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Recovery of arm-hand function after stroke:
developing neuromechanical biomarkers to
optimize rehabilitation strategies

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Recovery of arm-hand function after stroke: developing neuromechanical biomarkers to optimize rehabilitation strategies

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C h a p t e r

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General introduction

Stroke and impairment in arm-hand function

A cerebrovascular accident, or stroke, is defined by the World Health Organization as “an interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue”. The effects of a stroke depend on which part of the brain is injured and how severely it is affected [1]. Mortality directly after stroke is 15% [2].

Only 10% of stroke patients have a complete functional recovery [2]. In the Netherlands, it is estimated that the incidence of stroke is 0.5% [3] with a prevalence of 2.5%. That means that in a population of 17 million, there are around 85,000 new cases of stroke per year and over 400,000 persons living with the consequences of stroke. Among them, 32-60% experience a lasting impairment in arm-hand function [4,5] and movement disorders such as spasticity [6,7], with resulting limitations in activities of daily living or in participation [5,8], e.g. social functioning, sports or work.

Interventions directed at recovery of arm-hand function are either aimed at neural repair or at compensation methods and prevention of secondary complications. On the level of neural repair, early reperfusion with thrombolytic agents or mechanically by thrombectomy aim to minimize the damage in the first hours after stroke [9]; early hand therapy interventions aim to prevent learned non-use in the first days and weeks after stroke [10]. In the chronic phase after stroke, improvement in arm-hand function via neural repair is not to be expected [11]. Therefore, the focus in this phase lies on preventing secondary complications on the level of body structures and function; and on maximizing functioning on the level of activities and participation by compensation methods. Rehabilitation strategies range from task specific arm-hand training, robotics, splinting, stretching and botulinum toxin injections to surgery [12-15].

Clinical decision making

How to choose an appropriate rehabilitation strategy? Abovementioned therapies are often expensive and time consuming for both patients and therapists alike. Assigning the most effective intervention, however, not only depends on money and time, but also on an optimization of the time-window and selection of patients for a given intervention. Prediction models and biomarkers could support clinical decision making in this field [16]. For example: early return of wrist and finger extension and shoulder abduction after stroke is a key prognostic factor for regaining arm-hand function [4,10,17,18]. However, sensitivity and specificity of prediction models is seldom 100%. For example, prediction of proportional recovery fails in 30% of patients [19,20]. In this context, biomarkers of motor outcome play an important role, e.g. neuro-imaging and neurophysiological parameters to assess intactness of the corticospinal tract [16]. But these techniques do not fully bridge the gap towards endpoint joint behavior [21].

Endpoint joint behavior is determined by motor control, stretch reflex properties and tissue properties. Movement disorders after stroke are the result of a complex interaction between neural deficits and changes in non-neural tissue properties [22,23], leading to a recognizable triad of paresis, muscle overactivity and contracture. Paresis is determined by decreased voluntary motor unit recruitment. Muscle overactivity (e.g. over-excitability of stretch reflexes and decreased selectivity of movement) is determined by increased involuntary motor unit recruitment. Contracture is determined by altered tissue properties and a changed position of the joint [24,25]. Biomarkers that accurately represent endpoint joint behavior (i.e. parameters with a high sensitivity and specificity) are required to assign and evaluate therapies both in the acute and chronic phase, and to reduce numbers of patients needed in research [21]. These data need to be collected objective and reproducible, which cannot always be achieved by using clinical scales [26,27].

Neuromechanics

Could neuromechanics be the essential element to represent and further specify endpoint joint behavior? Clinically, endpoint joint behavior is mostly described in terms such as paresis and spasticity, and measured with clinical scales. Neuromechanics provide a quantitative description of joint properties, both under passive and active conditions and as a reaction to external mechanical perturbations [28]. Variation in measurement conditions and tasks allows for the separation of neural contributors (motor control and stretch reflex properties) and non-neural contributors (tissue properties) to movement disorders after stroke, and for a more precise analysis of the non-linear properties of endpoint joint behavior [29] (e.g. for non-linearity: twice as much stretching does not result in twice as much resistance of the joint).

Biomechanical measuring devices (such as haptic robots, force/torque transducers and electrogoniometers) in combination with electromyography [27,30-32] allow variation in measurement conditions to objectify motor control, stretch reflexes and tissue properties in a reproducible manner. Furthermore, degrees of freedom of movement may be controlled, to allow or restrict compensation methods, providing valuable information on the pathophysiological mechanisms underlying functional recovery. For example, neuromechanical parameters can describe paresis not only in terms of force or torque, but also as lack of selective muscle activation or diminished active range of motion. And in case of a clinical phenomenon such as spasticity: tissue stiffness, stiffness due to reflex activity and modulation of reflexes in a changed environment can be distinguished. In summary, neuromechanical parameters may provide a comprehensive description of endpoint joint behavior with a strong link to underlying pathophysiological mechanisms.

EXPLICIT-stroke project

The studies in this thesis were conducted within the framework of the Explaining PLastICITy after stroke (EXPLICIT-stroke) trial. This multicenter research program, consisting of a randomized clinical trial on the effects of early rehabilitation intervention on arm-hand function after stroke and a longitudinal survey into the dynamics of post-stroke recovery [10], aimed at improving arm-hand function by utilizing the window of opportunity for neural repair in the acute phase after stroke. Patients were stratified according to active wrist and finger extension within one week after stroke [10], based on the prediction model described earlier [4].

Parallel to clinical tests measuring arm-hand function, a selection of patients was assessed longitudinally by fMRI, TMS, kinematics and neuromechanics. The combination of clinical outcome measures, neuro-imaging, neurophysiological parameters and neuromechanics, aimed to enlarge the understanding of pathophysiological mechanisms of functional recovery after stroke. In short, EXPLICIT-stroke was designed to provide an answer to the key question whether improvement in arm-hand function in the first 6 months after stroke is due to a reduction of basic motor impairment by neural repair or by behavioral compensation methods.

Thesis outline

The aim of this thesis is to explore the neuromechanics of recovery of arm-hand function after stroke by assessing neural and non-neural contributors to movement disorders in the acute and chronic phase after stroke. Key questions are: How and to what extent does endpoint wrist joint behavior, as measured with neuromechanical parameters, change in the first 6 months after stroke? And how do those changes relate to functional outcome? [10]

First, the gap is explored between day-to-day practice (i.e. physical examination) and the biomechanical and electrophysiological techniques recommended by research to support clinical decision making. An overview is given of regularly used pathophysiological concepts and biomechanical and electromyographical outcome measures of movement disorders after stroke (chapter 2).

Then, methodological aspects on how to address the different (nonlinear) neural and non-neural properties of the wrist joint during flexion-extension movement are presented. The recommendations to apply multiple measurement and task conditions are assembled in a comprehensive and clinically applicable assessment protocol, to identify patients within the spectrum of neuromechanics and to understand the underlying pathophysiological mechanism of movement disorders after stroke (chapter 3).

Clinical responsiveness of the newly developed protocol and test-retest reliability are assessed in a cohort of stroke patients with impaired arm-hand function in the chronic phase after stroke and compared to a cohort of healthy participants (chapter 4). Complementary,

the roles of co-contraction and paresis on arm-hand function are investigated by assessing impairment in selective muscle activation. The methodology of measuring selective muscle activity by means of Activation Ratios is described and test-retest reliability and clinical responsiveness of this tool are presented (chapter 5).

Ultimately, changes in wrist neuromechanical parameters in the first 6 months after stroke are quantified by longitudinal data obtained with the comprehensive assessment protocol within the prospective cohort of the EXPLICIT trial. Neural and non-neural contributors to movement disorders after stroke i.e. paresis, stiffness and reflex modulation are related to functional outcome as determined by the Action Research Arm Test (ARAT) at 26 weeks after stroke. It is hypothesized that paresis, a high degree of stiffness and absence of reflex modulation will be related to poor functional outcome (chapter 6).

In the general discussion, the diverse aspects of measurement of impairment in arm-hand function after stroke are summarized, including clinical implications, methodological considerations and recommendations for future work (chapter 7).

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C h a p t e r

2

The gap between clinical gaze and systematic assessment of movement disorders after stroke

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ABSTRACT

Background

Movement disorders after stroke are still captured by clinical gaze and translated to ordinal scores of low resolution. There is a clear need for objective quantification, with outcome measures related to pathophysiological background. Neural and non-neural contributors to joint behavior should be separated using different measurement conditions (tasks) and standardized input signals (force, position and velocity).

Methods

We reviewed recent literature for the application of biomechanical and/or electromyographical (EMG) outcome measures under various measurement conditions in clinical research.

Results

Since 2005, 36 articles described the use of biomechanical and/or EMG outcome measures to quantify post-stroke movement disorder. Nineteen of the articles strived to separate neural and non-neural components. Only 6 of the articles measured biomechanical and EMG outcome measures simultaneously, while applying active and passive tasks and multiple velocities.

Conclusion

The distinction between neural and non-neural components to separately assess paresis, stiffness and muscle overactivity is not commonplace yet, while a large gap is to be bridged to attain reproducible and comparable results. Pathophysiologically clear concepts, substantiated with a comprehensive and concise measuring protocol will help professionals to identify and treat limiting factors in movement capabilities of post-stroke patients.

INTRODUCTION

Movement disorders after stroke are the result of a complex interaction of primary neural damage and secondary tendomuscular changes [1,2]. The combination of paresis, stiffness and muscle overactivity leads to a phenotype that is easy to recognize clinically, but hard to quantify [1]. The broadly used term “spasticity” is under debate. Different definitions are used, and while it is mostly used as an umbrella-term for the phenotype, it describes only a part of the movement disorder [3-7], and has little relation to the capabilities of a patient to perform under different circumstances.

Clinical gaze and manual tests to assess movement disorder after stroke are readily available to every physician and are currently used as a basis for clinical practice. However, there are some difficulties in evaluating interventions within patients and between studies. For example, resolution of clinical tests is low, rater dependency is variable and conditions are difficult to standardize [8,9]. Little is known about responsiveness of the clinical tests to change. Ordinal scales are often misused as linear entities. Also, the measured construct of tests is not always taken into account when choosing a test for the assessment of stroke patients [9], i.e. improvement in tests on the domains of body structures and functions of the International Classification of Functioning, Disability and Health (ICF) do not automatically lead to improvement in the domains of activities and participation.

Correct use of a meaningful pathophysiological construct will enable clinicians to target their expensive and labor intensive therapies such as botulinum toxin and exercise programs more efficiently and effectively. Evidently, this challenges the community of rehabilitation specialists to quantify and objectify the components of movement disorders according to their pathophysiological origin [10,11] and their relevance for performance in the different ICF domains. For the domain of Body Structures and Body Functions this means that, first of all, input signals (e.g. velocity, force, angle) should be standardized to enable comparability and repeatability. Second multiple measuring conditions should be applied to trigger the different pathophysiological components [10,11], i.e. active tasks to study voluntary muscle properties, passive tasks to study passive tissue properties, and multiple measurement velocities to elicit stretch reflexive behavior. This will allow for differentiation in neural and non-neural components (see Table 1), and will enable clinicians to direct their therapies more precisely. Simultaneously used biomechanical and electrophysiological techniques can support the identification of active, passive and reflexive components and their complex (non linear) interactions.

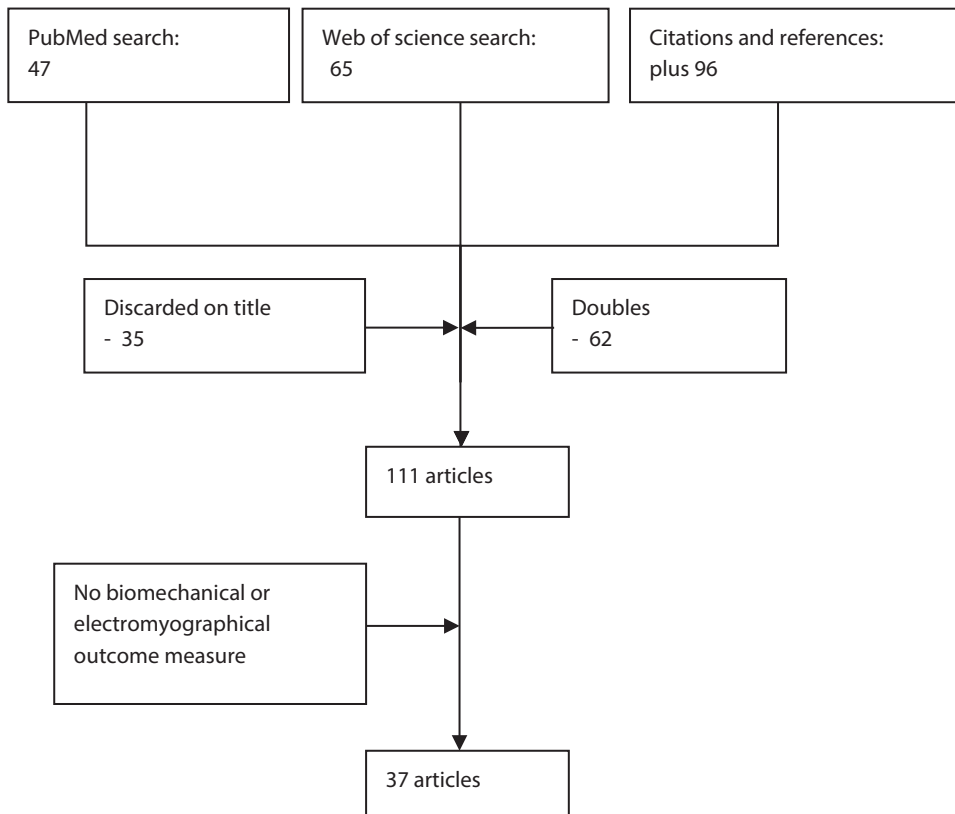
Recommendations for objective and quantitative assessment of movement disorders after stroke are readily available [6,9,12,13]. However, it is unclear to which extent these recommendations are implemented in current research and clinical practice. The aim of the present paper is to provide an overview of biomechanical and electrophysiological

outcome measures recently used to describe post-stroke movement disorders. In addition, the use of underlying pathophysiological constructs is investigated.

METHODS

We conducted a literature search on PubMed and Web of Science with the following search terms: PubMed: stroke AND biomechanics AND electromyography (limits: last 5 year, human, adult) (accessed dec 2010). Web of Science: TS = ((stroke AND outcome measures) AND (biomechanic OR electromyography)). We also tracked references and citations. Thereafter we checked for doubles and scanned titles and abstracts. For a flow chart of the search, see Figure 1.

Figure 1 | Flow chart of the search strategy and outcome.



Within the found references, we identified biomechanical and electromyographical (EMG) outcome measures, used in research on stroke patients. We searched for the pathophysiological construct of these outcome measures, given by the authors. Biomechanical and EMG outcome measures were examined for task instruction (active or passive) and for applied velocities of perturbations (slow, fast or multiple velocities). Subsequently, the outcome measures were separated in clusters, according to the applied method. For biomechanical outcome measures, the clusters were: range of motion, stiffness (or resistance to passive movement), maximum voluntary contraction, viscosity, work, mathematical models, other. For EMG outcome measures, the clusters were: magnitude, threshold (angle), onset (time), co-activation, other.

Table 1 | Division of components of post stroke movement disorder in non-neural and neural properties offers a construct for targeted therapy: an overview.

	Measuring condition	Construct
Non-neural	Passive	Stiffness, changed properties of connective tissue and joints
Neural	Active	Paresis, diminished voluntary muscular capacity
	Reflexive (velocities)	Muscle overactivity, stretch reflex behavior

RESULTS

The search yielded 37 articles. A flowchart of the search is illustrated in Figure 1. Study characteristics (measured segment, number of subjects, category of research) and the biomechanical and electrophysiological outcome measures found in each article, are summarized in Additional file 1.

Of the 37 articles, 3 were review articles [14-16]. In the other 34 articles, 30 included EMG outcome measures [17-45] and 31 included biomechanical outcome measures, while 25 articles included both. Active and passive tasks were found in 10 articles [17,19,20,26,27,29,33,34,38,46]. Different measuring velocities were found in 19 articles [18-22,24,27,30-35,37-39,43,44,47]. In 6 articles, all of the aforementioned properties were present (see Figure 2) [19,20,27,33,34,38].

In 6 articles the biomechanical and/or EMG were used to evaluate treatment of stroke patients [17,26,28,31,37,43], 10 articles addressed reliability or feasibility of the outcome measures in stroke patients [20,21,23,32,35,44,45,47-49] and 18 articles were observational (difference between healthy subjects and stroke patients) or tested a new measuring method [18,19,22,24,25,27,29,30,33,34,36,38-42,46,50]. A total of 682 stroke patients and 175 healthy subjects were included (see Additional file 1).

In 25 articles the biomechanical and EMG techniques were used to objectify or quantify a clinical concept (e.g. spasticity, muscle tone, muscle activity, impairment or coupling) [18,20,22-27,29-33,35,37,39-47,50]. Alongside this, a large part of the articles use these techniques to separate the underlying (neural and non-neural) mechanisms of the concept (n = 19) [18-24,30,31,33-35,37,39,40,42-45]. Finally, there is also a small number of articles that advocate standardized input (n = 6) [19-21,24,30,40].

Biomechanical outcome measures

An overview of biomechanical outcome measures is presented in Additional file 1.

Range of motion was assessed as passive range of motion (pain-free or comfortable range of movement about a joint) (n = 12), active range of motion (n = 3) or both (n = 3). An electrogoniometer was used in 7 articles [17,18,22,25,35,46-48], customized devices were used in 8 articles [19,20,32,34,38,44,45,49] and in 2 articles manual goniometry was used to measure the range of motion [23,28].

Maximum voluntary contraction was measured with a handheld dynamometer (n = 1) [17], or a torque transducer/load cell in a (customized) device (n = 11) [19,27-29,33,34,36,38,39,41,49]. Isometric conditions were applied in 11 articles, while in 1 article the peak active torque during flexion/extension movement was measured [19].

Stiffness or resistance to passive movement was measured as force or torque versus angle during passive movement, with the identical device as used for maximum voluntary contraction. The methods ranged from measuring peak resistance during movement (n = 2) [30,48], calculating the slope of the force-angle curve, linearized over a part [19,20,22,23,32,43] or the total [24,30,32,35,43] of the movement trajectory (n = 10), to a model fit (n = 5) [33,34,38,44,45]. A minority compared stiffness at different velocities (n = 5) [24,30,32,35,43].

Viscosity (n = 3) was derived from force and position at different velocities during passive movement [29,31,37]. Work (n = 2) was calculated as the area under the curve of moment-angle, during passive movement [18,30]. Mathematical models (n = 3) were used to compare the estimated or predicted parameter with the actual parameter. This was done once for muscle length [27], once for torque [33] and once for angle trajectory [42].

Other biomechanical parameters assessed (n = 25) were tracking index (correlation between target angle and actual angle) [19,20], relaxation index (difference in angle between initial angle and first drop in pendulum test) [25], velocity dependent torque [18,33-35,44,45], phase dependent torque (timing of joint resistance compared to movement) [29,37], movement pattern (range of motion related to duration of phase) [46], miscellaneous other torque parameters [18,23,30,38,40,50] and gains [44,45]. Most attempted to cipher some spasticity parameter, using different combinations of velocities or positions and resulting torque.

Electrophysiological outcome measures

All electrophysiological outcome measures were measured using surface electromyography (EMG). An overview of EMG outcome measures is presented in Additional file 1.

Magnitude of EMG signal was measured during maximum voluntary contraction (isometric) (n = 5) [27,28,33,39,41], with a target force or target EMG-level (n = 2) [27,39], during passive movement (n = 18) [17-20,22-26,30,33,36,38,40,43,44,46] or during active movement [46]. Tendon taps were used in 2 articles [23,40] and H-reflex stimulation were used in 2 articles [26,36]. In all cases the EMG was rectified and/or normalized. The EMG activity during maximum voluntary contraction was mostly used as a reference value for the magnitude of reflex EMG response. In 6 cases, EMG activation was compared between different velocities or task instructions [22,30,35,39,43,46].

Threshold was described as the angle at which EMG activity started during passive movement. Thresholds were compared between different velocities of perturbation [21,30,31,37]. Onset was described as the latency in time between start of perturbation and start of EMG activity [27,33,34,38,45].

