. In spite of the many metrics, there is no consensus on which metrics are best to quantify QoM and therefore behavioural restitution during functional tasks. The same applies to metrics for compensation. To address this issue some investigators use a global measure that does not presuppose that any specific kinematic measure should be used and instead rely on the task design itself to prevent compensation.[10] This makes a more general point that no kinematic measure can be interpreted outside of the behavioural context within which it was generated.

Figure 5.2 shows that in addition to visual inspection, movement trajectories can be quantified by many different kinematic metrics, each of which may be affected by different aspects of motor impairment and/or compensation. For instance, patients perform movements slower early after stroke, either due to weakness or to compensate for decreased accuracy.[58] Early post-stroke, peak hand velocity is often decreased and the time at which this peak is reached is often delayed, reflecting slowed muscle recruitment.[45] Movement smoothness is a widely acknowledged metric of QoM.[47,59] Different smoothness metrics have been reported during reaching, which quantify different aspects of motor control. Metrics which have been reported include, amongst others, jerk (3rd derivative of hand position) and peaks metric (number of velocity peaks in the velocity profile), both have been associated with feedback corrections and the number of sub-movements.[27,47,49,57] The deviation in movement trajectory can also be quantified by comparing the performed hand trajectory to a straight line between start position and the target (e.g. path error, reach efficiency). Quality of performance in a multi-joint reaching movement can also be quantified as the accuracy in arriving at the target location (e.g. endpoint accuracy), which requires adequate coordination of different joints during the movement. Besides the hand, kinematic data can be obtained from other segments of the upper extremity, which allows estimates of joint rotations (e.g. elbow, shoulder, trunk), which can also reflect either QoM or compensation.[24,60]

Overview of reported metrics

In total, 46 different kinematic metrics have been investigated during a reaching task in longitudinal studies starting in or before the sub-acute phase post-stroke (**Table 5.2**). The most frequently investigated metrics were *movement time* and *peak hand velocity* (**Figure 5.3**). Other metrics investigated in more than 20% of the studies were: *average hand velocity, jerk, speed metric*, *endpoint accuracy* and *reach efficiency*.

None of the studies investigated kinetic metrics during reaching. An overview of the investigated metrics per study, including details on metric definitions as provided by the authors, and when applicable their psychometric properties, can be found in Supplementary Table 4.

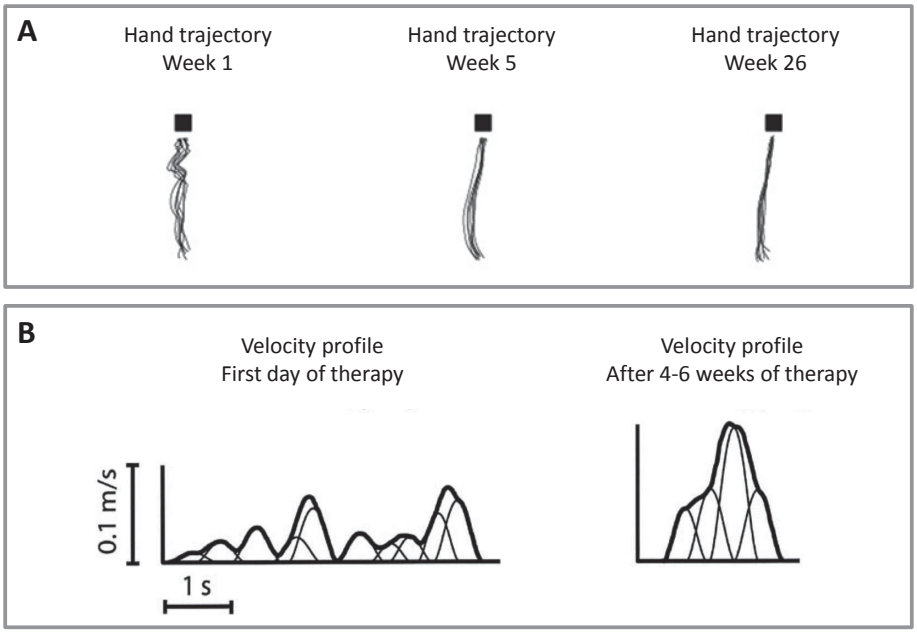

Figure 5.2 *(A) (adapted from Van Kordelaar et al., 2014) Reaching trajectories of the hand of one patient in weeks 1, 5, and 26 after stroke onset. Patients move their hand from the start position to a block, in this figure visualized as a black square. Each trace represents one reach-to-grasp movement. (B) (adapted from Rohrer et al., 2004) Typical velocity profile of a stroke patient during a point-to-point movement at the first day of therapy and after 4-6 weeks of therapy.*

Responsiveness and longitudinal association with clinical measures

Here, we report the responsiveness to change over time and the longitudinal association between kinematics and the FM-UE since this particular clinical measure was often reported by the studies. **Table 5.2** provides an overview of responsiveness of all reported kinematic metrics to change over time and their association with clinical measures.

Figure 5.3 *Percentage of studies which investigated a particular metric.*

Movement time, average hand velocity and *peak hand velocity* were shown to significantly change over time, mainly in the early sub-acute phase post-stroke. The longitudinal association between movement time and FM-UE was not significant.[40,49] Average hand velocity showed a poor longitudinal association with FM-UE.[38] The longitudinal association between peak hand velocity and FM-UE was found to be weak[38] or not significant[40,49]. *Time to peak velocity* did not change over time[40], nor was it longitudinally associated with FM-UE.[40,49]

The movement smoothness metrics that were most frequently investigated in longitudinal studies after stroke were: *jerk, speed metric* and *peaks metric* (**Figure 5.2**). These metrics were shown to change over time post-stroke, mainly in the early sub-acute phase.[8,28,30,32,38,40,41,43] Studies showed varying outcomes for the longitudinal association between *peaks metric* and FM-UE[47,49]. Inconclusive results were reported for the longitudinal association between *speed metric* and FM-UE. One study showed a significant longitudinal association with FM-UE (Pearson's r: 0.40)[47], while another study found a significant but poor longitudinal association with FM-UE[38], and yet another study found no significant longitudinal association[49]. Rohrer and colleagues[47] found a significant longitudinal association between *jerk* and FM-UE (Pearson's r: -0.48), while Palermo and colleagues[40] did not. For the smoothness metrics *mean arrest period ratio* and *tent metric,* change over time was not investigated. *Mean arrest period ratio* was longitudinally associated with FM-UE (Pearson's r:0.33), while *tent metric* was not.[47]

Endpoint accuracy and *reach efficiency* were both responsive to change over time in the early sub-acute phase post-stroke. *Endpoint accuracy* was stated to be poorly longitudinally associated with FM-UE.[38] *Reach efficiency* showed no significant longitudinal association with FM-UE.[40,49] *Path error* was responsive to change over time and longitudinally associated with FM-UE (Spearman's ρ: -0.51).[38]

In 11 out of 32 studies, the reaching task also included grasping. In five of these studies, kinematic metrics for grasping were investigated[8,37,50,51,54]. Grasp-related metrics such as *aperture speed, peak aperture* and *jerk grasp aperture* are responsive to change over time, which was not the case for *aperture efficiency* or *time of peak aperture*.[8,51]

A combination of simultaneously-measured joint-rotation metrics reflecting *elbow extension* and *shoulder abduction* were stated to be relevant since they are main components of stroke-related abnormal muscle synergies.[9] In one study, a principal component analysis showed that during a reach-to-grasp task, elbow and shoulder rotations are most associated early after stroke, and become more dissociated

mainly within the first 8 weeks post-stroke.[9] In the chronic phase post-stroke, elbow and shoulder joint rotation during reaching remain more associated compared to healthy individuals.[9] The kinematic metric *trunk displacement* is acknowledged to be a reflection of a compensation strategy to overcome the shoulder-elbow synergy that prevents elbow extension and thereby induces restriction of reaching area. The longitudinal association with clinical measures was not investigated.

Metrics reflecting behavioural restitution or compensation strategies

Attempts in the literature to investigate recovery of QoM by quantifying behavioural restitution and compensation

Trunk movement is a common compensatory strategy shown by stroke patients with any degree of motor impairment during reaching to distances that are at arm's length.[24,61] Trunk displacement assists the endpoint of the arm when the range of voluntary elbow extension is restricted, for example due to affected coordination between the elbow and shoulder joints.[24] Half of the studies intentionally restricted trunk movement during the reaching task in order to obtain kinematic data of a reaching movement which was not influenced by this form of compensation (**Table 5.1**). Three studies deliberately sought to measure compensatory movements of the trunk during a reaching task.[9,34,40]

Several studies explicitly addressed whether changes in particular metrics reflect either behavioural restitution or compensation. For example, Konczak and colleagues (2010)[53] showed that stroke patients perform pointing movements at a slower speed compared to controls, which was independent of whether the subjects had to point in the air or at a target. From this, they concluded that moving slower is not a compensatory strategy per se. Buma and colleagues (2016)[37] suggested that decreased movement smoothness may result from corrections of deviations from the intended optimal movement pattern. They state that jerk may reflect the control strategy to correct these deviations, which may be interpreted as a quantification of compensation.

Three studies focus on the time period in which behavioural restitution is argued to take place.[8–10] Van Kordelaar and colleagues (2013)[9] showed that recovery of the control over DOFs during a reach-to-grasp task, reflecting the ability to perform movements dissociated from abnormal muscle synergies[62], is restricted to the first five weeks post stroke, while FM-UE increased until eight weeks post stroke. Similar findings were shown for movement smoothness.[8] Therefore, they conclude that these kinematic metrics may quantify behavioural restitution of motor control. Cortes and colleagues (2017)[10] investigated improvement of motor control of the upper extremity during a 2D-reaching

task using the Kinereach™, which is designed to decrease strength requirements by providing anti-gravity support and reducing friction, while the trunk was restricted to limit compensation strategies. Thereby, the reaching task is in line with one of the performance assays suggested by the SRRR[12]. The gravitational support does not interfere with the planar movements assayed, and allows them to be properly measured. In addition, gravity support is used to overcome shoulder weakness and thereby reduce intrusion of flexor synergies.[63] Cortes and colleagues (2017)[10] showed that motor control of horizontal reaching plateaued within the first five weeks post stroke, whereas the FM-UE and ARAT continued to show improvements until 14 weeks post stroke. They suggest that this difference in time window may be due to strength improvements and learning of compensatory movements contaminating the FM-UE and the ARAT, respectively. They concluded that kinematics of performance assays such as quality of 2D-reaching better isolate the underlying process of spontaneous recovery compared to clinical motor impairment scales such as FM-UE and capacity scores such as ARAT[10].

Lang and colleagues (2006b)[51] compared recovery of reaching versus grasping after stroke. They showed that reaching accuracy recovered post stroke, while grasping efficiency did not. It is currently unclear what the contribution of different descending pathways is concerning restitution or compensation, and what causes the difference in recovery of reaching versus grasping.

Only one study measured performance assays alongside a functional task longitudinally.[52] Wagner and colleagues (2007)[52] performed a reaching task and two performance assays: isolated joint movements and grip strength. Deficits in isolated (fractionated) movements were shown to be present by comparing the composite score of the individuation index of the shoulder, elbow and wrist to healthy controls. Also, maximal grip strength was significantly decreased in stroke patients when compared to controls. Both performance assays showed improvement over time from the acute to the subacute phase post-stroke. However, deficits in grip strength and isolated movement control remained. Normal values of kinematic metrics such as reaching accuracy and efficiency were shown during a 3D goal-directed forward reaching task, despite the remaining deficits revealed by the performance assays. On the other hand, peak wrist velocity during a reaching task remained deviated from healthy values. From this, they conclude that "*performance of functional movement can be normal or near-normal, despite the presence of underlying sensorimotor impairments. This may reflect the idea that not all functional movements require full sensorimotor capacity*".[52] This conclusion is in line with the present dichotomy of behavioural recovery, whereby motor function at the activity domain of the ICF is achieved by two components: behavioural restitution and compensation.

Table 5.1 Characteristics of included studies

Authors	Objective	Study type and number of subjects	Participants	Stroke
Authors; Cohort	***Objective of the article***	***Study type; Subject type (N)***	***Age: Mean (SD); Gender: (male / female)***	***Inclusion in days post-stroke (SD); type (I/H); Affected side (L/R or *D/ND)***
Platz et al. 2001; NR	Test the efficacy of the arm ability training on a sample of patients with central arm paresis after traumatic brain injury or stroke.	Interventional; S_{AAT} (S:16, TBI:4) S_{AAT+KR} (S:14, TBI:6) $S_{no\ AAT}$ (S:15, TBI:5)	49(17.9); 11/9 54(18.0); 14/6 58(15.3); 11/9	42.7(25.2); NR; 12/8 43.4(49.7); NR; 14/6 72.1(139.3); NR; 11/9
Rohrer et al. 2002; NR	To provide additional evidence to literature that recovery proceeds by progressive blending of sub-movements, by quantifying the smoothness of movements made by stroke patients and how it changed over the course of recovery.	Interventional; $S_{subacute}$ (12) $S_{chronic}$ (19)	55.7(13.7), 56.2(17.3); 21/10	30; NR; NR 914.2(45.7) ; NR; NR
Lang et al. 2006a; VECTORS[1]	Examine the responsiveness and validity of the Action Research Arm Test (ARAT) in a population of subjects with mild-to-moderate hemiparesis within the first few months after stroke.	Interventional; S (51)	63.7(13.6); 21/29	9.5(4.5); 39/11; *21/29
Lang et al. 2006b; VECTORS[1]	Examine the relative recovery of reach versus grasp from the acute to chronic phase following stroke.	Interventional; S (23) C (10)	64.5(12.8); 12/11 59.1(12.5); 5/5	9.1(3.5); 10/5; *9/14
Wagner et al. 2007; VECTORS[1]	How do sensorimotor impairments relate to reaching performance in the subacute phase after stroke and how do sensorimotor impairments measured in the acute phase after stroke relate to reaching performance measured several months later.	Interventional; S (39) C (10)	63.9(11.5); 15/24 59.1(12.5); 5/5	8.7(3.6); 25/8; 18/21

	Assessment moments	Reaching task; postural restrictions	Additional performance assays investigated	Clinical measures	Protocol	Equipment
	Mean ± SD in days / weeks / months	***Task as described by the authors; trunk compensation restricted (yes/no)***	***To identify behavioural restitution in absence of compensation***	***Clinical tests and neuro-physiological techniques***	***Dimensions (1D/2D/3D); Number of repetitions; Sample frequency***	***System; segments***
	Pre and post 3 weeks of intervention	Horizontal forward reach of 200mm, start and end on table; No	x	TEMPA	2D; 20; 100Hz	Tablet; Stylus
	Pre and post intervention	Point to Point reaching; No	x	FM-UE	2D; as many as possible; NR	MIT Manus; Ha
	9.5±4.5d PS, 25.9±10.6d PS, 110.8±20.7d PS.	Move the hand from thigh to the target at 90% of arm's length in front of the affected shoulder; Yes	x	ARAT, NIHSS, FIM, sensory assessment	3D; 3; 60Hz	6-Camera's; Tr, UE, Fa, dorsum of Ha, Th, IF, T.
	9.1±3.5d PS, 105.3±18.8d PS, 383.4 ±16.3d PS.	Move the hand from thigh to the target at 90% of arm's length in front of the affected shoulder; Yes	x	ARAT, sensory assessment, MAS, muscle strength	3D; 3; 60Hz	6-Camera's; Tr, UE, Fa, dorsum of Ha, Th, IF, T.
	8.7±3.6d PS, 108.7±16.5d PS	Forward reaching from thigh to 90% of arm's length at shoulder height in front of affected shoulder; Yes	Individuation indexes (shoulder, elbow, wrist). Max grip strength, Jamar handheld dynamometer.	ARAT, FM-UE, sensory assessment, MAS, AROM	3D; 3; 60Hz	6-Camera's; Tr, UE, Fa, dorsum of Ha, Th, IF, T.

Table 5.1 Continued

Authors	Objective	Study type and number of subjects	Participants	Stroke
Konczak et al. 2010; NR	How is lesion site and arm dysfunction associated in the acute stage and what is the course of upper limb recovery during the first 4 months.	Observational; S (16) C (10)	60.1(14.4); 11/5 59.0(10.3); 7/4	14.5 range 1-33; 16/0; 7/9
Dipietro et al. 2012	Investigate whether untrained and trained movements were characterized by similar changes in smoothness and sub movements.	Interventional; $S_{subacute}$ (42) $S_{chronic}$ (116)	61.3(1.8); 24/18 58.8(1.2); 73/43	19.1(1.2); NR; 32/10 1150(90); NR; 53/63
Edwards et al. 2012; VECTORS[1]	Examine the internal consistency, validity, responsiveness, and advantages of the WMFT and compare these results to the ARAT in participants with mild to moderate hemiparesis within the first few months after stroke.	Interventional; S (51)	63.7(13.6); 21/29	9.5(4.5); 39/11; 21/29
Tan et al. 2012; NR	Identify the effects of CIMT on anticipatory hand posture selection and movement time for task-specific reach-to-grasp performance.	Interventional; S_{CIMT} (10) $S_{No\ CIMT}$ (10) C (6)	59.7(11.2); 7/3 58.2(13.4); 5/5 43.8(5.0); NR	228(56); NR; 11/9 1191(1225); NR; 4/6
Colombo et al. 2013; HUMOUR	We aimed to analyze how time since the acute event may influence the motor recovery process during robot-assisted rehabilitation of the upper limb.	Interventional; $S_{subacute}$ (20) $S_{chronic}$(21)	58.4(12.9); 8/12 50.7(11.3); 14/7	69(42); 15/5; 12/8 876(1221); 17/4; 10/11

	Assessment moments	Reaching task; postural restrictions	Additional performance assays investigated	Clinical measures	Protocol	Equipment
	14.5 range[1-33] d PS, 2w after session 1, 3m after session 1.	1. Point at a ball suspended from the ceiling in front at 90% of arm's length at shoulder height, 2. Point at the same location in absence of the target; No	x	MCS, MRI	3D; 10; 100Hz	3D ultrasound-based motion analysis system; Finger
	pre, halfway and post intervention	Eight targets, surrounding a center target, were displayed on a monitor. Subjects moved from the center 14cm to each target, stopped, then returned to the center; No	x	FM-UE	2D; 80; NR	MIT-Manus and its commercial version InMotion2; Ha
	9.5±4.5d PS, 25.9±10.6d PS, 110.8±20.7d PS	Move the hand from thigh to the target at 90% of arm's length in front of the affected shoulder; Yes	x	WMFT, ARAT, sensorimotor impairments, FA, FIM, NIHSS.	3D; 3; 60Hz	6-Camera's; Tr, UE, Fa, dorsum of Ha, Th, IF, T.
	Pre and post 2 weeks of intervention	2 different objects, 2 different grasp types. Grab the object and place it in the hole 15cm from the edge of the table; Yes	x	WMFT, MAL	1D; 7; NR	Electric switches at home position, object and target; NA
	pre and post 3+ weeks of intervention	The handle of the robot is grasped by the patient and moved through the workspace of the device (i.e. in the horizontal plane). The task consisted of a sequence of point to point reaching movements in the shape of a geometrical figure; Yes	x	FM-UE, MAS	2D; NR; 100Hz	2 DoF elbow-shoulder manipulators MEMOS; end effector

Table 5.1 Continued

Authors	Objective	Study type and number of subjects	Participants	Stroke
Duret and Hutin 2013; NR	Analyze clinical and kinematic motor outcomes during an intensive upper limb robot-assisted training program performed as an adjunct to a standard rehabilitation program over an extended period in the subacute phase after stroke in patients with moderate to severe paresis.	Observational; S (10)	47.5(19.6); 3/7	53.5(15.8); 8/2; 6/4
Metrot et al. 2013a; NR[2]	To assess the natural evolution of reaching kinematics during standard poststroke rehabilitation, focusing on bimanual coordination.	Observational; S (12)	65.6(9.7); 9/3	20.6(7.1); 8/4; 5/7
van Kordelaar et al. 2013; EXPLICIT[3]	Assess longitudinal improvements in dissociated upper limb movements during a standardized reach-to-grasp task in patients with a first-ever ischemic stroke.	Observational; S (31) C (12)	60.0(11.2); 18/13 52.8(5.9); 7/5	14(6); 31/0; 19/12
Krebs et al. 2014; NR	Predicting clinical outcomes with robot-assisted measurement of kinematic and kinetic with sufficient accuracy to serve as their surrogates.	Observational; $S_{completers}$ (87) $S_{non\text{-}completers}$ (121)	69.7(13.5); 45/42 75.7(13.0); 61/60	7; 87/0; 44/43 7; 121/0; 67/54
Van Dokkum et al. 2014; NR[2]	Addressing the link between clinical and kinematic assessment of motor performance during early poststroke recovery.	Observational; S (13) C (12)	63.9(9.4); 10/3 32.5(11.4); 0/12	21.2(7.2); 9/4; 5/8
van Kordelaar et al. 2014; EXPLICIT[3]	Investigate the time course of recovery in terms of smoothness of upper limb movements in the first 6 months post stroke, and assess how progress of time contributes to normalization of this metric	Observational; S (44)	58(12); 25/19	< 7(NR); 44/0; 27/17
Bang et al. 2015; NR	To investigate the effects of a modified constraint-induced movement therapy (mCIMT) with trunk restraint in subacute stroke patients.	Interventional; S_{exp} (9) $S_{control}$ (9)	60.2(5.8); 5/4 59.3(8.2); 4/5	90(34); 6/3; 6/3 107(30); 5/4; 4/5

	Assessment moments	Reaching task; postural restrictions	Additional performance assays investigated	Clinical measures	Protocol	Equipment
	1±1d; 40±4d; 80±6d; 120±13d PI	Reaching task towards targets set in 4 compass directions. Each movement was 14cm; No	x	FM-UE, MSS	2D; 1-3; NR	InMotion 2.0 robot; End effector
	inclusion, 1w, 2w, 3w, 4w, 5w, 6w and 12w PI.	Grasp a ball on the table 25cm away from the starting position of the hand; Yes	x	FM-UE	3D; 5; 30Hz	Electromagnetic motion tracker; Ha
	14d, 25d, 38d, 57d, 91d and 189d PS	Move hand from edge of the table in front of affected shoulder to grasp a block at maximum reaching distance of the non-paretic arm; No	x	NIHSS, ARAT, FM-UE, BI	3D; 4; 240Hz	Electromagnetic motion tracker; Tr, Sc, E, Wr
	7d, 14d, 21d, 30d and 90d PS	Visually guided and visually evoked reaching and circle drawing movements, and attempts to move against resistance; No	x	NIHSS, mRS, FM-UE, MP	2D; as many as possible; NR	MIT Manus; Ha
	1w, 2w, 3w, 4w, 5w, 6w and 3m PI	Grasping a ball on the table 20cm in front of the patient and bring it to a target 5cm from the edge of the table; Yes	x	FM-UE	3D; 5; 30Hz	Electromagnetic motion tracker; Ha
	1w, 2w, 3w, 4w, 5w, 8w, 12w and 26w PS	Move hand from edge of the table in front of affected shoulder to grasp a block at maximum reaching distance of the non-paretic arm; No	x	NIHSS, FM-UE, ARAT, BI	3D; 7; 240Hz	Electromagnetic motion tracker; Tr, Sc, UA, Fa, Ha, Th, IF.
	Pre and post 4 weeks of intervention	Reaching forward to grasp a cube, placed in the sagittal plane in the trunk midline at mid-sternal height at arm length; Yes	x	ARAT, FM-UE, BI, MAL	3D; 3; NR	Dartfish motion analysis software; S, E, Wr

Table 5.1 Continued

Authors	Objective	Study type and number of subjects	Participants	Stroke
Li et al. 2015; NR	Investigate the concurrent validity of kinematic variables before and after the intervention and the predictive validity after the intervention during reaching tasks with and without a trunk constraint in individuals with stroke.	Interventional; S (95)	57.1(10.9); 30/65	519(NR); NR; 42/53
Prange et al. 2015; Early Arm Support	To examine the effect of weight-supported arm training combined with computerized exercises on arm function and capacity, compared with dose-matched conventional reach training in subacute stroke patients.	Interventional; S_{exp} (33) $S_{control}$ (33)	60.3(9.7); 17/18 58.0(11.4); 24/19	51.1(23.8); 28/7; NR 47.6(21.7); 25/8; NR
Semrau et al. 2015; NR	Quantify proprioceptive and motor deficits using robotic technology during the first 6 months post stroke to characterize timing and patterns in recovery, and compare robotic assessments with traditional clinical measures.	Observational; S (113)	NR; NR	10.6(6.6); NR; NR
Yoo et al. 2015; NR	Examine the effects of upper limb robot-assisted therapy in the rehabilitation of stroke patients	Interventional; S (15)	40-49:8, 50-59:3, 60+:4; 13/2	0-6 m: 10, >7m: 5; 11/4; 7/8
Buma et al. 2016; EXPLICIT[3]	Investigate the association between jerk and recruitment of secondary sensorimotor areas. Is this association different in the early sub-acute phase compared to the chronic phase post stroke.	Observational; S (17)	59.9(12.6); 14/3	41(8); 17/0; 12/5

	Assessment moments	Reaching task; postural restrictions	Additional performance assays investigated	Clinical measures	Protocol	Equipment
	Pre and post 3-4 weeks of intervention	Reach the index finger towards the bell at 90% of arm's length; Yes/No depending on condition.	x	FM-UE, ARAT, MAS	3D; 3; 120Hz	7-camera's (VICON); Tr, Sh, UA, Fa, Wr, IF
	Pre and post 6 weeks of intervention	Start with hand as close to the sternum as possible and reach forward maximally. Movement was performed in free space to prevent any support; Yes	x	FM-UE, SULCS	2D; 5; NR	Arm support device (ArmeoBoom); Wr
	1w, 6w, 12w and 26w PS	8-target center-out reaching task. Each movement was 10cm; No	x	TLT, CMSA, FIM, Purdue Pegboard	2D; NR; NR	Exoskeleton (KINARM); Robot reflects position of Ha
	Pre and post 4 weeks of intervention	Move the hand from centre position to targets in each of eight compass directions (distance not clarified); No	x	FM-UE, MBI	2D; NR; NR	MIT MANUS; Sh, E
	5.9±1.1w PS 28.8±1.2w PS	Move hand from edge of the table in front of affected shoulder to grasp a block at maximum reaching distance and transport it to target location at the contralateral side at reaching distance; No	x	FM-UE, ARAT, NHPT, fMRI	3D; 7; 240Hz	Electromagnetic motion tracker; Tr, Sc, UA, Fa, Ha, Th, IF.