Co-activation (or cocontraction) compared agonistic and antagonistic EMG-activity during passive movement (n = 4) [19,20,44,45], during active movement (n = 1) [46] or maximum voluntary contraction (n = 1)[34].

Other parameters of EMG (n = 9) that were assessed, include velocity dependent EMG signal [35], tonic threshold (extrapolation of thresholds from different velocities to zero velocity) [21], duration of activity [29], modulation of activity [29], volitional response time [27,39], slope of recruitment curve and H-reflex related parameters [36].

Pathophysiological construct of outcome measures

Observed pathophysiological constructs were spasticity (n = 16) [17,21-26,32,33,35,37,44-48], muscle tone [18,30,31,42,43], muscle overactivity [28,39,40,50], paresis [49], motor control [29], impairment [19,20], coupling between extremities [27,36,38], secondary changes [34] and normalization of signals [41]. Observed underlying mechanisms used to underpin the pathophysiological constructs were paresis [17,19-21,24,34,49], limited range of motion [19,20,46,50], stiffness/hypertonia [18-25,30-35,37,38,42-45,47,50], muscle overactivity/hyperreflexia [17,20-25,27-31,34-40,43,45,50] and motor control/dexterity [19,20,29,33,46,49]. An overview of the cross-links between observed pathophysiological constructs and underlying mechanisms is presented in Table 2.

The most addressed concept was that of spasticity (n = 16), although different definitions and interpretations were given [17,21-26,32,33,35,37,44-48]. The observed underlying mechanism was in either non-neural (stiffness, resistance) (n = 4) [32,33,45,47], neural (muscle overactivity, hyperreflexia) (n = 2) [17,46], or a combination (n = 8) [21-25,35,37,45]. The remaining articles concerning the concept of spasticity did not discriminate between neural and non-neural components (n = 2) [26,48].

The second most addressed concept was that of muscle tone ($n = 5$) [18,30,31,42,43]. All five use non-neural components of muscle tone as underlying mechanism (i.e. stiffness, inertia, mechanical characteristics of passive tendomuscular and connective tissue, mechanical characteristics of activated muscle), while neural components (muscle overactivity, hyperreflexia) were separately addressed in 3 articles [30,31,43].

The concept of muscle overactivity was the main topic in 4 articles [28,39,40,50]. two articles distinguish between neural and non-neural properties ($n = 2$) [39,40].

The underlying mechanisms of stiffness and muscle overactivity were combined in 15 out of the 37 articles [19,21-25,30,31,34,35,37,38,40,43,45].

Table 2 | Concepts and pathophysiological mechanisms categorized in articles measuring movement disorder after stroke.

Concept	Articles (n)	Pathophysiological mechanisms				
		Paresis	Limited range of motion	Stiffness/ hypertonia	Muscle overactivity/ hyperreflexia	Motor control/ dexterity
Spasticity	16	3	2	12	9	2
Muscle tone or hypertonia	5	0	0	5	3	0
Muscle overactivity	4*	0	1	1	4	0
Other						
paresis	1	1	0	0	0	1
motor control impairment	1	0	0	0	1	1
coupling	2	2	2	2	1	2
secondary changes	3 [#]	0	0	1	3	0
normalization	1	1	0	1	1	0
normalization	1	0	0	0	0	0

*muscle overactivity ($n = 2$), reflex response ($n = 2$); # affected & non affected side ($n = 1$), upper & lower extremity ($n = 1$), proximal & distal segment of extremity ($n = 1$).

DISCUSSION

Since 2005, 37 articles described the use of biomechanical and/or EMG outcome measures to describe post-stroke movement disorder. Nineteen of the articles strived to separate neural from non-neural components. The most frequent pathophysiological constructs were spasticity, muscle tone and muscle overactivity. Only 6 of the articles measure

biomechanical and EMG outcome measures simultaneously, while applying active and passive tasks and multiple velocities.

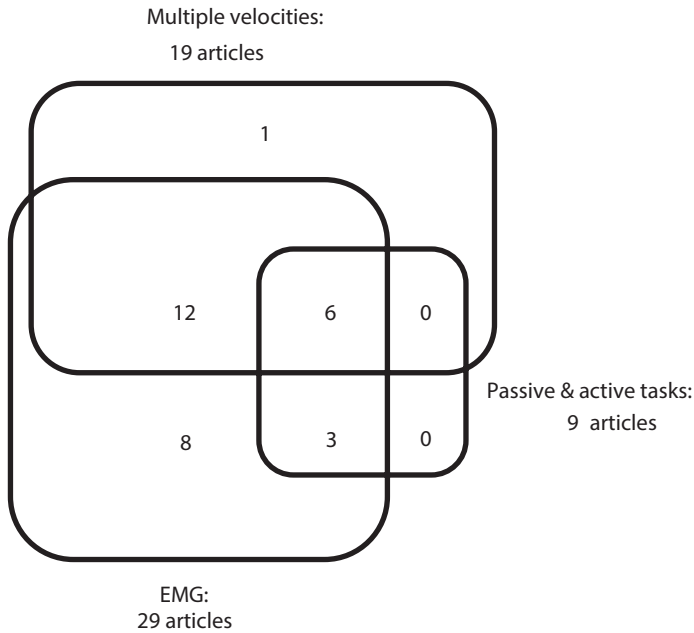
Whilst this study limited the use of search engines to PubMed and Web of Science, it is likely that the main bulk of relevant literature is identified by using generic search terms and cross-checking references. The restriction to search only recent literature is justified by the specific aim of the study, namely, to identify current methods.

This review shows that in recent years initiatives have been taken to quantify and objectify measurements in post stroke movement disorders. It also indicates that the conceptual mainframe of separating movement disorder into neural and non-neural components was not always taken into account, i.e. active, passive and reflex contributions were not always divided. In some articles, there was a lack of consistency in administration of the underlying pathophysiological mechanism (paresis, increased stiffness and muscle overactivity) or pathophysiological concept (spasticity, muscle tone). For example: one [50] of the 4 papers on muscle overactivity did not use EMG. Another example is spasticity, which was described as velocity dependent in 13 of the 16 papers [17,21,23-26,32,33,35,44,45,47,48], while only 8 of the 16 papers use multiple velocities in their tests [21,22,24,32,33,35,37,47].

Measuring in different operating points is not commonplace yet, while it will allow for a more complete understanding of the capabilities of a patient with a movement disorder. Active and passive tasks instructions will give information about paresis and involuntary muscle activity, and a variation of velocities of perturbations will illuminate stiffness and reflex contributions. A more specific knowledge of the capabilities of a patient will probably lead to a more specific treatment. For example, patients with movement disorder due to severe paresis or reduced range of motion through secondary changes will not benefit from spasmolytic or neurolytic treatment. Yet, before treatment in spastic patients, these disorders are not systematically separated from muscle overactivity. This does not benefit the individual patient, is not cost effective and will introduce a bias in research of effect measurements after treatment.

The techniques as described in this review are mostly not available in clinical practice yet. This has led to prolonged use of clinical scores, despite their known disadvantages. We recommend that future work on movement disorder in stroke patients should be based on a clear concept and include a comprehensive and concise measurement protocol which is easily applied on and well tolerated by stroke patients. Outcome measures should be pathophysiologically meaningful and applicable in decision making for clinicians. Additionally, to increase the understanding of primary and secondary changes, longitudinal studies will be essential [51]. This will enable specialists in physical medicine and rehabilitation to tailor their therapies and, moreover, allow them to assess the effect of (experimental) interventions.

Figure 2 | Number of articles conforming to recommendations for measuring movement disorder after stroke: measuring active and passive tasks, measuring at multiple velocities and including EMG-techniques.



CONCLUSION

In the last 6 years a number of initiatives were developed to quantify and objectify movement disorder after stroke. However, the distinction between non-neural and neural components to separately assess paresis, stiffness and muscle overactivity, is not commonplace yet. A large gap has to be bridged to attain reproducible and comparable results. Pathophysiologically clear concepts, substantiated with a comprehensive and concise measuring protocol will help professionals to identify and treat limiting factors in movement capabilities of post-stroke patients.

Abbreviations

EMG: Electromyography;

H-reflex: Hoffmann reflex, EMG response of muscle after electrical stimulation of the afferent nerve fibers;

EXPLICIT-stroke: "EXplaining PLasticITY after stroke";

mAS: Modified Ashworth Score;

ICF: The International Classification of Functioning, Disability and Health is a classification of health and health-related domains. These domains are classified from body, individual and societal perspectives by means of two lists: a list of body functions and structure, and a list of domains of activity and participation. Since an individual's functioning and disability occurs in a context, the ICF also includes a list of environmental factors [www.who.int accessed May 6th 2011].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JMK contributed to the design of the study, carried out the literature search and wrote the manuscript. CGM is co-PI of the EXPLICIT study, contributed to the design of the present study, assisted in data interpretation and commented on the manuscript. JDG contributed to the design of the study, assisted in data interpretation and commented on the manuscript. AK contributed to the design of the study, assisted in data interpretation and commented on the manuscript. JHA is co-PI of the EXPLICIT study, contributed to the design of the study, assisted in data interpretation and commented on the manuscript. All authors read and approved of the manuscript.

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C h a p t e r

3

Design of a concise and comprehensive protocol for post stroke neuromechanical assessment

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ABSTRACT

Functional recovery post stroke is determined by a complex interplay of neural and mechanical (muscular/ tissue) changes. In the present paper, we elaborate on a methodology to assess neuromechanical joint properties in a comprehensive and concise way. A measurement protocol applicable to the wrist joint is introduced and outcome is described for illustrative purposes.

By means of a single axis manipulator, a variety of conditions are applied including different exerted loadings and a passive or active task instruction. The combination of different tasks and loadings systematically excites the nonlinear neuromechanical joint system. Output of the joint system is measured in terms of torques, angular rotation and muscle activation. Both signal analysis and system identification methods are applied to translate the measured variables into physiologically meaningful parameters, describing passive and active (muscle) tissue properties and reflexive characteristics.

A severely impaired and a well-recovered stroke patient show clear differences in outcome parameters. Furthermore, parameters are shown to change over condition, indicating that multiple conditions need to be applied to identify their potentially varying role in movement disorders. The protocol is used in a longitudinal study to explore post-stroke upper limb recovery mechanisms, i.e. the EXPLICIT-stroke study.

INTRODUCTION

Movement disorders after stroke may have a major impact on daily life. Almost two thirds of the stroke survivors suffer from sustained deterioration of arm-hand function which threatens physical independency [1]. Besides cortical and corticospinal tract integrity, functional movement and motor deficits are largely determined by joint neuromechanics. In the acute phase after stroke, mechanical behaviour at joint level is characterized by flaccidity and paresis, while in the sub acute phase, signs of muscle over-activity and joint stiffening become more prominent [2,3]. Although this is a common recovery pattern, several different phenotypes may develop in the chronic phase [4]. These phenotypes will be the result of a complex and varying interplay between neurological and biomechanical changes over time. A better understanding of the interplay and changing contributions of aforementioned neuromechanical processes to movement disorders is needed to address the full functional recovery potential. The EXPLICIT-stroke (EXplaining PLastICity after stroke) study was designed to explore the functional impact of the time-dependent changes in cortical neuroplasticity and neuromechanics, as well as the adaptive compensation strategies that are applied to cope with ischemic brain lesion related motor deficits [5].

Current clinical assessment of joint neuromechanics is restricted to ordinal rating scales such as the Medical Research Council scale for muscle force, goniometry for impaired range of motion (ROM) and Ashworth score for spasticity. The latter however, is incapable of discriminating between the possible neural and/or mechanical sources of increased joint resistance [4,6,7]. The use of robotics (e.g. a wrist manipulator) to evoke controlled force and torque perturbations, electromyography (EMG) to record muscle activity and neuromuscular modelling potentially allows for an individual assessment of neurological and biomechanical joint properties [6,8-11].

Nonlinear dynamics of the neuromuscular system greatly influence joint behaviour, yet their role has not been fully recognised. For example, the stretching of tissue yields nonlinear force curves: twice as much stretching does not result in twice as much resistance of the joint [12]. Another example is the sensitivity of the stretch reflexes, which may be modulated at spinal cord level [13]. While linear mass-spring-damper-like concepts are far easier to apply and are regularly used to simplify mechanical behaviour, they do not comprehensively describe biomechanical properties of the joint under different environmental conditions (tasks and loadings). Using prior knowledge of nonlinearities, the joint can be conditioned such that the nonlinear dynamics of the neuromuscular system can be accounted for, or even parameterized.

In this paper we present the methodological aspects on how to individually address the different properties of the (nonlinear) neurological and biomechanical components of wrist joint behaviour in during flexion-extension movement. This resulted in a comprehensive and clinically applicable assessment protocol. Longitudinal measurements with this specific

protocol, within a longitudinal measurement framework such as the EXPLICIT-stroke study, will enhance our knowledge of primary and secondary changes in neuromechanics when functional changes are observed.

METHODS I. LINE OF THOUGHT

Assessment of neurological and biomechanical contributors to movement disorders after stroke should result in structure specific parameters that are potentially modifiable by therapeutic intervention. Treatment is commonly aimed at muscle activation or strength in case of paresis, reduction of reflex sensitivity or neural input in case of hyperreflexia or the stretching of passive tissue in case of joint stiffening. Therefore, we define the neuromechanical system on a therapeutically attainable level into passive, active and reflexive torque components:

- *Passive* = all joint resistance observed when no neural input is fed to the muscles
- *Active* = muscle torque generation due to neural input (supraspinal and reflexive)
- *Reflexive* = active muscle torque solely due to proprioceptive feedback

The interconnection between passive, active and reflexive contributors is represented in Figure 1. By differentiating the contributions of each of these elements to joint level mechanics, their individual roles in movement disorders can be better defined, allowing for targeted therapy.

In order to characterize the phenotype of post-stroke patients properly, the neuromechanical system needs to be sufficiently triggered i.e. different conditions need to be applied. Passive, active and reflexive components will be dependent on the state of the wrist (i.e. joint torque, joint angle and muscle activity) and the externally applied loading. The state represents the current operating point of the system and subsequently its dynamical properties, observed at endpoint level in torque (and angle). A haptic wrist manipulator combined with electromyographic (EMG) measurement is an easy-to-use combination of tools that allows for applying angle or torque controlled perturbations and the subsequent assessment of changes in joint state. The different modes in combination with task instruction enable us to impose a desired state. Properties of passive, active and reflexive contributors can be estimated from the measured in- and output data. When torque is the input, angular displacement is the output and vice-versa. Output signals including EMG, as a representative of active muscle state, may also be used to inform the subject on actual task performance.

For analysis, we define two different approaches. The first approach will be referred to as signal analysis. This approach aims to induce large variations regarding the role of model components by applying specific conditions to the system. Slow movements will exclude

reflexive activity, while the amount of voluntary contraction can be modulated, and therefore controlled, by proper task instruction. This gives contributor-specific tests that aim to assess passive, active or reflexive contributors individually. The second approach, referred to as system identification, is based on the fact that reflexive resistance is dynamically different from passive or active resistance. Differentiation between the feedback pathways can be done using torque-angle correlation analysis, keeping the closed loop configuration of reflexive (neural) and muscular (mechanical) components into account. Both approaches make it possible to express system performance in terms of its underlying properties, yet conditions are significantly different. System identification methods are not yet sophisticated enough to perform well over a nonlinear domain, and additional signal analysis methods are still needed. Furthermore, limit behaviour, such as ROM or maximal voluntary contraction (MVC), is easier to assess using basic signal analysis. The following subsections describe a listing of interesting outcomes that together result in a comprehensive set for assessment of joint neuromechanics. These outcomes were used as a basis for the protocol discussed in the following section, i.e., "The EXPLICIT-stroke protocol".

Signal analysis

Passive tests (slow movement while instructed to "do nothing")

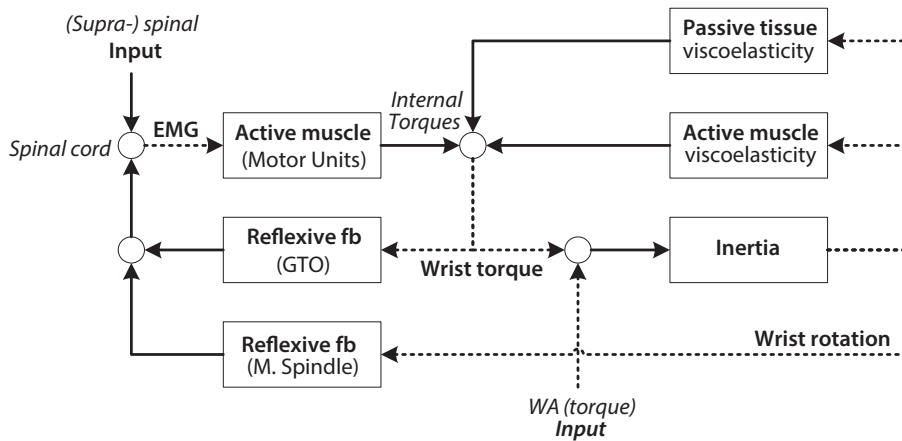
Of functional interest are the ROM and the resistance that subjects experience when their joint is moved passively through the ROM. The equilibrium angle of the joint, or rest angle represents a stiffness balance between agonist and antagonistic muscles. Passive tests aim to assess the passive joint structures in subjects, as given in Figure 1. For the assessment of the passive structures, subjects are instructed to do nothing. Movement of the wrist at a slow velocity then results in stretching of passive tissues, while minimizing the contribution of active muscle contraction and reflexive activity. The resulting joint torque will be the result of the stiffness and viscosity arising from predominantly passive contractile and non-contractile tissue. EMG measurements should be used to check for interfering muscle activation during measurement and for data analysis. The following outcomes can be listed for passive tasks:

- responsive range of motion
- stiffness and damping
- rest angle (angle of joint flexion-extension torque equilibrium)

In stroke patients, relative to controls, we expect restrictions in ROM, higher joint stiffness and a rest angle that tends towards flexion [2].

Figure 1 | Simplified graphical model of the components of the wrist joint, depicted with active, passive and reflexive elements, corresponding with areas for target therapy.

Dotted lines indicate non-invasively measurable connections, EMG (left), torque (center) and rotation (right). Rotation includes angle and rotational velocity.



Active tests (slow movement while instructed to “move / push / resist”)

These tests address the ability of the patient to actively generate torque at the joint level, preferably in a controlled manner (Figure 1). Applied torque levels should exceed resistance of passive tissue or antagonistic muscles. A subject’s ability to generate this particular torque level can be easily tested (also in the clinic) by asking them to flex or extend maximally (i.e. the active ROM). Alternative active tests are performed in a standard position (i.e. the rest angle) or during imposed slow movement to minimize reflex activity. Subjects are provided with visual feedback on their actual task performance. Joint angle (relating to overlap of muscle filaments and muscle moment arm, tissue strain) and joint velocity (relating to cross-bridge turnover dynamics and tissue viscosity) also contribute to the potential production of joint torque [14]. Applying an active and a passive test in similar test conditions, defined in terms of joint angle and angular velocity, allows for subtraction of torques generated by the passive structures from the data, under the assumption that the active muscle does not influence stiffness/viscosity values of surrounding passive structures.

From these measurements the following outcomes can be listed for active tasks:

- self induced ROM
- control over joint torque build-up (i.e. quality of motor control)
- maximally attainable torque
- angular/velocity dependent joint torque production

In stroke patients, relative to controls, we expect a smaller self induced ROM, a lower maximally attainable joint torque and less control over joint torque. Furthermore, it is expected that angular-dependency of torque production increases, with an optimum angle (e.g. muscle filament overlap) tending more towards flexion [15].