Table 5.1 Continued

Authors	Objective	Study type and number of subjects	Participants	Stroke
Duret et al. 2016; NR[4]	Investigate the relationships between clinical and kinematic motor outcomes after an upper limb robot-assisted training program added to usual care in patients with severe paresis, in the sub-acute phase of stroke.	Interventional; S (38)	56(17); 19/19	55(22); 29/9; 23/15
Cortes et al. 2017; SMARTS	To isolate and characterize the time course of recovery of arm motor control (kinematics of anti-gravity reaching movement) and clinical tests over the first year post stroke.	Observational; S (18) C (12)	55.0(12.9); 9/9 58.4(NR); NR	13.13(13.23); 18/0; *6/12
Pila et al. 2017; EudraCT Trial	Measure overall changes associated with a 3-month robot-assisted training program coupled with conventional care, on motor impairment and pointing task kinematics of the upper limb in late subacute stroke. Also, to compare the course of the various kinematic parameters over time, and the associated clinical changes at different joints.	Observational; S (22) C (17)	53(18); 13/9 53(18); 8/9	63(29); 15/7; 10/12
Palermo et al. 2018; NR	Investigate whether kinematic indices, based on motion capturing a 3D daily-life inspired gesture, improved after the administration of an RMT protocol, which involved an exoskeleton for 3D upper limb rehabilitation, and how these indices are in agreement with patient assessments that have been assessed using the most widely adopted clinical scales for post-stroke motor impairment.	Interventional; S (10)	60.1(18.3); 8/2	120(45); NR; 5/5
Mazzoleni et al. 2018; NR	(i) to investigate the relationship between wrist training and proximal segment recovery; (ii) to compare the recovery of subacute and chronic stroke patients after wrist robot-assisted rehabilitation training.	Interventional; S (20)	66.4(16.2); 9/11	25.4(16.0);17/3; 8/12

	Assessment moments	Reaching task; postural restrictions	Additional performance assays investigated	Clinical measures	Protocol	Equipment
	pre and post intervention (35 days in between)	Center-out point-to-point unconstrained reaching tasks without assistance towards visual targets set in 8 compass directions (14cm apart) and presented in a clockwise order; No	x	FM-UE, MSS	2D; 80; NR	InMotion 2.0 arm robot; End effector
	1.5w, 5w, 14w, 27w and 54w PS	Straight movement to a target arrayed radially at 80mm from a central starting point, 8 directions; Yes	x	FM-UE, ARAT, strength of m. biceps	2D; 80; 130Hz	Kinereach apparatus with anti-gravity support and Flock of Birds; Ha
	63±29d PS, 98±32d PS, 131±28d PS, 167±31 d PS	Reaching towards visual targets in 3 directions, each movement was a 14cm horizontal hand displacement; Yes	x	FM-UE	2D; >300; NR	InMotion; Ha
	Pre and post 4 weeks of intervention	Reach and point at a target, placed on the subject's sagittal plane, at shoulder height, and at a distance from the body equal to the patient's arm length; No	x	FIM, BI, FAT, FM-UE	3D; 6; 120Hz	Optoelectronic System (BTS SMART-DX 300) consisting of 6 infrared CCD cameras; Both arms: Fa, Ha, Wr_{ulna}, Wr_{radio}, E, C7, Sacrum, targets
	Pre and post 6 weeks of intervention	Move the cursor from the center of the screen to each of eight peripheral targets. Only N/E/S/W directions were used for analyses; Yes	x	FM-UE, $FM_{Shoulder-Elbow}$, FM_{wrist}, MAS_{wrist}, MI-UE, Box and Block test.	2D; 16; NR	InMotion WRIST robot. 3 DOF (abduction-adduction, flexion-extension, pronation-supination); Wr

Table 5.1 Continued

Authors	Objective	Study type and number of subjects	Participants	Stroke
Duret et al. 2019; NR[4]	examine a range of variables in order to identify reliable indictors of upper-limb motor performance following an intensive rehabilitation program that combined 16 sessions of robot-assisted training (3 days/ week) with usual care during the sub-acute phase in patients with moderate-to-severe upper-limb paresis following stroke.	Interventional; S (46)	57(17); 25/21	58(22); 32/14; 24/22
Mazzoleni et al. 2019; NR	investigate the effectiveness of combining tDCS and wrist robot-assisted rehabilitation in subacute stroke patients and whether this combination therapy would provide additional benefits in comparison with robotic therapy only.	Interventional; S_{exp} (18) $S_{control}$ (16)	67.5(16.3), 8/12; 68.7(15.8), 7/12	25(7); 13/7; 9/11 25(7); 16/3; 8/11
Goffredo et al. 2019; NR	Analyse built-in kinematic data registered by a planar end-effector robot for assessing the time course of motor recovery and patient's workspace exploration skills.	Interventional; S (68)	65.28(12.71); 45/23	NR;49/19;39/29
Hussain et al. 2020; SALGOT[5]	Determining how the relationship between objective kinematic variables obtained from the target-to-target pointing task and self-reported manual ability varies during the first year after stroke.	Observational; S(66)	65.7(13.4); 39/27	9.54d;53/13;29/37
Thrane et al. 2020; SALGOT[5]	To quantify longitudinal changes and residual deficits in movement performance and quality during the first year after stroke using kinematic analysis of drinking task.	Observational; S(56) C(60)	64.0(13.4), 35/31; 63.4(12.6), 33/27	NR;NR;30/22 (4other)

[1-5] Partial overlap of included patients between studies with the same number. *Abbreviations:* AAT: arm ability training, ARAT: Action Research Arm Test, AROM: Active Range of Motion, AS: Arm Support, C: healthy controls, CIMT: Constraint Induced Movement Therapy, CMSA: Chedoke-McMaster Stroke Assessment, CON: Conventional, d: days, D: Dominant, E: Elbow, Fa: Forearm, FA: functional ability, FIM: Functional Independence Measure, fMRI: functional MRI, FM-UE: Fugl-Meyer motor assessment of the Upper Extremity, $FM_{sensation}$: Fugl-Meyer domain for sensation, Ha: Hand, H: haemorrhagic, I: ischaemic, IF: Index Finger, KR: Knowledge of results, L: left, M: months,

	Assessment moments	Reaching task; postural restrictions	Additional performance assays investigated	Clinical measures	Protocol	Equipment
	Pre and post 5 weeks of intervention	80 point-to-point reaching movements towards 8 visual targets, each 14 cm from the centre position; No	x	FM-UE, $FM_{shoulder-elbow}$	2D; 80; NR	InMotion 2.0 Arm robot, with two active translational degrees-of-freedom to assist shoulder (flexion/extension) and elbow (flexion/extension) movements in the horizontal plane; Ha
	Pre and post 6 weeks of intervention	Move the cursor from the center of the screen to each of 8 peripheral targets. Only N/E/S/W directions were used for analyses; Yes	x	FM-UE, $FM_{Shoulder-Elbow}$, FM_{wrist}, MAS_{wrist}, MI-UE, Box and Block test.	2D; 16; NR	InMotion WRIST robot. 3 DOF (abduction-adduction, flexion-extension, pronation-supination); Wr
	Session 1, 5, 10, 15, and 20 of robotic therapy.	point-to-point reaching movements towards a visual target and back, each target 14 cm from the centre position; Yes	x	BI, MI-UE,	2D; 32 per target; 200Hz	InMotion 2.0. Two DOF robotic device; Ha
	10d, 4w, 3m, 6m, 12m PS	Reach and point at the target using the stylus; No	x	ABILHAND questionnaire, FM-UE	3D; 32; NR	Phantom Omni haptic stylus; Ha
	3d, 10d, 4w, 3m, 6m, 12m PS	Reach and grasp the glass, lifting the glass and bringing it to the mouth, taking on sip of water, placing the glass back down on the table and return the arm to its initial position; No	x	NIHSS, FM-UE, $FM_{sensation}$	3D; 3; 240 Hz	motion capture system (ProRe- flex MCU240 Hz, Qualisys) with 5 optoelectronic cameras; Ha, Wr, E, Sh_L, Sh_R, Tr, head, top and bottom of the glass

MAL: Motor Activity Log, MAS: Modified Ashworth Scale, (M)BI: (Modified) Barthel Index, MCS: motor control scores, MFS: Modified Frenchay Scale, MP: Motor Power, MRI: magnetic resonance imaging, MSS: Motor Status Scores, NA: not applicable, ND: Non-Dominant, NHPT: Nine Hole Peg Test, NIHSS: National Institutes of Health Stroke Scale, NR: not reported, PI: Post Inclusion, PS: Post Stroke, R:right, S: Stroke patients, Sc: Scapula, SD: standard deviation, Sh: Shoulder, SIS: Stroke impairment Scale, SULCS: Stroke Upper Limb Capacity Scale, T: Target, TBI: Traumatic Brain Injury, TEMPA: Test Evaluant les Membres superieurs de Personnes Agees, Th: thumb, TLT: Thumb Localization Test, Tr: Trunk, UA: Upper Arm, W: weeks, Wr: Wrist, WMFT: Wolf Motor Function Test.

Table 5.2 Overview of metrics, their responsiveness to change over time and their clinical association.

Metric in this review	**Metric name in study** (first author, year)
Movement time	Movement time (Platz 2001)
	Movement duration (Rohrer 2002)
	Movement time (Lang 2006b)
	Movement time (Wagner 2007)
	Total movement time (Konczak 2010)
	Total movement time (Tan 2012)
	Movement duration (Dipietro 2012)
	Movement duration (Van Kordelaar 2013)
	Movement time (Metrot 2013a)
	Movement duration (Van Kordelaar 2014)
	Movement time (Van Dokkum 2014)
	Movement time (Semrau 2015)
	Movement time (Li 2015)
	Movement duration (Buma 2016)
	Movement time (Palermo 2018)
	Task completion time (Goffredo 2019)
	Movement time (Hussain 2020)
Movement distance	Displacement (Yoo 2015)
	Endpoint displacement (Li 2015)
	Reach distance (Prange 2015)
Movement efficacy	Movement efficacy (Duret 2013)
Path error	Root-mean-square (Duret 2013)
	Path error (Duret 2016)
	Movement path error (Duret 2019)
Active movement index	Active movement index (Colombo 2013)
Trajectory length	Trajectory length (Van Dokkum 2014)

Responsiveness Significant change over time (yes/no); time period post stroke (T1-T2) or passed time (T)	**Clinical association** Type: longi/cross (time point); clinical measure, correlation coefficient/NR/NS
Yes; 3w	x
x	x
Yes; 1w-90d	x
Yes; 9d-109d	x
Yes; 2w-4w	x
Yes; 2w	x
Yes; NR	x
Yes; 14d-57d	x
Yes; 2w, 3w	x
Yes; 1w-5w	x
X	Longi: FM-UE, *NS*
X	Cross (all): FIM, PP, CMSA, *strength NR*
X	Cross (pre): ARAT, FM-UE, *strength NR* Cross (post): FM-UE, *strength NR*
Yes; 6w-29w	x
Yes; 4w	Longi: FIM, BI, FAT, FM-UE; *NS*
Yes, NR	x
X	Cross (10d/4w): ABILHAND, *NS* Cross (3/6/12m): ABILHAND, *ρ:-0.46/-0.49/-0.75*
No; 4w	x
X	Cross (pre): ARAT, *strength NR* Cross (post): ARAT, *strength NR*
Yes; 6w	x
Yes; 40d	x
No; 80d	x
Yes; 35d	Cross (pre): FM-UE, *ρ:-0.63;* MSS, *ρ: -0.63* Longi (correlation between change score): FM-UE, *ρ: -0.51*; MSS, *ρ:-0.49*
Yes; 5w	x
Yes; 3w	x
X	Longi: FM-UE, *NS*

Table 5.2 Coninued.

Metric in this review	**Metric name in study** (first author, year)
Trunk displacement	Trunk displacement (Palermo 2018)
Velocity	Hand velocity (Duret 2013)
	Posture speed (Semrau 2015)
Average hand velocity	Mean speed (Rohrer 2002)
	Movement mean speed (Dipietro 2012)
	Mean velocity (Colombo 2013)
	Average speed (Krebs 2014)
	Mean velocity (Van Dokkum 2014)
	Mean movement speed (Duret 2016)
	Mean velocity (Mazzoleni 2018)
	Mean movement speed (Duret 2019)
	Mean velocity (Mazzoleni 2019)
	Movement speed (Goffredo 2019)
	Mean velocity (Hussain 2020)
Peak velocity	Peak speed (Rohrer 2002)
	Reach speed (Lang 2006a)
	Reach speed (Lang 2006b)
	Peak wrist velocity (Wagner 2007)
	Max had velocity (Konczak 2010)
	Peak wrist velocity (Edwards 2012)
	Movement peak speed (Dipietro 2012)
	Max reaching velocity (Metrot 2013a)
	Peak speed (Krebs 2014)

Responsiveness Significant change over time (yes/no); time period post stroke (T1-T2) or passed time (T)	**Clinical association** Type: longi/cross (time point); clinical measure, correlation coefficient/NR/NS
Yes; 4w	Longi: FIM, BI, FAT, FM-UE, *NS*
Yes; 40d	x
X	Cross (all): FIM, PP, CMSA; *strength NR*
X	x
Yes; NR	x
Yes; 3w	x
X	x
X	x
Yes; 35d	Cross (pre): FM-UE, *ρ:0.73*; MSS, *ρ: 0.73* Longi (correlation between change score): FM-UE, MSS, *reported as weak*.
Yes (ab/ad component during forward and backward direction, fl/ex component during left/right direction); 6w	x
Yes; 5w	x
Yes (forward, backward and left direction); 5w	x
Yes, NR	x
X	Cross (10d/4w/3m/6m): ABILHAND, *NS* Cross (12m): ABILHAND, *ρ:0.54*
X	x
X	*Cross (0d): ARAT, *R:0.4* *Cross (14d): ARAT, *NS* *Cross (90d): ARAT, *R:0.55*
Yes; 1w-90d	x
Yes; 9d-109d	Cross (109d): C-STR, *ρ:0.55*; C-AROM, *ρ: 0.43*
Yes; 2w-4w	x
X	*Cross (0/14/90d): WMFT function, *R:0.63/0.35/0.45;* WMFT time, *R:-0.58/NS/-0.42*; WMFT grip, *R:0.55/0.42/0.59*.
Yes; NR	x
Yes; NR	x
X	x

Table 5.2 Coninued.

Metric in this review	**Metric name in study** (first author, year)
	Peak hand velocity (Van Dokkum 2014)
	Max speed (Semrau 2015)
	Peak velocity (Li 2015)
	Peak movement speed (Duret 2016)
	Peak velocity (Palermo 2018)
	Peak velocity (Hussain 2020)
	Peak hand velocity (Thrane 2020)
Mix/max speed difference	Mix/max speed difference (Semrau 2015)
Time to peak velocity	Time of max velocity (Van Dokkum 2014)
	Time to peak velocity (Palermo 2018)
	Percentage of peak velocity (Li 2015)
	Acceleration time (Konczak 2010)
	Relative time to peak velocity (Thrane 2020)
Max hand acceleration	Max hand acceleration (Konczak 2010)
Deceleration time	Deceleration time (Konczak 2010)
Number of hand trajectory reversals	Number of hand trajectory reversals (Duret 2013)
Speed maxima count	Speed maxima count (Semrau 2015)
Velocity index	Velocity index (Pila 2017)
Normalized reaching speed	Normalized reaching speed (Mazzoleni 2019)
Sub-movements speed profile characteristic	Number, overlap, duration, peak interval, skewness of sub-movements (Krebs 2014)
Jerk	Jerk metric (Rohrer 2002)
	Jerk (Dipietro 2012)
	Mean magnitude of jerk normalized by peak speed (Krebs 2014)
	Root mean square of the jerk normalized by the duration of movement (Krebs 2014)
	Normalized hand displacement jerk (Van Kordelaar 2014)

Responsiveness Significant change over time (yes/no); time period post stroke (T1-T2) or passed time (T)	**Clinical association** Type: longi/cross (time point); clinical measure, correlation coefficient/NR/NS
X	Longi: FM-UE, *NS*
X	Cross (all): FIM, PP, CMSA, *strength NR*
X	Cross (post): ARAT, (significant for constrained) *strength NR*
Yes; 35d	Cross (pre): MSS, *ρ:0.60*; FM-UE, *NS* Longi (correlation between change score): FM-UE, MSS, *reported as weak.*
No	Longi: FIM, BI, FAT, FM-UE, *NS*
X	Cross (all): ABILHAND, *NS*
Yes; 3d-6m	x
X	Cross (all): FIM, PP, CMSA, *strength NR*
X	Longi: FM-UE, *NS*
No	Longi: FIM, BI, FAT, FM-UE, *NS*
X	Cross (post): ARAT (significant for unconstrained); *strength NR*
X	x
Yes; 3d-3m	x
Yes; 2w-4w	x
X	x
Yes; 80d	x
X	Cross (all): FIM, PP, CMSA, *strength NR*
Yes; 2m-3m, 2m-4m, 2m-5m; 3m-5m	x
Yes (abduction component during reaching in forward direction); 5w	x
x	x
x	Longi (correlation between change scores): FM-UE, *R:-0.48*
Yes; NR	x
x	x
x	x
Yes; 1w-5w	x

Table 5.2 Coninued.

Metric in this review	**Metric name in study** (first author, year)
	Normalized Jerk (Palermo 2018)
	Normalized jerk (Mazzoleni 2018)
	Normalized jerk (Mazzoleni 2019)
Speed metric	Speed metric (Rohrer 2002)
	Speed shape (Dipietro 2012)
	Mean over peak speed (Krebs 2014)
	Movement irregularity (Van Dokkum 2014)
	Smoothness (Yoo 2015)
	Speed shape (Duret 2016)
	Smoothness (Duret 2019)
Mean arrest period ratio	Mean arrest period ratio (Rohrer 2002)
Peaks metric	Peaks metric (Rohrer 2002)
	Number of peaks (Dipietro 2012)
	Number of velocity peaks (Metrot 2013a)
	Movement smoothness (Colombo 2013)
	Number of velocity peaks (Van Dokkum 2014)
	Number of peak speed (Goffredo 2019)
	Number of velocity peaks (Hussain 2020)
Tent metric	Tent metric (Rohrer 2002)
Smoothness index	Smoothness index (Pila 2017)
Endpoint accuracy	Accuracy (Platz 2001)
	Reach Accuracy (Lang 2006a)
	Reach Accuracy (Lang 2006b)
	Endpoint error (Wagner 2007)

Responsiveness Significant change over time (yes/no); time period post stroke (T1-T2) or passed time (T)	**Clinical association** Type: longi/cross (time point); clinical measure, correlation coefficient/NR/NS
Yes; 4w	Longi: FIM, BI, FAT, FM-UE, *NS*
Yes (forward and backward direction); 6w	x
Yes (abduction component during reaching in forward direction); 5w	x
x	Longi (correlation between change scores): FM-UE, *R:0.40*
Yes; NR	x
x	x
x	Longi: FM-UE, *NS*
Yes; 4w	x
Yes; 35d	Cross (pre): FM-UE, *ρ:0.75*; MSS, *ρ:0.72* Longi (correlation between change score): FM-UE, MSS, *reported as weak.*
Yes; 5w	x
x	Longi (correlation between change scores): FM-UE, *R:0.33*
x	Longi (correlation between change scores): FM-UE, *NS*
Yes; NR	x
Yes; 2w, 3w	x
Yes; 3w	x
x	Longi: FM-UE, *strength NR*
Yes, NR	x
x	Cross (10d/4w/3m/6m/12m): ABILHAND, *ρ:-0.45/NS/NS/-0.54/-0.66*
X	Longi (correlation between change scores): FM-UE, *NS*
Yes; 2m-3m, 2m-4m, 2m-5m	X
Yes; 3w	X
X	*Cross (0/14/90d): ARAT, *R:-0.53/-0.50/-0.45*
Yes; 1w-90d	X
Yes; 9d-109d	Cross (109d): C-STR, *ρ:-0.34;* C-AROM, *NS*

Table 5.2 Coninued.

Metric in this review	**Metric name in study** (first author, year)
	Reach Accuracy (Edwards 2012)
	Reach error (Yoo 2015)
	Reach error (Duret 2016)
	Active range of motion (Duret 2019)
Reach efficiency	Reach efficiency (Lang 2006a)
	Reach efficiency (Lang 2006b)
	Reach path ratio (Wagner 2007)
	Reach efficiency (Edwards 2012)
	Normalized path length (Colombo 2013)
	Trajectory directness (Metrot 2013a)
	Deviation from Straight line (Krebs 2014)
	Trajectory directness (Van Dokkum 2014)
	Path length ratio (Semrau 2015)
	Hand path ratio (Palermo 2018)
	Movement accuracy (Goffredo 2019)
Averaged squared Mahalanobis distance	Averaged squared Mahalanobis distance (Cortes 2017)
Distance Index	Distance Index (Pila 2017)
Initial direction error	Initial direction error (Semrau 2015)
Initial distance ratio	Initial distance ratio (Semrau 2015)
Accuracy index	Accuracy index (Pila 2017)
Quality index	Quality index (Mazzoleni 2018)
	Movement error (Mazzoleni 2019)

Responsiveness Significant change over time (yes/no); time period post stroke (T1-T2) or passed time (T)	**Clinical association** Type: longi/cross (time point); clinical measure, correlation coefficient/NR/NS
X	*Cross (0/14/90d): WMFT function, *R:-0.65/-0.72/-0.50;* WMFT time, *R: 0.66/0.66/0.45*; WMFT grip, *R:-0.52/-0.38/-0.39*
Yes; 4w	X
Yes; 35d	Cross (pre): FM-UE, ρ:-0.79; MSS, ρ:-0.79 Longi (correlation between change score): FM-UE, MSS, reported as weak.
Yes; 5w	x
X	*Cross (0/14/90d): ARAT, *R:-0.35/-0.55/-0.43*
Yes; 1w-90d	x
Yes; 9d-109d	Cross (109d): C-AROM, *ρ:-0. 44;* Cross (109d): C-STR, *ρ:-0.47*
X	*Cross (0/14/90d): WMFT function, *R:-0.50/-0.43/-0.55;* WMFT time, *R: 0.56/0.56/0.55*; WMFT grip, *R:-0.30/-0.48/-0.45*
Yes; 3w	x
Yes; NR	x
X	x
X	Longi: FM-UE, *NS*
Yes; NR	Cross (all): FIM, PP, CMSA, *strength NR*
Yes; 4w	Longi: FAT, *strength NR* (mentioned as strong); FIM, BI, FM-UE, *NS*
No	x
Yes; 1w-5w	x
Yes; 2m-3m, 2m-4m, 2m-5m	x
Yes; NR	Cross (1/6/12/24w): FIM, *ρ:-0.61/-0.56/-0.47/-0.52* PP, *ρ:-0.79/-0.73/-0.72/-0.77* CMSA, *ρ:-0.79/-0.74/-0.66/-0.72*
X	Cross (all): FIM, PP, CMSA, *strength NR*
Yes; 2m-5m	x
Yes (forward, backward and left direction); 6w	x
Yes (forward, backward and left direction); 5w	x

Table 5.2 Coninued.

Metric in this review	**Metric name in study** (first author, year)
Aperture speed	Aperture speed (Lang 2006a)
	Aperture speed (Lang 2006b)
	Aperture speed (Edwards 2012)
Aperture efficiency	Aperture efficiency (Lang 2006a)
	Aperture efficiency (Lang 2006b)
	Aperture efficiency (Edwards 2012)
Peak aperture	Peak aperture (Lang 2006a)
	Peak aperture (Lang 2006b)
	Peak aperture (Edwards 2012)
Time of peak aperture	Time of peak aperture (Lang 2006b)
Jerk grasp aperture	Jerk grasp aperture (Van Kordelaar 2014)
	Normalized jerk grasp (Buma 2016)
Trunk rotation	Trunk rotation (Van Kordelaar 2013)
Shoulder rotation	Shoulder rotation (Van Kordelaar 2013)
	Shoulder flexion (Li 2015)
	Shoulder adduction (Li 2015)
Elbow rotation	Elbow rotation (Van Kordelaar 2013)
	Elbow extension (Li 2015)

Responsiveness Significant change over time (yes/no); time period post stroke (T1-T2) or passed time (T)	**Clinical association** Type: longi/cross (time point); clinical measure, correlation coefficient/NR/NS
X	*Cross (0/14/90d): ARAT, *R:0.58/0.35/0.39*
Yes; 1w-90d	x
X	*Cross (0/14/90d): WMFT function, *R:0.65/0.40/NS;* WMFT time, *R:-0.55/-0.38/-0.39*; WMFT grip, *R:0.59/0.53/NS.*
X	*Cross (0/14/90d): ARAT, *R:-0.45/-0.6/-0.45*
No; 1w-1y	x
X	*Cross (0/14/90d): WMFT function, *R:-0.61/-0.55/-0.55;* WMFT time, *R: 0.52/0.55/0.50*; WMFT grip, *R:-0.45/-0.43/-0.41*
X	*Cross (0/14/90d): ARAT, *R: 0.58/0.62/0.45*
Yes; 1w-90d	x
X	*Cross (0/14/90d): WMFT function, *R:0.61/0.68/0.45;* WMFT time, *R:-0.52/-0.62/-0.59*; WMFT grip, *R:0.72/0.83/0.52*
No; 1w-1y	x
Yes; 1w-5w	x
Yes; 6w-29w	Cross (w6): ARAT, *R:-.64*; FM-UE, NHPT, *NS*; fMRI, *R:[0.62 0.83]*
X	x
X	x
X	x
X	Cross (pre): FM-UE (significant for unconstrained), *strength NR* Cross (post): ARAT (significant for unconstrained), *strength NR* Cross (post): FM-UE, *strength NR*
X	x
X	Cross (pre): ARAT; significant for unconstrained, *strength NR*

Table 5.2 Coninued.

Metric in this review	**Metric name in study** (first author, year)
	Maximal elbow extension (Bang 2015)
Peak elbow velocity	Peak angular velocity (Thrane 2020)
Forearm rotation	Forearm rotation (Van Kordelaar 2013)
Wrist rotation	Wrist rotation (Van Kordelaar 2013)
Composite score	Composite score (Semrau 2015)
Reaction time	Reaction time (Semrau 2015)
	Reaction time (Li 2015)

Responsiveness was noted as change between two moments post stroke, or the passed time when measurement moments were not fixed post stroke. When available, the strength of the relation was provided, R: Pearson correlation coefficient, ρ: Spearman rank correlation coefficient, *Interpreted from graph. *Abbreviations:* ABILHAND: ABILHAND questionnaire, ARAT: Action Research Arm Test, C-AROM: composite score Active Range of Motion, CMSA: Chedoke-McMaster Stroke Assessment,

SRRR recommendation compatibility

None of the longitudinal studies met all recommendations provided by the SRRR, one reason of course being that these recommendations were published only recently.[12] The SRRR recommendations were predicated on the idea that it is important to distinguish between behavioural restitution and compensation. The recommendation to include longitudinal measurements of performance assays besides a functional task was met by one out of 32 studies. In 24 out of 32 studies, the first measurement was performed after the acute phase post-stroke, and measurements were repeated limited number of times. Furthermore, 24 out of 32 studies did not include healthy reference data, and were thereby not able to determine whether observed recovery was complete. An overview of which recommendations of the SRRR were met by the individual studies is provided in Supplementary Table 3 and Supplementary Figure 4. A checklist that contains all recommendations of the SRRR consensus papers is provided in Appendix C. This checklist can be used to design or evaluate stroke recovery studies that also target QoM by using kinematics and kinetics.

	Responsiveness Significant change over time (yes/no); time period post stroke (T1-T2) or passed time (T)	**Clinical association** Type: longi/cross (time point); clinical measure, correlation coefficient/NR/NS
	Yes; 4w	x
	Yes; 3d-6m	x
	X	X
	X	X
	X	Cross (all): FIM, PP, CMSA, *strength NR*
	X	Cross (all): FIM, PP, CMSA, *strength NR*
	X	Cross (pre): FM-UE, *strength NR* Cross (post): FM-UE (significant for unconstrained), *strength NR*

Cross: cross-sectional association, C-STR: composite score muscle strength, d: days post stroke, FM-UE: Fugl-Meyer motor assessment of the upper extremity, FIM: Functional Independence Measure, Longi: longitudinal association, m: months post stroke, MSS: Motor Status Scale, NHPT: Nine Hole Peg Test, NR: Not reported, NS: Not significant, Post: Post-intervention, PP: Purdue Pegboard, Pre: pre-intervention, WMFT: Wolf Motor Function Test, w: weeks post stroke, x: not investigated, y: years post stroke.

The only study which investigated recovery by performing both a functional task and performance assays[52] met many of the recommendations of the SRRR, except for the minimal number of repetitions within a measurement, and the number of longitudinal measurements was restricted to two measurements per patient.

Discussion

Despite the large number of cross-sectional kinematic post-stroke studies,[23] longitudinal studies that track recovery of quality of upper limb movement early post stroke remain scarce. Thirty-two longitudinal post-stroke studies were found that measured kinematic metrics during a reaching task. However, just a few of these studies addressed the need to distinguish between behavioural restitution and compensation. Only one study investigated the combination of performance assays and a functional task longitudinally,[12] showing that metrics such as reaching accuracy and reaching efficiency normalized, while peak wrist velocity and performance assays, such as grip strength and isolated movement control, showed recovery but remained affected. This is in line with the present dichotomy of behavioural recovery, whereby performance assays reflect behavioural restitution, while the observed recovery of function in the activity domain is the sum of behavioural restitution and compensation. More longitudinal studies should investigate performance assays early after stroke in addition to functional tasks. The recommendations recently provided by the SRRR, together with the overview of reported metrics reflecting QoM, may serve as inspiration and starting point for designing stroke studies which will bring us closer to kinematics that can distinguish between behavioural restitution and compensation.

From a translational perspective, it is of interest to study the longitudinal association between the recommended performance assays and common clinical assessments. For example, in case of the FM-UE, such studies would help elucidate precisely what the measure is capturing, whether it mainly quantifies the degree to which out-of-synergy movements can be made, as was originally intended[64,65], or the degree to which it is contaminated by other motor impairment components, both neural and musculoskeletal.[21,22,66] However, although some of the available studies investigated longitudinal associations between kinematics and clinical outcomes[37,38,46,50,52,54], these analyses did not concern kinematics obtained from performance assays.

A difference in recovery between reaching and grasping was observed by Lang and colleagues (2006)[51]. It is currently unclear what causes the difference in recovery of reaching versus grasping and what the contribution is of different descending pathways with regard to restitution and compensation. This has to be investigated by obtaining longitudinal neurophysiological data alongside kinematic data within the first months post-stroke.

Smoothness is assumed to be a good reflection of QoM. However, many different kinematic metrics have been used to quantify smoothness [67], which all have a different mathematical basis and therefore show varying recovery patterns. Moreover, smoothness of the hand trajectory during a reaching task can be influenced by several components of motor impairment across different joints in the upper extremity. Whether smoothness metrics are able to reflect behavioural restitution remains inconclusive and should be studied in a longitudinal study post-stroke, as recently recommended[68].