Reflexive tests (fast movement)

Reflexive tests are aimed to assess the reflexive pathways, as given in Figure 1. Higher reflex activity is known to be triggered by high joint angular velocity [11] and together with reflexive time delay (loop-time) it is considered to play an important role in reflex loop stability. To measure the reflexes we commonly use EMG recordings together with controlled, repeated perturbations. This will deliver reproducible data on reflexively triggered muscle activity (e.g. short and long latency reflexes). Perturbations are to be applied at random intervals to minimize anticipation (as subjects can influence their reflexive sensitivity, i.e. reflex modulation). Note however that active components should also be considered when assessing reflexive activity, as functional impairment is defined by the level of joint resistance. In signal analysis methods the possibilities are limited, because the dynamics of reflexively activated muscle are often difficult to distinguish from passive resistance, especially when reflexive activity is small or quickly occurring after perturbation. Clinical measures for spasticity include sudden increase in resistance or EMG and the angle at which this increase occurs, during movement through the ROM (i.e. threshold angle).

These conditions result in the following reflex-related outcomes:

- reflex loop-time (short and long latency reflex time)
- reflex magnitude (e.g. area under normalized EMG response)
- reflexively induced joint torque
- threshold angle

In stroke patients, relative to controls, we expect a longer short-latency reflex time, a stronger influence of reflex activity on joint resistance, and a threshold angle located more towards the flexion side of the ROM.

System Identification

These tests aim at measuring the full joint dynamics in an integral way, while taking the closed loop relation into account. Particular interest lies with the reflexive contributions to joint torque. Continuous random small amplitude torque perturbations induce high velocities and have been proven to allow for the quantification of intrinsic and reflexive components during either a passive or an active (postural control) task [5]. Based on these experiments, active modulation of the reflexive feedback gains, e.g. presynaptic inhibition on muscle spindles and Golgi tendon organs sensory feedback, have been studied using simple linear models. Different signal types include multisines and continuous ramp and

hold like perturbations such as ramped block waves or pseudo-random binary sequences. Still the effect of nonlinearity on measurement is unknown and may change over type of perturbation. Clear findings from the wide bandwidth multisine studies were that reflex gains increased with an active task and with the amount of damping provided by the environment.

These integral tests result in the following outcomes:

- stiffness and damping (of passive plus active structures)
- reflex loop time
- reflex magnitude (also referred to as reflex gain: torque contribution to joint dynamics)
- reflex modulation

In stroke patients we expect an increased short-latency reflex time, a stronger influence of reflex activity on joint resistance, higher reflex gains, smaller differences between active and passive tasks and less modulation with increase in external damping.

METHODS II. A COMPREHENSIVE NEUROMECHANICAL ASSESSMENT PROTOCOL

A protocol has been set up that assesses passive, active and reflexive components under different conditions, according to the aforementioned line of thought. This protocol is used in the EXPLICIT-stroke study, which aims to assess the relation between primary neural recover and behavioral compensation strategies in arm function recovery after stroke. The measurement set-up comprises a haptic manipulator and EMG-system (Appendix I). Specifications of the set-up have also been validated by Grimaldi et al. [16]. The protocol consists of multiple tests, all of which are either instrumented versions of tests from the clinic or have been tested previously tested on different setups, e.g. Schuurmans et al. [17] on analysis of the reflexive pathway (neural looptime test) and van der Helm et al. [18] and Meskers et al. [19] (amongst others) on multisine perturbations combined with system identification methods. The described neuromechanical protocol uses a combination of tests that all contribute to a post-stroke patient specific signature, and is new in extensively measuring both the structural and functional side of neuromechanical recovery.

Measurement protocol

The measurement protocol starts with tests which also provide the safety boundaries for later tests (ROM) or feedback target (MVC, restangle). Most tests are applied twice, one for the flexor carpi radialis (FCR) and one for extensor carpi radialis (ECR) muscle activity. Visual feedback of force, position or EMG is provided depending on the task instruction. For maximal active tasks, visual feedback is provided to increase subject motivation. Displayed

EMG levels are rectified and averaged over half a second (refresh rate 16Hz). Subjects are allowed to practice. To prevent fatigue, resting time is provided between tests. Total measuring time is approximately 45 min (including instructions and practice; excluding EMG placement). A full list of used tests and their properties is also given in Table 1. The analysis of each test is outlined below. After the title of each test an abbreviation is given that refers to the corresponding row in Table 1.

Passive tests (slow movement while instructed to “do nothing”)

1. Range Of Motion Passive – ROMP (P_{ROM})

Applied torques systematically vary between -2 and 2Nm. Movement is smoothed by keeping the torque derivative to time low for small torques. The P_{ROM} parameter is obtained by taking the difference between the minimal and maximal angle during the ROM test, as given in Figure 2 (left).

2. Stiffness In Rest – SIR (P_{RA} , P_k and P_d)

After obtaining the P_{ROM} position controlled movement is allowed. The stiffness in rest is tested with a constant velocity, position controlled perturbation. Movement is performed in two directions, resulting in a hysteresis curve [8,20], as shown in Figure 3. The defined angle of rest P_{RA} is taken as the angle where the average hysteresis curve per angle crosses 0Nm (hence assuming linear damping for small positive and negative velocities). The stiffness and damping related parameters (P_k and P_d) are, respectively, the average negative tangent and the average difference of the hysteresis curve over 0.2 rad around the rest angle (Figure 3), divided by the difference in velocity (0.2 rad/s). The latter will approximate the actual damping if stiffness in both movement directions is equal.

Active tests (slow movement while instructed to “move / push / resist”)

3. Range Of Motion Active – ROMA (A_{ROM})

For the ROMA test, the Wristalyzer was set to a nonresistant mode. The subject was asked to show his or her maximal ROM. Analysis of the A_{ROM} parameter equals the analysis of P_{ROM} parameter, given in Figure 2 (right).

4. Maximal Voluntary Contraction – MVC (A_{MVC})

A magnetic break was set and the subject was asked to contract maximally. Torque data was filtered with a 3rd order Butterworth filter of 20 Hz to reduce the influence of measurement noise. A_{MVC} is the maximum measured torque over two repetitions. For clarity, only one dataset (including the A_{MVC}) out of two repetitions has been shown in Figure 4.

Table 1 | Test specifications of the tests in the EXPLICIT-stroke protocol including: task instruction, visual feedback to the patient Wristalyzer controller mode (WA), Wristalyzer controller reference signal and resulting outcome parameters.

Test	Task	Visual feedback	WA	WA Reference signal	Parameter
ROMP	passive	none	Torque	slow increase, max 2 Nm	P_{ROM}
SIR	passive	none	Angle	ramp 0.1 rad/s through full ROM	$P_k P_d$
	passive	none	Angle	ramp 0.1 rad/s through full ROM	P_{RA}
ROMA	active: maximal angular excursion	attained angles and current angle	Torque	free (zero torque)	A_{ROM}
MVC	active: push max	attained torque and current torque	Angle	brake	A_{MVC}
CJT	active: push	Increasing torque target: ramp 1Nm/s	Angle	brake	A_{CJT}
ASH	passive	none	Angle	ramp 1 sec through full ROM	R_{ta}
	passive	none	Angle	ramp 0.5 sec through full ROM	$R_{ta,5}$
NL	passive	none	Angle	ramp and hold, speed 4 rad/s, amplitude 0.14 rad	R_{lt}
	active: push (const. EMG)	EMG target level 10% MVC EMG	Angle	ramp and hold, speed 4 rad/s, amplitude 0.14 rad	R_{lt}
WB	active: hold position	Reference angle incl. history	Torque	crested multisine 0.3-50 Hz	$P_{b_st}, P_{k_st}, R_{kv_st}, R_{td_st}$
			Torque	crested multisine 0.3-50 Hz	$P_{b_sl}, P_{k_sl}, R_{kv_sl}, R_{td_sl}$
	passive	none (EMG for researcher)	Torque	crested multisine 0.3-50 Hz + damping	$P_{b_da}, P_{k_da}, R_{kv_da}, R_{td_da}$
			Torque	crested multisine 0.3-50 Hz + damping	$P_{b_da}, P_{k_da}, R_{kv_da}, R_{td_da}$

Figure 2 | Range of motion data for patient A (light grey, solid —) and B (dark grey, dashed ---). Passive ROM (P_{ROM} , left) and active ROM (A_{ROM} , right) are indicated with thick horizontal lines.

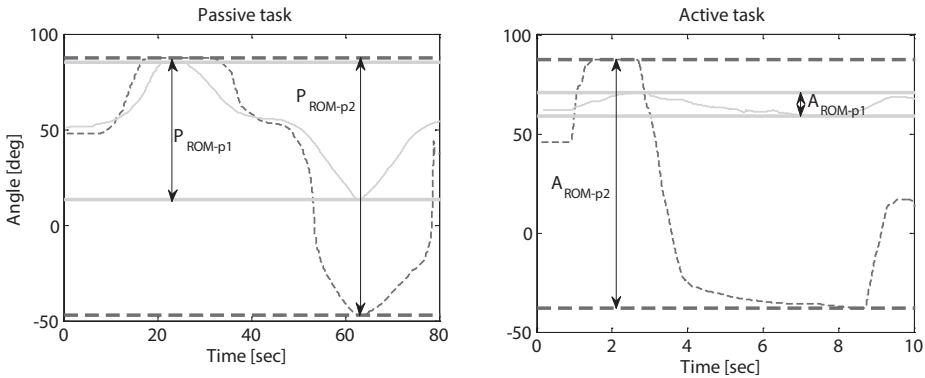
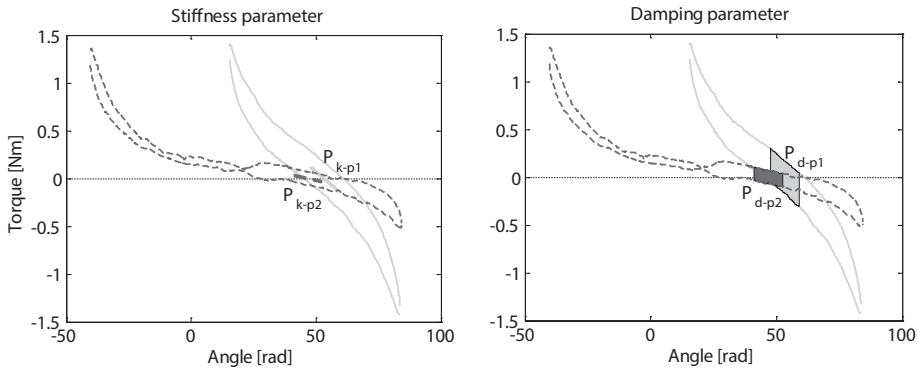


Figure 3 | Stiffness in rest test result for patient A (light grey, solid —) and patient B (dark grey, dashed ---). Thick lines around zero (left figure) indicate average slope of the data at those angles (P_k) and intervals around zero (right figure) show the (P_d).



5. Control over Joint Torque – CJT (A_{CJT})

The Control over Joint Torque (CJT) test is added to address the quality of motor control of the subject. The magnetic break was applied and the subject was asked to steadily increase his or her level of contraction (1Nm/s). Torque data was again filtered for analysis with a 3rd order Butterworth filter of 20 Hz to reduce influences measurement noise. The level at which the patient fails to follow the reference torque (A_{CJT}) is determined by the point at which the patient generated torque is lower than 1Nm under the reference torque (circle in Figure 5). The maximal force during the test (thick horizontal line in Figure 5) is used as an upper boundary for A_{CJT} .

Figure 4 | Maximal voluntary contraction data for patient A (light grey, solid —) and patient B (dark grey, dashed ---). Flexion MVC (A_{MVC} , left) and extension MVC (A_{MVC} , right) are indicated with thick horizontal lines.

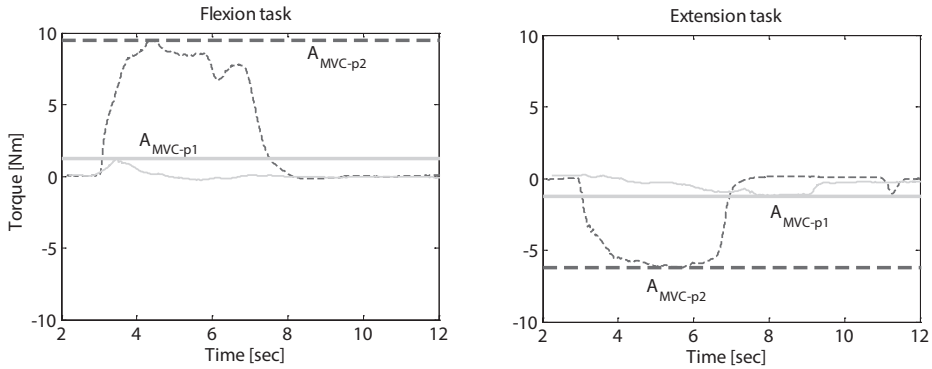
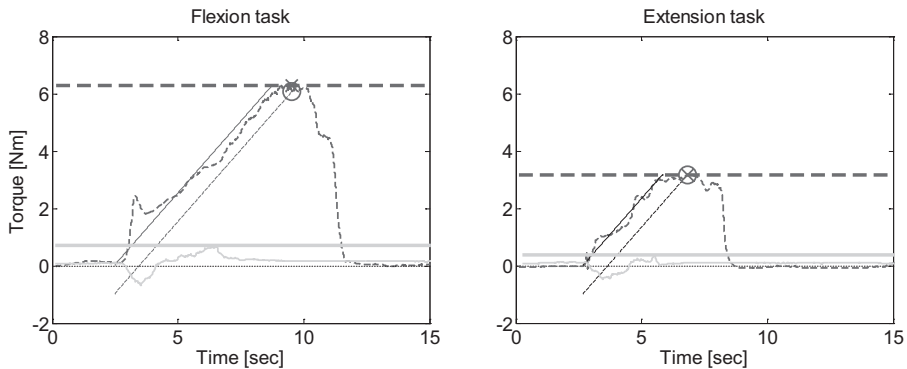


Figure 5 | Control over Joint Torque data A_{CJT} for patient A (light grey, solid —) and patient B (dark grey, dashed ---), for extension (left) and flexion (right). The diagonal straight solid line indicates the reference force over time, the diagonal dashed line shows the maximal follow lag. Circles indicate where the patient fails to follow the reference torque; parameters A_{CJT} for patient B are indicated with a cross.



Reflexive tests (fast movement)

6. Ashworth-ASH (R_{ta} and $R_{ta,S}$)

An instrumented version of the clinical modified Ashworth test has been included in the protocol to address the reflexive system. The Ashworth test gives insight into the reflexive properties during a large sweep through the ROM. Moreover, it allows for validation of the use of an Ashworth test in the clinic.

For the analysis, the EMG signal is rectified and filtered with a 3rd order low pass Butterworth filter of 80Hz. We first determined the angle for which the EMG signal exceeds 5 times

the standard deviation of the background EMG (horizontal dotted line in Figure 6). The preceding point where the EMG signal exceeds 2.81 times the standard deviation (i.e. resulting in 0.25% probability of being background signal if normally distributed) is taken as the onset of the EMG response to the perturbation. The corresponding angle at that onset time is the threshold angle (R_{it}).

7. Neural Looptime-NL (R_{it} and R_{auc_M1})

The neural looptime tests consist of nine ramp (2 rad/s) and hold (0.75s) perturbations that occur at random time intervals. After the hold phase a returning phase using a minimal jerk profile is initiated. For the analysis, the data of each of the runs is averaged over the nine perturbations to reduce noise. This sequence is performed in a passive and active condition; first the subject is asked to relax, second to push against the handle with constant EMG at 10% of measured MVC EMG. For the latter rectified and filtered EMG (averaging 8 times/sec) is shown to the subject as a vertical bar with a target area at 10+/-2.5% for the stretched muscle. Color of the bar changed from red to green when entering the target area. Subjects were instructed to ignore perturbations as much as possible and to return to the target area after perturbations, when necessary. Figure 7 shows the resulting average EMG signal with its cross-trial standard deviation. The EMG signal is rectified and filtered with a 3rd order low pass Butterworth filter of 80Hz. The base level (BL) of the EMG is determined as the average EMG over the time window [-400,-20]ms with respect to the start of the perturbation [17]. The EMG signal E is then normalized to the signal E_n using the baselevel BL:

$$E_n(t) = E(t)/BL - 1$$

Reflexive EMG response to the input stretch is assumed to be significant if the signal exceeds 2.81 times the standard deviation of the baselevel, indicated with the horizontal dotted line in Figure 7. The short-latency reflex onset R_{it} and area under the curve R_{auc_M1} are then obtained (time window for both parameters limited to [20, 50] ms, with respect to pulse onset [17]).

System Identification

8. Multisine perturbations-WB ($P_k, P_d, R_{td}, R_{kv_st}, A_{k_act}, A_{d_act}, R_{rm_act}$ and R_{rm_env})

A set of multisine perturbations has been added to address the subjects capabilities in disturbance rejection and adaptation to a changing environment (increased damping). Multisine perturbations represent a functional disturbance and may be supported by findings from the neural looptime test.

Possible low frequent compensational behavior of the patient (against drift away from the target angle), will be corrected for by first pre-filtering the raw data using a 3rd order butterworth high pass filter of 1 Hz. A frequency response function (FRF) is then estimated using a closed loop estimator on the pre-filtered data,

$$H_{FRF} = S_{da} / S_{dT}$$

Where S_{da} and S_{dT} are the estimated cross spectral densities of the externally applied disturbance torque d with the measured angle a and interaction torque T , using a Fast Fourier Transform [18].

Figure 6 | Ashworth data of patient A (left) and patient B (right).

Measured FCR EMG data (dark solid lines —), 2.81 times the standard deviation of the background (dashed lines ---) and the derivation of the threshold angle parameter R_{TA} (dashed-dotted lines -.-) are shown. Both figures represent the condition of 1ROM/sec angular velocity and movement towards extension.

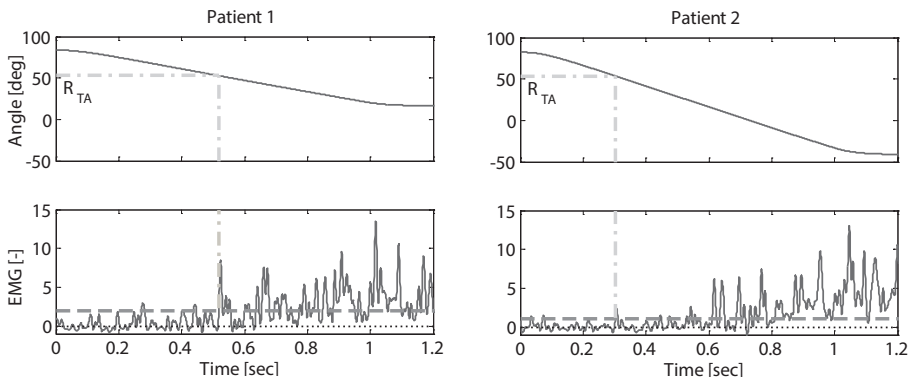
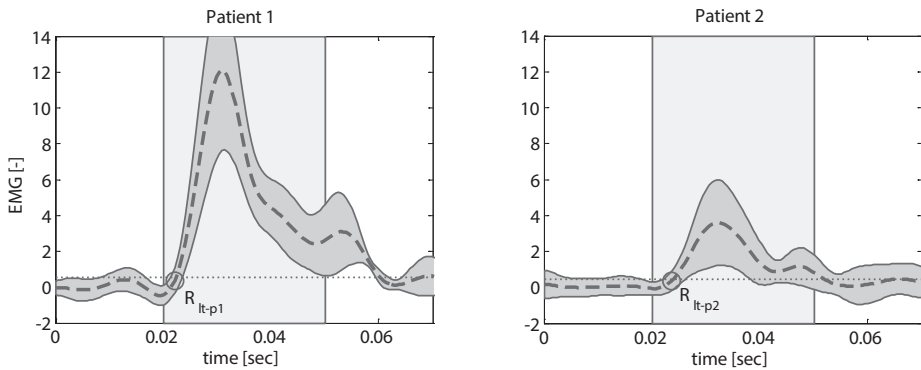


Figure 7 | Neural looptime test datasets for patient A (left) and patient B (right).

Average and standard deviation of nine FCR EMG responses (mean: dashed line ---, standard deviation: grey surrounding surface) and corresponding analysis interval and values (R_{It} : circle O and R_{AUC} : surface under --- within the indicated interval [0.02 – 0.05] sec). Dotted line (---) indicates the 2.81 times the standard deviation of the background EMG.