In sum, this review shows that despite the growing number of cross-sectional kinematic and kinetic post-stroke studies, there is still a need for longitudinal studies that separate behavioural restitution from compensation over the course of recovery. Thus, measuring QoM remains in its infancy in stroke recovery and rehabilitation studies. Further research is necessary to provide better means to interpret neuroimaging studies[12,69,70], and insight into which aspects of post-stroke arm function deficits are targeted during CIMT[71,72] and neuromodulation therapies such as rTMS[73] and tDCS[74]. Finally, understanding recovery of QoM may aid in the design of better rehabilitation approaches targeting restitution.[12,69,75]

Barriers in kinematic research post-stroke

There are a number of possible explanations for the paucity of longitudinal studies. First, collecting longitudinal datasets in a post-stroke cohort is challenging: having to adhere to fixed time points, at higher frequency early on; the need to restrict inclusion to those patients that can be captured in the first few weeks post stroke; and losing patients because they often change locations during their clinical trajectory. Second, while there is agreement on QoM as proxy for true neurological recovery[69], consensus on which metrics reflect QoM is lacking. Third, there may be technology-based barriers. High-resolution optical tracking systems[12] are typically not portable and pose a challenge for serial assessments as patients need to return to the movement laboratory for follow-up measurements, which increases the chances of drop-out. User-friendly, portable, high-resolution measurement setups or a validated setup of wearables in which inertial measurement units provide information using accelerometers and gyroscopes, would greatly improve feasibility of investigating kinematics post-stroke. An overview of the ease of application and practicality of different motion capture systems to measure kinematic metrics was recently provided.[76] In line with the SRRR task force, authors state that markerless systems are promising for implementation in hospitals and clinics, yet require validation.[76] Examples of such systems are the Microsoft Kinect, electromagnetic motion capture systems and miniature inertial measurement units.[76]

Performed reaching task

The performed task in the studies included in the present systematic review could either be a reach-to-grasp or reach-to-point task. It should be noted that the kinematics of these closely related tasks may differ, for example the velocity profile. The velocity profile of a reach-to-point movement mimics a minimum jerk model[77], whereas the profile of a reach-to-grasp movement is more skewed.[78] Therefore, kinematic metrics should be compared among similar tasks and no kinematic measure should be interpreted outside of the behavioural context within which it was generated. Stroke research focuses on recovery over time within subjects and comparisons with healthy subjects. This emphasizes the need for standardized tasks and the availability of reference data in healthy subjects.

The SRRR recommended to perform a functional drinking task to investigate how behavioural restitution and compensation may interact.[12] However, only one longitudinal study included in the present review[45] actually performed a drinking task. Studies that incorporated a drinking task were nevertheless excluded if they were either only cross-sectional[79] or quantified the drinking task as a complete task.[80,81] In the latter case, a global measure was obtained rather than decomposition into each kinematic phase of the drinking task (reaching, transporting glass to mouth, drinking, transporting glass to table, and returning hand). It should be noted that datasets that include a functional task like drinking might still be useful for separating restitution and compensation, if information for each separate phase can be extracted from the raw data by applying either post-hoc analyses or when machine learning techniques are able to quantify quality of a complete task. A disadvantage of the drinking task is that it includes grasp, and thereby excludes patients who have very limited dexterity. Recently, an alternative task was proposed in the form of turning on/off a light switch which does not require hand function.[82] Appropriate metrics that quantify movement quality during the light switching task are however required. Included studies investigated reaching tasks in 2D as well as in 3D. The performance assays suggested by the SRRR concern 2D movements. Currently, there are no validated 3D performance assays. Thus currently, 3D movements, as discussed above, remain in the functional domain.

Limitations

Due to our search restrictions regarding databases and language, some relevant studies may have been missed. Studies in which no reaching task was performed were excluded. Studies which measured performance assays but did not include a reaching task will therefore be missed. Articles often describe only part of the data obtained during the main study instead of all investigated tasks. Therefore, it might be the case

that the main study meets more recommendations of the SRRR than the appraised articles. Such information can be obtained from protocol papers, which were not analyzed in this review. Finally, some of the authors (GK, EW, JK) who contributed to the current manuscript were also part of the SRRR taskforce.

Future directions

In order to understand *what* occurs during true recovery from motor impairments after stroke and *how* innovative therapies may interact with such behavioural restitution, there is an urgent need for longitudinal studies that use kinematic and kinetic performance assays. In line with the SRRR recommendations, future studies should perform frequently repeated measurements in the first three months post stroke, measurement time points should be defined as elapsed time since the moment of stroke onset and healthy reference data should be provided regarding metrics reflecting QoM. Moreover, studies targeting QoM after stroke should use different performance assays such as strength, finger individuation, reaching dexterity and the ability to execute isolated movements for quantification of behavioural restitution. The contributions of these different motor impairment components and their relation to underlying mechanisms that drive behavioural restitution and neural repair early post-stroke need further investigation. In addition, performance assays and improvements in QoM will also allow better interpretation of observed changes in neuroimaging modalities such as EEG[83] and fMRI[84] obtained early post stroke. A checklist for study design and evaluation of longitudinal kinematic/kinetic stroke studies is provided as Appendix to this manuscript (Appendix C).

From a technical and practical point of view, there are a number of barriers that hinder the use of high-fidelity systems outside the laboratory. Therefore, we recommend the development of minimal and portable movement analysis systems or validation of existing ones to measure QoM outside the laboratory. Such portable systems will decrease patients burden and improve feasibility of longitudinal studies. Moreover, quick and easy to use systems are more likely to ultimately make the transition to routine clinical practice. These systems along with analysis packages that provide a small number of interpretable measures will be essential to make studying recovery using kinematics useful for clinicians.

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Declaration of Conflicting Interests
The authors declare that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Supplementary files
Supplementary files and Appendices can be found online.

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6

Smoothness metrics for reaching performance after stroke. Part 1: Which one to choose?

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Abstract

Background: Smoothness is commonly used for measuring movement quality of the upper paretic limb during reaching tasks after stroke. Many different smoothness metrics have been used in stroke research, but a 'valid' metric has not been identified. A systematic review and subsequent rigorous analysis of smoothness metrics used in stroke research, in terms of their mathematical definitions and response to simulated perturbations, is needed to conclude whether they are valid for measuring smoothness. Our objective was to provide a recommendation for metrics that reflect smoothness after stroke based on: (1) a systematic review of smoothness metrics for reaching used in stroke research, (2) the mathematical description of the metrics, and (3) the response of metrics to simulated changes associated with smoothness deficits in the reaching profile.

Methods: The systematic review was performed by screening electronic databases using combined keyword groups *Stroke*, *Reaching* and *Smoothness*. Subsequently, each metric identified was assessed with mathematical criteria regarding smoothness: (a) being dimensionless, (b) being reproducible, (c) being based on rate of change of position, and (d) not being a linear transform of other smoothness metrics. The resulting metrics were tested for their response to simulated changes in reaching using models of velocity profiles with varying reaching distances and durations, harmonic disturbances, noise, and sub-movements. Two reaching tasks were simulated: reach-to-point and reach-to-grasp. The metrics that responded as expected in all simulation analyses were considered to be valid.

Results: The systematic review identified 32 different smoothness metrics, 17 of which were excluded based on mathematical criteria, and 13 more as they did not respond as expected in all simulation analyses. Eventually, we found that, for reach-to-point and reach-to-grasp movements, only Spectral Arc Length (SPARC) was found to be a valid metric.

Conclusions: Based on this systematic review and simulation analyses, we recommend the use of SPARC as a valid smoothness metric in both reach-to-point and reach-to-grasp tasks of the upper limb after stroke. However, further research is needed to understand the time course of smoothness measured with SPARC for the upper limb early post stroke, preferably in longitudinal studies.

Introduction

Stroke is one of the main causes of adult disability.[7-9] Goal-directed upper limb movements after stroke are characterized by slowness, spatial and temporal discontinuity (i.e., lack of smoothness), and abnormal stereotypic patterns of muscle activation or movement synergies.[10,11]

Currently, stroke literature offers several ways for objective measurement of upper limb movement, and standardization is lacking.[12-13] Measuring changes in smoothness during reaching, pointing or grasping using the upper paretic limb is suggested to reflect quality of movement (QoM) early after stroke.[5,6] Smoothness of movement is regarded as the result of 'learned, coordinative processes in sensorimotor control', although the underlying neuronal and mechanical substrates that cause lack of smoothness in motor control are still poorly understood.[14,15] Smoothness is therefore interpreted as a reflection of the level of sensorimotor coordination and movement proficiency.[16,17]

Balasubramanian and colleagues defined *movement smoothness* as continuity or non-intermittency of a movement, independent of its amplitude and duration.[6] Maximizing the smoothness of a movement is considered to be prioritized by the neuro-muscular system, as it reduces the control burden on the brain.[18] Nonetheless, the neurophysiological mechanisms of smoothness deficits after stroke are yet to be understood. Muscle activity patterns observed during reaching after stroke have been shown to be impaired.[19] Smoothness deficits could, for example, be caused by the inability to synchronize motor units or control agonists and antagonists in the right proportions[14,20], or may be due to changes in cortico-spinal tract excitability following stroke[21].

A prerequisite for investigating smoothness deficits after stroke is identifying a 'valid' smoothness metric. Unfortunately, there is currently no commonly accepted metric for quantifying movement smoothness, and many types have been used in the literature to investigate smoothness of reaching movements post stroke.[13] The use of many smoothness metrics in clinical research is limited by several methodological concerns. For instance, some metrics are not clearly described and therefore not reproducible. Other metrics depend on the duration or distance of reaching or are not dimensionless. In both cases, they could be confounded by the shape, *i.e.*, the duration and amplitude, of the movement.[16] Some proposed smoothness metrics are based on position, and do not truly reflect smoothness per se as they do not measure the rate of change of position.[6,22] Furthermore, some metrics are linear transformations of other smoothness metrics, and are therefore proxies of existing metrics. Finally, some metrics lack robustness against measurement noise.[6]

Several narrative reviews about smoothness have discussed the strengths and weaknesses of a limited set of available metrics.[6,3,14,16] The relations between these metrics and smoothness were assessed either by using simulation models, or by studying post-stroke correlations with clinical scales. However, these studies reviewed the literature narratively, rather than systematically. Therefore, a comprehensive overview of metrics used to measure smoothness after stroke is lacking. Furthermore, these metrics have not been validated in terms of whether they reflect smoothness.[23] As a result, proper recommendations for a valid smoothness metric are currently lacking in the literature.

Our goal was to identify the most valid metrics for quantifying smoothness of upper paretic limb movement after stroke during reaching tasks.[24] Reaching can be used to extend or point the hand/arms (reach-to-point) or touch or grasp something (reach-to-grasp). To this end, several subsidiary questions were formulated. Firstly, to identify available metrics, we addressed the question '*Which metrics have been used in the literature to assess movement smoothness in reaching by persons with stroke?*'. Secondly, we filtered metrics sequentially, using a set of criteria derived from the literature to assess whether their mathematical definitions regarding smoothness were sound.[6,14,16] This was done to answer the question '*Which of the available metrics are mathematically defined, reproducible, not linear transforms of another metric, dimensionless, and defined using the rate of change in position?*'. Thirdly, we assessed how each metric responds to smoothness deficits in the reaching task, to answer the question '*How does each smoothness metric respond to a simulated change in the velocity profile of a reaching task?*'. In this study, metrics that satisfy the two latter questions can be said to be valid smoothness metrics that have been applied in stroke research.

Materials and methods

Systematic Literature Review

The literature search was performed in accordance with the PRISMA statement, using keyword groups 'Stroke', 'Reaching' and 'Smoothness'[25] (Full search query in Additional File 1.A). PubMed, Scopus, Cochrane Library, EMBASE and CINAHL databases were searched for all records up to October 2019. The screening of the literature was performed by one author (BLS) and ambiguities were resolved with another author (MRMI). Articles were excluded if they were in a language other than English, or if they were reviews. Eventually, we included articles in which (1) reaching or aiming movements of persons with stroke were studied and (2) a metric was used to determine the smoothness of a reaching movement. The International Classification of Functioning, Disability, and Health (ICF) definition of a *reaching* movement (code: d4452) is '*Using the hands and arms to extend outwards and touch and grasp something, such as when reaching across a table or desk for a book*'.[26] The references of the included articles were scanned for additional suitable articles. The review has been registered in the PROSPERO registry under CRD42020173211.

Metrics mathematically reflecting smoothness

Metrics should reflect the definition of movement smoothness, i.e., the continuity or non-intermittency of the movement profile, independent of its amplitude and duration.[6] Additionally, as smoothness reflects continuity, it should be based on rate of change of position or a higher derivative. Based on the requirements stated in the introduction above, the definition of a metric was not sound if:

E1. the metric was not dimensionless,
E2 the metric was not reproducible from the literature,
E3. the metric was not based on velocity or a derivative of velocity, or
E4. the metric was linearly related to another metric by (a) scaling or (b) addition of a constant.

Response of metrics to changes in velocity profile

The response of each metric to four different types of simulated perturbations, applied to two reaching velocity profiles, viz. reach-to-point and reach-to-grasp, were studied. A reach-to-point movement was simulated using a minimal jerk model[27]:

$$v_{\mathrm{mj}}(t) = \mathrm{d_t}\left(\frac{30t^4}{T^5} - \frac{60t^3}{T^4} + \frac{30t^2}{T^3}\right)$$

where v_{mj} is the minimal jerk velocity profile, d_t is the total reaching distance, *T* is the total movement time and *t* is the time scale from 0 to *T*. Using this, a symmetrical velocity profile (v_{symm}) was created with a d_t of 0.3 m, and a *T* of 1 s. While this velocity profile reflects a reach-to-point movement, it does not truly reflect reach-to-grasp movements, as the latter movements have to account for a higher accuracy when nearing the target position.[28] An initial analysis on healthy subjects showed that an asymmetrical velocity profile (v_{asymm}) was better suited for this purpose. This was modelled using a polynomial curve (Additional File 1.B). Both velocity profiles are shown in Additional File 1.C, and have been further investigated.

Of the four simulated perturbations, the first three are analytical evaluations of the smoothness metrics, and the last one is specifically based on theories regarding recovery of movement after stroke.[14]

- *Shape Simulation (SS)*: The movement duration and distance of the base velocity profiles were varied. The smoothness metric must not depend on either of these parameters.

The durations and distances of both velocity profiles were varied from 0.5 to 6.0 s in steps of 0.1 s, and from 0.2 to 0.7 m in steps of 0.01 m. A total of 2856 combinations were used to calculate the outcomes of the metrics. The ranges for movement duration and distance were chosen such that they were within the physiological range of human reaching.

- *Harmonic Disturbances (HD)*: In this analysis, tremor or weak control of reaching movement was simulated using harmonic disturbances added to the base velocity profiles.[29] This included sinusoids with varying amplitude and frequency. The relation between frequency or amplitude and the metric should be monotonic. Smoothness is expected to decrease with increasing amplitude for a given frequency, and also with increasing frequency for a given amplitude.

Sinusoids of frequencies between 2 and 25 Hz in steps of 0.5 Hz, and amplitudes between 0 and 0.2 m/s in steps of 0.005 m/s were added to the base velocity profile. A total of 1927 unique combinations were explored. The ranges chosen were within the physiological ranges of movement.[4,30]

- *Measurement noise (MN)*: A more robust smoothness metric is less sensitive to measurement noise.[6] The noise was modelled as normally distributed white noise (mean = 0, standard deviation = 1) and added to the base velocity profiles.

The root mean square (RMS) of the noise was varied from 0 to 0.08 m/s in steps of 0.002 m/s. Twenty-five different realizations for each RMS were generated, and the metrics were estimated for each realization. The minimum, maximum, mean and standard deviation of the metrics were calculated and reported. In an additional analysis of noise we filtered the noise-added velocity profile using a zero phase 4th order low pass Butterworth filter with cut off of 20 Hz.[6] The mean of the metric outcome across the 25 realizations after filtering was determined.

- *Sub-movement Simulation (SMS)*: A smoothness metric must reflect movement intermittency, and the change in the progressive blending of sub-movements.[6,31] The smoothness metric should therefore decrease monotonically with increasing number of sub-movements and increasing delays between each sub-movement.

This is an extension of previous work applied to a set of metrics.[4,14] The reaching profiles were modelled as a composition of two or more sub-movements, each defined as the base velocity profile with a duration of 1 s. The sub-movements were separated by a varying lag, denoted as *Ks*. *Ks* ranged from 0 s, were the sub-movements fully overlap, to 1.2 s, where there was 1.2 s between the starting points of the two sub-movements. The lag was increased in steps of 0.02 s. Note that when the lag was greater than 1 s, there were instances of zero velocity between subsequent sub-movements. The total duration of the movement increased with *Ks*. Simulations were performed for 2 – 4 sub-movements.

Analysis of the simulations

The responses of each metric to the four different simulated perturbations were individually assessed. For the *Shape Simulation* and *Harmonic Disturbances,* the percentage change (%Δ) of the metric from its value estimated using the respective base profile was identified as

$$\%\,\Delta = \frac{metric_i - metric_1}{metric_1} * 100$$

where $metric_i$ corresponds to metric values for each combination of parameters in the simulations, and $metric_1$ is the value for the first combination used. For *Shape Simulation*, $metric_1$ corresponded to the smoothness of a base profile with reaching distance 0.2 m and duration 0.5 s. We considered a change of more than 10% as meaningful, and the maximum %Δ was identified.

For *Harmonic Disturbances*, $metric_1$ corresponded to a base profile of reaching distance 0.3 m and duration 1 s. The %Δ was estimated for each combination of frequency and amplitude. Then, a Combinations Exceeded (CE) parameter was marked as the percentage of the combinations that exceeded 10%. A higher value of CE meant that there were more combinations of frequency and amplitude that caused a meaningful change in the value of the metric from its base velocity profile.

For the *Measurement Noise* simulation, the ratio of signal-to-noise power (SNR) was estimated to quantify the robustness to noise. First, the power of the measurement noise was estimated. Then, the power of the signal was estimated as the power of the base velocity profile with added measurement noise. The lowest RMS of added noise was 0.002 m/s, which corresponds to SNRs of 45.0 dB for v_{symm} and 45.4 dB for v_{asymm}. Subsequently, the highest noise RMS added was 0.08 m/s, which corresponded to SNRs of 13.2 dB for v_{symm} and 13.6 dB for v_{asymm}. The SNR at which the mean value of the metric differed from the base velocity profile by at least 10% is reported. Metrics that reached a 10% threshold only at a high RMS of added measurement noise, and therefore a low SNR, were deemed to be more robust to noise. On the other hand, metrics that crossed the threshold at lower RMS values, and therefore a higher SNR, were highly sensitive to noise. An SNR threshold to distinguish between high and low robustness was determined using the distribution of the SNR values obtained at the 10% cut-off for each metric. Metrics with an SNR lower than the 25th percentile were considered to have *high* robustness to noise, and all others were deemed to have *low* robustness to noise.

Finally, in the *Sub-movements Simulations*, the change in the direction of the derivative of the metrics for increasing delays was assessed to study monotonicity. All computations were performed using MATLAB (2018b, The Mathworks, Natick, MA, USA).

Data availability

The MATLAB scripts used to generate the different simulations, the scripts for estimating the smoothness metrics, and the resulting metrics are provided with this manuscript (Additional File 4).

Results

Systematic Literature Review

A total of 476 unique articles were identified, 102 of which were found to be eligible for inclusion using Rayyan.[32] A total of 32 different metrics (Additional Files 1.D and 1.E) were identified. **Figure 6.1** shows the PRISMA flow chart (Additional File 3 reports the PRISMA checklist).

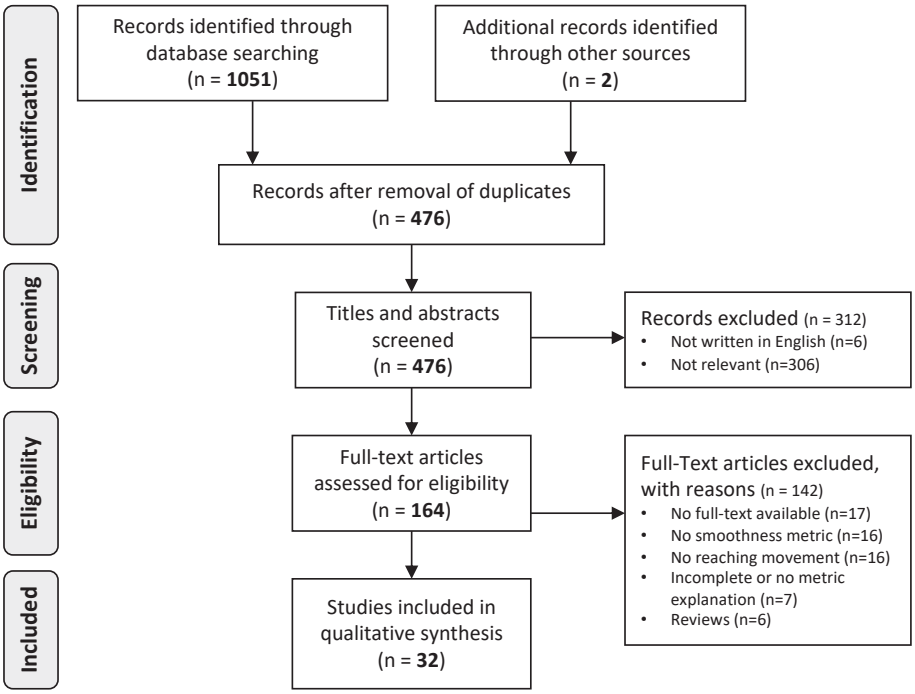

Figure 6.1 *PRISMA Flow chart*

Table 6.1 Overview of Smoothness metrics identified from the literature

Metric (Abbreviation)	Units	Articles used[a]	Exclusions	Category	Earliest Citation
Index of curvature (IC)	[ ]	1	E3	Trajectory	[33]
Standard deviation in 2D plane (SD_XY)	[ ]	1	E3	Trajectory	[72]
Number of sub-movements (NOS)	[ ]	1		Velocity	[37]
Speed metric (SM)	[ ]	15		Velocity	[14]
Normalized reaching speed (NRS)	[ ]	2	E4 (*SM*)	Velocity	[35]
Movement arrest period ratio (MAPR)	[ ]	3		Velocity	[34]
Tent Metric (TM)	[ ]	1	E2	Velocity	[14]
Velocity Arc Length (VAL)	[ ]	1		Velocity	[4]
Correlation Metric (CM)	[ ]	2		Velocity	[38]
Peaks Metric (Peaks)	[ ]	61		Acceleration	[39]
Number of Movement Units (NMU)	[ ]	3	E4a (*Peaks*)	Acceleration	[73]
Number of peaks normalized by movement duration (NPt)	$[s^{-1}]$	1	E1	Acceleration	[40]
Number of peaks normalized by movement distance (NPd)	$[m^{-1}]$	3	E1	Acceleration	[41]
Inverse number of peaks and valleys (IPV)	[ ]	1		Acceleration	[44]
Acceleration metric (AM)	[ ]	2	E1	Acceleration	[35]
Integrated absolute jerk (IAJ)	$[ms^{-2}]$	2	E1	Jerk	[74]
Mean absolute jerk (MAJ)	$[ms^{-3}]$	2	E1	Jerk	[33]
Mean absolute jerk normalized by peak speed (MAJPS)	$[s^{-2}]$	7	E1	Jerk	[14]
Integrated squared jerk (ISJ)	$[m^2s^{-5}]$	1	E1	Jerk	[75]
Root mean squared jerk metric (RMSJ)	$[ms^{-3}]$	1	E1	Jerk	[76]
Normalized integrated jerk (NIJ)	$[ms^{-3}\sqrt{s}]$	1	E1	Jerk	[77]
Dimensionless squared jerk (DSJt)	[ ]	12		Jerk	[3]
Log dimensionless squared jerk (LDSJt)	[ ]	1		Jerk	[5]
Dimensionless squared jerk (DSJm)	[ ]	1	E4a (*DSJt*)	Jerk	[2]
Dimensionless squared jerk (DSJb)	[ ]	1		Jerk	[4]
Log dimensionless squared jerk (LDSJb)	[ ]	1		Jerk	[4]
Rotational jerk (RJ)	[ ]	1	E3	Jerk	[48]
Spectral metric (SPMR)	[ ]	1		Frequency	[49]
Spectral method (SPM)	[ ]	1		Frequency	[1]

Table 6.1 Continued

Metric (Abbreviation)	Units	Articles used [a]	Exclusions	Category	Earliest Citation
Spectral arc length 2012 (SPAL)	[ ]	8		Frequency	[4]
Spectral arc length (SPARC)	[ ]	1		Frequency	[6]
Combined smoothness metric (CSM)	[--][b]	1	E1	Other	[78]

[a] Number of articles in the systematic review that used the metric. [b] Units were not available. Exclusion criteria include E1: metric was not dimensionless; E2: metric not reproducible from the literature; E3: metric not based on velocity or its derivative; and E4: metric linearly related to another metric (shown in brackets) by (a) scaling or (b) addition of a constant.

Metrics mathematically reflecting smoothness

Table 6.1 shows an overview of all metrics identified from the literature, and the ones that did not meet the four exclusion criteria (E1-E4). *The metrics identified in the systematic review were classified into categories based on their mathematical definitions. Metrics defined in the time domain were classified as 'Trajectory metrics', or 'Velocity metrics', or 'Acceleration metrics', or 'Jerk metrics'. Metrics defined in the frequency domain were classified as 'Frequency metrics'. Metrics that did not fit in any of these categories, or fitted in more than one category, were classified as 'Other metrics'.*

Trajectory-based smoothness metrics: The Index of Curvature *(IC)*[33] and the standard deviation of the position perpendicular to the movement direction *(SD_XY)* measured smoothness using only the discrete position information of the reaching movement. As these are not based on the rate of change of position as a function of time, they cannot be used to measure continuity and thereby smoothness of reaching (criterion E3). This holds for any proposed metric that belongs to this category.

Velocity-based smoothness metrics: Of the seven velocity-based metrics, Movement Arrest Period Ratio (*MAPR*), Speed Metric (*SM*), Number of Sub-movements (*NOS*), Velocity Arc Length (*VAL*) and Correlation Metric (*CM*) were found to be mathematically sound for measuring smoothness and were used for further analysis.

MAPR is the proportion of time that the movement speed exceeds a given percentage of the peak speed.[34] *SM*, defined as the mean speed of the whole movement normalized by the peak speed, was found to decrease with the severity of the stroke.[14] Normalized Reaching Speed (*NRS*) is the ratio of the difference in peak and mean speed over the peak speed.[35] As *NRS* = 1 – *SM*, it is a linear transform of the *SM* metric, and is expected to behave congruently. Therefore, *NRS* was excluded from further analysis

(criterion E4). The definition and mathematical description of the Tent Metric (*TM*) was incomplete in the study[14], and therefore could not be evaluated further (criterion E2). *NOS* counts the sub-movements that make up the norm of the velocity profile[36] and has been used to assess smoothness in persons with stroke[37]. *VAL* is based on the arc length of the speed profile normalized by the peak speed.[4] It assumes that a bell-shaped velocity profile has a shorter arc length than one with velocity fluctuations. *CM* determines the correlation between the velocity profile extracted from the minimal jerk model and the actual hand velocity profile during reaching.[38]

<u>*Acceleration-based smoothness metrics:*</u> In this category, six metrics were identified, of which peaks (*Peaks*) and Inverse Number of Peaks and Valleys (*IPV*) were analysed further.

Peaks was the most frequently used metric (61 citations). The metric reflects the number of local maxima in the velocity profile for a given movement[39], which is inversely proportional to the smoothness of a movement. *Peaks* can also be defined as zero crossings in the acceleration domain when the derivative of the acceleration is negative. *Peaks* were additionally normalized either to the movement duration (*NPt*)[40] or to the movement distance (*NPd*)[41]. However, doing so causes the metric to be dependent on movement duration or movement distance. Therefore, these adapted definitions of *Peaks* (*NPt* and *NPd*) were excluded (criterion E1). Smoothness was also estimated using the Number of Valleys[42] or the Number of Valleys and Peaks[43]. Since these definitions are linear transforms of *Peaks*, they are assumed to show congruent behaviour to *Peaks*, and were excluded from further analysis (criterion E4). *IPV*, on the other hand, is not a linear transform of *Peaks*, and was included in further analysis.[44] Although a few studies employed additional criteria for peak detection[45,46], the choices for these criteria, and the difference with *Peaks* was not explicitly provided, and they were not considered for the present study. The Acceleration Metric (*AM*) is the ratio between the mean acceleration and the peak acceleration.[35] A point-to-point reaching movement should have zero velocity both at the beginning and end of the movement, which implies that the mean acceleration over this movement must be zero. However, this was not the case in the referenced studies, suggesting that some aspect of its definition is missing.[35,47] According to the textual description, the metric definition is not face-valid, and it was therefore excluded (criterion E2).

<u>*Jerk-based smoothness metrics:*</u> There were a total of 12 different jerk-based metrics, of which only two types of dimensionless squared jerk metrics, *DSJt* and *DSJb,* and their respective log transformations, *LDSJt*, and *LDSJb*, were further analysed.

Jerk, the third derivative of position, has often been used as a measure of smoothness in different ways; either as the integral of the squared jerk or the integral of the absolute jerk.[3,14,16] Furthermore, the results were scaled using different terms, which introduces a unit to the metric. As smoothness metrics have to be dimensionless (criterion E1), only the dimensionless jerk metrics were considered. Three types of dimensionless squared jerk metrics, *DSJt*[3], *DSJb*[4], and *DSJm*[2], were introduced to measure smoothness. The suffixed letter corresponds to the author's name. These jerk metrics differ in the normalizations used in their definitions. As *DSJm* is a linear transform of *DSJt*, it was excluded (criterion E4a). A natural logarithm transform of the *DSJb* metric was performed to improve its sensitivity (*LDSJb*).[4] The same was applied to *DSJt*, thereby introducing *LDSJt*.[5] As *LDSJb* and *LDSJt* employ the peak velocity, and the average velocity respectively in their equations, they are not linear transformations of each other. Rotational Jerk (*RJ*) measures movement smoothness using the orientations of the wrist during the movement.[48] This form of smoothness quantifies the variability of hand orientation. However, as we analysed changes to a tangential velocity profile, we have no models for the changes in orientation during the reaching movement. Therefore, this metric was not analysed further.

<u>*Frequency-based smoothness metrics:*</u> All four metrics from this category, including Spectral Method (*SPM*), Spectral Arc Length 2012 (*SPAL*), Spectral Arc Length (*SPARC*), and Spectral Metric (*SPMR*), were analysed further.
The *SPM*, *SPAL*, and *SPARC* were developed by the same authors[1,4,6], and are directly proportional to the increase in smoothness of the movement. The *SPM* measures smoothness as the sum of all peaks in the amplitude-normalized Fourier transform of the velocity profile.[1] The *SPAL* uses the negative arc length of the amplitude and the frequency-normalized Fourier transform of the velocity profile.[4] The frequency range used in *SPAL* was further limited in order to define *SPARC*.[6] Finally, *SPMR* expresses smoothness using the energy within a 0.2 Hz bin around the dominant frequency in the Fourier transform of the accelerations, normalized by the entire energy.[49]

<u>*Other metrics:*</u> Kostić and Popović[50] defined a smoothness metric (Combined Smoothness Metric [*CSM*]) in the context of a drawing task in which a patient, while seated at a desk, draws a pre-defined square. The smoothness metric uses information from the movement velocity and jerk, and consists of four different terms. As the formula uses different dimensions incorrectly, the metric was excluded (criterion E1).

Table 6.2 Simulation Analysis for each metric and its changes

Metric (Feasible Range)	Base Velocity Profile	Shape			Sinus		
		Min	Max	%Δ (%)	Min	Max	CE (%)
NOS* (1 – 7)	v_{symm}	1	2	**50**	1	7	10.7
	v_{asymm}	3	7	**N.A.**	3	7	1.2
SM (0 – 1)	v_{symm}	0.5	0.5	0	0.4	0.6	63.6
	v_{asymm}	0. 5	0.5	0	0.4	0.5	56
MAPR (0 – 1)	v_{symm}	0.8	0.8	0	0.8	1	3.2
	v_{asymm}	0.8	0.8	0	0.7	0.9	0.6
VAL* (-∞ – ∞)	v_{symm}	-2E-04	-1.6E-05	**91.7**	-1E-03	-5.7E-04	21.6
	v_{asymm}	-2E-04	-1.7E-05	**91.7**	-1E-03	-6.6E-04	16.2
Peaks* (1 – ∞)	v_{symm}	1	1	0	1	25	92.2
	v_{asymm}	1	1	0	1	25	93.4
IPV (-∞ – 1)	v_{symm}	1	1	0	0	1	92.2
	v_{asymm}	1	1	0	0	1	93.4
DSJt* (0 – ∞)	v_{symm}	19	19	0	17.4	8.2E+3	96.3
	v_{asymm}	36.4	36.7	0.1	34.4	8.2E+3	94
LDSJt* (0 – ∞)	v_{symm}	2.9	2.9	0	2.9	9	95.1
	v_{asymm}	3.6	3.6	0	4	9	90.9
DSJb* (0 – ∞)	v_{symm}	204.6	204.8	0.1	162.5	2.1E+07	96.9
	v_{asymm}	548	549.3	0.3	489.1	1.6E+07	95
LDSJb* (0 – ∞)	v_{symm}	5.3	5.3	0	5.1	16.9	95.1
	v_{asymm}	6.3	6.3	0	6.2	16.6	91.6
CM (-1 – 1)	v_{symm}	1	1	0	0.8	1	34.5
	v_{asymm}	0.6	0.6	0.1	0.4	0.6	26.7
SPMR (0 – 1)	v_{symm}	0.1	1	**774.4**	0.1	0.2	93.5
	v_{asymm}	0.1	0.9	**1E+03**	0.1	0.2	76.9
SPM (0 – ∞)	v_{symm}	-1	-1	0	-1.4	-1	57
	v_{asymm}	-1	-1	0	-1.4	-1	55
SPAL (0 – ∞)	v_{symm}	-2.1	-1.9	**11**	-3	-2	50
	v_{asymm}	-2	-1.8	**12.2**	-3	-1.8	54.7
SPARC (0 – ∞)	v_{symm}	-1.4	-1.4	1	-2.9	-1.4	66.9
	v_{asymm}	-1.4	-1.4	0.4	-2.8	-1.4	66.3

Assessing the response of each metric by comparing the effect of perturbation against the base velocity profile: Δ%: percentage difference in metric value from the base velocity profiles (instances where the metric depends on the shape are in bold), CE(%): percentage of combinations where the metric value differs by at least 10% from base velocity profiles, SNR(dB): the signal-to-noise ratio at which the metric differs by at least 10% from the base profile. Note that a higher added RMS noise value corresponds to a lower SNR value, and hence to a greater robustness to noise.

Noise			Filtered noise			Sub-movements (N=2)	
Min	Max	SNR (dB)	Min	Max	SNR (dB)	Min	Max
1	7	N.A.	1	7	N.A.	1	3
4	7	N.A.	4	7	N.A.	3	7
0.4	0.5	18.6	0.4	0.6	-	0.5	0.7
0.3	0.5	18.6	0.4	0.5	-	0.4	0.5
0.8	0.9	-	0.8	0.9	-	0.7	0.9
0.7	0.9	-	0.7	0.9	-	0.7	0.9
-9.7E-03	5.6E-03	25	-9.7E-03	-7.2E-03	19	-4.9E-03	-2E-03
-9.7E-03	4.2E-03	24.6	-9.7E-03	-7.9E-03	18.2	-4.9E-03	-2E-03
1	36	45	1	16	43.3	1	3
1	35	45.4	1	16	43.7	1	2
0	1	45	0	1	43.3	0.2	1
0	1	45.4	0	1	43.7	0.3	1
18.7	5.2E+03	45	18.5	885.6	49.3	18.8	95.6
34.4	5.2E+3	45.4	33.3	889.8	49.7	34.6	179.6
2.9	8.6	45	2.9	6.8	49.3	2.9	4.6
3.5	8.6	45.4	3.5	6.8	43.7	3.5	5.2
194.8	9.9E+06	45	191.4	3.8E+05	49.3	199.7	4.3E+03
478.6	8.5E+06	45.4	457	2.7E+05	49.7	437	1.1E+04
5.3	16.1	45	5.3	12.9	49.3	5.3	8.4
6.2	16	45.4	6.1	12.5	46.7	6.1	9.3
0.9	1	-	1	1	-	-0.2	1
0.6	0.7	-	0.6	0.7	-	-0.1	0.8
0	0.2	39	0	0.2	35.3	0.2	0.5
0	0.2	39.4	0	0.2	32.8	0.1	0.3
-2.1	-1	27	-1.6	-1	25.8	-1.8	-1
-2.1	-1	27.4	-1.6	-1	26.8	-2	-1
-2.3	-2	-	-2.3	-2	-	-3.4	-1.9
-2.2	-1.9	-	-2.2	-1.8	-	-3.8	-1.9
-2.2	-1.4	15.1	-2.2	-1.4	19	-2.7	-1.4
-2.1	-1.4	14.7	-2.1	-1.4	18.2	-3.1	-1.4

Metrics included are NOS* (number of sub-movements), SM (speed metric), MAPR (movement arrest period ratio), VAL* (velocity arc length), Peaks* (number of peaks), IPV (inverse of number of peaks and valleys), DSJt* and DSJb* (Dimensionless squared jerk), LDSJb* and LDSJt* (log of DSJt* and DSJb*), CM (correlation metric), SPMR (spectral metric), SPM (spectral method), SPAL (spectral arc length 2012), and SPARC (spectral arc length).

Response of metrics to changes in velocity profile

In the previous section, fifteen metrics were identified as mathematically sound, and therefore subjected to further analysis: *NOS*, *SM*, *MAPR*, *VAL*, *Peaks*, *IPV*, *DSJt*, *LDSJt*, *DSJb*, *LDSJb*, *CM*, *SPMR*, *SPM*, *SPAL* and *SPARC*. **Table 6.2** describes the selected metrics' range of feasible mathematical values obtained for each type of perturbation. The parameters used to interpret the response of metrics to the simulations (%Δ, CE, and SNR) are also shown. Metrics *SM, MAPR, IPV, CM*, *SPM*, *SPMR*, *SPAL* and *SPARC* should decrease with decreasing smoothness of movement. However, the other metrics increase with decreasing smoothness. To enable comparison across metrics, we append a * to these latter metrics. This includes *NOS**, *VAL**, *Peaks**, *DSJt**, *LDSJt**, *DSJb**, and *LDSJb**.

In this section, we discuss the results of the simulation analyses using v_{symm} as the base velocity profile. As the changes in the values of the smoothness metrics for the v_{asymm} were similar, their results have been placed in Additional File 1.F. The main difference between using the two base velocity profiles was the magnitude of the resulting values, as shown in **Table 6.2**. Where other differences in the response to the simulation analyses were found, they are addressed in the following sections.

Shape Simulation (SS)

Figure 6.2 shows the response of each metric to changes in movement duration and movement distance for the symmetric velocity profile. The percentage of change (%Δ) shows that *NOS**, *VAL**, *SPAL*, and *SPMR* were sensitive to changes in this simulation for both velocity profiles (Table 2). The inconsistencies in the number of sub-movements as measured by the *NOS** shows that this metric is not suitable as a smoothness metric. Metrics *SM*, *MAPR*, *Peaks**, *IPV*, *LDSJt**, *LDSJb**, *CM*, and *SPM* were truly insensitive to changes in this simulation.

Harmonic Disturbances (HD)

Figure 6.3 shows the metric outcomes with added sines of varying frequencies and amplitudes. The algorithm used to estimate *NOS** failed to converge to an optimal solution for higher frequencies (missing data in **Figure 6.3**). All other metrics behave as expected to this simulation and show a lower smoothness outcome as the amplitude of the added sine increases. However, all metrics except *SM*, *MAPR* and *CM* showed lower smoothness outcomes at higher frequencies for the same amplitude. *SPAL* and *SPARC* were insensitive to sine disturbances with frequencies higher than 20 Hz, as their definitions include the use of a cut-off frequency. The CE values for *NOS**, *MAPR*, *VAL**, and *CM* are less than 50% (**Table 6.2**) suggesting that these metrics are relatively less sensitive to harmonic disturbances, and might not be useful to reflect presence of tremor or weak control of reaching movement.

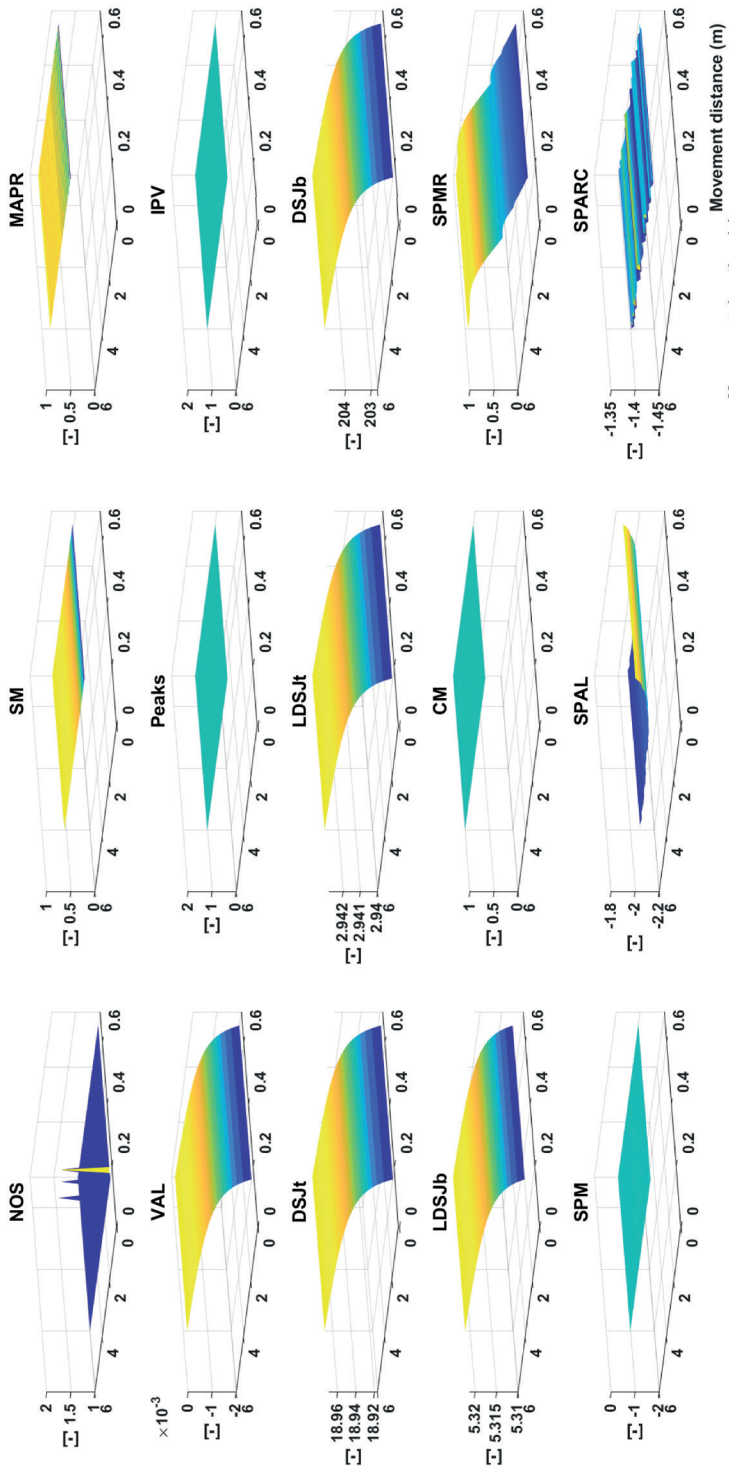

Figure 6.2 Shape simulation. *The vertical axis represents the metric value decreasing from yellow to blue. The horizontal axes represent the movement duration and movement distance. Metrics included are NOS* (number of sub-movements), SM (speed metric), MAPR (movement arrest period ratio), VAL* (velocity arc length), Peaks* (number of peaks), IPV (inverse of number of peaks and valleys), DSJt* and DSJb* (Dimensionless squared jerk), LDSJb* and LDSJt* (log of DSJt* and DSJb*), CM (correlation metric), SPMR (spectral metric), SPM (spectral method), SPAL (spectral arc length 2012), and SPARC (spectral arc length). By definition, the metrics with a * increase with decreasing smoothness.*

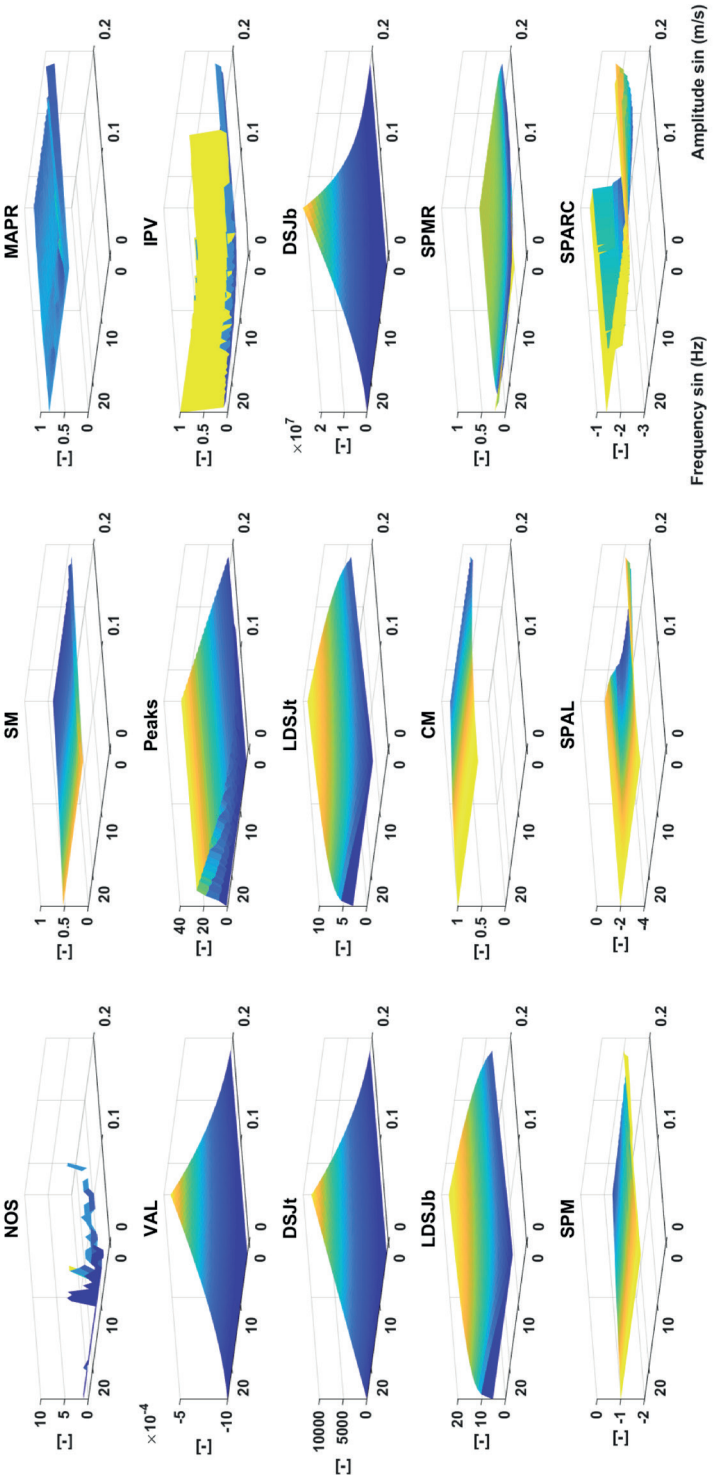

Figure 6.3 Harmonic Disturbances. *The vertical axis represents the metric value decreasing from yellow to blue. Metrics included are NOS* (number of sub-movements), SM (speed metric), MAPR (movement arrest period ratio), VAL* (velocity arc length), Peaks* (number of peaks), IPV (inverse of number of peaks and valleys), DSJt* and DSJb* (Dimensionless squared jerk), LDSJb* and LDSJt* (log of DSJt* and DSJb*), CM (correlation metric), SPMR (spectral metric), SPM (spectral method), SPAL (spectral arc length 2012), and SPARC (spectral arc length). By definition, the metrics with a * increase with decreasing smoothness.*

Measurement Noise (MN)

*NOS** is only capable of analysing the smoothness at low noise powers up to an RMS of 0.008 m/s (**Figure 6.4**). For higher noise powers, the algorithm that counts *NOS** fails to converge to an optimal solution (indicated by N.A. in **Table 6.2** in the SNR column). The other metrics show lower outcomes of smoothness as the RMS of the noise is increased (**Figure 6.4**). *MAPR*, *CM*, and *SPAL* did not cross the 10% threshold for any noise power included in the simulation (unfilled entries '-' in **Table 6.2**). This indicates that these metrics are robust to the range of measurement noises added in this study. *Peaks**, *IPV,* and all jerk-based smoothness metrics were very sensitive to measurement noise.

Sub-movements Simulation (SMS)

The algorithm used to estimate *NOS** calculated incorrect values at certain instances (**Figure 6.5**). This was because the algorithm did not converge to an optimal solution within the provided boundary constraints with increasing number of sub-movements. We found that only the *VAL** was truly monotonic to changes in lag between sub-movements (Additional File 1.G). *SPMR* surprisingly increased with increasing numbers of sub-movements which shows that the metric fails in this analysis. All other metrics showed a lower outcome for smoothness with increasing number of sub-movements and increasing delay between them. For *Peaks** and *IPV*, a third peak was detected at 0.3 and 0.5 s (**Figure 6.5**). Although non monotonic overall, the metrics *Peaks**, *IPV*, *SPM*, *SPAL*, and *SPARC* showed jumps only at certain discrete intervals. The *CM* was seen to be monotonic only if the delay between sub-movements was larger than 0.2 s. Further, when considering increases in delays (*Ks*) of 0.06 s, the *SPAL* and *SPARC* metrics also showed a monotonic change for delays larger than 0.2 s. Furthermore, the monotonicity was influenced by the base velocity profile used for all metrics except *VAL**, *SPMR*, and *SPARC* (Additional File 1.G).

Summary of findings

Table 6.3 summarizes the simulation analysis results and indicates whether the responses of each metric were as expected. For the measurement noise analysis, the robustness of each metric to added noise was studied. Descriptive statistics of the SNR values as shown in **Table 6.2** were used to divide the metrics into two groups: *high* and *low* robustness to measurement noise. Note that a higher added RMS noise value corresponds to a lower SNR value, and hence to greater robustness to noise. We find that only *SPARC* responded as expected to the *Shape Simulation*, *Harmonic Disturbances*, and *Measurement Noise* simulations. For the *Sub-movement Simulation*, *SPARC* responded as expected by showing a monotonic change for increase in delays between sub-movements greater than 0.2 s (20% of sub-movement duration) only when the delay was increased in steps of 0.06 s (6% of sub-movement duration).

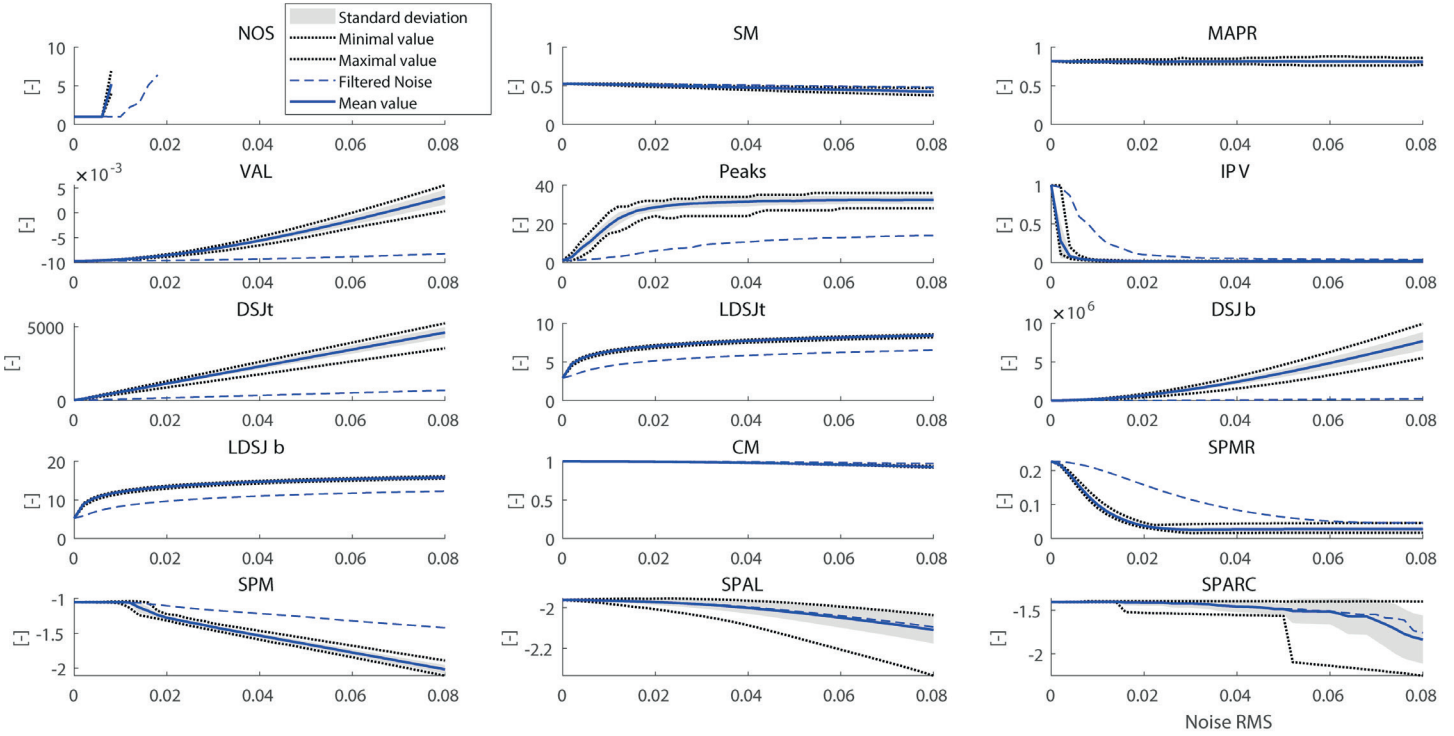

Figure 6.4 Measurement Noise. *The thick blue line represents the mean value of 25 different realizations of the noise for each measurement noise level added, and the shaded area is the corresponding standard deviation. The dotted black lines denote the minimum and maximum values of the metric found at that RMS value. The dashed blue line shows mean values of the filtered noise sets. Metrics included are NOS* (number of sub-movements), SM (speed metric), MAPR (movement arrest period ratio), VAL* (velocity arc length), Peaks* (number of peaks), IPV (inverse of number of peaks and valleys), DSJt* and DSJb* (Dimensionless squared jerk), LDSJb* and LDSJt* (log of DSJt* and DSJb*), CM (correlation metric), SPMR (spectral metric), SPM (spectral method), SPAL (spectral arc length 2012), and SPARC (spectral arc length). By definition, the metrics with a * increase with decreasing smoothness.*

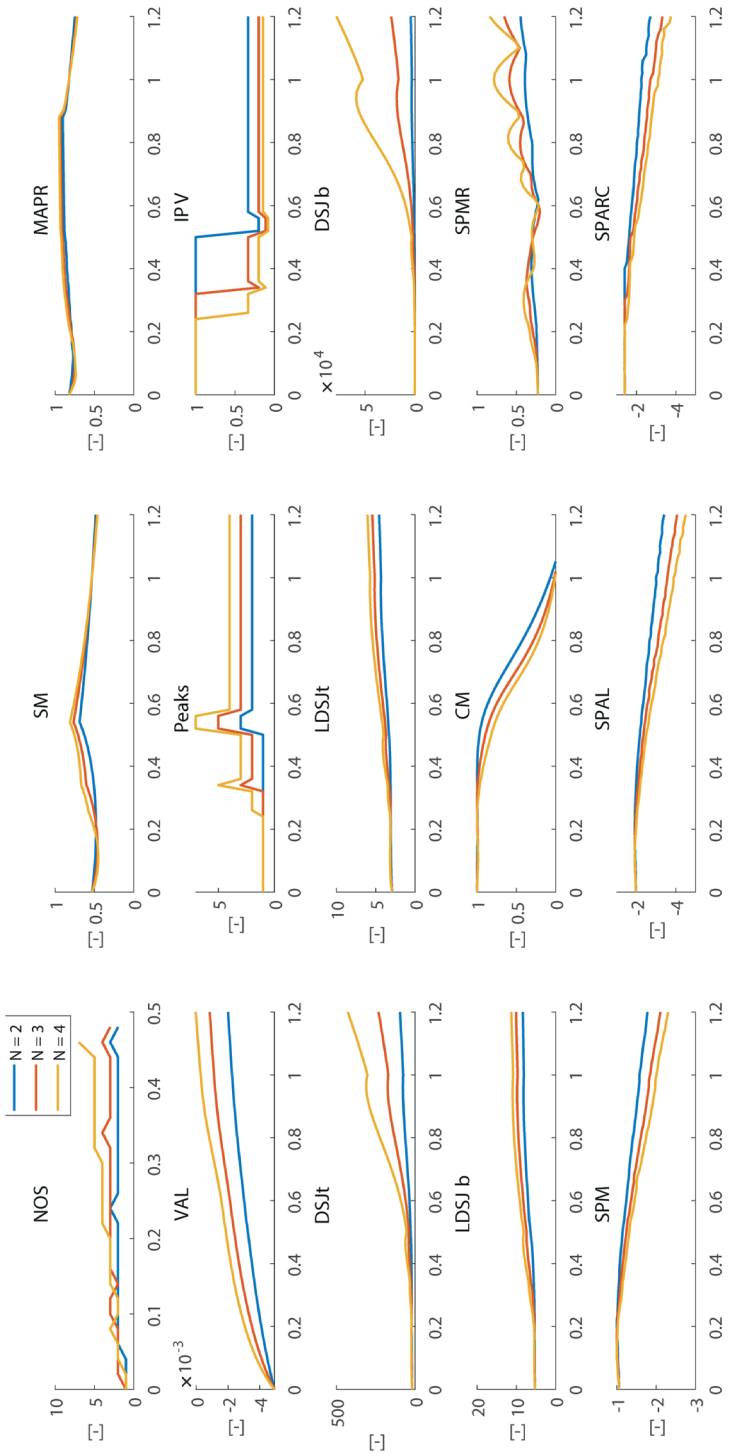

Figure 6.5 Sub-movements simulation. *The colours denote the number of sub-movements. The horizontal axis represents the lag between two sub-movements. Metrics included are NOS* (number of sub-movements), SM (speed metric), MAPR (movement arrest period ratio), VAL* (velocity arc length), Peaks* (number of peaks), IPV (inverse of number of peaks and valleys), DSJt* and DSJb* (Dimensionless squared jerk), LDSJb* and LDSJt* (log of DSJt* and DSJb*), CM (correlation metric), SPMR (spectral metric), SPM (spectral method), SPAL (spectral arc length 2012), and SPARC (spectral arc length). By definition, the metrics with a * increase with decreasing smoothness.*

Table 6.3 Summary of the analysis results.