The resulting FRF is then averaged in groups of 8 frequency points to improve the estimate. Finally, a model [18,19], based on the block scheme depicted in Figure 1 is fitted to the acquired FRF (Figure 8). Inertia, spring ($P_{k_{<condition>}}$), damper ($P_{d_{<condition>}}$), eigenfrequency of muscle activation, velocity dependent reflex gain ($R_{kv_{<condition>}}$), reflex speed ($R_{td_{<condition>}}$) and grip dynamics parameters are all included in the model [18]. Different types of reflexive feedback (position, velocity and force) were tested, yet only velocity feedback gave low parameter variability, in accordance with earlier results of Meskers et al. [19]. Microneurographic studies imply velocity feedback is muscle spindle feedback, as opposed to Golgi Tendon Organ feedback [21]. Using different conditions (stiff, slack and damp, see Table 3) the changes of the system over condition can be investigated. The difference in stiffness and damping between passive and active conditions yields the activation induced stiffness and damping $A_{k_{act}}, A_{d_{act}}$:

$$\begin{aligned} A_{k_{act}} &= A_{k_{st}} - A_{k_{sl}} \\ A_{d_{act}} &= A_{d_{st}} - A_{d_{sl}} \end{aligned}$$

Difference in reflex gain over conditions results in the modulation parameters $R_{rm_{act}}$ and

$$\begin{aligned} R_{rm_{env}} &: \\ R_{rm_{act}} &= R_{kv_{st}} - R_{kv_{sl}} \\ R_{rm_{env}} &= R_{kv_{da}} - R_{kv_{st}} \end{aligned}$$

RESULTS

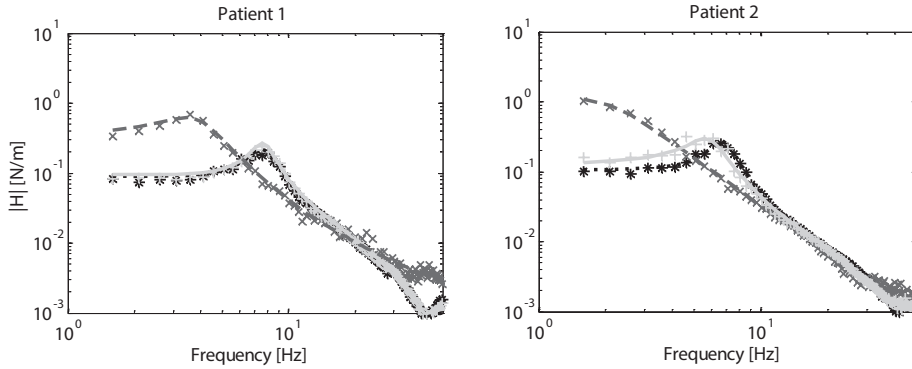
Parameter values taken from two stroke patients are given in Table 2 and 3, for illustration purposes. Both patients A and B are female (aged 55 and 45, respectively) and were measured more than one year post-stroke. Ashworth scores for the measured and impaired left wrist joint of both patients were manually determined to be 3 and 0 respectively.

Passive parameters

Patient A shows a smaller passive ROM (P_{ROM}) and an increased stiffness (P_k) and viscosity (P_v) at the restangle, both for large and small perturbations, as shown in Table 2 and 3, respectively. This indicates a higher resistance against movement from passive structures, as muscle activation is checked for using EMG. Differences between Table 2 and Table 3 values are expected as they differ greatly in condition. The data underlying the system identification method contains only small angular deviations, while the data underlying the signal analysis is performed during a long sweep through the ROM. Earlier research on passive stiffness has shown that in the initial phase of movement the stiffness is larger [12]. Furthermore, the rest angle (P_{RA}) of patient A is located more towards flexion (Table 2). It is known that in the sub-acute phase the restangle moves towards flexion [2].

Figure 8 | Bode magnitude plot of multisine-test data from patient A (left) and B (right).

Bode magnitude representation of the model fits of the data for the 3 measurement conditions: stiff (fit: dotted ---, FRF estimate: *), slack (fit: dashed ---, FRF estimate: x) and damp (fit: solid line —, FRF estimate: +).



Active parameters

In Table 2, the combination of a decreased active ROM (A_{ROM}) and a low MVC (A_{MVC}) is seen in the resulting parameters of patient A. Movement is determined by both the potential voluntary torque and the stiffness of the joint, for each angle. Therefore we can expect a smaller value for the A_{ROM} parameter given low voluntary contraction (e.g. A_{MVC} in the restangle) and stiffness of passive structures (e.g. P_k in the restangle). Control over Joint Torque (A_{CJT}) values show the amount of joint torque control in a slowly increasing tracking task. A_{CJT} values are expected to be slightly lower than the MVC and are found to be approximately 60 % of the MVC value for patient B. The A_{CJT} is set to zero for patient A as the maximal force in test does not exceed 1Nm (see appendix II for more details on analysis). Table 3 coincidentally shows equal values for stiffness ($A_{k_{act}}$) and damping ($A_{d_{act}}$), induced by the “hold position” task instruction. This shows that both patients were able to increase their joint stiffness voluntarily, yet the control over the unilaterally produced joint torque (A_{CJT}) is a lot lower for patient A.

Reflexive parameters

The reflex loop time (R_{lt}) of about 23 ms is comparable to the values found in literature [17]. The higher value for patient A was due to low reflexive activity for that condition ($R_{m1_{auc}}$). The looptime parameter resulting from the system identification procedure (Table 3, $R_{td_{st}}$) is generally higher. This difference is expected to be of methodological nature; for system identification procedures the best fit may lie more towards the long latency response, instead of the short latency response onset. Still, the two are assumed to be equal in their physiological background and do not yield additional information. For patient B the area under the curve $R_{m1_{auc}}$ is similar for FCR and ECR. The $R_{m1_{auc}}$ value for the ECR of patient A

is substantially lower than the other values, indicating a very small reflex, if at all present. The FCR muscle shows a very high response, possibly indicating hyperreflexia. Additional looptime (R_{lt}) and reflexive activity ($R_{auc,m1}$) are believed to contribute to joint instability. Threshold angles (R_{ta}) are similar for both patient A and B (the flexion angle prior to movement is with 85 degrees also equal for both patients, see P_{ROM} Table 1). The angular velocities at which these were determined differ significantly (72deg/sec and 135deg/sec for patient A and B, respectively), which, as reflexes are velocity dependent, explains the quick response of the more recovered subject. Threshold angles are only given for the FCR muscle as the stretching of the ECR muscle did not result in reflexive activation. Reflexive contributions to joint resistance (R_{kv_stiff}) are stronger in patient B. For both patients activation of the muscles has a large influence on the modulation of reflexes (R_{rm_act}). Furthermore, a more stable, damped environment does not trigger reflex modulation (R_{rm_env}) for patient A and unexpectedly [19] causes negative reflex modulation for patient B.

Table 2 | Parameters following from the signal analysis technique tested on a paretic chronic stroke patient (pt. A) and a functionally recovered chronic stroke patient (pt. B).

E refers to Extension and *F* to Flexion. All angles, except for ROM parameters, are given in degrees from the zero angle of the Wristalyzer.

Parameter		Patient A	Patient B
Passive			
ROM Passive	P_{ROM}	72 deg [13,6 – 85,1]	135 deg [-46,9 – 87,7]
Rest angle	P_{RA}	53 deg flexion	34 deg flexion
Active			
ROM Active	A_{ROM}	17 deg [49,1 – 65,9]	126 deg [-38,1 – 87,7]
Maximal Voluntary Contraction (MVC) at rest angle	A_{MVC}	F: 1,2 Nm E: 1,3 Nm	F: 9,5 Nm E: 6,2 Nm
Control over Joint Torque (CJT)	A_{CJT}	F: 0 Nm E: 0 Nm	F: 6,2 Nm E: 3,2 Nm
Reflexive			
Reflexive Looptime	R_{lt}	F: 22ms E: 32ms	F: 24ms E: 23ms
Area under the M1 curve	$R_{auc,m1}$	F: 0,16 E: 0,01	F: 0,05 E: 0,05
Threshold angle	R_{ta}	F: 53 deg E: -	F: 55 deg E: -

Table 3 | Parameters following from the system identification technique tested on a paretic chronic stroke patient (pt. A) and a functionally recovered chronic stroke patient (pt. B).

Parameter		Patient A	Patient B
Passive			
Stiffness at Restangle	P_k	2,8 Nm/rad	1,0 Nm/rad
Damping at Restangle	P_d	0,07 Nms/rad	0,05 Nms/rad
Active			
Additional activation induced muscle stiffness at Restangle	$A_{k_{act}}$	8,3 Nm/rad	8,3 Nm/rad
Additional activation induced muscle damping at Restangle	$A_{d_{act}}$	0,08 Nms/rad	0,08 Nms/rad
Reflexive			
Reflexive Looptime	$R_{td_{st}}$	30 ms	29 ms
Reflexive contributions to joint resistance	$R_{kv_{st}}$	0,080 Nms/rad	0,092 Nms/rad
Reflex modulation due to activation	$R_{m_{act}}$	0,06 Nms/rad	0,06 Nms/rad
Reflex modulation due to environmental changes	$R_{m_{env}}$	0,01 Nms/rad	-0,06 Nms/rad

DISCUSSION

We presented a methodology that can be used to obtain insight into the potential roles of passive, active and reflexive contributors to movement disorders. Using a combination of test conditions and available analysis methods it is possible to discriminate different contributors of the movement disorder. We used this methodology to design a protocol that can be used to assess the role of neuromechanics in stroke recovery, to be used in the EXPLICIT-stroke study. This specific protocol is responsive to changes in severity of movement disorder. Passive parameters show altered stiffness, active parameters show paresis and diminished control. Reflexive parameters show altered reflex gain, loop time and modulation. Furthermore, differently conditioned tests have shown different values for the same parameter, potentially resulting in an altered role in joint dynamics for that specific contributor.

Compared to current, manual clinical tests such as the Ashworth test, a full protocol might seem cumbersome. However, a combination of different conditions or tests is required to determine the major contributors to a movement disorder. The presented protocol, in combination with a haptic manipulator (the Wristalyzer), is comprehensive yet concise, safe and non-invasive.

With the current setup it is not possible to discern continuous involuntary active tissue from passive viscoelastic properties during passive tasks. Furthermore, specifically for some of the active tests in the EXPLICIT-stroke protocol, a certain amount of independent control of agonist and antagonist muscles is required, which some patients will not be able to

perform. However, these tests can still give valuable results. The issued parameters reflect the properties of a highly non-linear system. As such, presented parameters are to be considered a mean over e.g. a movement trajectory. Non-linear identification techniques should be developed to assess instantaneous determinant characteristics during true functional tasks. Furthermore, there are some indications that patients particularly have trouble adapting from one state to the next [19], as opposed to attaining that new state at all. Adding time variance (e.g., in task instruction or virtual environments) during tests could highlight differences between stroke patients and healthy subjects.

The primary outcome measures will be validated in a larger group of chronic patients versus a control group of healthy subjects. Furthermore, longitudinal analysis of changes in neuromechanics in acute and subacute stroke patients will be conducted in the EXPLICIT-stroke program [5], a program targeted at understanding the relation of primary neural repair to behavioural compensation in arm function recovery. This multicenter research project comprises the longitudinal assessment of parameters of functional recovery (clinimetrics), recovery of cortical activation (fMRI), intactness of corticospinal tract (TMS) and compensation strategies (kinematics). Neuromechanics describe the integration of neural and muscle activation, determining actual functional performance. As such, the assessment of neuromechanics within the EXPLICIT-stroke study is essential in understanding the relation between primary (neural) lesion and functional performance.

CONCLUSION

A comprehensive, yet concise assessment protocol was developed to identify tissue, active muscular and reflexive properties at joint level. Application of the protocol illustrates the necessity to apply multiple measurement and task conditions to identify patients within a spectrum of neuromechanical system functions and to ultimately understand the underlying mechanism of a movement disorder after neural lesions.

APPENDIX I | MEASUREMENT SETUP

Based on the earlier work on wrist manipulators [22] a torque controlled haptic wrist manipulator has been developed, called the Wristalyzer®, (MOOG, Nieuw Vennepe, the Netherlands) [16] in collaboration with the Delft University of Technology and the Leiden University Medical Center (Figure 9). The setup consists of a main drive of a vertically positioned servo motor (Parker SMH100 series). The arm is fixated to the Wristalyzer and the hand is fixated to the handle. The motor axis is aligned with the rotation axis of the wrist joint. Movement of the motor is therefore directly coupled to flexion/extension of the wrist. The handle has an ellipsoidal shape which, because of its length, prevents finger flexion (Figure 9).

Wristalyzer

Handle ROM $\approx 180^\circ$; accuracy 0.35°

Nominal motor torque is $6Nm$

Magnetic break torque $20Nm$

Maximal angular velocity $2000deg/s$ [16]

Encoder (Hiperface absolute single turn)

Strain gauge (mounted between the axis and handle)

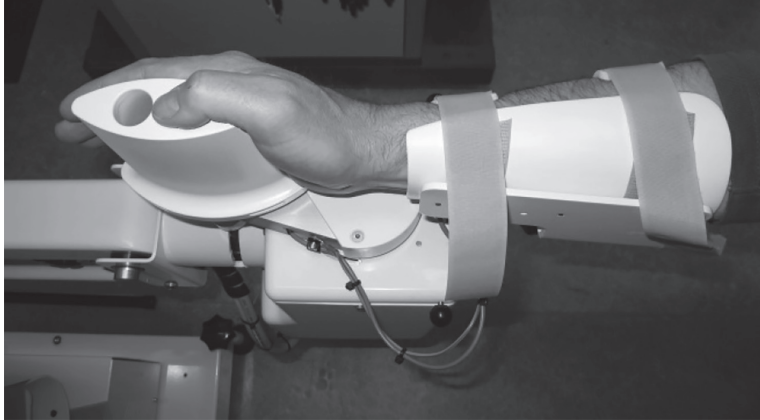
EMG

Muscle activation was measured using a Delsys Bagnoli-8 system with bipolar surface electrodes on the Flexor Carpi Radialis (FCR) and two on the Extensor Carpi Radialis (ECR).

Measurement computer

A laptop is used for data processing and visualization. Matlab® R2007a was used for communication with the Wristalyzer and Matlab® R2008b was used for data analysis.

Figure 9 | Top-view of the Wristalyzer®, (MOOG, Nieuw Venneep, the Netherlands).



Abbreviations

ECR – Extensor carpi radialis;

EMG – Electromyography;

EXPLICIT-stroke – EXplaining PLasticITY after stroke;

FCR – Flexor carpi radialis;

FRF – Frequency response function;

ROM – Range of motion;

Conflict of interest statement

The authors declare that there is no conflict of interest that could influence the scientific content of the presented work.

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C h a p t e r

4

Comprehensive neuromechanical assessment in stroke patients: reliability and responsiveness of a protocol to measure neural and non-neural wrist properties

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ABSTRACT

Background

Understanding movement disorder after stroke and providing targeted treatment for post stroke patients requires valid and reliable identification of biomechanical (passive) and neural (active and reflexive) contributors. Aim of this study was to assess test-retest reliability of passive, active and reflexive parameters and to determine clinical responsiveness in a cohort of stroke patients with upper extremity impairments and healthy volunteers.

Methods

Thirty-two community-residing chronic stroke patients with an impairment of an upper limb and fourteen healthy volunteers were assessed with a comprehensive neuromechanical assessment protocol consisting of active and passive tasks and different stretch reflex-eliciting measuring velocities, using a haptic manipulator and surface electromyography of wrist flexor and extensor muscles (Netherlands Trial Registry number NTR1424).

Intraclass correlation coefficients (ICC) and Standard Error of Measurement were calculated to establish relative and absolute test-retest reliability of passive, active and reflexive parameters. Clinical responsiveness was tested with Kruskal Wallis test for differences between groups.

Results

ICC of passive parameters were fair to excellent (0.45 to 0.91). ICC of active parameters were excellent (0.88 – 0.99). ICC of reflexive parameters were fair to good (0.50 – 0.74). Only the reflexive loop time of the extensor muscles performed poor (ICC 0.18). Significant differences between chronic stroke patients and healthy volunteers were found in ten out of fourteen parameters.

Conclusions

Passive, active and reflexive parameters can be assessed with high reliability in post-stroke patients. Parameters were responsive to clinical status. The next step is longitudinal measurement of passive, active and reflexive parameters to establish their predictive value for functional outcome after stroke.

BACKGROUND

Upper extremity movement disorder is a major contributor to impaired activity and participation levels in post-stroke patients [1,2]. In the acute phase after stroke, paresis is the dominant factor of impairment [3,4]. However, in the chronic phase, the complex interaction between inappropriate neural activation of muscles and secondary biomechanical changes in contractile muscle tissue and passive viscoelastic connective tissue becomes more prominent [3-6]. The dynamical interactions between neural capacity and contractile and connective tissues during daily functioning in patients are poorly understood.

Unraveling movement disorder after stroke into non-neural (passive) and neural (active and reflexive) contributors and assess their separate influence over time, is essential to understand functional recovery after stroke and to aim therapy at the most dominant contributing factor at the most appropriate moment in time [7-10]. Physical examination is currently the most utilized clinical tool for assessment of paresis, inappropriate muscle activity and secondary biomechanical changes [11].

Biomechanical and electrophysiological techniques support standardization of input signals and uniform registration of output signals. A comprehensive neuromechanical assessment should be able to discriminate between non-neural and neural contributors to movement disorder [7-10,12]. Non-neural contributors, i.e. passive tissue properties, should be measured by passive movement at low velocity to minimize background muscle activation [13]. Neural contributors should be measured during active tasks to study voluntary muscle properties and during multiple measurement velocities to study the role of stretch reflexes [3,4,7-10,12]. System Identification and Parameter Estimation techniques assist in separation of neural and non-neural contributors independently of task and condition [14].

Earlier work on measurement of joint neuromechanics [15-19] provided a comprehensive assessment protocol including passive, active and reflexive tests to measure non-neural and neural contributors to movement disorder after stroke [20]. To ensure standardized input signals and registration of output signals, a haptic wrist manipulator [21,22] was combined with surface-EMG measurements.

Clinical implementation of this newly developed protocol required validation. The aim of this study was to assess test-retest reliability and to determine clinical responsiveness in a cohort of stroke patients with upper extremity impairments compared to a cohort of healthy volunteers.

METHODS

Participants

We identified patients who survived a first ischemic stroke between 1999 – 2009, and were between 18 – 80 years at time of stroke, at the outpatient clinics of the Department of Rehabilitation in LUMC and Rijnlands Rehabilitation Center. Inclusion criteria were: a perceived remaining impairment of arm-hand function by the participant, being able to travel to the research laboratory, and being able to sit on a chair and follow instructions for one hour. To establish the perceived impairment of arm-hand function, respondents were asked if they still perceived any impairment of the arm and/or hand. Possible answers were: no impairment, moderate impairment or severe impairment. Patients with moderate to severe perceived impairment were invited for measurements. Exclusion criteria were: limitations of arm-hand function prior to stroke, a history of other neurologic impairments besides stroke. Participants were measured on two occasions within a month, assuming that their clinical status would remain stable. A volunteer sample of healthy volunteers served as a reference group. The study was approved by the Medical Ethical Committee of the LUMC. All participants were compensated for travel expenses.

Protocol

Measurements were carried out in a laboratory setting at the LUMC. Before the test protocol started, the modified Ashworth Scale (mAS) was measured. Participants were extensively instructed and were given ample opportunity to practice. The protocol consisted of nine tests, with a total duration of approximately 45 minutes.

Measurement set-up

The measurement set-up [20] consisted of a haptic manipulator (“Wristalyzer”, Moog FCS, the Netherlands) and a surface EMG-system (“Bagnoli”, Delsys Inc., USA). The manipulator delivered precise torque or position perturbations through a vertically positioned servomotor (Parker SMH100 series), connected to a handle (Meester techniek, the Netherlands). The hand of the participant was fixed to the handle, which had an ellipsoidal shape to prevent finger flexion (Figure 1). The arm was stabilized in an arm rest. The motor axis was aligned with the rotation axis of the wrist joint. Movement of the motor was therefore directly coupled to flexion/extension of the wrist.