Metric	Duration/Distance independence		Harmonic Disturbances		Sub-movements		Robustness	
	v_{symm}	v_{asymm}	v_{symm}	v_{asymm}	v_{symm}	v_{asymm}	v_{symm}	v_{asymm}
NOS*	No	No	No	No	No	No	No Data+	
SM	Yes[1]	Yes[1]	Yes	Yes	No	No	High	High[4]
MAPR	Yes[1]	Yes[1]	No	No	No	No	High[4]	High[4]
VAL*	No	No	No	No	Yes	Yes	High	High
Peaks*	Yes[1]	Yes[1]	Yes	Yes	No	No	Low	Low
IPV	Yes[1]	Yes[1]	Yes	Yes	No	No	Low	Low
DSJt*	Yes[1]	Yes	Yes	Yes	No	No	Low	Low
LDSJt*	Yes[1]	Yes[1]	Yes	Yes	No	No	Low	Low
DSJb*	Yes	Yes	Yes	Yes	No	No	Low	Low
LDSJb*	Yes[1]	Yes[1]	Yes	Yes	No	No	Low	Low
CM	Yes[1]	Yes	No	No	No[2]	No[2]	High[4]	High[4]
SPMR	No	No	Yes	Yes	No	No	Low	Low
SPM	Yes[1]	Yes[1]	Yes	Yes	No	No	Low	Low
SPAL	No	No	Yes	Yes	No[2,3]	No[2,3]	High[4]	High[4]
SPARC	Yes	Yes	Yes	Yes	No[2,3]	No[2,3]	High	High

'Yes' means that the metric responded to the perturbations as expected, whereas 'No' means otherwise. [1]There was no instance in the analysis where the metric value crossed the 10% threshold. [2]The metric showed monotonic change for lag values greater than 0.2 s. [3]The metric showed monotonic change when the derivative was estimated using steps of 0.06 s for the lag between sub-movements. [4]The metric was robust to all noise values added in the simulation. [+] Incomplete data. Metrics included are NOS* (number of sub-movements), SM (speed metric), MAPR (movement arrest period ratio), VAL* (velocity arc length), Peaks* (number of peaks), IPV (inverse of number of peaks and valleys), DSJt* and DSJb* (Dimensionless squared jerk), LDSJb* and LDSJt* (log of DSJt* and DSJb*), CM (correlation metric), SPMR (spectral metric), SPM (spectral method), SPAL (spectral arc length 2012), and SPARC (spectral arc length).

Discussion

The aim of this study was to identify valid smoothness metrics to investigate the QoM of the upper paretic limb during reaching tasks by persons with stroke. A smoothness metric used in stroke research was valid if it was mathematically sound, and responded to the simulation analyses as expected. The systematic literature review revealed 32 different metrics used in stroke research, however, only 15 unique metrics had a sound mathematical definition relating to smoothness.[16] Many metrics were sensitive to reaching distance and duration, or were not found to be useful to reflect presence of tremor or weak control of reaching movement, or were not robust to added measurement noise. We find that almost all metrics do not change monotonically to increasing delay between the sub-movements. Further, we observe in some cases (**Table 6.3**) that the reaching task influences the behaviour of smoothness metric, which was a disadvantage to certain metrics. Our simulation analyses showed that Spectral Arc Length (*SPARC*) responded favourably in all simulation analyses, for both base velocity profiles, and therefore is a valid metric to measure smoothness of reach-to-point or reach-to-grasp movements post stroke.

The simulation analyses performed in this study builds on and agrees with the trends for the shape, noise, and sub-movement simulations shown in literature.[4,6,14,16] However, this study offers an exhaustive analysis of all available smoothness measures and also offers insight on influence of added sinusoids.

Clinical Relevance

Smoothness is considered a result of learned coordinative processes, and increased motor control results in improved smoothness during reaching, pointing and grasping.[5,6,14] Identifying and using valid smoothness metrics is essential for proper clinical research, and results in accurate observations of the recovery of motor control while improving the identification of true treatment effects on QoM. The present study showed that only *SPARC* is a valid smoothness metrics in spite of the plethora available in the literature.

Neurological recovery occurs spontaneously after stroke and results in normalization of neurological measures such as EEG patterns, whereas behavioural restitution is rather restricted to regaining normal behaviour, not denying that neuronal restitution is taking place.[51,52] Clinical assessments which are most closely related to behavioural restitution and thereby neurological recovery, take into account the ability to perform movements outside the pathologic synergies.[53] Whether smoothness metrics reflect neurological recovery after stroke can be determined by investigating the longitudinal

association between clinical outcomes that measure behavioural restitution and smoothness metrics.[54] Furthermore, studying the associations between the recovery of neurological pathways and changes in movement smoothness will reveal the influence of behavioural restitution and compensation on smoothness. Additionally, identifying neurological recovery along with changes in movement smoothness post stroke and eventually the underlying physiology that governs smoothness, will provide an indication whether smoothness can be used as a target or outcome measure in training and in designing rehabilitation robotics. In these cases, smoothness measured during reaching in healthy age- and gender-matched individuals can be used as reference values.[54]

This study used simulations to offer a systematic analysis of changes to the reaching profiles. In case of harmonic disturbance analysis, the upper limit of the sinusoidal frequency range tested (25 Hz) was beyond known frequencies in stroke, and therefore covers all potential disturbances.[55] In case of noise simulation analysis, the robustness of metrics to added measurement noise was tested. However, if the noise is a result of weak human control, the resulting movement would be less smooth, as reflected by the smoothness metric. Therefore, efforts to distinguish between measurement noise and perturbations due to actual human motion control must be undertaken in order to distinguish abnormal, pathologically reduced movement smoothness from that seen in healthy, age- and gender-matched subjects.

Practical Barriers

In order to measure smoothness, the measurement system should be capable of measuring velocity (or a higher derivative) of reaching. Measuring smoothness using motion tracking systems or high-end kinematic measurement sensors is relatively simple using the *SPARC* metric. However, practical requirements need to be considered when the metric is applied in either a clinical setting or an ambulatory or daily life setting. For ambulatory or daily life settings, metrics that can be estimated using wearable on-body sensors are preferred. Inertial and Magnetic Measurement Units (IMUs) are commonly used as wearable sensors for measuring the kinematics of movement. However, as an IMU measures accelerations, estimating velocity from it would require additional processing and is usually prone to drift.[56] In this study, we measured *SPARC* using linear velocities.[6] Alternatively, in a recent study, Melendez-Calderon and colleagues suggest that during reaching, *SPARC* can be measured using angular velocities obtained from IMUs.[22] However, techniques to correct drift due to strapdown integration[56] were not employed in their study, as the authors suggest that it warrants a systematic analysis of the errors introduced in the smoothness estimate.[22] Therefore, if the errors are accounted for, it should be possible to reliably measure

SPARC using corrected linear velocities obtained from IMUs for a standardized pre-defined movement with a clear start and end posture. Given the advantages of using IMUs, their validity in measuring QoM after stroke requires further research.[57]

Generalizability of current findings

Besides stroke, smoothness is highly relevant for studying the impact of neurological disease in other populations, such as those with Parkinson's and Huntington's disease.[16] For instance, smoothness has been used to study *fluidity* of movement in the upper limb, reflecting bradykinesia and rigidity in patients with Parkinson's disease.[58] Furthermore, the generalizability of smoothness should be investigated for the lower limb allowing to differentiate between affected and healthy gait, as well as to examine effects of medication on smoothness, and to identify fall risk.[59] In addition, the level of smoothness is highly relevant in sports as a measure of proficiency.[60,61] The present findings may serve as inspiration for related fields to determine how smoothness varies for the movement task they analyse.

Limitations and future directions

The first limitation of the current review was that it was restricted to smoothness metrics investigated in post-stroke reaching. Additional metrics for measuring movement smoothness could have been identified if our review was not limited to stroke studies. Generalization to other neurological diseases is therefore limited. The same is true for other movement tasks such as rhythmic drinking tasks[62] or self-paced, isolated elbow flexion movements[63].

Secondly, only English language articles were considered for our systematic review. Thirdly, we model different reaching tasks with different velocity profiles; reach-to-point or aiming movements with symmetrical velocity profiles based on minimum jerk models[27], and reach-to-grasp movement with an asymmetrical velocity profile based on a polynomial curve[28]. The minimum jerk profile was shown to be a good approximation for reaching in healthy individuals.[14,64-69] The asymmetric profile was modelled by applying a polynomial fit to reach-to-grasp movements in healthy individuals using a polynomial fit. This fit was found to be better than averaging the reaching profiles from the healthy individuals (Additional File 1.B). However, a true measure of smoothness should not be influenced by the movement profile.

Fourthly, the sub-movement analysis shows that a minimum detectable change in smoothness as measured by *SPARC* reflects a change in delay between sub-movements that were at least 6% of the sub-movement duration or longer. Furthermore, as the metric is non-monotonic for delays less than 20% the duration of a sub-movement,

it should be used with caution when studying differences in smoothness amongst fully recovered or healthy individuals. This needs to be considered when studying populations with good recovery. Finally, smoothness metrics such as *RJ* are based on rotational movements and had to be rejected as they could not be tested with the current simulations.

As QoM is studied by comparing task performance with normative values, *CM* could have been a suitable metric.[70] It is defined using correlation with a minimal jerk profile and it might be interesting to consider a *CM* measure that takes account of correlation with a velocity profile that models the reaching task. However, in our analysis, we saw that the metric might not be useful in measuring tremor or weak control of reaching movement. Additionally, the need for prior knowledge of the intended reaching task is a big drawback of the metric.

Although our simulations mimicked features of reaching in persons with stroke, such as varying duration or distance, and sub-movement segmentation[11], they cannot truly replace actual reaching by subjects who have suffered a stroke. Moreover, longitudinal studies of patterns of smoothness metrics in patients early post stroke will show how sensitive the smoothness metric over time and how these values relate to values measured in healthy age- and gender-matched subjects. We performed this analysis in our companion paper[71], where SPARC was seen to be responsive to change over time in the early phase post stroke and longitudinally associated with clinical measures of motor impairment within subjects.

Conclusion

We recommend the use of SPARC as a valid metric to measure the smoothness of the upper limb reaching after stroke. Longitudinal studies are further required to understand the relationship between the time course of recovery and smoothness early post stroke.

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Author's contributions
MIMR and BS equally contributed to the conception of the study, systematic review and analysis, the simulation analyses and in writing and editing the manuscript. MS contributed to the systematic review, interpretation of results, and in writing and editing the manuscript. JvK, JBJB, PV, and JB contributed by revising the manuscript. CM and EvW contributed to the interpretation of results and substantially revised the manuscript. GK and BJvB contributed to the conception and design of the study and substantially revised the manuscript. All authors read and approved the final manuscript.

Additional files
Additional files can be found online.

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Smoothness metric during reach-to-grasp after stroke. Part 2: Longitudinal association with motor impairment.

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Abstract

Background: The cause of smoothness deficits as a proxy for quality of movement post stroke is currently unclear. Previous simulation analyses showed that spectral arc length (SPARC) is a valid metric for investigating smoothness during a multi-joint goal-directed reaching task. The goal of this observational study was to investigate how SPARC values change over time, and whether SPARC is longitudinally associated with the recovery from motor impairments reflected by the Fugl-Meyer motor assessment of the upper extremity (FM-UE) in the first 6 months after stroke.

Methods: Forty patients who suffered a first-ever unilateral ischemic stroke (22 males, aged 58.6±12.5 years) with upper extremity paresis underwent kinematic and clinical measurements in weeks 1, 2, 3, 4, 5, 8, 12, and 26 post stroke. Clinical measures included amongst others FM-UE. SPARC was obtained by three-dimensional kinematic measurements using an electromagnetic motion tracking system during a reach-to-grasp movement. Kinematic assessments of 12 healthy, age-matched individuals served as reference. Longitudinal linear mixed model analyses were performed to determine SPARC change over time, compare smoothness in patients with reference values of healthy individuals, and establish the longitudinal association between SPARC and FM-UE scores.

Results: SPARC showed a significant positive longitudinal association with FM-UE (B: 31.73, 95%-CI: [27.27 36.20], $P<0.001$), which encompassed significant within- and between-subject effects (B: 30.85, 95%-CI: [26.28 35.41], $P<0.001$ and B: 50.59, 95%-CI: [29.97 71.21], $P<0.001$, respectively). Until 5 weeks post stroke, progress of time contributed significantly to the increase in SPARC and FM-UE scores ($P<0.05$), whereafter they levelled off. At group level, smoothness was lower in patients who suffered a stroke compared to healthy subjects at all time points ($P<0.05$).

Conclusions: The present findings show that, after stroke, recovery of smoothness in a multi-joint reaching task and recovery from motor impairments are longitudinally associated and follow a similar time course. This suggests that the reduction of smoothness deficits quantified by SPARC is a proper objective reflection of recovery from motor impairment, as reflected by FM-UE, probably driven by a common underlying process of spontaneous neurological recovery early post stroke.

Introduction

Motor impairments of the upper extremity are estimated to occur in about 80% of patients who survived a stroke.[1,2] These impairments are characterized by weakness, diminished dexterity, spatial and temporal discontinuity (i.e., lack of smoothness), and abnormal stereotypic patterns of muscle activation or muscle synergies during goal-directed movements.[3,4] Spontaneous motor recovery occurs mainly in the first 10 weeks post stroke, depending on stroke severity.[5] Smoothness of movements, for example during reaching, is an important indicator of quality of movement (QoM)[6-9], which is valuable for computational models of neurological recovery when studying motor control after stroke [10-12]. Enhanced smoothness has been argued to reflect improved sensorimotor coordination and movement proficiency.[13,14] Unfortunately, the underlying neurophysiological mechanisms of post-stroke smoothness deficits during multi-joint movements such as reaching are poorly understood.[11]

Several theories have been proposed, for example less smooth movements may reflect unstable co-contractions between agonists and antagonists due to a lack of reciprocal inhibition.[15,16] In line with this, muscle activity patterns observed during reaching after stroke were shown to be more synchronized.[17,18] An EMG study suggested that a reduced motor unit discharge rate post stroke would explain the decreased smoothness.[19] Buma and colleagues (2016) found an association between an increase in jerk and additional cortical recruitment in secondary sensorimotor areas as shown by fMRI in subjects with subacute stroke, which supports the hypothesis of enhanced online feedback corrections to prevent movement errors during upper limb reaching early after stroke.[20] One may also hypothesize that the lack of smoothness is a reflection of increased segmentation of multi-joint movements[16], observed together with abnormal muscle synergies[21-23]. Although the underlying neurophysiological cause of smoothness deficits are unknown, improvement of smoothness deficits after stroke has been assumed to reflect neurological recovery. Therefore, one may hypothesize that recovery of smoothness will occur in the same time window as that of spontaneous neurological recovery post stroke. As a consequence, smoothness may serve as a fine-grained marker for measuring recovery of motor control early post stroke.[10]

In our previous study, we showed that out of 32 different smoothness metrics which have been used in stroke studies, only *spectral arc length* (SPARC)[10] is a valid metric to reflect smoothness during a multi-joint reach-to-grasp movement.[24] The frequency spectrum of a movement is dependent on the sub-movements dispersed in time. Smooth movements are assumed to be composed of mainly low-frequency

components, whereas less smooth movements show a larger amount of higher-frequency components and thereby show a more complex magnitude spectrum. The smoothness metric SPARC is based on the complexity of the shape of a Fourier magnitude spectrum of the velocity profile during a reaching task.[25] However, recovery of SPARC during reaching movements has not been investigated longitudinally early after stroke, nor its within-subject association with motor recovery measured with the Fugl-Meyer motor assessment of the upper extremity (FM-UE).

Assuming that recovery of smoothness reflects a decreasing segmentation of motor performance due to progressive blending of sub-movements[16], we hypothesized that an increase in SPARC values would be associated with recovery from motor impairments as measured with FM-UE. In addition, we hypothesized that SPARC would improve mainly in the early phase, whereafter it would level-off, within the time window of spontaneous neurological recovery. Therefore, the present paper addresses three key questions. First, whether smoothness, reflected by SPARC during a reach-to-grasp movement, is longitudinally associated with FM-UE scores in the first six months post stroke. Second, whether the observed time window of recovery of smoothness is in line with the time window of FM-UE recovery. Third, whether patients attain healthy reference values of smoothness within the first six months post stroke.

Materials and methods

Participants and procedures

Patients admitted to one of the acute stroke units of eleven participating hospitals in the Netherlands were screened. This prospective longitudinal multicentre cohort study, which was part of a translational research programme to explain plasticity after stroke (EXPLICIT-stroke[26]) included 40 patients who suffered a stroke (22 males, 18 females). Inclusion criteria were: (1) ≤1 week after a first-ever ischemic hemispheric stroke, as revealed by computerized axial tomography or magnetic resonance imaging scan; (2) being able to sit independently without trunk support for at least 30 seconds; (3) upper limb motor deficits, but with the ability to grasp objects within 3 weeks post stroke; (4) aged between 18 and 80 years; and (5) having provided written informed consent. Exclusion criteria were: (1) severe cognitive deficits (Mini-Mental State Examination score <23); (2) comorbidities such as cardiac, pulmonary, orthopaedic or other neurological disorders; and (3) participating in other studies. By using their paretic arm, patients performed clinical assessments, as well as a 3-dimensional kinematic reach-to-grasp task to estimate their movement smoothness. This was done weekly between week 1 and week 5 post stroke, and at weeks 8, 12, and 26. Patients were allowed to receive movement therapy during the study.

Twelve age- and gender-matched healthy individuals without reported history of neurological and/or orthopaedic disorders (7 males, 5 females) were included to obtain healthy reference values for smoothness.

The EXPLICIT-stroke study was approved by the Medical Ethics Committee of the VU University medical centre, Amsterdam, The Netherlands, and carried out in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki[27].

Clinical assessment

A clinical measure of motor impairment commonly used in stroke studies is the Fugl-Meyer motor assessment of the upper extremity (FM-UE, range [0-66]), which shows excellent inter-rater and intra-rater reliability and construct validity.[28] Although the FM-UE originates from the evolution of abnormal muscle synergies[3,29], it is also influenced by other impairments such as upper limb paresis[30], and is widely used to describe neurological motor impairment after stroke. Bamford classification[31] was used to establish the type of stroke; the National Institutes of Health Stroke Scale (NIHSS)[32] was used to assess the global neurological deficit; clinical assessments to

determine functional ability included the Action Research Arm Test (ARAT)[33] of the paretic upper extremity and the Barthel Index (BI)[34]; sensory deficits were monitored by performing the Erasmus MC modification of the Nottingham Sensory Assessment (EmNSA)[35] of the upper extremity.

Kinematic measurement

Participants were seated on a chair, with their paretic hand placed in front of their shoulder on the edge of a table with a height of 76 cm. A block of 5x5x5 cm (150 g) was placed in front of their shoulder at a participant-specific maximum reaching distance, obtained using the less affected arm. Participants were asked to reach towards the block, grasp the block with their thumb and index finger, lift it, and place it on the indicated position at the less affected body side (**Figure 7.1**). Participants were instructed not to slide the block or upper limb over the table, but to move the hand through the air. Participants started after the experimenter gave a verbal "go" signal. During this movement, participants were not allowed to slide or twist over the seat of the chair, but were allowed to move their trunk away from the back of the chair if this was more comfortable. Each measurement involved recording seven repetitions. Healthy individuals performed the reach-to-grasp movement with their non-dominant hand.

Kinematic data were recorded using a portable electromagnetic motion tracking device (Polhemus Liberty) consisting of an electromagnetic source and seven motion sensors of size 2.3x2.8x1.5 cm. The source was placed on the edge of the table at the paretic side[22] (**Figure 7.1**). Sensors were attached to the thorax, and to six segments of the paretic upper extremity (scapula, upper arm, forearm, hand, thumb, and index finger), using double-sided adhesive tape (**Figure 7.1**). Only the data of sensors placed on the forearm and hand were used for the present study. The sampling frequency during the motion recordings was 240 Hz. All 3-dimensional kinematic assessments were conducted by one researcher (JvK). This portable setup enabled measurements at the participants' place of residence (e.g., stroke unit in a hospital, rehabilitation centre, nursing home or their home situation), limiting the burden on patients in this longitudinal study.

Kinematic data analysis

The reach-to-grasp part of the movement performed was extracted and analysed. The start of the movement was defined as the moment at which the hand sensor exceeded 5% of the maximum tangential speed during the forward reach.[36] The end of the reaching movement was defined as the moment at which the forearm sensor exceeded 5% of the maximum tangential speed for the first time during the

displacement of the block.[37] Time series for displacement of the hand were filtered using a 2nd order recursive Butterworth low-pass filter with a cut-off frequency of 20 Hz. All computations were performed in MATLAB (2015b, The Mathworks, Natick, MA, USA). A detailed description of the computation of SPARC can be found in the first part of this twin paper.[10,24] Higher SPARC values (i.e., less negative) reflect smoother movements.

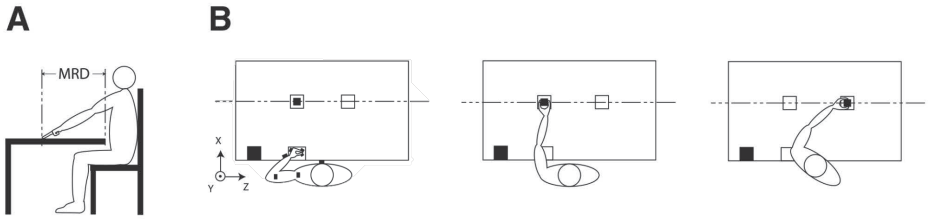

Figure 7.1 Kinematic measurement set-up

(A) Determination of the maximum reaching distance (MRD), also indicated by a dashed line. (B) Visualization of the task performance. Left panel: initial position and visualization of sensor placement on the subject. Middle panel: reaching forward towards the block (small black square), grasping the block between thumb and index finger. Right panel: lifting and moving the block without sliding and placing it at the indicated end position. The large black square at the corner of the table indicates the position of the electromagnetic source of the Polhemus Liberty system.

Statistical analysis

The longitudinal association between smoothness metric SPARC and FM-UE within the first six months post stroke, and their change over time, were both analysed using a linear mixed model.

For the first analysis, the smoothness metric SPARC served as independent variable, while FM-UE served as dependent variable. A random intercept was added for each individual to account for dependency within subjects. The regression coefficient of a regular longitudinal association is a combination of a within- and between-subject effect. These two effects can be distinguished by applying a hybrid model.[38] The between-subject covariate was determined as the individual average value of the smoothness metric over time, while the within-subject covariate was calculated as the observed value minus the individual average. The hybrid model results in two regression coefficients. The within-subject regression coefficient is the most interesting for the present analysis. It reflects whether the change of the dependent variable within a subject over time is associated with a change of the independent variable within a subject over time.

For the second analysis, the factor ‘week of measurement’ was included as the main fixed effect; a random intercept per individual was added to account for dependency within subjects. Two separate models were applied for SPARC and FM-UE as dependent variables.

SPARC values of patients who suffered a stroke were compared with reference values obtained from healthy participants at every time point using independent samples t-tests. Multiple testing was accounted for using the Holm-Bonferroni method.[39]

Statistical analyses were performed using IBM SPSS Statistic for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). For each regression model, the distribution of residuals was tested for normality by inspecting histograms and Q-Q plots.

Results

Participants

Table 7.1 displays the baseline characteristics of the 40 included patients who suffered a stroke (22 males; mean age ± SD: 58.6±12.5 years) and the 12 healthy age- and gender-matched participants (7 males; mean age ± SD: 52.8±5.9 years). All recruited patients had the ability to grasp the object in the third week post stroke. Twenty patients were able to perform the kinematic assessment starting in the first week after stroke onset, 13 starting in the second week, and seven starting in the third week post stroke.

Table 7.1 Participant characteristics at baseline

Characteristics	Values[a]
Stroke patients (N = 40)	
Age (years)	58.6±12.5
Sex (male/female)	22/18
Most affected body side (left/right)	25/15
Hand dominance (left/right/forced right)	2/37/1
Bamford classification (LACI/PACI/TACI)	29/9/2
Time post stroke of the first clinical assessment (days)	7.3±2.9
Clinical scores at baseline (week 1 post stroke)	
FM-UE (0-66)	43.5 (29.3-54.5)
$FM\text{-}UE_{arm}$ (0-52)	34 (21.0-44.0)
NIHSS (42-0)	4.0 (2.0-5.0)
ARAT (0-57)	25.0 (7.3-36.0)
BI (0-20)	15.0 (11.0-17.0)
EmNSA (0-40)	40.0 (34.8-40.0)
Healthy participants (N = 12)	
Age (years)	52.8±5.9
Sex (male/female)	7/5

[a] *Values are number, mean ± standard deviation or median (interquartile range). Abbreviations: N, number of participants; LACI, lacunar anterior circular infarct; PACI, partial anterior circular infarct; TACI, total anterior circular infarct; FM-UE, Fugl-Meyer motor assessment of the upper extremity;* $FM\text{-}UE_{arm}$*, FM-UE without hand function scores; NIHSS, National Institutes of Health Stroke Scale; ARAT, Action Research Arm Test; BI, Barthel Index; EmNSA, Erasmus MC modified Nottingham Sensory Assessment of the upper extremity.*

Longitudinal association between SPARC and FM-UE

SPARC showed a significant positive longitudinal association with FM-UE (B: 31.73, 95%-CI: [27.27 36.20], *P*<0.001). The hybrid model showed that this association encompassed a significant within- and between-subject effect (B: 30.85, 95%-CI: [26.28 35.41], *P*<0.001 and B: 50.59, 95%-CI: [29.97 71.21], *P*<0.001, respectively). **Figure 7.2** shows smoothness against motor impairment at each measurement moment. **Figure 7.3** shows for each measurement moment the average smoothness in the investigated population against the average motor impairment score. These figures visualize that when patients show recovery of smoothness, they also show recovery from motor impairment in parallel. Moreover, the kinematic metric SPARC suffers less from a ceiling effect compared to the clinical measure FM-UE.

Change over time and comparison with reference values

Figure 7.4 shows the change of SPARC and FM-UE over time post stroke, and how the values of patients who suffered a stroke compare with the reference values of the healthy individuals. The effect of time after stroke was significant for weeks 1 to 4 after stroke for SPARC and FM-UE (*P*<0.05, **Table 7.2**). SPARC showed a gradual increase over time towards the reference values of the healthy individuals; it levelled off in week 5 (**Table 7.2**) yet remained lower in the patients who suffered a stroke than the age-matched healthy individuals (*P*<0.05/N_s, **Table 7.3**). FM-UE showed an increase over time and levelled off in week 5 (**Table 7.2**).

Table 7.2. Regression coefficients of SPARC and FM-UE relative to week 26 post stroke

Time points		***SPARC***			***FM-UE***	
	B	***95%-CI***	***P***	***B***	***95%-CI***	***P***
(Intercept)	-1.48	[-1.52 -1.43]	**<0.001**	61.40	[58.60 64.20]	**<0.001**
Week 1	-0.26	[-0.20 -0.32]	**<0.001**	-21.48	[-18.76 -24.19]	**<0.001**
Week 2	-0.18	[-0.13 -0.23]	**<0.001**	-9.89	[-7.11 -12.67]	**<0.001**
Week 3	-0.09	[-0.04 -0.14]	**<0.001**	-5.46	[-2.47 -8.46]	**<0.001**
Week 4	-0.06	[-0.01 -0.11]	**0.025**	-3.25	[-0.32 -6.18]	**0.030**
Week 5	-0.05	[0.00 -0.10]	0.062	-2.62	[0.12 -5.35]	0.061
Week 8	-0.03	[0.02 -0.08]	0.290	-0.94	[1.91 -3.79]	0.515
Week 12	-0.01	[0.04 -0.06]	0.558	-0.66	[2.12 -3.43]	0.643
Week 26	0[a]	-	**-**	0[a]	-	**-**

Abbreviations: B, regression coefficient; 95%-CI, 95% confidence interval; P, probability value; SPARC, spectral arc length; FM-UE, Fugl-Meyer motor assessment of the upper extremity. [a]*This parameter is set to 0 because it is redundant. Significant values are indicated in bold font. A P-value below 0.05 indicates a significant difference from the reference time point (week 26). For both SPARC and FM-UE, the contribution of time was significant until week 5 post stroke.*

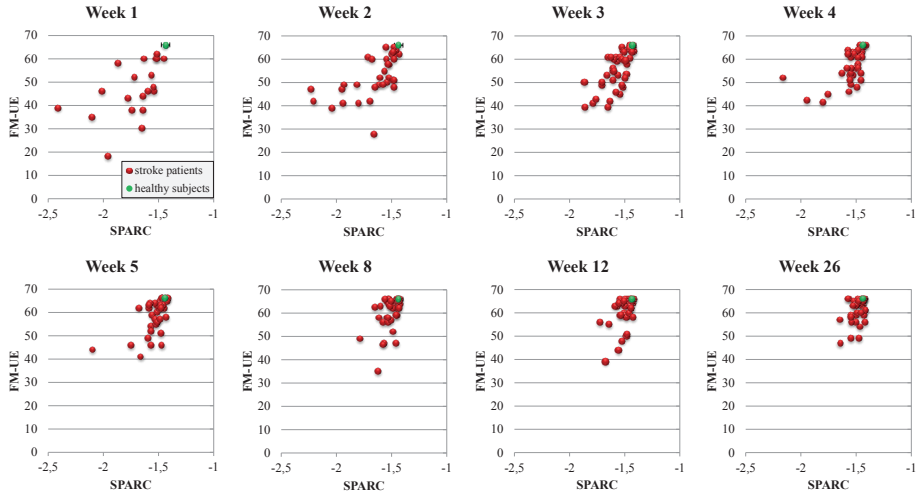

Figure 7.2 Smoothness against motor performance at each measurement moment post stroke.