Tasks, conditions and outcome parameters

An overview and more elaborate description of applied Passive, Active and Reflexive tests and their outcome parameters is shown in Table 1. The tests were performed in a fixed order, starting with Passive tests, followed by Active and Reflexive tests respectively [20].

Participants were provided with visual feedback on torque, angle or EMG-level, depending on the test and task instruction.

Table 1 | Description of Passive, Active and Reflexive parameters.

Adapted from Klomp et al¹⁹.

Parameter		Description
Passive		
Range of motion passive	(degrees) P_{ROM}	Slow passive movement through range of motion, maximum torque is 2Nm. Range of motion equals the difference between minimal and maximal angle.
Stiffness in rest	(Nm rad ⁻¹) P_k	Resistance to passive movement during a slow, position controlled, passive movement through range of motion. Average negative tangent of the hysteresis curve over 0.2 rad around P_{RA} .
Rest angle	(degrees) P_{RA}	Angle at which the resultant torque during a slow, position controlled, passive movement through range of motion is zero.
Active		
Range of motion active	(degrees) A_{ROM}	Voluntary movement through range of motion, no resistance from haptic robot. Range of motion equals the difference between minimal and maximal angle.
Maximal voluntary contraction	(Nm) A_{MVC}	Maximal torque generated by participant. Fixed position at P_{RA} .
Control over joint torque	(Nm) A_{CT}	Ability of participant to achieve steadily increasing target torque. Fixed position at P_{RA} .
Reflexive		
Threshold angle	(degrees) R_{ta}	Angle at which the EMG exceeds 5 times the standard deviation of baseline during a fast, position controlled passive movement through total range of motion.
Reflex loop time	(s) R_{lt}	Time from perturbation onset to M_1 -reflex onset. Participant is asked to deliver 10% of maximum EMG-activity during a position controlled movement over 0.14 rad at 3 rad/s.
Reflex contribution to joint resistance	(Nms rad ⁻¹) R_{kv}	Participant is asked to resist fast multisine force perturbations. Velocity dependent reflex gain is computed using system identification methods.
Reflex modulation to environment	(Nms rad ⁻¹) $R_{m,env}$	Participant is asked to resist fast multisine force perturbations in a damped environment. Velocity dependent reflex gain in a damped environment is computed.

Passive tests were performed at low velocity to avoid stretch reflexes, and included a task instruction to “do nothing”. First, a force controlled movement was applied in flexion and extension direction, to establish passive range of motion passive (P_{ROM}). Then a position

controlled movement was applied, also in both flexion and extension direction. The following outcome parameters were extracted: Stiffness in rest (P_k) and Rest angle (P_{RA}) (Table 1).

Active tests comprised task instructions to “move/push/resist”, i.e. exert a voluntary torque or complete a voluntary movement. This part commenced with an active, maximal movement from flexion to extension and back to establish active range of motion active (A_{ROM}). Then, the position of the handle was fixed at the P_{RA} and participants were asked to complete and repeat a maximal voluntary isometric contraction in both flexion and extension direction to establish active maximal voluntary contraction (A_{MVC}). Subsequently, participants were asked to match a gradually inclining torque level. This was also performed in both flexion and extension direction and repeated once. The following outcome parameter was extracted: Control over joint torque (A_{CJT}) (Table 1).

Reflexive tests were performed at velocities above the assumed stretch reflex threshold, and had either passive or active task instructions. A high velocity, position controlled movement through the P_{ROM} was applied once, in both flexion and extension direction (passive task instruction) to calculate Threshold angle (R_{ta}). Short ramp and hold position perturbations were applied 9 times in each direction at random time intervals (active task instruction) to extract Reflexive loop time (R_{lr}). A multisine force perturbation was applied for 20 seconds (active task instruction) and repeated three times: once in the same environment and twice in a damped environment. The following outcome parameters were extracted: Reflexive contributions to joint resistance (R_{kv}) and Reflex modulation due to environmental changes ($R_{m_{env}}$) (Table 1).

Statistical analysis

Data was retrieved and processed with Matlab 2007b (Mathworks, USA) [20]. Calculations and statistics were performed with SPSS Statistics 20 (IBM, USA). Sample size was calculated on the outcome parameter with the expected largest variability: R_{kv} . In an earlier study, a standard deviation of 0.17 Nms/rad was found [17], with a mean difference between patients and controls of 0.12 Nms/rad. Based upon $\alpha = 0.05$ and with a target power of 80%, a sample size of minimally 10 participants was estimated to be required to detect an existing difference between measurements of 0.12 Nms/rad with sufficient power.

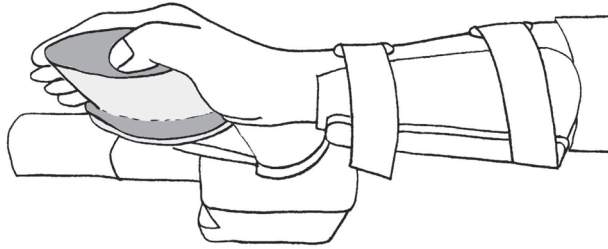
Intraclass correlation coefficients (ICC) were calculated using the two-way mixed model for absolute agreement. Values above 0.75 represent excellent reliability, values between 0.4 and 0.75 represent fair to good reliability and values below 0.4 represent poor reliability [23]. As ICC is a relative measure dependent on variance within a group [24], Bland Altman plots were used to illustrate variability and Standard Error of Measurement (SEM) values (Equation 1) and Smallest Detectable Difference (SDD) (Equation 2) were calculated to further substantiate ICC.

$$\text{Equation 1.} \quad SEM = SD * \sqrt{1-ICC}$$

$$\text{Equation 2.} \quad SDD = 1.96 * \sqrt{2 * SEM}$$

Figure 1 | Illustration of Wristalyzer handle and arm-rest.

For a better view of the hand position, the hand straps are not represented in this illustration.



Normality of distribution was assessed by visual inspection of histograms and equality of variance was tested with Levene's test. Median, minimum and maximum were calculated per parameter. Levene's test showed wider variances in the group of chronic stroke patients compared to healthy volunteers, therefore chronic stroke patients were split in two groups according to mAS ($mAS = 0$ and $mAS \geq 1$), a clinimetric observation. This allowed for a more specific description of phenotypes and more equally dispersed values within each group, which was illustrated with box plots. An exploratory comparison was made between parameters of the group of healthy volunteers, the group of chronic patients with $mAS = 0$ and the group of chronic patients with $mAS \geq 1$, using the non-parametric Kruskal-Wallis test. The Kruskal-Wallis test was performed on the average outcome of the two visits per parameter, after testing for systematic differences between the two visits. This comparison was further substantiated by pairwise testing between each of the groups with the non-parametric Wilcoxon Rank Sum test.

RESULTS

Descriptive data

We identified and invited 102 post stroke patients. Response rate was 64% ($n = 65$). Of the responders, 17 patients declined to participate and 16 patients had either no current impairment of arm-hand function or had severely impaired mobility preventing them from travelling to the clinic. Therefore, 32 patients were included in the study. Fourteen healthy volunteers served as a reference group. All healthy volunteers completed the two visits and 28 out of 32 patients completed all visits (87.5%). Reasons for dropping out were: unable to schedule the second visit ($n = 2$), visit was too tiresome ($n = 1$), patient was treated with botulinum toxin in period between first and scheduled second visit ($n = 1$). In chronic stroke patients, the affected hand was dominant in 14 patients (right hand $n = 13$, left hand $n = 1$) and non-dominant in 18 patients (right hand $n = 2$, left hand $n = 16$). Average age at stroke

was 55.2 years. Average time after stroke was 40 months. Descriptive data are presented in Table 2.

Reliability

Test-retest reliability for Passive parameters was excellent for P_{ROM} and P_k (ICC 0.81 and 0.91 respectively) and fair to good for P_{RA} (ICC 0.45). For Active parameters, test-retest reliability was excellent (ICC 0.88-0.99). For Reflexive parameters, the ICC's of R_{ta} (flexor and extensor), R_{lt} (flexor), R_{kv} and $R_{m_{env}}$ were fair to good (ICC 0.50 – 0.74). ICC for R_{lt} (extensor) was poor (ICC 0.18). ICC's are summarized in Table 3. Bland Altman plots are shown in Figure 2, depicting the mean of the two measurements (x-axis) compared to the difference between two measurements (y-axis). The values are scattered around the mean difference (solid line), illustrating the absence of a systematic difference or learning effect between the two measurements. In parameters with a lower ICC, the 95% confidence interval of the difference between the measurements is wider, illustrating a larger measurement error. SEM values (Table 3) provide an indication of the dispersion of the measurement errors and SDD are given for future reference (Table 3).

Table 2 | Descriptive data of the study population.
Means and standard deviation or percentages for healthy volunteers and chronic stroke patients.

Study population	Healthy volunteers (n = 14)	Chronic patients mAS = 0 (n = 21)	Chronic patients mAS >= 1 (n = 11)
Age (years) (SD)	49.4 (15.1)	60.4 (13.1)	54.5 (12.7)
Men (n) (%)	9 (64%)	10 (48%)	3 (27%)
Right side dominant (n) (%)	13 (93%)	21 (100%)	8 (73%)
Measured side dominant (n) (%)	14 (100%)	10 (48%)	4 (36%)
Time between measurements (days) (SD)	27 (21)	18 (7)	29 (17)
Time after stroke (months) (SD)	–	30 (27.6)	53 (34.3)
Age at moment of stroke (years) (SD)	–	58 (13.1)	50 (14.5)

Table 3 | Median, minimum and maximum, Intraclass correlation coefficients (ICC) , Standard Errors of Measurement (SEM) and Smallest Detectable Difference (SDD) for Passive, Active and Reflexive parameters for all participants.

P_{ROM} : Range of motion passive, P_k : Stiffness in rest, P_{RA} : Rest angle. A_{ROM} : Range of motion active, A_{MVC} : Maximal voluntary contraction, A_{CJT} : Control over joint torque. R_{th} : Threshold angle, R_{lt} : Reflexive loop time, R_{kv} : Reflexive contributions to joint resistance, $R_{m_{env}}$: Reflex modulation due to environmental changes. *: average of SEM and SDD for R_{ta} flexor and R_{lt} extensor, valid around median of both parameters. Because of heteroscedasticity, SDD and SEM might be smaller towards minimum of parameter and might be larger towards maximum of parameter.

Parameter		All participants median [min;max]	ICC	SEM	SDD
Passive					
P_{ROM}	(degrees)	132 [42; 151]	0.91	7	20
P_k		1.16 [0.29; 4.84]	0.81	0.36	1
P_{RA}	(degrees)	-44 [-73; 1]	0.45	14	39
Active					
A_{ROM}	(degrees)	127 [0; 158]	0.99	5	14
A_{MVC}	(Nm) flexor	17.8 [0.1; 28.7]	0.95	2.1	6
	extensor	10.0 [0.1; 25.4]	0.93	1.8	5
A_{CJT}	(Nm) flexor	12.6 [0.0; 21.1]	0.92	1.9	5
	extensor	7.8 [0.0; 18.4]	0.88	1.9	5
Reflexive					
R_{ta}	(degrees) flexor	-68 [-84; 47]	0.67	19*	53*
	extensor	22 [-69; 55]	0.50	26	73
R_{lt}	(s) flexor	0.029 [0.021; 0.045]	0.51	0.0039	0.0109
	extensor	0.035 [0.020; 0.049]	0.18	0.0056*	0.0154*
R_{kv}	(Nms rad ⁻¹)	0.019 [-0.059; 0.395]	0.52	0.0634	0.18
$R_{m_{env}}$	(Nms rad ⁻¹)	-0.007 [-0.086; 0.444]	0.74	0.0557	0.15

Figure 2 | Bland Altman plots for Passive, Active and Reflexive parameters.

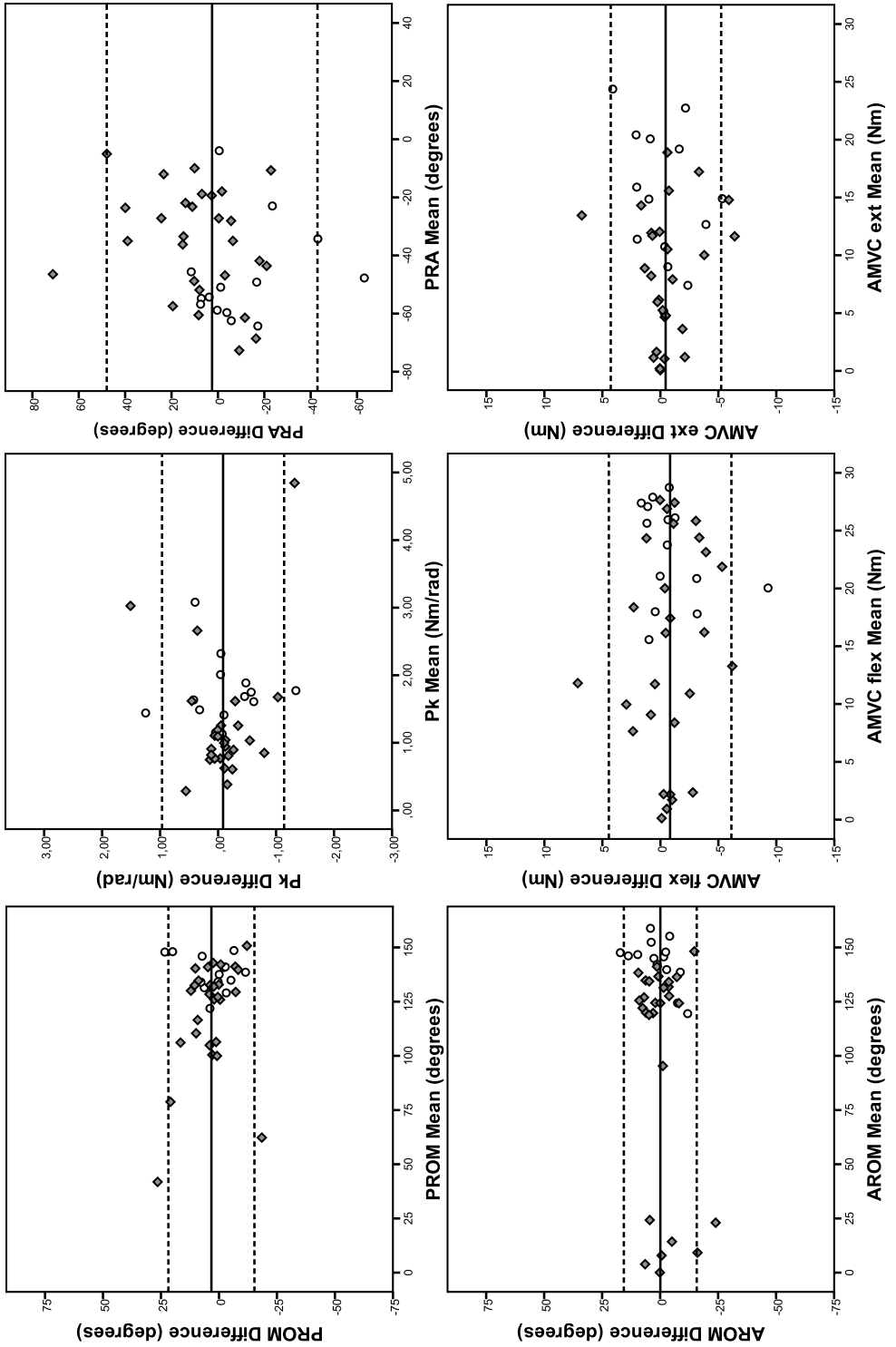


Figure 2 | Bland Altman plots for Passive, Active and Reflexive parameters.

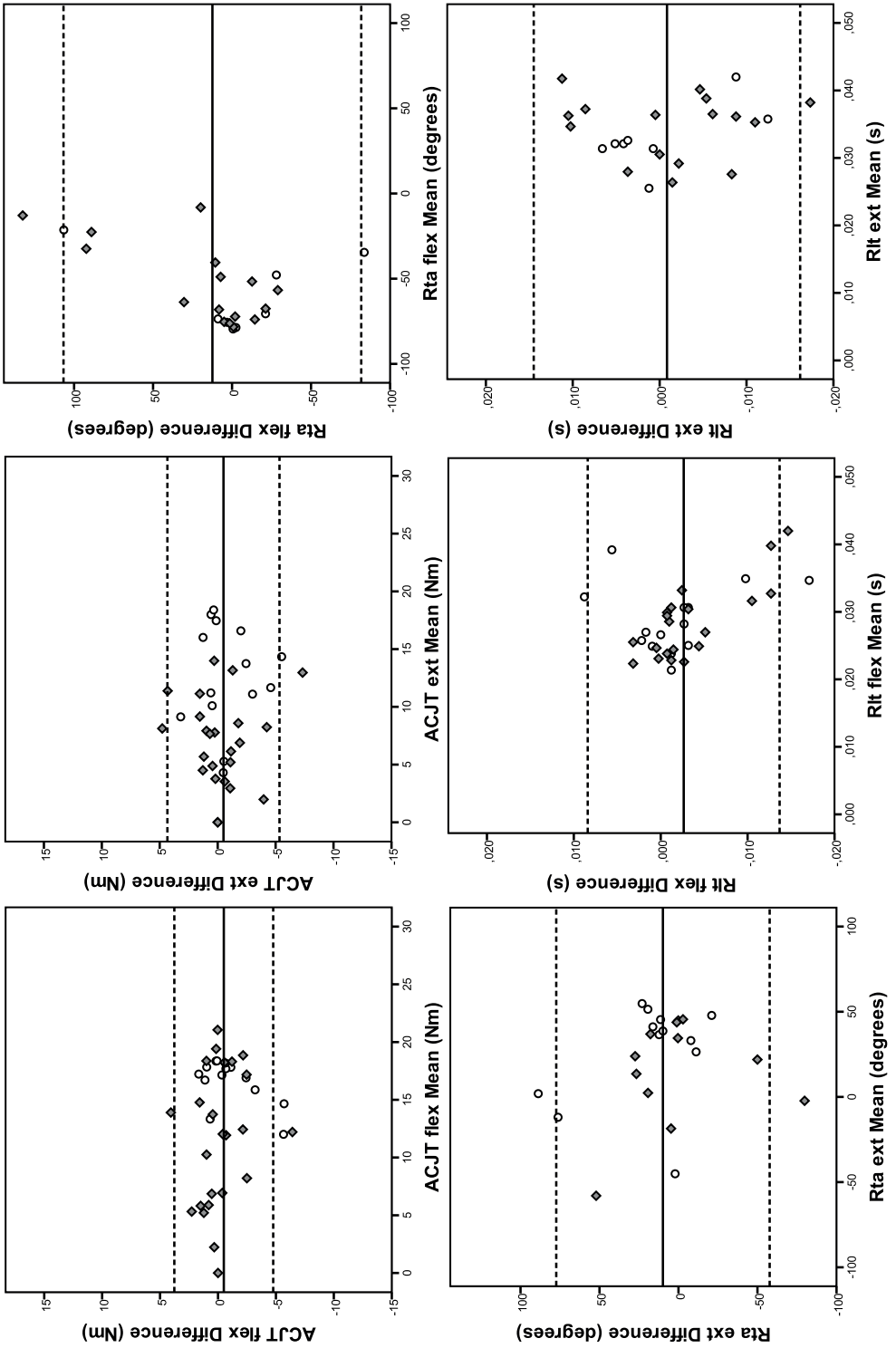
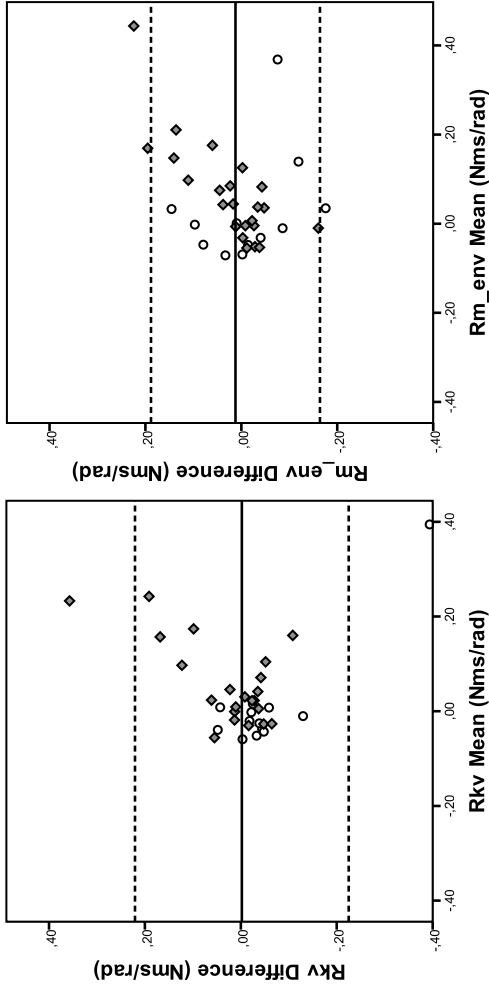


Figure 2 | Bland Altman plots for Passive, Active and Reflexive parameters.

P_{loop} : Range of motion passive, P_r : Stiffness in rest, P_{RA} : Rest angle, A_{ROM} : Range of motion active, A_{VMC} : Maximal voluntary contraction, A_{CT} : Control over joint torque, R_{thr} : Threshold angle, R_r : Reflexive loop time, R_{vz} : Reflexive contributions to joint resistance, $R_{m,env}$: Reflex modulation due to environmental changes. Open circle: Healthy participant. Gray circle: Post-stroke patient. Solid line: mean of the difference between first and second visits. Dotted line: upper and lower limit of 95% confidence interval for difference between first and second visits.



Responsiveness to clinical status

An overview of outcomes per group is summarized in Table 4. Dropout rates were similar in both chronic patient groups ($mAS = 0$: $n = 2$ and $mAS \geq 1$: $n = 2$). Differences between healthy volunteers, chronic stroke patients with $mAS = 0$ and chronic stroke patients with $mAS \geq 1$ are illustrated by box plots in Figure 3. Corresponding quartiles are given in Appendix A. In 10 out of 14 parameters, these differences were statistically significant, based on the exploratory Kruskal Wallis test (Table 4). When tested pairwise with the Wilcoxon Rank Sum test (Appendix B), there were significant differences between healthy volunteers and the $mAS=0$ group in the Passive parameters P_k and P_{RA} ; the Active parameters A_{ROM} , A_{MVC} (flexor and extensor) and A_{CJT} (flexor and extensor); and the Reflexive parameters R_{it} (extensor) and R_{kv} . Differences between healthy volunteers and the $mAS \geq 1$ group showed significance in P_{ROM} , all Active parameters, R_{ta} (extensor) and R_{kv} . When comparing the $mAS=0$ group and $mAS \geq 1$ group, there were significant differences in P_{ROM} , P_k and all Active parameters, but no significant differences in Reflexive parameters.

DISCUSSION

Using a dedicated, comprehensive neuromechanical assessment protocol, Passive and Active parameters could be assessed with excellent reliability in a cohort of stroke patients with upper extremity impairments and healthy volunteers. Repetitive assessment of the Passive parameter P_{RA} and Reflexive parameters had fair to good reliability, except for poor reliability of R_{it} (extensor). Parameters were responsive to clinical status, i.e. results demonstrated differences between healthy volunteers and chronic stroke patients.

The use of a haptic robot in combination with surface EMG provides standardized application of input signals and registration of output signals. Participants could comfortably tolerate the position in the measurement set-up and the length of the protocol. Previous publication of measurement set-up, protocol and data processing [20] and current assessment of test-retest reliability and clinical responsiveness add to the clinical validity of our method, which is advantageous for prospective implementation of this method in clinical practice.

Relative reliability expressed by ICC's is both determined by heterogeneity of the study group and the variance on the repeated measurements. In homogenous study groups, relative reliability may drop. For future assessment of longitudinal changes, variability of neuromechanical outcome parameters is unknown and may be dependent on the time of measurement, i.e. low heterogeneity early after stroke when the paresis component prevails and large heterogeneity when secondary biomechanical changes become manifest. We therefore adopted the present cohort-approach to minimize a-priori assumptions on heterogeneity within groups.

Table 4 | Median, minimum and maximum for healthy volunteers, chronic patients with modified Ashworth score (mAS) = 0 and chronic patients with mAS ≥ 1 , and p-value of the Kruskal Wallis test for differences between groups for Passive, Active and Reflexive parameters.

P_{ROM} : Range of motion passive, P_k : Stiffness in rest, P_{RA} : Rest angle. A_{ROM} : Range of motion active, A_{MVC} : Maximal voluntary contraction, A_{CT} : Control over joint torque. R_{ta} : Threshold angle, R_{lv} : Reflexive loop time, R_{kv} : Reflexive contributions to joint resistance, $R_{m_{env}}$: Reflex modulation due to environmental changes. #: significant difference between groups.

Parameter	Healthy volunteers	Chronic patients mAS = 0	Chronic patients mAS ≥ 1	Kruskal Wallis	
	median [min;max]	median [min;max]	median [min;max]		
Passive					
P_{ROM} (degrees)	138 [118; 148]	132 [100; 151]	100 [42; 133]	p < 0.001 [#]	
P_k (Nmrad ⁻¹)	1.72 [1.13; 2.95]	0.85 [0.29; 1.68]	1.44 [0.90; 4.84]	p < 0.001 [#]	
P_{RA} (degrees)	-52 [-64; 1]	-33 [-61; -10]	-52 [-73; -5]	p = 0.013 [#]	
Active					
A_{ROM} (degrees)	146 [119; 158]	128 [26; 148]	14 [0; 120]	p < 0.001 [#]	
A_{MVC} (Nm)	flexor	25.2 [16.4; 28.7]	18.4 [0.3; 27.6]	2.2 [0.1; 13.3]	p < 0.001 [#]
	extensor	14.9 [4.6; 25.4]	10.5 [0.1; 18.9]	1.1 [0.1; 6.0]	p < 0.001 [#]
A_{CT} (Nm)	flexor	17.3 [12.0; 18.4]	12.4 [0.0; 21.1]	2.2 [0.0; 8.2]	p < 0.001 [#]
	extensor	12.7 [4.1; 18.4]	7.8 [0.0; 14.0]	0.0 [0.0; 4.9]	p < 0.001 [#]
Reflexive					
R_{ta} (degrees)	flexor	-71 [-80; 9]	-72 [-84; 47]	-54 [-68; -8]	p = 0.221
	extensor	35 [-45; 55]	19 [-63; 46]	-64 [-69; 14]	p = 0.031 [#]
(s)	flexor	0.028 [0.022; 0.039]	0.030 [0.022; 0.045]	0.027 [0.021; 0.033]	p = 0.537
	extensor	0.032 [0.022; 0.042]	0.037 [0.020; 0.049]	0.036 [0.028; 0.044]	p = 0.097
R_{kv} (Nmsrad ⁻¹)	-0.015 [-0.059; 0.395]	0.025 [-0.056; 0.242]	0.053 [0.005; 0.160]	p = 0.017 [#]	
$R_{m_{env}}$ (Nmsrad ⁻¹)	-0.006 [-0.086; 0.368]	0.044 [-0.068; 0.444]	0.032 [-0.006; 0.126]	p = 0.192	

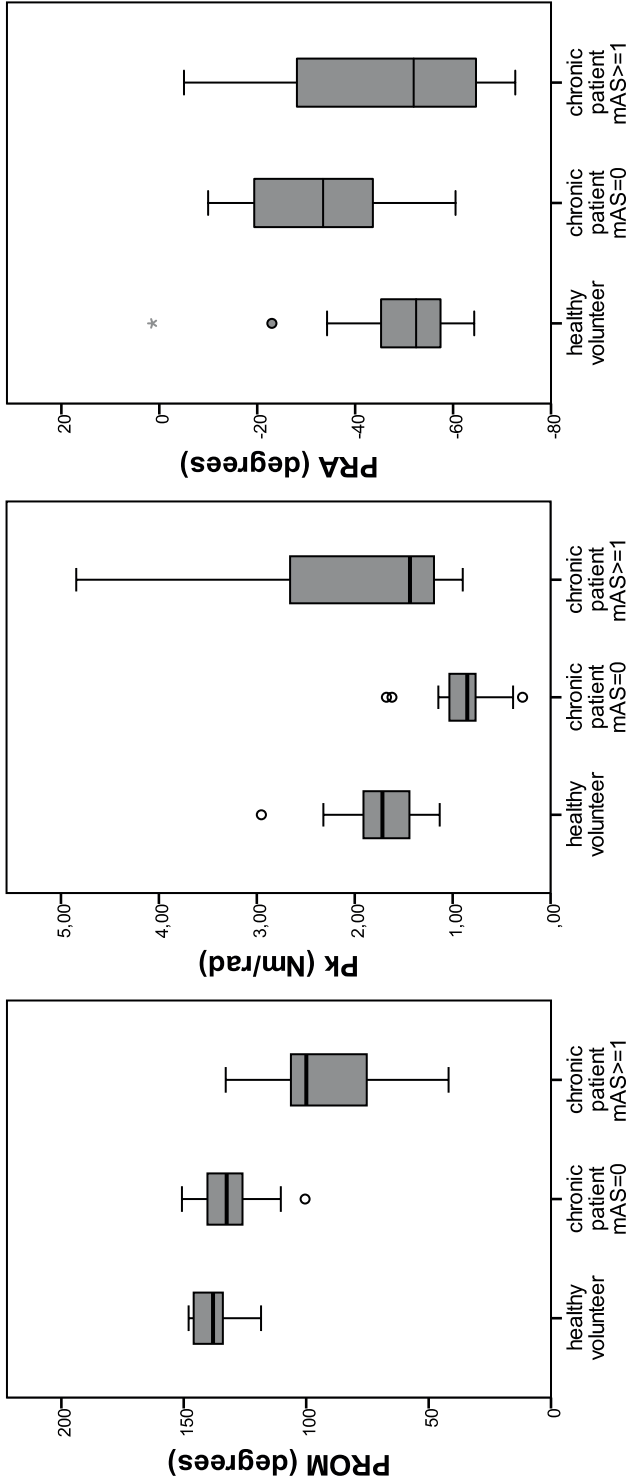


Figure 3 | Box plots for Passive, Active and Reflexive parameters.

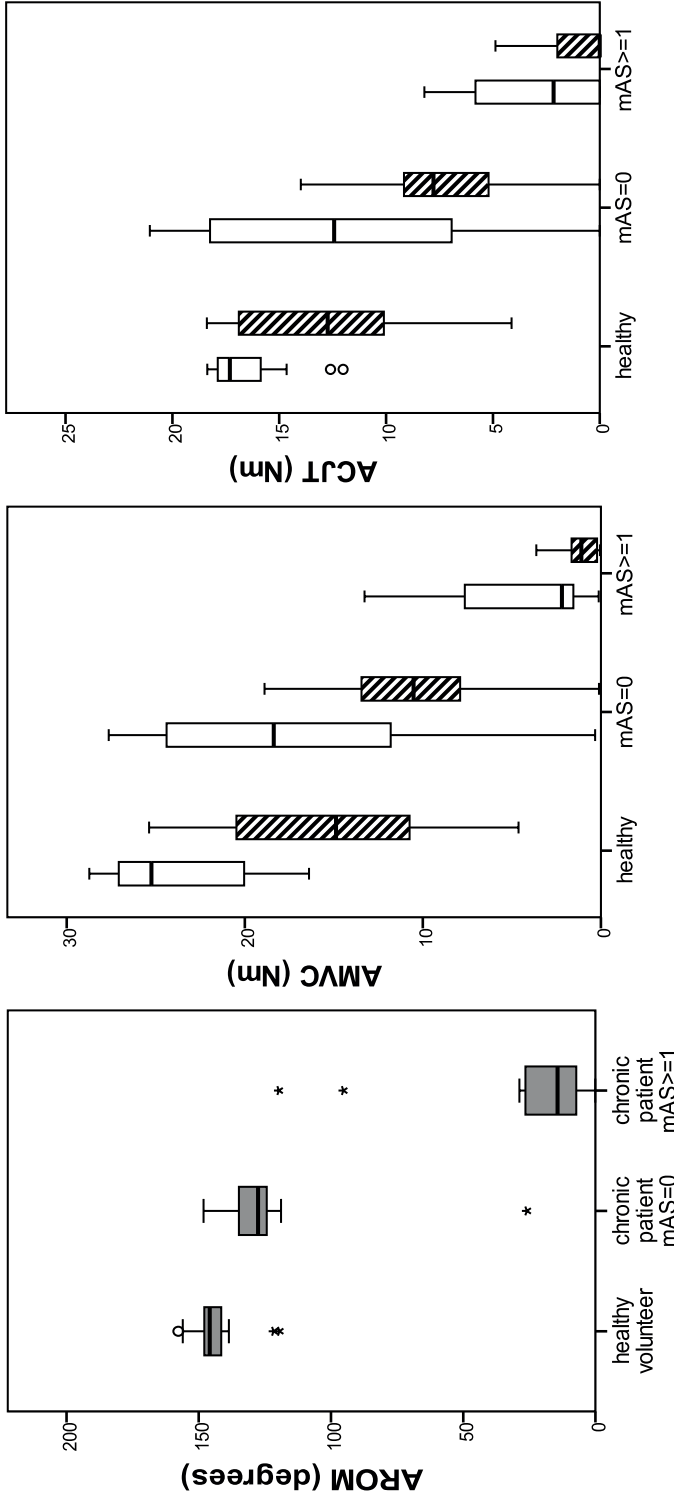
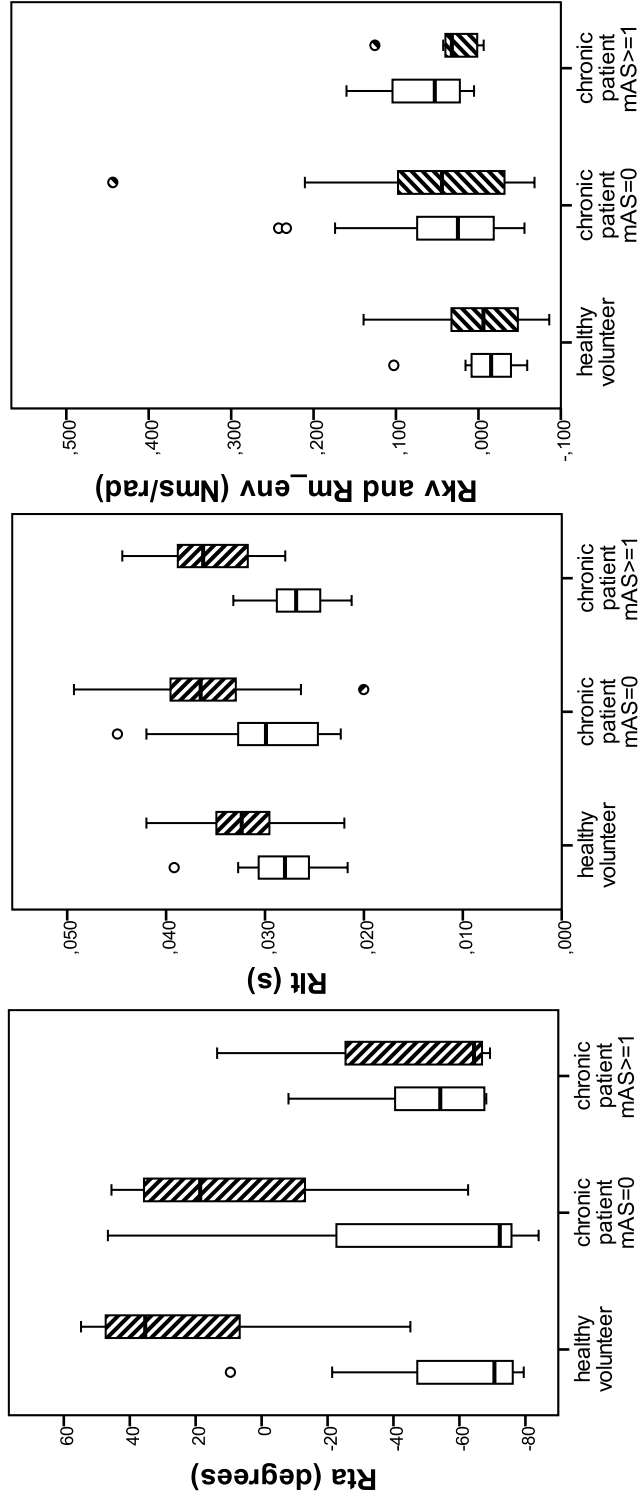


Figure 3 | Box plots for Passive, Active and Reflexive parameters.

Figure 3 | Box plots for Passive, Active and Reflexive parameters.

Groups divided in healthy volunteers, chronic stroke patients with mAS = 0 and chronic patients with mAS ≥ 1. P_{ROMF} : Range of motion passive, P_{r} : Rest angle, A_{ROMF} : Range of motion active, A_{VC} : Maximal voluntary contraction, A_{CJT} : Control over joint torque, R_{t} : Threshold angle, R_{r} : Reflexive loop time, R_{V} : Reflexive contributions to joint resistance, $R_{\text{m,env}}$: Reflex modulation due to environmental changes. White bars: flexor (and R_{v} in the lower right panel). Striped bars: extensor (and $R_{\text{m,env}}$ in the lower right panel).



Measures of absolute reliability can be used to calculate the SDD, i.e. the difference between measurements that can be attributed to real system changes. For example in A_{ROM} the SDD is 14 degrees, meaning that a change of 14 degrees or over can be attributed to a genuine change in patient characteristics in 95% of cases. SEM values for P_{ROM} , $P_{k'}$, A_{ROM} , A_{MVC} and A_{CJT} were low. These are sensitive parameters for real system changes, indicative for both passive as well as active contributors to observed movement disorders. We therefore recommend these parameters for future assessment of longitudinal neuromechanical changes.

In all Passive, Active and Reflexive parameters except $P_{k'}$, P_{RA} and R_{it} (extensor), differences between healthy volunteers and patients in the $mAS \geq 1$ group were more pronounced than differences between healthy volunteers and patients in the $mAS = 0$ group. However, parameters did not always increase or decrease proportionally between groups, which illustrates the complex and non-linear nature of movement disorder after stroke. In the $mAS = 0$ group, the paresis component probably plays an important role, while the ability for voluntary motor control is more preserved than in the $mAS \geq 1$ group (as can be seen from A_{MVC} and A_{CJT}), leading to a lower stiffness ($P_{k'}$) in passive structures (i.e. muscle, tendon, ligament). Test-retest results showed good reproducibility, however, the remarkable inter-individual variation in passive and active parameters in the group of chronic patients may represent the different phenotypes in post stroke motor control.

Strengths and limitations

The perturbations in our protocol may not have been enough to trigger the stretch reflex threshold of the extensor muscles, which are more difficult to trigger [25]. This could have contributed to a lower repeatability in Reflexive parameters R_{it} (extensor) and R_{ta} (extensor), and a larger SDD than expected for R_{kv} . Other contributing factors may be found in a low signal to noise ratio, i.e. absence of inappropriate muscle activity in healthy volunteers and in chronic stroke patients with $mAS = 0$. Furthermore, variability in Reflexive parameters is known to be present in both healthy volunteers and chronic patients [26-29], even in optimal circumstances. Stretch reflex behavior is more variable than passive tissue properties and voluntary muscle properties [29-31]. Apart from day-to-day variability in stretch reflex behavior [27,29], there is also variability due to level of arousal, audiovisual stimuli and other environmental factors [32,33], as well as conscious down- or up-regulation [34]. These methodological considerations, combined with the unequal variances in subgroups, might account for heteroscedasticity, especially in R_{ta} flexor and R_{it} extensor. SEM and SDD for these values should be interpreted bearing in mind that SDD and SEM might be smaller towards the minimum of the parameter and might be larger towards the maximum of both parameters.

Although sufficient for the aim of this study, group sizes were small. Current subdivision of clinical phenotypes according to mAS is a fairly rough approximation of clinical status and more participants may be needed for a more elaborate post-hoc analysis. The adopted

cohort approach is an estimation of group heterogeneity. The neuromechanical assessment protocol aimed to identify passive, active and reflexive contributors to movement disorder by differences in task and measurement conditions. For example: the protocol was designed to minimize the effects of active and reflexive (neural) contributors during passive (non-neural) tasks and vice versa. However, this might not yet give a completely true reflection of neuromechanical behavior, as system behavior under active task conditions involves a combination of both neural and non-neural contributors. The same goes for passive conditions, where neural components may be present through increased baseline activation [13]. Further development of System Identification and Parameter Estimation techniques might help to zoom in even closer on the specific contributors to neuromechanical behavior.