Scatter plots of Spectral Arc Length (SPARC) against Fugl-Meyer motor assessment score of the Upper Extremity (FM-UE) at each measurement moment. Red solid dots represent data of stroke patients. Green dots with error bars represent the average value and standard deviation of the healthy age- and gender-matched controls.

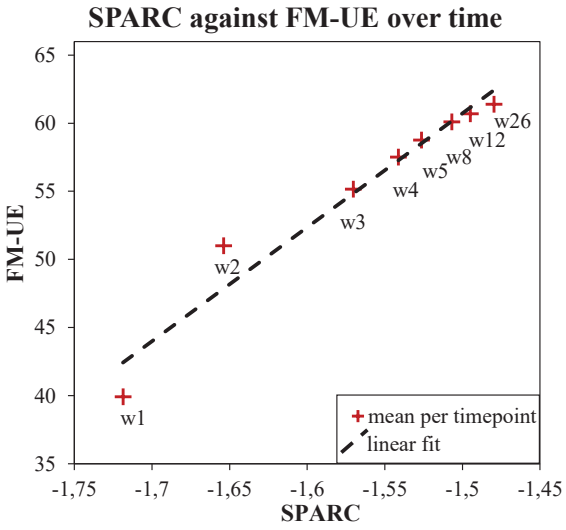

Figure 7.3. Smoothness against motor performance change in parallel post stroke.

Mean Spectral Arc Length (SPARC) against mean Fugl-Meyer motor assessment score of the Upper Extremity (FM-UE) at each measurement moment indicated by red crosses. The dashed black line concerns a linear fit.

Table 7.3. Reach-to-grasp smoothness of stroke patients compared to healthy reference values.

	SPARC			
	mean	**SD**	**t(df)**	***P***
Week 1	-1.719	0.243	3.98(30)	**<0.001**
Week 2	-1.654	0.218	3.42(43)	**0.001**
Week 3	-1.570	0.114	3.98(50)	**<0.001**
Week 4	-1.541	0.145	2.47(50)	**0.017**
Week 5	-1.526	0.118	2.59(50)	**0.013**
Week 8	-1.507	0.076	3.11(50)	**0.003**
Week 12	-1.495	0.070	2.77(50)	**0.008**
Week 26	-1.480	0.059	2.43(50)	**0.019**
Healthy age- and gender-matched individuals	-1.436	0.038	-	-

Abbreviations: SPARC, spectral arc length (less negative values reflect smoother movements); SD, standard deviation; t, t-statistic of the independent samples t-test; df, degrees of freedom; P, probability value. Significant probability values after Holm-Bonferroni corrections are indicated in bold font ($P<0.05/N_s$).

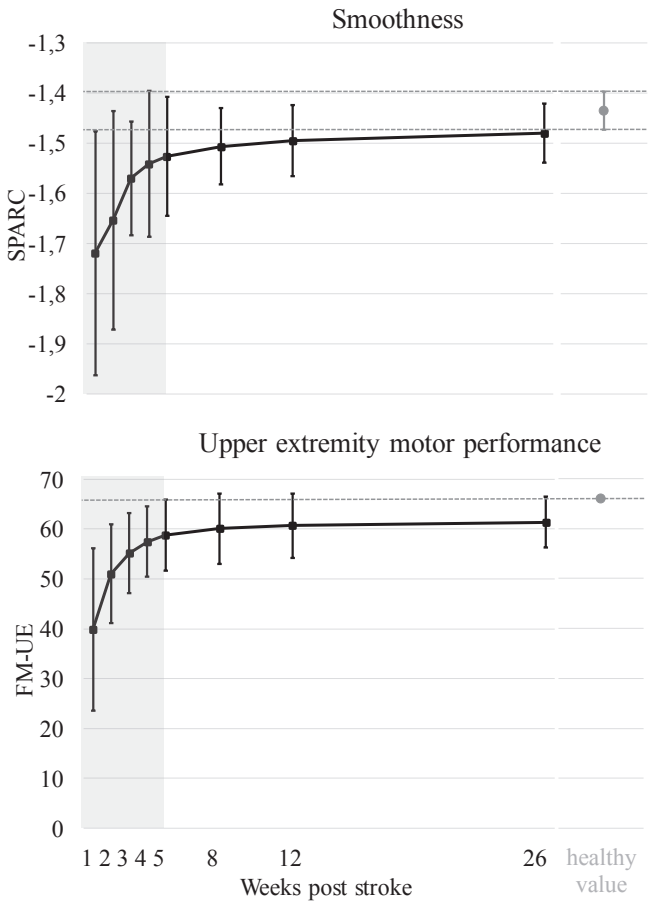

Figure 7.4. Smoothness and motor performance of the upper extremity as a function of time post stroke.

The black squares and corresponding error bars represent the average and standard deviation of SPARC and FM-UE. Shaded area indicates the time period for which the contribution of time was significant (i.e., until week 5 post stroke) for SPARC and FM-UE. Thereafter, recovery levelled off. The grey dots and broken lines display the average and standard deviation of reference values of age- and gender-matched healthy individuals, from which patients who suffered a stroke deviated at all time points. Abbreviations: SPARC, spectral arc length; FM-UE, Fugl-Meyer motor assessment of the upper extremity.

Discussion

The present longitudinal study is the first to show that recovery of smoothness reflected by the *spectral arc length* (SPARC) is highly associated with recovery of FM-UE within moderately to mildly affected patients early after stroke. Both measures show a non-linear time course, with the greatest change taking place within the first 5 weeks post stroke, whereafter their recovery gradually levels off. The significant longitudinal association between SPARC and FM-UE within subjects and their similar time window of recovery of 5 weeks post stroke suggest that their recovery may be driven by a common underlying process responsible for spontaneous neurological recovery early post stroke.

Our findings show that recovery of smoothness during a multi-joint reaching movement, as quantified by SPARC, follows a similar time course as recovery from motor impairment, as reflected by FM-UE scores, within the first 6 months post stroke. Therefore, this objective kinematic metric reflecting smoothness may be an alternative for clinical measures to reflect motor impairment.

Besides this likely similar time course, we showed a longitudinal within-subject association between SPARC and FM-UE. The yielded within-subject regression coefficient estimate reflects the degree of increase of one variable when the other variable increases with 1.0 within a subject.[38] Our findings show that observed time-dependent changes of smoothness and recovery of FM-UE scores are associated with each other within subjects. These findings suggest that both measures may be driven by the same underlying processes of spontaneous neurological recovery. Despite the likely similar time courses of SPARC and FM-UE, and longitudinal within-subject association, the underlying neurophysiological cause of diminished smoothness after stroke remains unclear and requires further investigation.

The lower movement smoothness observed in the investigated group of mildly to moderately affected patients at 6 months post stroke, compared to reference values of age-matched healthy individuals, suggests that residual movement smoothness deficits remain present in most patients who suffered a stroke. The Stroke Recovery and Rehabilitation Roundtable task force (SRRR)[40] suggested that kinematics quantifying QoM may have added informative value to identify minor deficits in those who show full motor recovery based on clinical assessments. In our sample, the number of patients that show full recovery based on FM-UE scores was too small to perform a sufficient-powered analysis to determine whether smoothness quantified as SPARC is a more responsive biomarker to identify remaining motor impairments when compared to FM-UE. SPARC as a marker for full sensorimotor recovery requires further investigation.

It is important to note that during recovery early after stroke, not all kinematic metrics improve and follow a non-linear time course. For example, endpoint accuracy of the hand during reaching, shows a poor longitudinal association with FM-UE.[7] Obviously, a metric that allows multi-joint compensation strategies during reaching prevents to measure 'true' neurological recovery post stroke. This finding suggests that understanding how uniquely a metric reflects underlying neurological impairment, is an important feature for designing stroke recovery and rehabilitation trials targeting quality of movement early post stroke, as recently emphasized by the SRRR.[40]

Limitations

Only patients who were moderately to mildly affected due to a stroke were included in the present study since participants had to be able to perform the reach-to-grasp task within 3 weeks post stroke. Despite this bias in patient selection, the current longitudinal study strongly suggests that recovery of FM-UE closely parallels recovery of smoothness and levels off after 5 weeks post stroke. Such a restricted time window has been shown to be typical of this subpopulation.[5] The generalisability of our findings is restricted to smoothness of reach-and-grasp tasks performed using a block of 5x5x5cm. This object could be picked-up by most patients, and thereby resulted in the most complete dataset. When using larger objects, one should consider the weight of the object since strength is a confounder for motor control during reaching after stroke.[30] A reach-to-point task, not requiring the ability to grasp, would allow for smoothness to be measured in more severely affected patients, reducing the selection bias. In addition, currently, consensus on how to determine the exact end of a reaching movement is lacking. Our method is in line with the approach as described by Alt Murphy and colleagues (2018)[37], and Michaelsen and Levin (2004)[36]. Secondly, the present analyses used FM-UE total scores, which also assess the functioning of the fingers, while pathological synergisms are mainly present in the more proximal part of the upper extremity (i.e., wrist, elbow, shoulder). However, we found similar associations when FM-UE hand scores were ignored ([Additional file], Section C). Finally, earlier studies suggested that recovery of smoothness deficits reflects neurological recovery[11,16], which is in line with the findings of the present study. However, in contrast to the performance assays recommended by the SRRR[40], smoothness during multi-joint movements may be influenced at different degrees of motor control. In these cases, the underlying neurophysiological cause remains unclear and its association with compensation strategies cannot be ruled out. Therefore, we recommend to also measure smoothness during single-joint experiments, preventing compensation strategies.

Future directions

Although smoothness is seen as an important measure of movement quality, recovery from smoothness deficits after stroke is poorly understood. The present findings do not rule out any hypothesized cause of smoothness deficits early post stroke. Determining which neurophysiological deficit after stroke is the main cause of decreased smoothness requires further investigation. One might think of combining repeated measurements of kinematics to measure smoothness, with EMG to determine muscle activity patterns, and non-invasive neuroimaging techniques such as MRI, fMRI or DTI.

Although FM-UE is considered to be a clinical measure for assessment of muscle synergies during recovery post stroke, it is important to note that FM-UE is not purely measuring muscle synergies. The systematic coupling by co-activation of muscles across multiple joints are influenced by strength.[30] Thereby, strength is a confounding factor for the true coupling between different joints during reaching.[41] How the increased muscle synergies during reaching after stroke are longitudinally associated with SPARC within subjects remains to be investigated. For example, Ellis and colleagues showed that increased shoulder-elbow coupling is associated with reduced work area during a 2D drawing task, while the work area improves by arm-weight support.[30] In a similar way, Bartolo and colleagues showed that arm-weight support in robotics results in a significantly reduced amount of jerk.[42] Therefore, we suggest to repeat our measurements using weight support. In addition, a more advanced method than the FM-UE is required to quantify muscle synergies, which prevents against the confounding influence of strength and does not suffer from ceiling effects.[30,41] This may enable to investigate the longitudinal within-subject association between muscle synergies and smoothness after stroke.

Smoothness is used as reflection of quality of movement and the degree of motor control in many studies. In line with the findings in the present study, recovery of smoothness deficits after stroke has been suggested to be associated with neurological recovery. Therefore, SPARC may serve as outcome measure in studies which investigate the effect of interventions such as upper limb robotics or brain stimulation. In the present study, statements about similarity in time course of recovery are based on visual inspection and the determined time window of recovery. However, further mathematical underpinning is necessary to determine whether the time course of SPARC and FM-UE post stroke are truly similar (e.g., by performing an exponential fit or principal component analysis[43]).

We recommend that future kinematic studies investigating smoothness during multi-joint reaching movements use SPARC. We showed previously, by performing simulation analyses, that SPARC meets the requirements of internal validity to reflect smoothness during reaching tasks.[24] In the present study, we examined the external validity based on longitudinal data of stroke patients who perform a reach-to-grasp task. Furthermore, to determine whether smoothness can serve as a performance assay, the improvement of smoothness should be related to true neurological repair in absence of compensation strategies. For this latter aim, the motor paradigm should focus on performing a single-joint task.

Healthy individuals, especially the elderly, may also show deviations from the optimal reaching trajectory, resulting in a certain decrease of smoothness.[44,45] Studies should include reference data from age-matched healthy subjects, in order to determine whether smoothness values are significantly different from what could be expected in healthy state. Obviously, the tasks performed should be similar in order to be able to compare smoothness values. Hence, no general task-independent cut-off to distinguish between normal and abnormal smoothness could be provided in the present study.

Finally, repeated measurements within subjects, which are required for stroke recovery studies, are highly demanding for participants. To limit the burden for patients by reducing preparation time and enabling measurements to take place at their place of residence, ambulant measurement systems for measuring smoothness should be simplified. Recently, it was shown that an ambulant system based on inertial measurement units was not capable of measuring SPARC for translational movements due to issues of drift commonly seen in these systems.[46] Further development of simple ambulant measurement systems is needed to enable valid and reliable measurements using wearables.

Conclusions

The present findings show that the recovery of smoothness during a multi-joint reaching task reflected by SPARC and the recovery from motor impairment reflected by FM-UE are longitudinally associated and highly likely to follow a comparable time course. This finding suggests that the reduction of smoothness deficits quantified by SPARC is a proper objective reflection of recovery from motor impairment, as reflected by FM-UE, and may be driven by a common underlying process of spontaneous neurological recovery within the first 5 weeks post stroke in patients who are moderately to mildly affected due to a stroke.

Declarations

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of the VU University medical centre, Amsterdam, The Netherlands, and carried out in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki.[27]

Availability of data and materials

The datasets supporting the conclusions of this article and the Additional file can be found online.

Competing interests

The authors report no competing interests.

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Authors' contributions

MS analysed and interpreted the data, and was a major contributor in writing the manuscript. MIMR contributed substantially to the data processing and writing the manuscript. JvK performed the measurements and pre-processed the kinematic data. BS contributed substantially to the kinematic data processing. BJvB, JBJB, JB and PV contributed by revising the manuscript. EvW, CM and GK contributed to the conception and design of the study and substantially revised the manuscript. All authors read and approved the final manuscript.

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General discussion

General discussion

Stroke lesions often result in motor impairments of the upper extremities, which hinder patients in their daily life. Current stroke research aims to improve understanding of motor recovery after stroke. For this, it is a prerequisite to assess the underlying neurological recovery, but this cannot be measured directly. This thesis discusses two topics which were prioritized by an international group of neurorehabilitation experts, the Stroke Recovery and Rehabilitation Roundtable task force (SRRR).[1,2] First, the inability to monitor neurological recovery after stroke due to the absence of adequate quantification of neurological state. Secondly, the demand for additional prognostic biomarkers of motor recovery in more severely affected stroke patients.

Neurological recovery consists of neural restitution (i.e., neural recovery to pre-stroke state) and neural substitution (i.e., changed neural activation) which both contribute to behavioural recovery. Behavioural recovery in turn, can be distinguished in behavioural restitution (i.e., recovery of motor performance in the direction of pre-stroke, normal behaviour) which is assumed to be mainly driven by neural restitution, and behavioural compensation (i.e., alternative motor performance to improve upper limb capacity) which is mainly driven by neural substitution. This thesis aimed to investigate whether brain activity quantified using electroencephalography (EEG), and observed behavioural recovery quantified using kinematics, may serve as a biomarker for neurological recovery or neural state after stroke.

In **Part I**, the association between neurological and behavioural recovery after stroke is investigated. The Fugl-Meyer motor assessment of the upper extremity (FM-UE) is a clinical assessment which is currently assumed to be most closely related to behavioural restitution.[3] In **chapter 2**, a cross-sectional study shows that resting-state EEG parameters that reflect the power asymmetry of brain activity between hemispheres in the low frequency bands (e.g., BSI_{delta} and BSI_{theta}) are associated with FM-UE scores in the chronic phase post stroke. In **chapter 3**, a longitudinal study is described in which EEG recordings and clinical assessments were performed repeatedly between the early sub-acute and chronic phase post stroke. The observed longitudinal association between FM-UE and the quantitative resting-state EEG parameter $BSIdir_{delta}$ shows the potential of this EEG parameter to serve as monitoring biomarker of neurological recovery. In the future, such monitoring biomarkers may be used to quantify the state of the brain during recovery, which may reveal whether interventions induce neurological recovery. Furthermore, prediction models of behavioural recovery need to be improved. In **chapter 4**, we identified BSI_{theta} as the strongest prognostic EEG-based biomarker of chronic motor impairment, showing

additional prognostic value beyond initial motor impairment as measured by FM-UE. We thus concluded that EEG parameters may contribute to improving prediction models of motor recovery after stroke.

Part II addresses the potential of kinematics to distinguish behavioural restitution from compensation, as a proxy for neurological recovery which is assumed to be restricted to the first few weeks post stroke. In **chapter 5**, a systematic review of the literature is performed from which it is concluded that currently available longitudinal kinematic stroke studies show various approaches to quantify behavioural restitution and compensation, but do not comply with the consensus on *how* and *when* to apply kinematic measurements when studying recovery after stroke as recommended by the SRRR. A commonly used variable to quantify quality of movement as a measure of neurological recovery is movement smoothness during a reaching task. In **chapter 6**, 32 different kinematic metrics are identified in literature which are used to quantify smoothness, from which Spectral Arc Length (SPARC) is determined to be the most appropriate. SPARC reflects the complexity of the shape of a Fourier magnitude spectrum of the velocity profile of a movement. **Chapter 7** described that SPARC and FM-UE show a similar pattern of recovery within a similar time window of five weeks post stroke and are longitudinally associated within patients. These findings suggest that recovery of smoothness and recovery from motor impairments may be driven by a common underlying process of spontaneous neurological recovery. Thereby, the smoothness metric SPARC may serve as monitoring biomarker of neurological recovery after stroke.

8.1. Phenomenological model of upper extremity motor recovery after stroke

Figure 8.1 shows the phenomenological model of upper extremity motor recovery after stroke as introduced in **chapter 1**, which encompasses two main levels: neurological and behavioural recovery.

8.1.1. Neurological recovery

Neurological recovery covers all structural and functional changes occurring in the brain following stroke and has been argued to be a combination of neural restitution and neural substitution.

Neural restitution refers to restoring networks or 'true' recovery, probably caused by salvation of penumbral tissue and reversal of shock or diaschisis, in brain areas near the lesion and brain areas anatomically connected with the infarcted brain area. Mechanisms behind neural restitution in humans is poorly understood. Next to metabolic reperfusion-dependent processes, mainly responsible for elevation of

penumbra and shock, recovery of affected networks are heavily dependent on reactive neuroplastic changes such as neurogenesis, gliogenesis, and neural sprouting, which are enhanced in the first weeks post stroke[4–6]. Neural restitution results in recovery of various neurological impairments, such as muscle synergies[7], sensory deficits[8], visuo-spatial neglect[9], and speech[10], and is believed to be mainly restricted to the first 5-10 weeks post stroke. More precisely, quality of movement in terms of intralimb coordination[3] and smoothness during a reaching task[11] normalizes in the first 5 weeks post stroke. In line with this restricted time window of behavioural recovery, the present thesis shows for the first time that at neurophysiological level, normalization of resting-state EEG such as decreasing DAR_{AH} and $BSIdir_{delta}$ [12] occurs in the same time window as seen in clinical and kinematic outcomes.

In addition to neural restitution, alternative pathways formed by structural plasticity of intact cerebral tissue after stroke are responsible for the processes of behavioural recovery.[4] This process has been referred to as *neural substitution* for the first time in the eighties.[13] An example of neural substitution is activation of alternative cortical areas to enable to perform a motor task, resulting in adapted activity patterns and adapted functional connectivity within networks. In contrast to neural restitution, neural substitution is believed to continue beyond the first 10 weeks due to learning dependent plasticity.

Since it is difficult to measure what is changing at the molecular and cellular level, researchers use non-invasive techniques, such as fMRI, EEG, or MEG, to quantify brain activity to reflect neural processes of recovery early after stroke.

8.1.2. Behavioural recovery

The term behavioural recovery refers to *observed* improvement in performance of motor tasks, and likewise can be divided into two components, namely: behavioural restitution and behavioural compensation.[14,15] *Behavioural restitution* is defined as recovery of neurological impairments[2,16], leading to normal quality of movement (QoM). The closer patients' motor task execution matches the movement pattern of healthy age-matched controls, for example during reaching, the better the QoM.[2] Behavioural restitution, to restore QoM, is argued to require neural restitution, which is seen as its main driver.[13] Regaining the ability to perform a motor task can also be achieved by using muscles, joints, and effectors in a different way compared to pre-stroke behaviour, which is referred to as *behavioural compensation*.[15] Behavioural compensation is believed not to require neural restitution, and results mainly from neural substitution.[13]

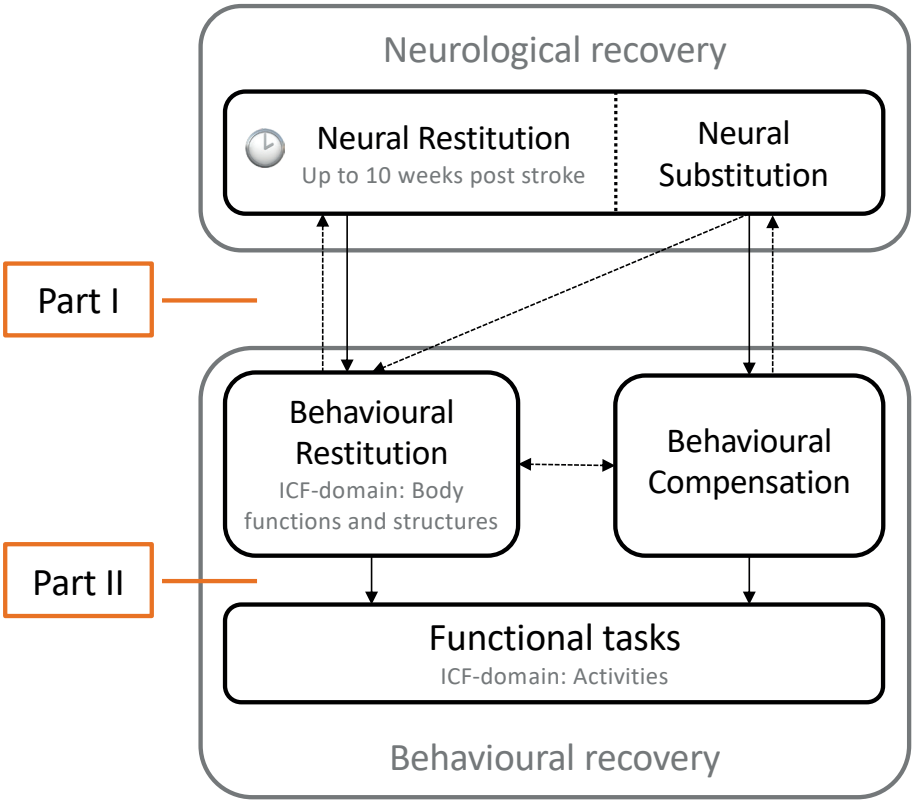

Figure 8.1 *Phenomenological model of upper extremity motor recovery after stroke. A visualisation of the scope of this thesis. In Part I of this thesis the association between neurological and behavioural recovery after stroke was investigated. In Part II of this thesis the current ability to discern behavioural restitution, as a proxy for neurological recovery, from behavioural compensation was investigated, focussing on quality of movement. Solid lines represent relations that are consented to exist, whereas dashed lines represent possible relations.*

8.2. Part I. The association between neurological recovery and behavioural restitution after stroke

8.2.1. Monitoring biomarkers of neurological recovery based on EEG parameters

Investigating whether quantitative resting-state EEG parameters may serve as monitoring biomarkers of neurological recovery requires EEG recordings performed from the acute phase up to the chronic phase post stroke. Early post stroke, *BSI* and *DAR* were increased compared to healthy individuals.[17–19] These parameters were previously found to be associated with global neurological deficits as defined by the National Institutes of Health Stroke Scale (NIHSS) and have predictive value for the modified Rankin Scale (mRS) scores reflecting dependency after stroke.[20–25] Our

studies, described in **chapter 2** and **chapter 3**, were the first to show that these quantitative resting-state EEG parameters still deviate in the chronic phase, change in the direction of normal early after stroke, and are longitudinally associated with behavioural recovery reflected by FM-UE.

Chapter 2 describes a cross-sectional study in which quantitative resting-state EEG parameters were compared between 21 chronic stroke patients, and eleven age- and gender-matched controls. Compared to healthy subjects, patients showed more power asymmetry over the hemispheres. This increased asymmetry was mainly present in the low-frequency bands (i.e., BSI_{delta} and BSI_{theta}). Directional BSI (BSIdir) elucidated that this asymmetry was mainly the result of increased low-frequency power in the lesioned hemisphere compared to the non-lesioned hemisphere. Furthermore, a higher power asymmetry was associated with more motor impairment of the upper extremity reflected by the FM-UE. By combining the findings of our cross-sectional study in the chronic phase, with findings of previous studies performed early post stroke, we hypothesized that quantitative resting-state EEG parameters (e.g., DAR and BSI) change over time in the direction of healthy age-matched controls in the sub-acute phase post stroke, and have thereby the potential to serve as monitoring biomarkers of neurological recovery. Testing this hypothesis required a longitudinal study combining resting-state EEG recordings and obtaining FM-UE scores repeatedly within subjects early post stroke.

Chapter 3 describes such a longitudinal observational study, in which 41 patients were measured repeatedly between stroke onset and six months after stroke. Each measurement encompassed an EEG recording and a clinical assessment encompassing FM-UE and NIHSS. The first measurement was performed within 3 weeks post stroke, and was repeated at weeks 5, 12 and 26. Compared to previously performed longitudinal quantitative EEG studies after stroke, our study had a longer follow-up time regarding brain activity recordings, a lower drop-out rate, and more responsive and motor recovery focused clinical outcome measures.[19,24] Within the first six months after stroke most of the investigated quantitative resting-state EEG parameters changed over time towards normative values observed in healthy individuals (e.g., DAR, DAR_{AH}, BSI, BSI_{delta}, BSI_{theta}, $BSIdir_{delta}$). In line with these findings, a previous longitudinal magnetoencephalography (MEG) study reported increased delta activity in the affected hemisphere in the acute phase, whereafter it deceased during the early subacute phase post stroke.[26] Since changes of DAR, DAR_{AH}, $BSIdir_{delta}$ and $BSIdir_{theta}$ within subjects over time are longitudinally associated with recovery of global neurological deficits, reflected by NIHSS, we concluded that these EEG parameters can be considered monitoring biomarkers of general neurological

recovery. Only BSIdir and $BSIdir_{delta}$ showed a longitudinal within-subject association with recovery of motor impairments, reflected by FM-UE, and may therefore serve as monitoring biomarkers of neurological motor recovery. Besides, results show that power asymmetry measures across the hemispheres relate more closely to motor recovery compared to the ratio between delta and alpha power within hemispheres. This suggests that motor impairment may be associated with the connectivity between hemispheres or within networks which spread across hemispheres. Currently, it is unclear how changes in power asymmetry indexes relate to recovery of cortical network integrity early after stroke.

8.2.2. Prognostic biomarkers of behavioural recovery post stroke based on resting-state EEG

Early performed clinical motor assessments explain a large portion of the variance in presence of motor impairments in the chronic phase post stroke.[7,27–29] For example, the ability to perform shoulder abduction and finger extension, as well as FM-UE scores, in the early phase post stroke, are predictors of motor function scores at six months post stroke.[29] In a recent study, the time course of 412 first-ever stroke patients was investigated, which showed that prediction of behavioural recovery based on FM-UE baseline scores is unreliable for patients who show moderate or poor scores (i.e., FM-UE≤18) within the first 3 days post stroke.[7] For this group of patients in particular, prognostic biomarkers based on neurophysiological data may improve prediction models of behavioural recovery.

In previous EEG studies, the presence of low frequency brain activity and power asymmetry were identified as predictors of the degree of disability or dependency in the daily activities after stroke reflected by the modified Rankin Scale (mRS).[21–23,25] These quantitative EEG parameters are obtained during resting-state, and therefore also suitable for more severely affected patients who are not able to perform voluntary motor tasks. In **chapter 4**, we showed that resting-state EEG parameters have prognostic value regarding behavioural recovery after a first-ever ischemic stroke. Larger power asymmetry across the hemispheres measured within three weeks post stroke predicts more severe upper limb motor impairment, reflected by low FM-UE scores, at six months post stroke. More specifically, the level of hemispheric power asymmetry in the theta frequency band (BSI_{theta}) appeared to be the strongest prognostic biomarker.

To date, only one available study which focused on the prognostic value of quantitative resting-state EEG parameters after stroke did also include clinical assessments as predictors, which is needed in order to conclude whether EEG

parameters have added value beyond clinical assessments.[25] The added value of quantitative EEG parameters beyond age and clinical scores as NIHSS to predict mRS scores was previously studied.[24] However, the mRS is a 7-point global disability scale which ranges from *no symptoms* (mRS 0) to *death* (mRS 6), which is of low resolution and lacks sensitivity. This could be a reason why in the aforementioned study no added predictive value of BSI was found. In a further analysis of our data in **chapter 4**, we took into account baseline values of motor impairment (FM-UE) and showed that quantitative resting-state EEG parameters derived early post stroke have additional prognostic value regarding motor impairment at six months post stroke. BSI_{theta} appeared to be the strongest additional prognostic biomarker. By adding this biomarker, the explained variance increased from 61.5% to 68.1%. This finding suggests that, in the early phase post stroke, resting-state EEG contains unique information concerning motor recovery post stroke, which could not be obtained from clinical assessments of motor impairment. EEG may contribute to the prediction of motor recovery, possibly as a reflection of cortical network integrity which is required for motor recovery but not yet detectible by the FM-UE. EEG parameters which were not investigated in the present thesis, such as connectivity measures and other network related parameters[30], deserve further investigation. Connectivity measures may provide a more accurate indication of cortical network integrity.[30] Besides EEG, also other imaging techniques, such as fMRI, DTI, and DWI, are used to quantify connectivity between brain areas. Further research should elucidate which neurophysiological biomarkers are most informative and feasible to be obtained in patients early after stroke. In order to construct a better prediction model for motor recovery post stroke, investigating the added prognostic value of neurophysiological information beyond clinical assessments should be prioritized. Ideally, a longitudinal study is set up in which MRI, DTI, EEG, and clinical assessment data is obtained in or before the early sub-acute phase post stroke, followed by conducting clinical assessments of relevant outcome measures at six months post stroke. However, such a longitudinal study would be less feasible for the severely affected patients, which is the group of patients for which prediction based on initial motor impairment scores is not sufficient. This emphasizes that it should be investigated which information can be obtained from data gathered during usual care (e.g., MRI or CT data) which does not impose an additional burden on the patient.

8.3. Part II. Measuring behavioural recovery using kinematics

Since clinical assessments cannot purely reflect neurological recovery, we were interested in identifying kinematic metrics that quantify QoM, a measure that is assumed to reflect neurological recovery. Ideally, these kinematic metrics would

reflect behavioural restitution in absence of compensation, and may thereby serve as proxy of neural restitution. Investigating whether a kinematic metric may reflect neurological recovery requires studying its time course early after stroke. Since an overview of studies which investigated kinematics longitudinally early post stroke was lacking, we performed a systematic review to collate currently used methodology that aimed to distinguish behavioural restitution from compensation. Moreover, our longitudinal kinematic study showed a similar time window for recovery of SPARC (reflecting movement smoothness) and FM-UE scores, from which we concluded that recovery of SPARC may reflect neurological recovery.

8.3.1. Quantifying quality of movement

The systematic review, presented in **chapter 5**, shows how currently available longitudinal kinematic stroke studies investigate QoM during reaching. Till July 2020, 32 longitudinal stroke studies were identified which included patients before the chronic phase post stroke. Together, these studies investigated 46 different kinematic metrics during reaching.

We identified several different approaches to quantify behavioural restitution and compensation during upper limb recovery. Trunk displacement is a kinematic metric which is acknowledged to reflect a compensation strategy to overcome the reaching restriction caused by the shoulder-elbow muscle synergy. The contribution of behavioural compensation during task performance can be quantified by measuring trunk displacement or minimized by restricting trunk displacement. Two studies focused on the time period in which upper limb recovery takes place.[31,32] It was suggested that metrics which reflect behavioural restitution would hardly improve beyond the time window of spontaneous neurological recovery. However, these metrics may still be contaminated by behavioural compensation. Some studies used anti-gravity support during reaching tasks, which is argued to enable a better reflection of neurological recovery, since the movement is not contaminated by impairment of strength. Nevertheless, in the longitudinal kinematic studies included in the systematic review, consensus on which metrics are able to quantify QoM to reflect behavioural restitution during a functional reaching task, especially in absence of compensation strategies, is lacking. This emphasizes the need for further research, for example by longitudinally studying changes in intralimb coordination.

In 2019, the SRRR provided recommendations for study designs to perform adequate longitudinal kinematic studies after stroke and suggested standardized tasks to enable to distinguish behavioural restitution and compensation. Amongst others,

the SRRR suggested to add performance assays as a proxy for behavioural restitution.[2] These tasks, that are assumed not to allow any compensation, encompass: grip strength, precision grip, finger individuation, and 2D planar reaching. Performance assays should be performed longitudinally within subjects next to a functional task such as reaching.[2] None of the studies included in our systematic review met all recommendations provided by the SRRR. However, one should keep in mind that the included studies were designed and performed before these recommendations were published and only showed part of the data obtained in their main study which may encompass more tasks.

The requirements for study designs to enable identification of biomarkers for restitution, as formulated in **chapter 5**, may serve as a starting point for future longitudinal kinematic studies about recovery of QoM of the upper extremity post stroke. We conclude that there is a need for studies that serially measure "performance assays" next to a standardized functional task to better understand motor recovery of the upper extremity post stroke, and to enable distinguishing between behavioural restitution and compensation. In order to support future kinematic studies on functional recovery after stroke, we developed a checklist inspired by the recommendations of the SRRR. This checklist can be used to evaluate study designs and provides guidance for designing future longitudinal kinematic stroke studies.

8.3.2. Recovery of smoothness deficits after stroke

QoM has often been quantified by kinematic assessment of reaching movements.[31,33–42] Smoothness is a metric which reflects the continuity or non-intermittency of the movement profile, independent of its amplitude and duration[43], and has been argued to reflect QoM (i.e., the degree of motor control)[31,43], whereby smoother movements reflect better movement quality. Improvement of smoothness after stroke may therefore reflect behavioural restitution. In **chapter 5**, we identified a variety of metrics from literature which were used to quantify smoothness. However, their validity was often not considered. In **chapter 6**, we presented a systematic review followed by simulation analyses to address the validity of available smoothness metrics used in stroke literature. In total, 32 different smoothness metrics were identified and checked for mathematical soundness to describe smoothness. Subsequently, simulations were performed to test their response to changes in reaching behaviour using models of velocity profiles with varying durations, amplitudes, harmonic disturbances, noises, and sub-movements. For reach-to-grasp tasks, it was concluded that only spectral arc length (SPARC) is a valid metric to reflect smoothness. The smoothness metric SPARC is based on the complexity of the shape of a Fourier magnitude spectrum of the velocity profile during a reaching task.[44] The frequency spectrum of a smooth

movement is composed of mainly low-frequency components, whereas less smooth movements show more high-frequency components and thereby a more complex magnitude spectrum. Future studies should use outcome measures which have been validated specifically for the investigated task and target population, for example as described in **chapter 6** by performing specific simulation analyses.

Recovery of SPARC during reaching movements has not been investigated longitudinally early after stroke, nor its longitudinal association with recovery from motor impairments of the upper extremity. In **chapter 7**, the recovery of upper extremity movement smoothness deficits during reaching was investigated in a longitudinal study. 40 first-ever stroke patients with initial upper limb paresis were followed from the early sub-acute phase till six months post stroke. FM-UE scores and 3-dimensional kinematic data of reach-to-grasp tasks were obtained weekly in the first five weeks post stroke, and repeated at week 8, 12, and 26. Twelve healthy age-matched individuals were included to obtain healthy reference values regarding smoothness during reaching. We showed that improvement of smoothness, reflected by SPARC, is longitudinally associated with recovery from motor impairments, reflected by FM-UE. Smoothness deficits and motor impairment showed to recover within a comparable time window of 5 weeks post stroke, whereafter their improvement levelled-off. These findings suggest that recovery of smoothness deficits and recovery from motor impairments are driven by a common underlying process of spontaneous neurological recovery. The more objective smoothness metric SPARC, which follows an asymptotic time course, may be more sensitive to detect abnormalities in quality of movement, and may thereby serve as a more genuine measure of motor recovery in patients with a minor stroke. The longitudinal within-subject association between smoothness deficits and motor impairment scores related to muscle synergies does not rule out other hypothesized causes of smoothness deficits early post stroke. Examples of other hypothesized causes of decreased smoothness after stroke are imbalanced co-contractions between agonists and antagonists due to a lack of reciprocal inhibition[33,45], deficiencies in motor unit discharge[46] and enhanced online feedback corrections to compensate for impaired feedforward control to prevent movement errors during reaching[47]. To determine which neurophysiological deficits after stroke cause decreased smoothness, further investigation is required. Combining repeated measurements of kinematics to measure smoothness, with EMG to determine muscle activity patterns, and non-invasive neuroimaging techniques such as MRI, fMRI, or DTI may enable to unravel underlying mechanisms of movement smoothness deficits. Kinematic measurements may be more feasible when performed using inertial measurement units[48] or markerless motion capture systems[49], although such systems require further development and validation.

8.4. Methodological considerations

A large portion of the available stroke studies is cross-sectional, while understanding of recovery requires longitudinal studies which enable within-subject analyses. Motor recovery is mainly restricted to the first 10 weeks post stroke, whereafter recovery levels off.[7] This non-linear recovery pattern emphasizes that the repeated measurements should take place most frequently in the first weeks since stroke onset, allowing to investigate the time window of recovery. To determine the presence of an association between behavioural and neurological recovery within a subject, it is important to distinguish the within-subject effect and the between-subject effect of a longitudinal association. Therefore, in **chapter 3** and **chapter 7**, a hybrid model[50] was used to discriminate between these two components.

The longitudinal studies presented in this thesis only included patients who suffered from a first-ever stroke. Although such a restriction limits the generalizability of our findings to the entire stroke population, it was necessary to ensure that observed remaining neurological or motor deficits did not result from a previous stroke.

Longitudinal studies on recovery of brain activity and QoM after stroke require a lot of resources and research staff, which is one of the reasons for the limited number of such studies. Moreover, participating in such studies requires a lot of effort from patients, resulting in a low inclusion rate and high drop-out rate.[19] In case of brain activity recordings, different measurement techniques are available, such as fMRI, MEG or EEG, which commonly requires patients to travel to the laboratory for each measurement. In this thesis, brain activity was recorded using EEG, which enables to perform ambulant measurements and thereby limit the burden of patients. In the studies described in **chapter 2**, **3**, and **4** of this thesis, resting-state EEG recordings were performed in a specially equipped measurement van. This laboratory on wheels enabled us to visit the patients and perform the recordings at their place of residence (e.g., hospital, rehabilitation centre, nursing home or home). Such an approach increases feasibility of participation in observational studies in parallel to rehabilitation interventions of patients in the sub-acute phase post stroke. Feasibility of EEG recordings in a very early phase may be further improved by reducing preparation time. For example, by limiting the number of used electrodes or performing recordings using dry electrodes or water-based electrodes for EEG, systems which are currently under development. Also 3-dimensional kinematic measurements to quantify QoM usually require patients to visit a laboratory. The protocol followed in **chapter 7** allowed to perform on-site 3-dimensional kinematic motion recordings, increasing the feasibility of repeated recordings early post stroke. The protocol may be even more feasible by using newly developed technology. To further limit the burden for patients and to increase

feasibility to include such measurements in usual care, preparation time should be reduced. For example, systems based on inertial measurement units (IMU)[48] or markerless motion capture systems[49] should be further developed and validated to enable clinical use. Reliability and accuracy of such measurement systems to quantify QoM have yet to be confirmed and requires further investigation.[51] Subsequently, such easy-to-use ambulant measurement systems may facilitate e-health by enabling home-based monitoring of recovery and rehabilitation programmes without visiting the physician.

Studies should include data of an age-matched control group as a reference for two reasons. First, parameters derived from EEG or kinematic data are influenced by measurement protocols and subsequent processing of the obtained data. Second, neuronal oscillations in the brain as well as QoM during reaching have been shown to be influenced by age. With increasing age, slowed alpha activity is observed in neuronal oscillations.[52] This also applies to QoM quantified using kinematics, since also healthy individuals, especially elderly, show deviations from the optimal reaching trajectory, which results in a certain level of decreased smoothness.[53,54] To determine which proportion of smoothness deficits is pathological, the age and performed task should be similar amongst patients and healthy controls. A general task-independent cut-off to distinguish between normal and abnormal smoothness cannot be provided. A solution for this issue could be to compose a, preferably, open-source database of healthy reference values, regarding neuronal oscillations in the brain and QoM of the upper extremity, for different age categories for a set of highly standardized tasks combined with a set processing procedure.

8.5. Directions for future research on neurological and behavioural recovery after stroke

In this thesis, it was shown that recording EEG and kinematics enable us to: 1) monitor neurological recovery early after stroke, 2) improve prediction of behavioural recovery, and 3) better represent behavioural restitution compared to clinical assessments. The main future steps for each of these three key elements will be discussed below. Future research is necessary to improve our understanding of motor recovery and prognosis early post stroke, which in turn is conditional to select the most appropriate intervention and thereby improve personalized medicine.

8.5.1. Biomarkers for monitoring of neurological recovery

Identified monitoring biomarkers obtained from resting-state EEG may be used to quantify the state of the brain during recovery, which may reveal whether patients show neurological recovery and may indicate whether interventions induce neurological

recovery. To unravel the actual cause of the observed changes in EEG early after stroke (**chapter 3**) is a challenging task for future research. The relationship with underlying structural deficits affecting network integrity, such as cortical spinal tract integrity, deserves further investigation. This may clarify why some patients barely show any recovery, while others show partial or good recovery. Besides EEG, also other neuroimaging techniques, for example those providing brain activity information (e.g., fMRI, MEG), structural information (e.g., MRI, DTI) or metabolic and perfusion related information (e.g., PWI), can be used to reflect brain damage early post stroke and may serve as source for monitoring biomarkers of neurological recovery. Techniques with high temporal resolution but low spatial resolution may compliment techniques with high spatial resolution but low temporal resolution, such as simultaneous acquisition of EEG and fMRI. This approach is promising and is continuously improved.[55,56] Furthermore, spontaneous neurological recovery has been argued to be restricted to the early sub-acute phase post stroke, while observed changes in resting-state EEG parameters were not always restricted to this time window. This suggests that resting-state EEG may be able to detect ongoing neurological recovery beyond a three-month time window, which is not detectable by the clinical outcome measures (e.g., FM-UE or NIHSS). Further research should provide evidence necessary for confidently accepting that motor recovery continues after 12 weeks, for example by measuring behavioural recovery using finer grained and more sensitive outcome measures compared to commonly used clinical assessments, for example by using kinematics.

8.5.2. Improving prediction models of motor recovery post stroke

Motor impairment in the early phase post stroke explains most variance of motor impairment in the chronic phase. Motor impairment of stroke patients in the chronic phase can be well predicted for patients with high initial FM-UE scores, while for patients with moderate or poor FM-UE scores (i.e., FM-UE≤20) prognosis of motor recovery based on a clinical motor assessment is unreliable.[7] This emphasizes the need for additional prognostic biomarkers for moderate to severely affected stroke patients. For this group, resting-state EEG parameters seem promising since these patients have no or limited voluntary muscle activity, and resting-state neurophysiological parameters may reflect the neural state of the brain necessary for behavioural recovery.

Chapter 4 showed that prognostic biomarkers based on resting-state EEG have potential to improve prediction models of motor recovery. Since EEG parameters do not explain enough variance to serve as single predictor, they should be used in addition to other predictors. Examples of alternative proposed prognostic biomarkers based on neurophysiology which deserve further investigation are: brain responsivity

(observed using EEG-TMS), white matter intactness of the CST (observed using DTI), and lesion volume and location (observed using MRI).[57–60] In a systematic review on neurological biomarkers to predict motor recovery after stroke, it was concluded that more high-quality studies are needed to establish which neurological biomarkers are proper predictors of behavioural recovery after stroke.[61] One could think of a study in which data are gathered from various sources, whereafter the best predictor can be identified. If collected in the same way within Europe or Worldwide[1], like the ENIGMA initiative[62], a big data set may allow artificial intelligence approaches like machine learning to extract useful information from sources such as genetics, clinical assessments, kinematics, and neuroimaging, to optimize patient-specific prognostic modelling. In addition, such prognostic models may help to better stratify patient groups at the baseline of clinical trials, and with that to limit the heterogeneity of the investigated patient population and prevent neutral trials due to a lack of sufficient statistical power.

The patient population described in this thesis showed a wide range of stroke severity in the early phase. Future studies which aim to improve prediction models of motor recovery after stroke should include more severely affected patients who could benefit most from adjusted prediction models. To obtain data from severely affected patients, it is of major importance to consider the measurement burden on the patient. Studies should investigate whether prediction models can be improved based on biomarkers derived from recordings in standard care by additional post-processing without the need for additional measurements. Data recorded during usual care neuroimaging (e.g., CT or MRI) may be useful to obtain neurophysiological parameters which have potential to serve as prognostic biomarkers, such as lesion location or white matter intactness. In addition, quantitative resting-state EEG parameters may be estimated during bedside testing, which lowers the burden on the patient and advances the time until it is feasible to perform the first measurement. By using fewer electrodes or a dry-EEG system, feasibility can be improved even more[63,64], although this requires further technical development.

8.5.3. Measuring behavioural restitution in absence of compensation

Quantifying behavioural restitution should be prioritized by studies which use kinematics to reflect neurological recovery. Kinematic metrics obtained during performance assays should encompass a specific stroke-induced motor impairment and should not be contaminated by behavioural compensation. With this, the data derived during performance assays may serve as monitoring biomarker of neurological recovery and will enable to investigate whether interventions can induce neurological recovery. This may enable to improve current interventions for stroke rehabilitation.

Obtaining these metrics will be mainly relevant for moderately affected stroke patients to monitor their motor recovery. For mildly affected patients no intensive rehabilitation is necessary, while severely affected patients will not be able to perform performance assays since they require a particular level of motor capacity.

Determining which neurophysiological deficit after stroke is the main cause of decreased smoothness requires further investigation. One might think of combining repeated measurements of kinematics to measure smoothness, with EMG to determine muscle activity patterns, and non-invasive neuroimaging techniques such as MRI, fMRI, and DTI. Future studies which quantify smoothness during reaching tasks after stroke are recommended to calculate this as SPARC. Since SPARC may reflect neurological recovery, it may serve as outcome measure in studies which investigate the effect of interventions such as upper limb robotics or brain stimulation.

Kinematic metrics that quantify quality of movement during performance assays may be the substitute of the frequently used FM-UE, which suffers from a ceiling effect for excellent recoverers. In addition, FM-UE scores are not a pure reflection of neurological recovery since the FM-UE is affected by muscle strength deficits. Kinematic metrics obtained during performance assays may better quantify behavioural restitution and thereby reflect neurological recovery. Such kinematic metrics may be incorporated in the design of rehabilitation robotics. Unfortunately, the evidence of robotic-assisted therapy for the upper paretic limb is weak when compared to usual care.[65] Future robotic therapy should target improvement of intralimb coordination, increase the degrees of freedom, and improving movement smoothness. Robotics should also provide feedback about ongoing motor recovery by quantifying QoM and thereby behavioural restitution. Acknowledging that FM-UE scores are influenced by strength deficits, robots may be able to quantify recovery of muscle synergies in a more genuine way. Development of valid ambulant kinematic measurement systems which have a short preparation time should be prioritized in order to limit the burden of patients and improve feasibility of clinical use. Recently, it was shown that an ambulant system based on inertial measurement units was not capable of measuring SPARC for translational movements due to issues of drift commonly seen in these systems.[66] Further development of a simple ambulant measurement system is needed to enable valid and reliable measurements using wearables.

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APPENDICES

Summary

Summary

Stroke is one of the main causes of serious adult disability in Europe. Around 80% of stroke survivors suffer from motor impairment, typically affecting unilateral motor control of the face, arm, and leg. Especially upper limb impairments limit patient's activities of daily living. While the majority of patients shows some level of spontaneous neurological recovery, about 20-30% do not recover at all. Most of the observed improvements in upper limb function occur in the first 10 weeks after stroke. However, the mechanisms underlying motor recovery are poorly understood. While primary and secondary prevention measures aim to reduce the number of stroke patients and to detect and treat the stroke as soon as possible, investing in tertiary prevention is important to predict, accelerate, and enhance post-stroke recovery. **Chapter 1** discusses two issues. First, the inability to monitor neurological recovery after stroke due to the absence of adequate quantification of neurological state. Secondly, the demand for additional prognostic biomarkers of motor recovery in more severely affected stroke patients.

Adequate quantification of neurological recovery is required to investigate whether neurorehabilitation interventions can induce neurological motor recovery after stroke. Unfortunately, neurological motor recovery cannot be measured directly. Therefore, derivatives of neurological state associated with behavioural recovery should be identified, referred to as biomarkers. In this thesis, we investigate biomarkers derived from observed behaviour and biomarkers derived from brain activity.

A clinical assessment which is often used in scientific research to monitor behavioural recovery after stroke is the Fugl-Meyer motor assessment of the upper extremity (FM-UE). The FM-UE reflects the ability to perform movements dissociated from abnormal muscle synergies and originates from the different stages of motor recovery after stroke. With this, the FM-UE is assumed to be closely related to behavioural restitution, and thereby neural restitution. However, the FM-UE suffers from a ceiling effect and is amongst others influenced by impairment of muscle strength. Quality of movement (QoM), derived from kinematic data, has been proposed as a more adequate quantification of behavioural recovery as it reflects the degree of motor control. Besides observed behaviour, also neural oscillations have been affected by stroke, which have been proposed to be measured to monitor neurological recovery.

Upper limb motor impairment in the chronic phase can be predicted quite well for mildly affected stroke patients, based on their initial upper limb motor impairment. However, especially in moderate to severely affected patients, prediction models are

unreliable and require improvement. There is a demand for additional prognostic biomarkers which can be obtained from patients who are not able to perform active motor tasks. Neurophysiological parameters, for example obtained from neural oscillations recorded using EEG in awake resting-state, may serve as additional prognostic biomarkers of behavioural recovery after stroke.

In **Part I** of this thesis, it is determined which quantitative EEG parameters can serve as monitoring or prognostic biomarkers of neurological recovery underlying behavioural recovery of the upper extremity after stroke. In **Part II** of this thesis, it is described how QoM is measured using kinematics to quantify behavioural restitution, and whether it may serve as monitoring biomarker of neurological recovery.

Chapter 2 shows a cross-sectional study in which quantitative resting-state EEG parameters were investigated in the chronic phase post stroke. We included 21 first-ever chronic stroke patients, who suffered from upper limb paresis at least in the acute phase after stroke, and eleven age- and gender-matched controls.

Compared to healthy subjects, patients showed higher Brain Symmetry Index (BSI) values which means that there is more power asymmetry over the hemispheres, mainly in the low-frequency bands (BSI_{theta} and BSI_{delta}). The directional BSI (BSI_{dir}) revealed that this asymmetry is mainly the result of increased low-frequency power in the lesioned hemisphere compared to the non-lesioned hemisphere. Delta/Alpha Ratio (DAR) did not differ between groups. Motor impairment was quantified by the FM-UE. Regression analyses showed that patients with lower FM-UE scores, reflecting more severe motor impairments, showed more power asymmetry in the low frequency bands (BSI_{theta} and BSI_{delta}). DAR showed no association with FM-UE.

Together with previous findings reported in literature concerning EEG deviations in the acute and subacute phase post stroke, our results suggest that quantitative resting-state EEG parameters change over time in the direction of healthy reference values, which may reflect spontaneous neurological recovery.

In **chapter 3**, the time course of aforementioned quantitative resting-state EEG parameters is investigated in the first 6 months after stroke. Moreover, their longitudinal association with global neurological recovery and upper-limb motor recovery was studied. For these analyses, data of 41 first-ever ischemic stroke patients was used. Resting-state EEG was recorded using 62 electrodes within the first 3 weeks post stroke and at 5, 12, and 26 weeks post stroke.

Quantitative EEG parameters (BSI, BSI_{theta}, BSI_{delta}, BSIdir, $BSIdir_{theta}$, $BSIdir_{delta}$, DAR, DAR_{AH}, and DAR_{UH}) showed normalization over time, within and beyond 12 weeks post stroke. Linear mixed models analyses show the presence of a longitudinal association between resting-state EEG parameters and both clinical measures (i.e. NIHSS and FM-UE). A hybrid model enabled us to distinguish within- and between-subject associations. A significant longitudinal within-subject association means that changes in brain activity within subjects were associated with changes observed using clinical assessments. DAR_{AH} shows a longitudinal within- and between-subject association with NIHSS. $BSIdir_{delta}$ shows a longitudinal within- and between-subject association with NIHSS and FM-UE. From this, we concluded that quantitative resting-state EEG parameters may serve as monitoring biomarkers of neurological recovery early after stroke.

In **chapter 4**, it is investigated whether quantitative resting-state EEG parameters recorded early post stroke can predict upper extremity motor impairment reflected by the FM-UE after six months. Moreover, it is investigated whether these EEG parameters have added value beyond initial FM-UE scores. For these analyses, resting-state EEG was used from 39 adults within three weeks after a first-ever ischemic hemispheric stroke. FM-UE scores were acquired within three weeks ($FM\text{-}UE_{baseline}$) and at 26 weeks post stroke ($FM\text{-}UE_{w26}$).

Regression analyses showed that BSI and BSI_{theta} early after stroke are significant predictors of $FM\text{-}UE_{w26}$. Patients with larger power asymmetry across the hemispheres within 3 weeks post stroke, show more severe motor impairment in the chronic phase. Moreover, BSI, BSI_{theta}, and BSI_{delta}, had added prognostic value in addition to initial motor impairment scores (i.e., $FM\text{-}UE_{baseline}$) when predicting $FM\text{-}UE_{w26}$. BSI_{theta} was the strongest predictor of the computed EEG parameters. This finding suggests that, in the early phase post stroke, resting-state EEG contains unique information concerning motor recovery post stroke, which could not be obtained from clinical assessments of motor impairment such as the FM-UE. From this, it is concluded that resting-state EEG parameters may serve as additional prognostic biomarkers of behavioural recovery after stroke.

The results presented in **chapter 2** to **4** confirm that quantitative resting-state EEG parameters may serve as monitoring and prognostic biomarkers of neurological and behavioural recovery after stroke. Although the underlying neurological mechanisms of the observed changes remain unclear, EEG parameters are able to quantify neurological changes associated with motor recovery and predict motor recovery beyond clinical assessments. Future prognostic studies should focus on more severely affected stroke patients, for whom current prediction models are not adequate.

Chapter 5 presents how currently available longitudinal kinematic stroke studies investigate QoM during reaching. In this systematic review, a total of 32 studies was included, in which 46 different kinematic metrics were investigated during reaching in the sub-acute phase post stroke. Various approaches were identified to quantify behavioural restitution and compensation during upper limb recovery. Trunk displacement is a kinematic variable which is acknowledged to reflect a compensation strategy to overcome the reaching restriction caused by the shoulder-elbow muscle synergy. The contribution of behavioural compensation during task performance can be quantified by measuring trunk displacement or reduced by restricting trunk displacement. Some studies focused on the time period in which recovery takes place, since metrics which reflect behavioural restitution were argued not to improve beyond the time window of spontaneous neurological recovery. It should be noted that these metrics may still be contaminated by behavioural compensation. Some studies used anti-gravity support during reaching tasks, which is argued to enable a better reflection of neurological recovery, since the movement is not affected by limitations of muscle strength. In 2019, the Stroke Recovery and Rehabilitation Roundtable (SRRR) task force recommended to perform tasks which capture important components of motor impairment but do not allow compensation strategies, referred to as performance assays. One study obtained kinematic metrics for both a performance assay and a functional task. Nevertheless, we concluded that to date, performed longitudinal kinematic stroke studies lack consensus on metrics which are able to quantify QoM to reflect behavioural restitution during a functional reaching task, especially in absence of compensation strategies.

Smoothness is a kinematic variable which is generally accepted to quantify quality of movement. In stroke research, various kinematic metrics are used to describe smoothness, while proper recommendations for a valid smoothness metric are lacking. **Chapter 6** provides a systematic review of smoothness metrics used in stroke research, followed by simulation analyses to determine which smoothness metric is most adequate to use. In total, 32 different smoothness metrics were identified. Metrics which were mathematically sound in describing smoothness (n=15) were subjected to simulation analyses to test their response to changes in reaching behaviour using models of velocity profiles with varying durations, amplitudes, harmonic disturbances, noises, and sub-movements. For reach-to-grasp tasks, only the spectral arc length (SPARC) was identified as a valid metric to measure upper limb movement smoothness during reaching. The calculation of SPARC is based on the complexity of the shape of a Fourier magnitude spectrum of the velocity profile of the movement. The frequency spectrum of a smooth movement is composed of mainly low-frequency components, whereas less smooth movements show a larger number

of high-frequency components and thereby a more complex magnitude spectrum. Future studies which investigate smoothness during reach-to-point or reach-to-grasp tasks after stroke are recommended to compute SPARC as a valid smoothness metric.