Implications for future work

One of the objectives of the EXPLICIT-stroke project [35] will be to combine the neuromechanical approach with extensive clinimetric data. Simultaneously, in this project, longitudinal measurements will be used to provide information on the changes in paresis, the development of secondary biomechanical changes and the increase of inappropriate muscle activity over time. This should provide the necessary data to enhance description of clinical phenotypes by clustering of neuromechanical parameters, and, moreover, to predict functional outcome.

CONCLUSIONS

Passive, Active and Reflexive parameters, representing passive tissue properties, voluntary muscle function and stretch reflex behavior respectively, can be measured in a reliable way. The comprehensive neuromechanical assessment protocol is responsive to clinical status and fulfills the requirements to separately assess non-neural and neural contributors to movement disorder around the wrist after stroke, using biomechanical, electromyographical and system identification techniques [7-10,12]. Therefore, this protocol gives momentum to future work on connecting pathophysiology to functional outcome, which will enable clinicians to substantiate their treatment.

Abbreviations

LUMC: Leiden University Medical Center;

mAS: modified Ashworth Scale;

ICC: Intraclass correlation coefficient;

SEM: Standard Error of Measurement;

SDD: Smallest Detectable Difference;

EMG: Electromyography.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JK participated in the design of the study, carried out the measurements, performed the statistical analysis and drafted the manuscript. AK participated in the design of the study, carried out the measurements and helped to draft the manuscript. JG participated in the design of the study and its coordination, and helped to draft the manuscript. EV participated in the design of the study and commented on the manuscript. FH participated in the design of the study and commented on the manuscript. CM conceived of the study, and participated in its design and coordination and helped to draft the manuscript. JA conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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APPENDICES

Appendix A | Quartiles of Passive, Active and Reflexive parameters for healthy volunteers, chronic patients with modified Ashworth score (mAS) = 0 and chronic patients with mAS \geq 1.

P_{ROM} : Range of motion passive, P_k : Stiffness in rest, P_{RA} : Rest angle, A_{ROM} : Range of motion active, A_{MVC} : Maximal voluntary contraction, A_{CT} : Control over joint torque, R_{th} : Threshold angle, R_{rl} : Reflexive loop time, R_{rv} : Reflexive contributions to joint resistance, $R_{m,env}$: Reflex modulation due to environmental changes.

Parameter		25 th percentile	50 th percentile	75 th percentile
Passive				
P_{ROM}	(degrees) healthy volunteer	133	138	146
	chronic patient mAS = 0	126	132	141
	chronic patient mAS $>$ = 1	75	100	112
P_k	(Nm rad ⁻¹) healthy volunteer	1.43	1.72	2.01
	chronic patient mAS = 0	0.76	0.85	1.06
	chronic patient mAS $>$ = 1	1.15	1.44	2.75
P_{RA}	(degrees) healthy volunteer	-58	-52	-43
	chronic patient mAS = 0	-45	-33	-19
	chronic patient mAS $>$ = 1	-66	-52	-27
Active				
A_{ROM}	(degrees) healthy volunteer	141	146	149
	chronic patient mAS = 0	124	128	136
	chronic patient mAS $>$ = 1	7	14	45
A_{MVC} flexor	(Nm) healthy volunteer	19.5	25.2	27.2
	chronic patient mAS = 0	11.8	18.4	25.0
	chronic patient mAS $>$ = 1	1.4	2.2	7.8
A_{MVC} extensor	(Nm) healthy volunteer	10.4	14.9	20.6
	chronic patient mAS = 0	7.0	10.5	13.9
	chronic patient mAS $>$ = 1	0.2	1.1	2.1
A_{CT} flexor	(Nm) healthy volunteer	15.6	17.3	17.9
	chronic patient mAS = 0	6.6	12.4	18.3
	chronic patient mAS $>$ = 1	0.0	2.2	6.1
A_{CT} extensor	(Nm) healthy volunteer	9.9	12.7	17.1
	chronic patient mAS = 0	4.9	7.8	10.2
	chronic patient mAS $>$ = 1	0.0	0.0	2.2

Appendix A | *Continued*

Parameter		25 th percentile	50 th percentile	75 th percentile
Reflexive				
R _{ta} flexor	(degrees) healthy volunteer	-77	-71	-41
	chronic patient mAS = 0	-76	-72	-13
	chronic patient mAS > = 1	-68	-54	-36
R _{ta} extensor	(degrees) healthy volunteer	3	35	47
	chronic patient mAS = 0	-16	19	36
	chronic patient mAS > = 1	-69	-64	
R _{lt} flexor	(s) healthy volunteer	0.025	0.028	0.031
	chronic patient mAS = 0	0.024	0.030	0.033
	chronic patient mAS > = 1	0.024	0.027	0.030
R _{lt} extensor	(s) healthy volunteer	0.029	0.037	0.035
	chronic patient mAS = 0	0.032	0.036	0.040
	chronic patient mAS > = 1	0.031	0.036	0.039
R _{kv}	(Nms rad ⁻¹) healthy volunteer	-0.040	-0.015	0.010
	chronic patient mAS = 0	-0.021	0.025	0,084
	chronic patient mAS > = 1	0.016	0.053	0.105
R _{m_env}	(Nms rad ⁻¹) healthy volunteer	-0.053	-0.006	0.033
	chronic patient mAS = 0	-0.032	0.044	0.122
	chronic patient mAS > = 1	-0.001	0.032	0.041

Appendix B | Pairwise comparison with Wilcoxon Rank Sum test between healthy volunteers, chronic patients with $mAS = 0$ and chronic patients with $mAS \geq 1$.

[#]: significant difference between pair. The Kruskal Wallis test results are repeated from Table 4 for reference. P_{ROM} : Range of motion passive, P_k : Stiffness in rest, P_{RA} : Rest angle. A_{ROM} : Range of motion active, A_{MVC} : Maximal voluntary contraction, A_{CJT} : Control over joint torque. R_{ta} : Threshold angle, R_{lt} : Reflexive loop time, R_{kv} : Reflexive contributions to joint resistance, R_{m_env} : Reflex modulation due to environmental changes.

Parameter	Kruskal Wallis	Wilcoxon rank sum test (between groups)		
		Healthy volunteers vs. Chronic patients $mAS = 0$	Healthy volunteers vs. Chronic patients $mAS \geq 1$	Chronic patients $mAS = 0$ vs. Chronic patients $mAS \geq 1$
Passive				
P_{ROM} (degrees)	$p < 0.001^{\#}$	$p = 0,059$	$p < 0.001^{\#}$	$p < 0.001^{\#}$
P_k (Nm rad ⁻¹)	$p < 0.001^{\#}$	$p < 0.001^{\#}$	$p = 0.682$	$p = 0.001^{\#}$
P_{RA} (degrees)	$p=0.013^{\#}$	$p = 0.004^{\#}$	$p = 0.725$	$p = 0.063$
Active				
A_{ROM} (degrees)	$p < 0.001^{\#}$	$p = 0.001^{\#}$	$p < 0.001^{\#}$	$p < 0.001^{\#}$
A_{MVC} (Nm)	flexor	$p < 0.001^{\#}$	$p = 0.026^{\#}$	$p < 0.001^{\#}$
	extensor	$p < 0.001^{\#}$	$p = 0.031^{\#}$	$p < 0.001^{\#}$
A_{CJT} (Nm)	flexor	$p < 0.001^{\#}$	$p = 0.086$	$p < 0.001^{\#}$
	extensor	$p < 0.001^{\#}$	$p = 0.002^{\#}$	$p < 0.001^{\#}$
Reflexive				
R_{ta} (degrees)	flexor	$p=0.221$	$p = 0.596$	$p = 0.094$
	extensor	$p=0.031^{\#}$	$p = 0.096$	$p = 0.032^{\#}$
R_{lt} (s)	flexor	$p=0.537$	$p = 0.711$	$p = 0.413$
	extensor	$p=0.097$	$p = 0.041^{\#}$	$p = 0.102$
R_{kv} (Nms rad ⁻¹)	$p=0.017^{\#}$	$p = 0.043^{\#}$	$p = 0.006^{\#}$	$p = 0.268$
R_{m_env} (Nms rad ⁻¹)	$p=0.192$	$p = 0.138$	$p = 0.076$	$p = 0.845$

C h a p t e r

5

Loss of selective wrist muscle activation in post-stroke patients

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ABSTRACT

Purpose

Loss of selective muscle activation after stroke contributes to impaired arm function, is difficult to quantify and is not systematically assessed yet. The aim of this study was to describe and validate a technique for quantification of selective muscle activation of wrist flexor and extensor muscles in a cohort of post-stroke patients. Patterns of selective muscle activation were compared to healthy volunteers and test-retest reliability was assessed.

Materials & Methods

Activation Ratios describe selective activation of a muscle during its expected optimal activation as agonist and antagonist. Activation Ratios were calculated from electromyography signals during an isometric maximal torque task in 31 post-stroke patients and 14 healthy volunteers. Participants with insufficient voluntary muscle activation (maximal electromyography signal < 3SD higher than baseline) were excluded.

Results

Activation Ratios at the wrist were reliably quantified (Intraclass correlation coefficients 0.77 – 0.78). Activation Ratios were significantly lower in post-stroke patients compared to healthy participants ($p < 0.05$).

Conclusion

Activation Ratios allow for muscle specific quantification of selective muscle activation at the wrist in post-stroke patients. Loss of selective muscle activation may be a relevant determinant in assigning and evaluating therapy to improve functional outcome.

INTRODUCTION

In post-stroke patients, impaired arm and hand function is determined by a complex interaction of primary neurological deficits and secondary changes in connective and contractile tissue [1-3]. Amidst these changes, loss of selective muscle activation plays a role [4-7]. The ability to voluntarily contract a muscle and to have selective control of antagonistic muscles predominantly defines the torque output a patient can generate during a task. Loss of selective muscle activation may result in energetically inefficient co-contraction and impaired dexterity in the affected limb [8-11]. Moreover, loss of selective muscle activation [12] may result in a lower torque output at joint level than expected by the level of paresis alone [13]. We expect clinical phenotypes to diverge from 1) patients with flaccid paresis, i.e. no selective muscle activation, to 2) patients with some loss of selective muscle activation, and 3) patients with normal selective muscle activation combined with either low or normal torque output. Addressing the role of selective muscle activation to loss of function is important in clinical decision making, e.g. to optimize patient selection and timing of costly or labor intensive therapies such as mCIMT or botulinum toxin.

Selective muscle activation is not yet assessed routinely in post-stroke patients. Current measures may have methodological drawbacks. For example, comparison of electromyography (EMG) signals of agonistic and antagonistic muscles is a frequently applied technique [14-18]. Yet the comparison of agonist and antagonist EMG-signals is for instance troubled by differences in volume of the muscles in an agonist-antagonist muscle pair [19,20] and complicated in case of spasticity [9], which makes quantification of selective muscle activation with this technique challenging. Furthermore, quantification of selective muscle activation by comparison of EMG-signals of the same muscle in the ipsilateral and contralateral sides [13,21] may be hampered, as muscle properties of the unaffected side should not be regarded as normal in post-stroke patients [22-26]. Moreover, proper address of selective muscle activation is of importance as morphological changes interfering with contractile behavior are already reported in the early phase after stroke [27].

In this study we describe selective muscle activation by comparing EMG-signals of wrist muscles during two isometric but antagonistic task conditions, using the normalized ratio of the EMG-signals per muscle group, also called Activation Ratio (AR) [28]. This method is methodologically advantageous because it describes the activation of both flexor and extensor muscles in relation to their expected agonistic and antagonistic function. AR may be applied to antagonist muscle pairs provided the axis of movement is controlled (limitation in degrees of freedom). Selective muscle activation around the wrist joint had our special interest because of its role in lasting impairment in arm-hand function after stroke, e.g. in case of flexion deformity. Muscle specific AR is assumed to assist in a better definition of clinical phenotypes in post-stroke patients. However, this method has not been evaluated in post-stroke patients yet. Our aim was to describe and validate this technique

for quantification of selective muscle activation of wrist flexor and extensor muscles in a cohort of post-stroke patients. Patterns of selective muscle activation were compared to healthy volunteers and test-retest reliability was assessed.

METHODS

Participants

The study cohort consisted of 31 stroke survivors and 14 healthy volunteers. Post-stroke patients were recruited from an outpatient rehabilitation department. Inclusion criteria were: first ischemic stroke between 1999 – 2009, age 18 – 80 years, a perceived persistent impairment of arm-hand function by the participant, being able to travel to the research laboratory, and being able to sit on a chair and follow instructions for one hour. Exclusion criteria were: previous orthopedic limitations of arm-hand function, a history of other neurologic impairments besides stroke. Participants were measured between November 2008 and January 2010 on two occasions within a month, under the assumption that clinical status would remain stable. Stroke onset was more than 6 months prior to assessment. Ethical approval for the study was received from the medical ethical committee at the Leiden University Medical Center and written informed consent was obtained from each participant prior to testing.

Protocol

Participants were instructed to perform a voluntary isometric maximal flexion or extension torque, starting from a relaxed condition. The voluntary maximal isometric torque (MIT) had to be attained within a 15 second timeframe, followed by a minimum of 60 seconds rest. This procedure was performed twice for both flexion and extension. The position of the wrist during the test was a neutral angle where the average measured torque during a slow passive movement through the range of motion was 0 Nm (Rest Angle) [29]. For motivational purposes, visual feedback was provided on a computer screen. This feedback consisted of a vertical bar which showed both instantaneous and maximal attained torque.

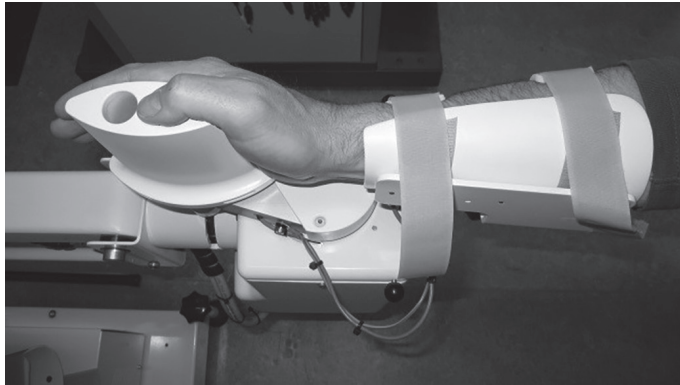
Measurement set-up

Tests were performed on a haptic wrist manipulator (Wristalyzer®, Moog FCS, Nieuw Vennep, the Netherlands) [30], on which torque and wrist joint angle were recorded. Participants were comfortably seated on a chair in front of a video screen. The forearm of the participant was positioned horizontally with the elbow in 90° flexion. The hand was strapped to an ellipsoidal shaped handle (Figure 1) to prevent finger flexion and hand closure. The skin at the electrode positions was cleansed with alcohol and lightly abraded with skin preparation gel (SkinPure, Nihon Kohden, Japan). EMG activity of the m. flexor carpi radialis (FCR) and

m. extensor carpi radialis longus and brevis (together abbreviated as ECR) was recorded by bipolar parallel bar surface electrodes (Bagnoli® DE-2.1, Ag, single differential, inter electrode distance 10 mm; Bagnoli-8 amplifier, Delsys Inc., Boston, USA). FCR and ECR were chosen to reflect overall muscle activity of wrist flexor and extensors. Both muscles are the less pennate muscles of the lower arm, have good accessibility with surface EMG and are therefore likely to suffer less from measurement artefacts. Two bipolar electrodes were placed on each muscle group to ensure that a signal was available and to compensate for spatial alterations in the affected (atrophic) muscle after stroke [31]. Position, force and EMG were sampled at 2048Hz using a 16 bit analog-to-digital card (USB 6221, National Instruments, Austin, USA) [29].

Figure 1 | Photograph of Wristalyzer handle and arm-rest.

For a better view of the hand position, the hand straps are not shown.



Data processing

Data were processed with Matlab® (Mathworks, Natick, USA). Selective activation of FCR and ECR were computed by means of Activation Ratio (AR). This is an EMG-based method [28], which requires voluntary muscle activation. In patients with flaccid paresis, voluntary muscle activation is insufficient to distinguish between resting state and active conditions, and therefore insufficient to determine selective muscle activation. In this study, insufficient voluntary muscle activation was defined as EMG activity during the isometric maximal torque task of less than three times standard deviation above baseline EMG. When insufficient EMG activity was established for a trial, the trial was excluded from analysis.

AR was calculated per bipolar electrode according to equation 1 [28], where AIP is the in-phase muscle activation, i.e. activity during the agonistic task; and AOP is the out-of-phase muscle activation, i.e. activity during the antagonistic task of the muscle. An AR close to one indicates optimal in-phase (selective) muscle activation. If the AR equals zero, muscle activation is equal during flexion and extension. A negative AR indicates out-of-phase

muscle activation, i.e. the muscle is more active during its antagonistic task than during its agonistic task.

$$\text{Equation 1} \quad AR = \frac{(A^{IP} - A^{OP})}{(A^{IP} + A^{OP})} \quad [-1 \leq AR \leq 1]$$

Raw EMG signals (online band pass filter 20-450 Hz) were rectified and smoothed by a 2Hz 3rd order Butterworth low pass filter [32]. Torque data were also smoothed with a 3rd order Butterworth low pass filter of 2 Hz. Smoothed torque data and corresponding EMG signals were sorted along torque magnitude with intervals of 0.01 Nm. Then AR were computed for each torque level using both flexor and extensor task data within the available torque range (containing matching torques from both flexion and extension task) per bipolar electrode. The average AR was then computed per bipolar electrode, resulting in two AR for FCR and two AR for ECR per trial.

Statistical methods

SPSS 20 (IBM, New York, USA) was used for statistical analysis. For each participant, the average AR_{flex} for FCR and average AR_{ext} for ECR per visit was computed from the mean AR per bipolar electrode per trial (EMG was recorded by two bipolar electrodes per muscle group and participants had two trials per visit), after checking for systematic differences between the electrodes and trials using Wilcoxon rank sum test and scatter plots.

Test-retest reliability of AR was established by Intraclass correlation coefficient (ICC) between the two visits. ICC were calculated using the two-way mixed model for absolute agreement. Values above 0.75 were assumed to represent excellent reliability, values between 0.4 and 0.75 to represent fair to good reliability and values below 0.4 to represent poor reliability [33]. As ICC is a relative measure dependent on variance between measurements compared to total variance [34], Bland Altman plots were used to illustrate variability. Standard Error of Measurement (SEM) values were calculated to further substantiate ICC according to equation 2.

$$\text{Equation 2} \quad SEM = SD \cdot \sqrt{1-ICC}$$

At parameter level, normality of distribution was inspected with histograms and equality of variances between healthy volunteers and post-stroke patients was tested with Levene's test. Age was normally distributed, equal variances were assumed (Levene's test $p = 0.78$). The independent samples t -test was used to compare age between healthy volunteers and post-stroke patients. AR were not normally distributed within groups and variance was not equal between groups (Levene's test for AR_{flex} $p = 0.018$, and for AR_{ext} $p < 0.001$), hence median and range were used and the non-parametric Independent Samples Median Test

was used for comparison between post-stroke patients and healthy volunteers. The relation between AR_{flex} and AR_{ext} was tested with Spearman's rho correlation coefficient. Ratio of men to women within the two groups (post-stroke patients and healthy volunteers) was tested with the chi-square test.

RESULTS

Participants

All healthy volunteers completed all visits (100%) and 28 out of 31 patients completed all visits (90.3%). Reasons for dropping out were: unable to schedule the second visit ($n = 2$), patient was treated with botulinum toxin in period between first and scheduled second visit ($n = 1$). Demographics of the study population are summarized in table 1. Mean age in post-stroke patients was 59 years (SD 13 year) and 50 years (SD 15 year) in healthy participants ($p = 0.04$ when tested for difference in age between group; 95% confidence interval for the difference: -18 years to -0.2 years). However, further analysis showed that age did not have a significant correlation with either AR_{flex} (Pearson correlation -0.079 with $p = 0.62$) or AR_{ext} (Pearson correlation -0.139 with $p = 0.38$), and in multivariate analysis, age was not a contributing factor. Therefore age was not corrected for in further analysis. The ratio of men to women was not statistically different in both categories ($p = 0.14$). Average time post-stroke was 3 years (SD 2.5 year). More information on limb dominance in the post-stroke patient group can be found in Supplementary Figure S1.