In **chapter 7**, the time course and longitudinal association of smoothness and motor impairments of the upper extremity is investigated in 40 first-ever stroke patients. Reach-to-grasp movements were measured using 3-dimentional kinematics, weekly in the first 5 weeks and at week 8, 12, and 26 post stroke. At these measurement moments, clinical measures were also obtained including amongst others the FM-UE, reflecting motor impairment. Twelve healthy age-matched individuals were recruited to obtain reference values. Smoothness, quantified as SPARC, showed a longitudinal within-subject association with recovery of FM-UE. Both, SPARC and FM-UE, improved significantly until 5 weeks post stroke, whereafter their recovery levelled-off. When comparing SPARC between groups, stroke patients showed impaired smoothness compared to healthy individuals at all time points. The findings of this study suggest that recovery of smoothness deficits and recovery from motor impairments may be driven by a common underlying process of spontaneous neurological recovery. Thereby, the smoothness metric SPARC may serve as monitoring biomarker of neurological recovery after stroke.

Chapter 8 discusses the findings presented in the chapters of this thesis and potential next steps for future research. In this discussion, it is mentioned that besides EEG also other neuroimaging techniques (e.g., MRI, fMRI, DTI, MEG) may be used to search for neurophysiological parameters which can be used to reflect the neural state of the brain and may serve as monitoring biomarkers of neurological recovery. Furthermore, it was emphasized that prognostic models of behavioural recovery require further development, especially for more severely affected stroke patients for whom the current prediction models based on clinical motor assessments lack sufficient precision in the first weeks after stroke onset. This target population emphasizes the need for additional prognostic biomarkers that do not require to perform motor tasks, are to be assessed with non-invasive methods, and have added value above current predictors based on clinical assessments. With that, the prognostic value of various neurophysiological parameters derived from neuroimaging data obtained during usual care (e.g., CT or MRI) deserves further research early after stroke. Finally, future kinematic stroke studies should prioritize quantifying behavioural restitution. Kinematic metrics obtained from performance assays should encompass a specific stroke-induced motor impairment and should not be influenced by behavioural compensation. These metrics may serve as monitoring biomarker of neurological recovery and will enable to investigate whether neurological recovery can be influenced

by rehabilitation interventions. When motor recovery is better understood and the accuracy of early prediction of behavioural recovery is improved, clinicians will be able to: 1) Better inform patients and their families early after stroke, 2) Improve the triage by preventing an over- or underestimation of patients' expected capacity, and 3) Select the most adequate rehabilitation therapy.

Samenvatting

Samenvatting

Een beroerte is één van de voornaamste oorzaken van invaliditeit bij volwassenen in Europa. Ongeveer 80% van de patiënten die een beroerte overleeft ervaart motorische beperkingen. Dit uit zich voornamelijk unilateraal in verminderde controle van de aansturing van het gezicht, de arm en het been. Vooral motorische beperkingen aan de bovenste extremiteiten belemmeren patiënten in de uitoefening van dagelijkse activiteiten. Hoewel het merendeel van de patiënten een zekere mate van spontaan neurologisch herstel ondervindt, herstelt ongeveer 20-30% helemaal niet. Herstel van de functionaliteit van de bovenste extremiteit vindt overwegend plaats in de eerste tien weken na de beroerte. Over de mechanismen die ten grondslag liggen aan motorisch herstel is echter nog maar weinig bekend. Primaire en secundaire preventieve maatregelen beogen het aantal beroertes te reduceren en een beroerte zo spoedig mogelijk te detecteren en te behandelen. Tertiaire preventie is van belang om het herstelproces na de beroerte beter te kunnen voorspellen, en het herstel te versnellen en te verbeteren. **Hoofdstuk 1** behandelt twee knelpunten. Allereerst, de problematiek rondom het monitoren van neurologisch herstel door het ontbreken van een gedegen kwantificatie van de neurologische staat van het brein. Ten tweede, de behoefte aan biomarkers om de voorspelling van het motorisch herstel bij zwaar aangedane patiënten te kunnen verbeteren.

Gedegen kwantificatie van neurologisch herstel is nodig om te onderzoeken of neurorevalidatie interventies het neurologisch herstel na een beroerte beïnvloeden. Helaas kan neurologisch herstel niet direct worden gemeten. Om deze reden moeten er afgeleiden van de neurologische staat van het brein worden geïdentificeerd die geassocieerd zijn met bewegingsherstel, aangeduid als biomarkers. In dit proefschrift worden zowel biomarkers onderzocht die zijn afgeleid van waargenomen bewegingen als biomarkers die zijn afgeleid van hersenactiviteit.

Een klinische test die in wetenschappelijk onderzoek vaak wordt gebruikt om bewegingsherstel na een beroerte te monitoren is de Fugl-Meyer motor assessment voor de bovenste extremiteit (FM-UE). De FM-UE weerspiegelt het vermogen om te bewegen buiten abnormale synergiën die zijn ontstaan door de beroerte, en is gebaseerd op de verschillende stadia van motorisch herstel die worden doorlopen. Om deze reden wordt de FM-UE beschouwd als de klinische test die het meest gerelateerd is aan bewegingsrestitutie, en daarmee neurale restitutie. Echter, de FM-UE kent een plafondeffect en wordt onder anderen beïnvloed door beperkingen van spierkracht. Kwaliteit van bewegen (QoM – *Quality of Movement*), afgeleid van kinematische data, weerspiegelt het vermogen van motorische aansturing en wordt daarom aangedragen

als een meer gedegen kwantificatie van bewegingsherstel. Naast bewegingen die we met het oog kunnen waarnemen is ook de hersenactiviteit aangedaan (e.g., neurale oscillaties). Daarom wordt ook het meten van neurale oscillaties geopperd als methode voor het monitoren van neurologisch herstel.

Bij patiënten die licht zijn aangedaan kan de mate van motorische beperkingen van de bovenste extremiteit in de chronische fase momenteel vrij goed worden voorspeld aan de hand van hun initiële motorische beperking. Bij mild tot zwaar aangedane patiënten blijkt echter dat predictiemodellen onbetrouwbaar zijn en verbetering behoeven. Er is vraag naar aanvullende voorspellende biomarkers die kunnen worden verkregen bij patiënten die niet in staat zijn om actieve motorische handelingen te verrichten. Neurofysiologische parameters, bijvoorbeeld parameters die worden verkregen op basis van neurale oscillaties gemeten met EEG, kunnen mogelijk dienen als aanvullende voorspellers van bewegingsherstel na een beroerte.

In **Deel I** van dit proefschrift wordt bepaald welke kwantitatieve EEG-parameters kunnen dienen als biomarkers voor het monitoren of voorspellen van neurologisch herstel dat ten grondslag ligt aan het bewegingsherstel van de bovenste extremiteit na een beroerte. In **Deel II** van dit proefschrift wordt beschreven hoe QoM wordt gemeten met behulp van kinematica om bewegingsrestitutie te kwantificeren, en of het zou kunnen dienen als biomarker om neurologisch herstel te monitoren.

Hoofdstuk 2 behandelt een cross-sectionele studie waarin kwantitatieve parameters uit rust-EEG worden onderzocht in de chronische fase na een beroerte. In deze studie werden 21 patiënten, die ten minste in de acute fase na de beroerte leden aan een parese van de bovenste extremiteit, en 11 qua leeftijd en geslacht overkomende controlepersonen geïncludeerd.

Vergeleken met de gezonde proefpersonen vertonen patiënten hogere Brain Symmetry Index (BSI) waarden wat duidt op meer asymmetrie van de hersenactiviteit tussen de hersenhelften, voornamelijk bij neurale oscillaties met een lage frequentie (BSI_{theta} en BSI_{delta}). De directionele BSI (BSI_{dir}) laat zien dat deze asymmetrie voornamelijk het resultaat is van een toegenomen sterkte van de laagfrequente neurale oscillaties in de aangedane hersenhelft ten opzichte van de niet-aangedane hersenhelft. De Delta/Alpha Ratio (DAR) vertoonde geen verschillen tussen de groepen. Motorische beperkingen werden gekwantificeerd met behulp van de FM-UE. Uit een regressieanalyse blijkt dat patiënten met lagere FM-UE scores, oftewel degene met meer ernstige motorische beperkingen, meer asymmetrie vertonen in de sterkte van laagfrequente neurale oscillaties tussen de hersenhelften (BSI_{theta} and BSI_{delta}). De DAR vertoont geen relatie met de FM-UE scores.

Samengenomen met eerdere bevindingen uit de literatuur, betreffende EEG-afwijkingen in de acute en subacute fase na een beroerte, suggereren onze resultaten dat kwantitatieve rust-EEG parameters veranderen over de tijd waarbij zij meer gelijkenis gaan vertonen met de referentiewaarden van gezonde proefpersonen. Dit kan duiden op spontaan neurologisch herstel.

In **Hoofdstuk 3** wordt onderzocht hoe de eerdergenoemde kwantitatieve rust-EEG parameters zich ontwikkelen in de eerste 6 maanden na een beroerte. Ook wordt hun longitudinale associatie met globaal neurologisch herstel (NIHSS) en herstel van motorische beperkingen aan de bovenste extremiteit (FM-UE) onderzocht. Voor deze analyses werd data gebruikt van 41 patiënten die voor het eerst een hemisferisch ischemische beroerte hebben doorgemaakt. Rust-EEG werd opgenomen binnen de eerste 3 weken na de beroerte, en na 5, 12 en 26 weken, met behulp van 62 electroden.

Kwantitatieve EEG-parameters (BSI, BSI_{theta}, BSI_{delta}, BSIdir, $BSIdir_{theta}$, $BSIdir_{delta}$, DAR, DAR_{AH}, and DAR_{UH}) vertoonden normalisatie over de tijd, zowel binnen als ná 12 weken na de beroerte. Lineaire mixed models analyses toonden aan dat er een longitudinale associatie is tussen rust-EEG parameters en beide klinische testen (i.e., NIHSS en FM-UE). Een hybride model maakte het mogelijk om binnen- en tussen-persoons effecten te onderscheiden. De aanwezigheid van een significante longitudinale associatie binnen personen betekent dat veranderingen in hersenactiviteit binnen personen is geassocieerd met veranderingen in klinische testscores over de tijd. DAR_{AH} liet een longitudinale binnen- en tussen-persoons relatie zien met NIHSS-scores. $BSIdir_{delta}$ liet een longitudinale binnen- en tussen-persoons relatie zien met NIHSS en FM-UE scores. Op basis van deze bevindingen concluderen we dat kwantitatieve rust-EEG parameters kunnen dienen als biomarkers voor het monitoren van neurologisch herstel na een beroerte.

In **Hoofdstuk 4** wordt onderzocht of kwantitatieve rust-EEG parameters in de vroege fase na de beroerte kunnen voorspellen wat de mate van motorische beperking van de bovenste extremiteit (FM-UE) zal zijn na zes maanden. Bovendien wordt onderzocht of deze EEG-parameters toegevoegde prognostische waarde hebben bovenop initiële FM-UE scores. Voor deze analyses werd rust-EEG data gebruikt van 39 volwassen personen gemeten binnen drie weken na hun eerste ischemische beroerte. FM-UE scores werden verkregen binnen drie weken ($FM\text{-}UE_{baseline}$) en op zes maanden ($FM\text{-}UE_{w26}$) na de beroerte.

Regressieanalyses laten zien dat BSI en BSI_{theta} vroeg na de beroerte voorspellers zijn van $FM\text{-}UE_{w26}$. Patiënten die meer asymmetrie vertonen in de sterkte van de hersenactiviteit tussen de hersenhelften in de eerste drie weken na de beroerte

hebben meer motorische beperkingen in de chronische fase. Bovendien hebben BSI, BSI_{theta} en BSI_{delta}, een toegevoegde prognostische waarde ten opzichte van initiële motorische beperkingen (i.e., $FM\text{-}UE_{baseline}$) bij het voorspellen van $FM\text{-}UE_{w26}$. BSI_{theta} was hierbij de sterkste van de geanalyseerde voorspellende EEG-parameters.

De bevindingen suggereren dat rust-EEG in de vroege fase na de beroerte unieke informatie bevat over toekomstig motorisch herstel dat niet kan worden verkregen met behulp van klinische testen die motorische beperkingen kwantificeren zoals de FM-UE. Er wordt daarom geconcludeerd dat rust-EEG parameters zouden kunnen dienen als aanvullende prognostische biomarkers voor bewegingsherstel na een beroerte.

De resultaten beschreven in **Hoofdstuk 2**, **3** en **4** bevestigen dat kwantitatieve rust-EEG parameters zouden kunnen dienen als biomarkers voor het monitoren en voorspellen van bewegingsherstel na een beroerte. Hoewel de neurologische mechanismen die ten grondslag liggen aan de waargenomen veranderingen in het EEG onbekend zijn, kunnen EEG-parameters neurologische veranderingen kwantificeren die geassocieerd zijn met bewegingsherstel en hebben ze toegevoegde prognostische waarde bovenop klinische testen van motorische beperkingen. Toekomstige predictiestudies zouden moeten focussen op zwaar aangedane patiënten, voor wie de huidige predictie modellen niet voldoen.

Hoofdstuk 5 laat zien hoe longitudinale studies na een beroerte tot nu toe QoM hebben onderzocht op basis van kinematica. In dit systematisch review zijn 32 studies geïncludeerd, die in totaal 46 verschillende kinematische metrics hebben onderzocht tijdens reiktaken in de subacute fase na een beroerte. In deze studies werden verscheidene benaderingen gebruikt om bewegingsrestitutie en compensatie tijdens bewegingsherstel van de bovenste extremiteit te kwantificeren. Rompverplaatsing is een kinematische variabele waarvan wordt erkend dat het een compensatiestrategie weerspiegelt om de reikbeperking, die wordt veroorzaakt door de synergie tussen de schouder en elleboog, te overwinnen. De bijdrage van compensatiestrategieën tijdens het uitvoeren van een taak kan daarom bijvoorbeeld worden gekwantificeerd door de verplaatsing van de romp te meten. Compensatiestrategieën kunnen worden verminderd door de verplaatsing van de romp te beperken. Sommige studies richtten zich voornamelijk op de tijdsperiode waarin het herstel plaatsvond. Hierbij wordt verondersteld dat meetwaarden die bewegingsrestitutie weerspiegelen niet zouden verbeteren buiten de beperkte periode die wordt beschreven voor spontaan neurologisch herstel. Het moet wel worden opgemerkt dat deze tijdsrestrictie er niet voor zorgt dat kinematische metrics geen bewegingscompensatie weerspiegelen.

Andere studies gebruiken anti-zwaartekrachtsondersteuning tijdens het uitvoeren van reiktaken. Zij beargumenteren dat deze methode een betere weergave van neurologisch herstel mogelijk maakt, omdat de beweging niet wordt beïnvloed door beperkingen in spierkracht. In 2019 adviseerde de Stroke Recovery and Rehabilitation Roundtable (SRRR) werkgroep om taken uit te voeren die belangrijke componenten van motorische beperkingen vastleggen, maar geen compensatiestrategieën toestaan. Dit worden ook wel *performance assays* genoemd. Tot nu toe heeft één studie kinematische metrics gemeten tijdens zowel een performance assay als een functionele taak. Desalniettemin hebben we geconcludeerd dat tot op heden uitgevoerde longitudinale kinematische studies na een beroerte geen consensus hebben over metrics die QoM kunnen kwantificeren om bewegingsrestitutie weer te geven tijdens een functionele reiktaak zonder beïnvloed te worden door compensatiestrategieën.

Smoothness (ook wel vloeiendheid in het Nederlands) is een kinematische metric die algemeen is geaccepteerd om de kwaliteit van bewegen te kwantificeren. Aanbevelingen voor valide smoothness metrics ontbreken, waardoor in onderzoek naar herstel van QoM na een beroerte verscheidene kinematische metrics gebruikt worden om smoothness te kwantificeren. **Hoofstuk 6** beschrijft een systematisch review van smoothness metrics die zijn gebruikt in onderzoek bij patiënten die een beroerte hebben gehad, gevolgd door simulatieanalyses om te bepalen welk van deze metrics het best gebruikt kan worden. In totaal werden 32 verschillende smoothness metrics geïdentificeerd. Metrics die een wiskundig correcte beschrijving waren van smoothness (n=15) werden onderworpen aan simulatieanalyses om te testen of en hoe zij beïnvloed worden door veranderingen in de reikbeweging. Dit werd gedaan met behulp van modellen van snelheidsprofielen met verschillende tijdsduur, amplituden, harmonische storingen, ruis en sub-bewegingen. Voor reik-en-grijp taken werd geconcludeerd dat alleen de Spectral Arc Length (SPARC) een valide metric is om smoothness van de reikbeweging met de bovenste extremiteit te kwantificeren. De berekening van SPARC is gebaseerd op de complexiteit van de vorm van de Fourier-magnitudespectrum van het snelheidsprofiel van een beweging. Het frequentiespectrum van een vloeiende beweging bestaat voornamelijk uit laagfrequente componenten, terwijl een minder vloeiende beweging een groter aantal hoogfrequente componenten laat zien wat resulteert in een complexer magnitudespectrum. Toekomstige studies die smoothness onderzoeken tijdens reik-en-wijs taken of reik-en-grijp taken na een beroerte worden aanbevolen om SPARC te gebruiken als smoothness metric.

In **Hoofdstuk 7** wordt het verloop over de tijd en de longitudinale associatie van smoothness en bewegingsbeperkingen van de bovenste extremiteit onderzocht in 40 patiënten die voor het eerst een beroerte hebben gehad. Reik-en-grijp bewegingen werden gemeten met behulp van 3-dimentionale kinematica. Dit gebeurde wekelijks

in de eerste 5 weken, en in week 8, 12 en 26 na de beroerte. Op deze meetmomenten werden ook klinische metingen van bewegingen uitgevoerd, onder anderen de FM-UE dat motorische beperkingen van de bovenste extremiteit weerspiegelt. Twaalf gezonde personen die qua leeftijd overeenkwamen met de patiëntengroep werden geworven om referentiewaarden te verkrijgen. Smoothness, gekwantificeerd door de kinematische metric SPARC, liet een longitudinale binnen-persoonsassociatie zien met herstel van bewegingsbeperkingen, gekwantificeerd door FM-UE. Zowel SPARC als FM-UE lieten herstel zien tot en met de vijfde week na een beroerte, waarna hun herstel afvlakte. Reikbewegingen van patiënten die een beroerte hebben doorgemaakt waren op alle meetmomenten minder vloeiend dan bewegingen van gezonde personen. De bevindingen in deze studie suggereren dat herstel van verminderde smoothness en herstel van bewegingsbeperkingen mogelijk gedreven zijn door een gemeenschappelijk onderliggend proces van spontaan neurologisch herstel. Daardoor zou SPARC mogelijk kunnen dienen als biomarker om neurologisch herstel na een beroerte te monitoren.

Hoofdstuk 8 bespreekt de bevindingen die zijn gepresenteerd in de verschillende hoofstukken van dit proefschrift en potentiele vervolgstappen voor toekomstig onderzoek. Naast EEG zijn er ook andere neuroimaging technieken (e.g., MRI, fMRI, DTI, MEG) die gebruikt kunnen worden om neurofysiologische parameters te identificeren die gebruikt kunnen worden als biomarker om neurologisch herstel na een beroerte te monitoren. Ook wordt opgemerkt dat modellen die bewegingsherstel voorspellen verdere ontwikkeling vereisen. Dit geldt vooral voor zwaar aangedane patiënten, voor wie de huidige voorspellingsmodellen op basis van klinische testen onvoldoende nauwkeurig zijn in de eerste weken na een beroerte. Voor deze zwaar aangedane groep patiënten moeten voorspellende biomarkers geïdentificeerd worden die geen motorische activiteit vereisen, niet-invasief te verkrijgen zijn, en toegevoegde waarde hebben bovenop reeds bekende voorspellers. Daarom zouden bijvoorbeeld neurofysiologische parameters die verkregen kunnen worden uit neuroimaging tijdens de gebruikelijke zorg (e.g., CT of MRI) verder onderzocht moeten worden. Tenslotte zouden toekomstige kinematische studies naar het herstel na een beroerte prioriteit moeten geven aan het kwantificeren van bewegingsrestitutie. Kinematische metrics die verkregen worden tijdens performance assays moeten daarbij een specifiek door een beroerte veroorzaakte motorische beperking weerspiegelen die niet beïnvloed wordt door compensatiestrategieën. Deze metrics zouden kunnen dienen als biomarkers voor het monitoren van neurologisch herstel en zouden het mogelijk maken om te onderzoeken of neurologisch herstel kan worden beïnvloed door middel van revalidatie interventies. Wanneer motorisch herstel beter wordt begrepen en de nauwkeurigheid van predictie van bewegingsherstel is verbeterd, zorgt dit ervoor

dat behandelaars in staat zullen zijn om: 1) patiënten en hun families beter te informeren in de vroege fase na de beroerte, 2) de triage te verbeteren door een over- of onderschatting van verwachtte capaciteit van de patiënt te verminderen, en 3) de meest geschikte revalidatietherapie te selecteren.

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Dankwoord (Acknowledgements)

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A

About the Author

Curriculum Vitae

Mique Saes was born on December 7, 1991 in Nieuwegein and grew up in IJsselstein, the Netherlands. In 2010, she completed pre-university secondary education (Dutch: Voorbereidend Wetenschappelijk Onderwijs, VWO) at Het Oosterlicht College in Nieuwegein.

In 2013, she graduated *cum laude* as a Human Movement Scientist and received her Bachelor of Science degree at the Vrije Universiteit in Amsterdam. She focused on movement rehabilitation and programming to develop simulation models and analyze movements. During this study she also completed the *honors program* in which she broadened her knowledge of, amongst others, philosophy, neuroimaging, and statistics.

In 2015, she graduated *cum laude* from the Research Master Human Movement Sciences at the Vrije Universiteit in Amsterdam. During this study she gained knowledge on neurorehabilitation and performing clinical studies. She received the *Elvire van Oudenaarde award*, which is awarded annually to an outstanding female research master student of the Research Master Human Movement Sciences. This allowed her to visit a conference and follow a course on regulations for clinical studies. Moreover, she was appointed as a *VU University Research Fellow* of Professor Kwakkel. This fellowship was financially supported by the Vrije Universiteit to provide an outstanding student the chance to gain experience in scientific research under supervision of an outstanding researcher. During her scientific internship she joined the 4D-EEG research group in the Amsterdam University Medical Center (VUmc) at the department of rehabilitation medicine, where she performed electroencephalography measurements in stroke patients. She gained more experience in quantitative data analysis, data visualization, and scientific writing. After her graduation, she joined the research group as junior researcher and was responsible for gathering data, research coordination, and data management of this unique multi-center study.

In 2017, she started her PhD under supervision of Prof.dr. G. Kwakkel, prof.dr. C.G.M. Meskers, and dr. E.E.H. van Wegen at the department of Rehabilitation Medicine, and thereby continued working in the field of neurorehabilitation focused on stroke. During her PhD she was still involved in the 4D-EEG study. She performed quantitative data analysis based on longitudinal data gathered during clinical and electroencephalography measurements in stroke patients. She also engaged in the AMBITION project, which focused on quantifying quality of movement using kinematics. Both projects are described in this thesis.

Currently, Mique works as a medical writer at an international contract research organization specialized in the Medical Device industry.

Portfolio

Name PhD student:	M. Saes
PhD period:	June 2017 – December 2021
Name PhD supervisor:	Prof.dr. G. Kwakkel
Names PhD co-supervisors:	Prof.dr. C.G.M. Meskers and Dr. E.E.H. van Wegen

1. PhD training

	Year	ECTS
General courses		
· BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2016	2,00
· Scientific writing in English	2018	3,00
· Writing a Data Management Plan	2019	1,00
· AMS Scientific Integrity	2017	2,00
Specific courses		
· EEG Advance analyses	2018	1,43
· NeuroControl Summer School	2016-2019	6,00
· Courses Epidemiology (EpidM)		
· V30 – Regressie technieken	2017	5,00
· K73 – longitudinal regression analysis	2018	3,00
· GRAIL – software and hardware	2017	1,00
Seminars, workshops, and master classes		
· NeuroCIMT symposium (presenter)	2016/18/19	3,00
· NeuroCIMT workshops		
· Clinical engineering	2019	0,29
· fMRI and ECoG	2018	0,29
· Biofeedback	2018	0,29
· Science Exchange Day – VUmc (presenter)	2018	1,11
· Science Exchange Day – VUmc (organization)	2017	3,00
· Colloquia - Amsterdam Movement Sciences	2017-2020	1,00
· Monthly department meeting researchers Revalidatiegeneeskunde	2017-2020	2,00
Presentations		
· Refereeravond revalidatieartsen Noord-Holland	2020	0,39
(Inter)national conferences		
· Brain Modes Congress: *Coordinated brain activity: foundations and applications* – Brussel (presenter)	2016	2,00

· Annual Meetings – Research Institute Amsterdam Movement Sciences.	2017-2020	1,11
· Amsterdam Movement Sciences – PhD Day	2017-2020	0,60
· Society for Neuroscience - Chicago (presenter)	2019	2,00
· American Society of NeuroRehabilitation annual meeting Chicago (attendee)	2019	1,00
· Neurorehabilitation and Neural Repair – Maastricht (presenter)	2017/19	2,00
· Dutch Biomedical Engineering conference – Egmond aan Zee	2019	2,00
Other		
· Organizing a multi-center study	2015-2019	2,00
· Preparing, guiding, and closing out of monitoring visits	2015-2019	2,00

2. Teaching

	Year	ECTS
Supervising		
Student Supervising - Master thesis		
· Elza van Duijnhoven, Research Master Human Movement Sciences	2017 2018	0,50 0,50
· Ilona Visser, Master Human Movement Sciences		
· Daphne Koning, Mens en Techniek - Bewegingstechnologie	2018	0,50

3. Parameters of Esteem

	Year
Awards and Prizes	
· Best Poster – Annual meeting Amsterdam Neurosciences	2019

4. List of Publications

	Year
Peer reviewed international publications (Included in this thesis)	
• **Saes M**, Meskers CGM, Daffertshofer A, de Munck JC, Kwakkel G, van Wegen EEH; 4D-EEG consortium. How does upper extremity Fugl-Meyer motor score relate to resting-state EEG in chronic stroke? A power spectral density analysis. Clin Neurophysiol. 2019; 130(5):856-862. DOI: 10.1016/j.clinph.2019.01.007	2019

4. List of Publications (Continued)

	Year
• **Saes M**, Zandvliet SB, Andringa AS, Daffertshofer A, Twisk JWR, Meskers CGM, van Wegen EEH, Kwakkel G. Is Resting-State EEG Longitudinally Associated with Recovery of Clinical Neurological Impairments Early Poststroke? A Prospective Cohort Study. Neurorehabil Neural Repair. 2020; 34(5):389-402. DOI: 10.1177/1545968320905797	2020
• **Saes M**, Meskers CGM, Daffertshofer A, van Wegen EEH, Kwakkel G; 4D-EEG consortium. Are early measured resting-state EEG parameters predictive for upper limb motor impairment six months poststroke? Clin Neurophysiol. 2021; 132(1):56-62. DOI: 10.1016/j.clinph.2020.09.031.	2021
• Mohamed Refai MI, **Saes M**, Scheltinga BL, van Kordelaar J, Bussmann JBJ, Veltink PH, Buurke JH, Meskers CGM, van Wegen EEH, Kwakkel G, van Beijnum BF. Smoothness metrics for reaching performance after stroke. Part 1: which one to choose? J Neuroeng Rehabil. 2021; 18(1):154. DOI: 10.1186/s12984-021-00949-6.	2021
• **Saes M**, Mohamed Refai MI, van Kordelaar J, Scheltinga BL, van Beijnum BF, Bussmann JBJ, Buurke JH, Veltink PH, Meskers CGM, van Wegen EEH, Kwakkel G. Smoothness metric during reach-to-grasp after stroke. Part 2: longitudinal association with motor impairment. J Neuroeng Rehabil. 2021; 18(1):144. DOI: 10.1186/s12984-021-00937-w.	2021
• **Saes M**, Mohamed Refai MI, van Beijnum BF, Bussmann JBJ, Jansma EP, Veltink PH, Buurke JH, van Wegen EEH, Meskers CGM, Krakauer JW, Kwakkel G. Quantifying Quality of Reaching Movements Longitudinally Post Stroke: A Systematic Review. Neurorehabil Neural Repair. 2022; online ahead of print. DOI: 10.1177/15459683211062890.	2022
Other publications	
• Haring L, **Saes M**, Zandvliet S, Winters C, Andringa A; namens het 4D-EEG-consortium. De relatie tussen hersenactiviteit en herstel van arm- en handfunctie na een beroerte. Ned Tijdschr Revalidatiegeneeskd. 2016; 4: 79-81.	2016
• Mohamed Refai MI, van Beijnum BF, Buurke JH, **Saes M**, Bussmann JBJ, Meskers CG, Wegen EV, Kwakkel G, Veltink PH. Portable Gait Lab: Zero Moment Point for Minimal Sensing of Gait. Annu Int Conf IEEE Eng Med Biol Soc. 2019; 2019:2077-2081. DOI: 10.1109/EMBC.2019.8857314.	2019

Amsterdam Movement Sciences

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Amsterdam Movement Sciences conducts scientific research to optimize physical performance in health and disease based on a fundamental understanding of human movement in order to contribute to the fulfillment of a meaningful life.