Table 1 | Demographics of the study population.
Data expressed as mean (SD) or number (%), n.a. = not applicable.

Population	Healthy volunteers (n = 14)	Chronic patients (n = 31)
Age (years) (SD)	49.4 (15.1)	58.5 (13.1)
Men (n)	9 (64%)	13 (42%)
Right side dominant (n)	13 (93%)	29 (94%)
Measured side dominant (n)	14 (100%)	14 (45%)
Rest Angle (degrees) (range)	-52 [-64; 1]	-35 [-72; -5]
Time between measurements (days) (SD)	27 (21)	22 (12)
Time after stroke (years) (SD)	n.a.	3.1 (2.6)
Age at moment of stroke (years) (SD)	n.a.	55.2 (13.8)
modified Ashworth Score = 0 (n)	n.a.	21
modified Ashworth Score ≥ 1 (n)	n.a.	10

Voluntary muscle activation

Three out of 172 trials were excluded because of recording errors. Insufficient voluntary muscle activation was observed in both FCR and ECR in three post-stroke patients, indicating flaccid paresis. The trials of these three patients were excluded from analysis. In two additional post-stroke patients, there was insufficient voluntary muscle activation in the ECR only. Therefore, all trials regarding the extensor muscles of these two patients were excluded from analysis.

Quantification of selective muscle activation

A typical recording of a healthy participant is illustrated in Figure 2. Voluntary maximal isometric torque (MIT) were 28.3 Nm (flexion) and 18.4 Nm (extension). EMG activity of the FCR during extension was low and EMG activity of the ECR during flexion was low, as expected. Resulting AR in this participant were therefore close to one ($AR_{flex} = 0.82$, $AR_{ext} = 0.81$), indicating a high selectivity of FCR and ECR muscle activation.

Figure 2 | Wrist torque and EMG activity in a healthy volunteer with selective muscle activation.

Right arm measured. EMG FCR: EMG signal of m. flexor carpi radialis. EMG ECR: EMG signal of m. extensor carpi radialis longus and brevis.

Upper panel: red line represents flexion wrist torque. Blue line represents extension wrist torque.

Middle and Lower panel: red lines represent EMG activity during flexion. Blue lines represent EMG activity during extension.

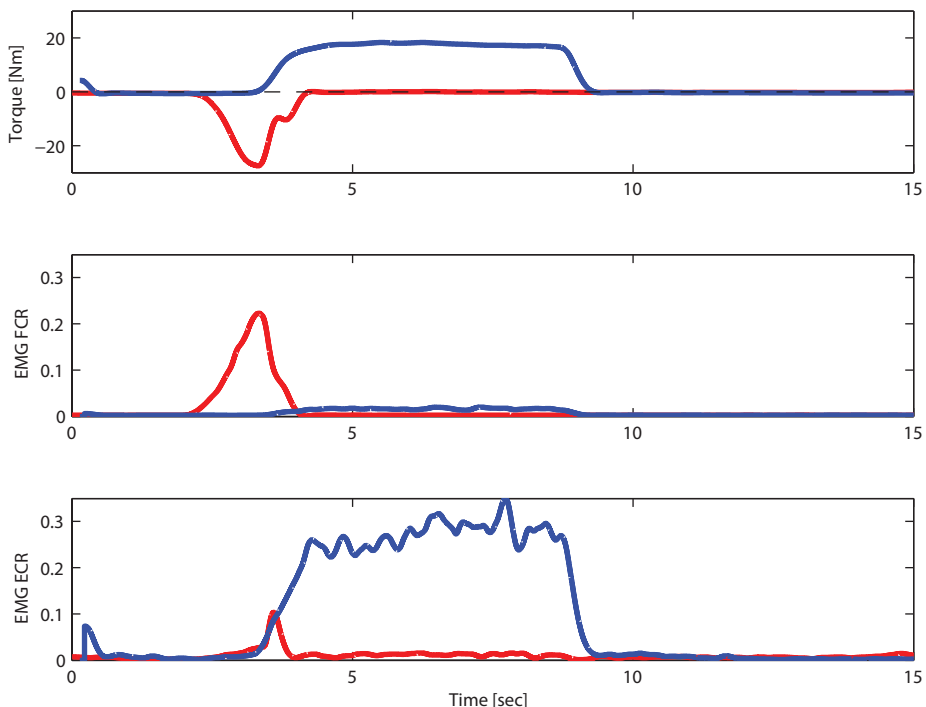
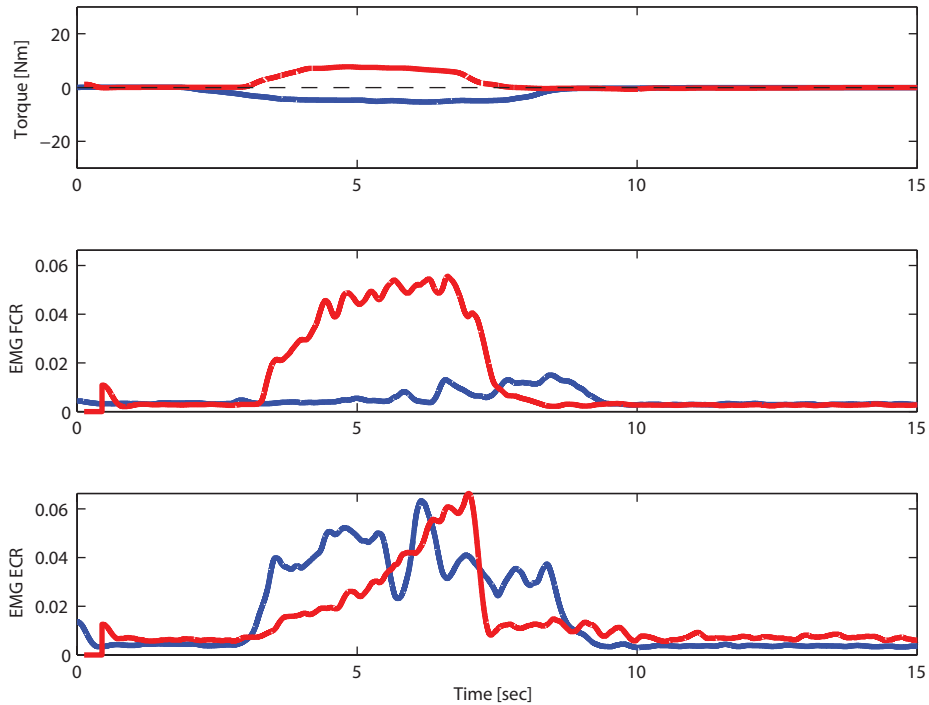


Figure 3 | Wrist torque and EMG activity in a post-stroke patient with loss of selective muscle activation.

Left arm measured. EMG FCR: EMG signal of *m. flexor carpi radialis*. EMG ECR: EMG signal of *m. extensor carpi radialis longus* and *brevis*.

Upper panel: Red line represents flexion wrist torque. Blue line represents extension wrist torque.

Middle and lower panel: Red lines represent EMG activity during flexion. Blue lines represent EMG activity during extension.



An example of a post-stroke patient with loss of selective function of the ECR is shown in Figure 3. Voluntary MIT were 7.8 Nm (flexion) and 5.4 Nm (extension). There was an increased EMG activity of the ECR during flexion. This EMG activity was almost equal to the EMG activity of the ECR during extension. Therefore the AR_{ext} in this participant was close to zero ($AR_{ext} = 0.01$). The FCR showed more selective activation ($AR_{flex} = 0.55$).

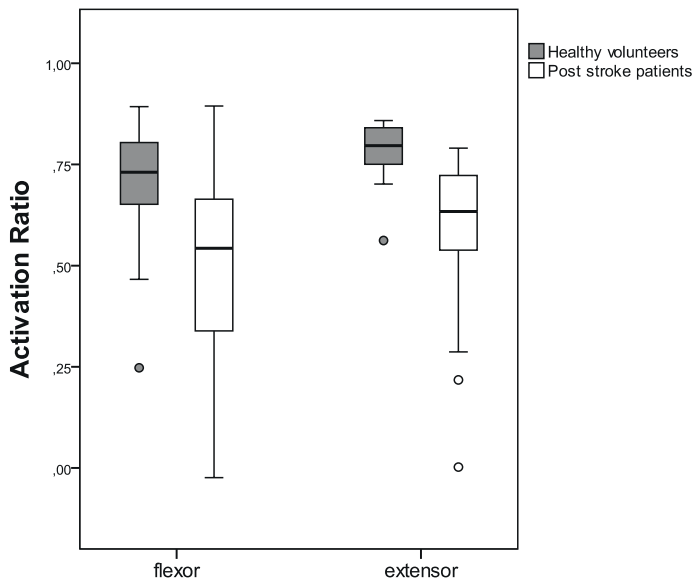
Activation Ratios in post-stroke patients and healthy volunteers

Median AR_{flex} was 0.62 and median AR_{ext} was 0.71 overall in all participants. Median and range of AR in post-stroke patients and healthy participants, as well as voluntary MIT per group are summarized in table 2. Median AR_{flex} and AR_{ext} in post-stroke patients were significantly lower than in healthy participants ($p = 0.022$ and $p = 0.003$ respectively), this is graphically represented in Figure 4. AR_{flex} and AR_{ext} were significantly correlated in post-stroke patients (Spearman's rho 0.486, $p = 0.012$), but not in healthy participants (Spearman's rho 0.262,

$p = 0.366$), which can be inferred from Figure 5. Test-retest reliability of AR_{flex} and AR_{ext} was excellent with ICC of 0.77 and 0.78 respectively. Bland Altman plots are shown in figure 6, depicting the mean of the two measurements (x-axis) compared to the difference between two measurements (y-axis). The values are scattered around the mean difference (solid line), which is close to zero, illustrating the absence of a systematic difference or learning effect between the two measurements. The 95% confidence interval of the difference between the measurements (dotted lines) illustrates measurement error. SEM values provide an indication of the dispersion of the measurement errors. SEM were 0.11 for AR_{flex} and 0.10 for AR_{ext} . More information on the influence of variance on ICC and SEM can be found in Supplementary Figure S2.

Figure 4 | Box plot for Activation Ratios of m. flexor carpi radialis (AR_{flex}) and m. extensor carpi radialis communis (AR_{ext}) in post-stroke patients and healthy volunteers.

Differences between post-stroke patients and healthy volunteers are significant as tested with Independent Samples Median Test. P-values: $p(AR_{flex}) = 0.022$, $p(AR_{ext}) = 0.003$.



Clinical Phenotypes

As introduced, clinical phenotypes were expected to diverge from 1) patients with flaccid paresis i.e. no selective muscle activation, to 2) patients with some loss of selective muscle activation combined with low torque output, and 3) patients with normal selective muscle activation combined with either low or normal torque output. To substantiate these phenotypes, combinations of AR and MIT can be used. In the first phenotype, voluntary muscle activation is insufficient to distinguish between resting state and active conditions, so AR cannot be quantified. In the second phenotype, combinations of low AR with both

high and low MIT are found. In the third phenotype, a high AR in combination with either a high MIT or a low MIT is expected. Patients of phenotype 2 and 3 are graphically represented in Figure 7, with the dotted line representing the lowest value in healthy volunteers (AR_{flex} 0.15 and AR_{ext} 0.56; MIT_{flex} 16.4 Nm and MIT_{ext} 4.6 Nm). High AR (representing high selective muscle activation) occurred within patients with both high and low MIT (right upper and lower quadrant in all panels), while low AR (representing low selective muscle activation) predominantly coincided with low MIT (left lower quadrant in all panels). The exception is low AR_{ext} , which coincided with both high and low MIT_{ext} (left upper and lower quadrant in lower right panel).

Figure 5 | Scatter plot illustrating the correlation of Activation Ratio for m. flexor carpi radialis (AR_{flex}) and m. extensor carpi radialis communis (AR_{ext}).

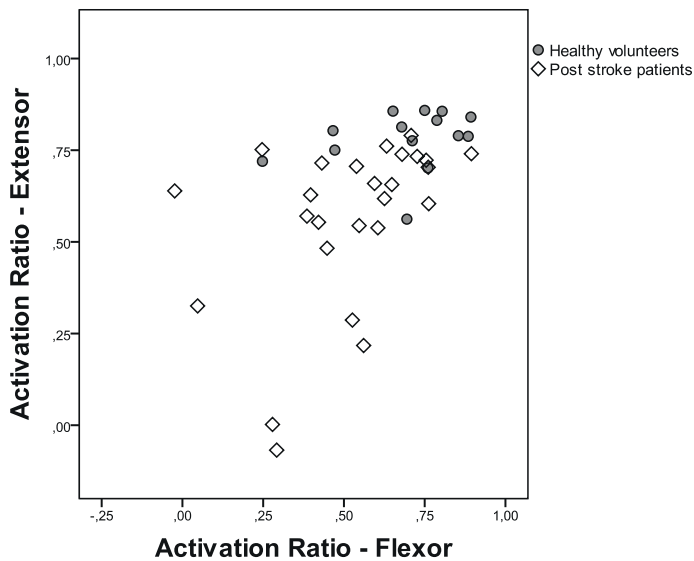


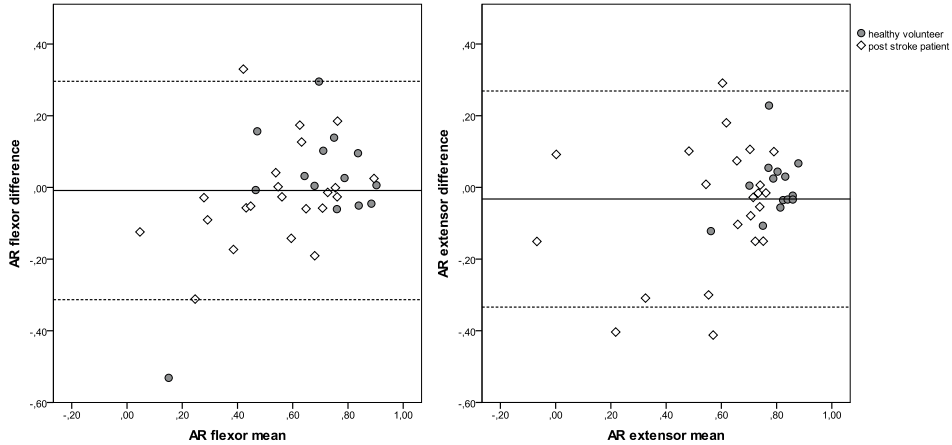
Table 2 | Median and range of Activation Ratio and voluntary Maximal Isometric Torque in post-stroke patients and healthy volunteers.

AR_{flex} = Activation Ratio for m. flexor carpi radialis; AR_{ext} = Activation Ratio for m. extensor carpi radialis communis; MIT_{flex} = Maximal Isometric Torque towards flexion (Nm); MIT_{ext} = Maximal Isometric Torque towards extension (Nm).

	Post stroke Median [min;max]	Healthy Median [min;max]
AR_{flex}	0.54 [-0.02; 0.89]	0.73 [0.15; 0.90]
AR_{ext}	0.63 [-0.07; 0.79]	0.80 [0.56; 0.88]
MIT_{flex}	14.7 [0.9; 27.6]	25.2 [16.4; 28.7]
MIT_{ext}	8.8 [1.1; 18.9]	14.9 [4.6; 25.4]

Figure 6 | Bland Altman plots for Activation Ratio for m. flexor carpi radialis (ARflex) and m. extensor carpi radialis communis (ARext).

Solid line: mean of the difference between first and second visits. Dotted line: upper and lower limit of 95% confidence interval for difference between first and second visit.



DISCUSSION

Although essential, establishing selective muscle activation does not reflect the full potential for treatment of a patient yet. Inappropriate muscle activation, i.e. exaggerated stretch reflexes, and secondary biomechanical properties, such as increased stiffness should also be taken into account [29,35-39]. For example, loss of selective muscle activation might coincide with spasticity, for which botulinum toxin could be beneficial [40-42], while loss of selective muscle activation combined with structural shortening of a muscle unresponsive to physical therapy might benefit more from surgery [43,44]. In order to tailor treatment to patient characteristics, each clinical phenotype requires a different approach.

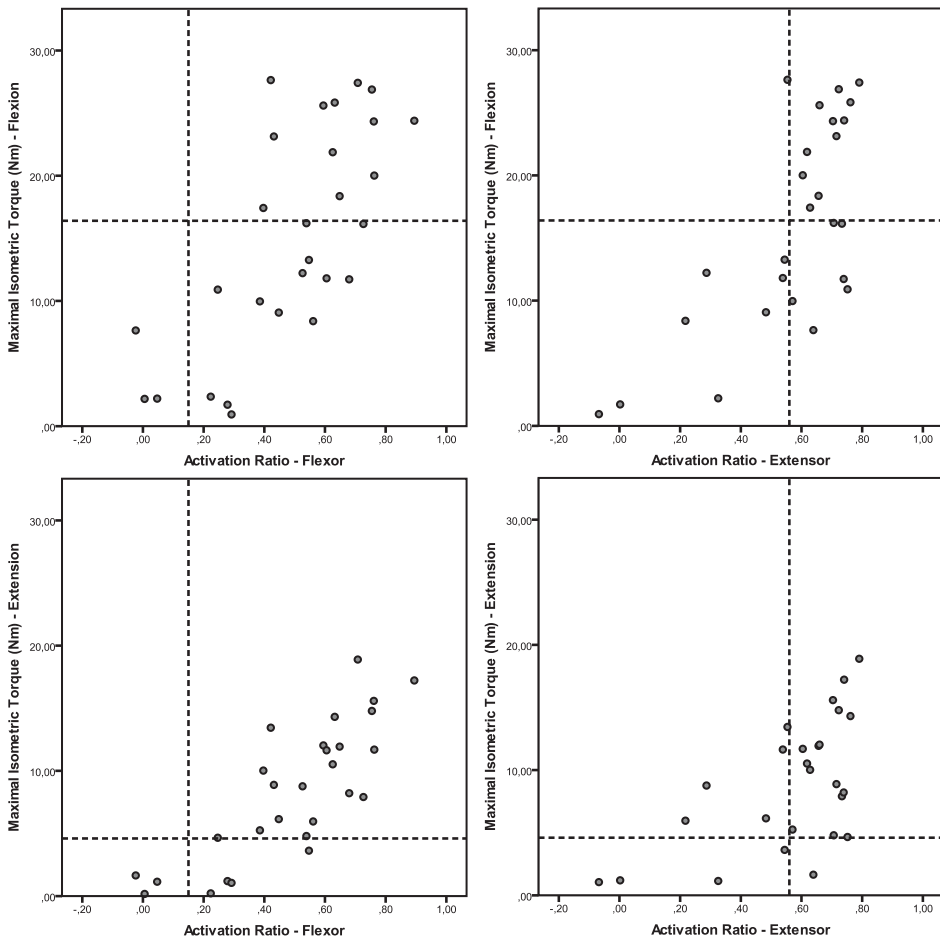
Strengths and limitations

The isotonic torque task preferred in earlier work [28] was modified to an isometric task during a maximal voluntary contraction. Voluntary maximal isometric torque is a widely used and easily applied clinimetric parameter that was already part of our test procedure. The necessary sorting technique to align EMG-signals along torque magnitude (that is not necessary in isotonic tasks) proved to be feasible. The current short task in a single torque direction also had the advantage of avoiding fatigue and signal modifications due to steering. The present measurement set-up allowed for standardization, however, further analysis of the dependence on orientation of the upper limb is required when test results are to be translated to functional task performance (i.e. reaching, grabbing). Visual feedback

might have supported any participants with diminished sensory functions, e.g. of the hand (visual feedback to compensate for lack of sensory feedback) or hemi-inattention or neglect (vertical bar), however, this was not tested. ICC might be different in a more homogenous population selected on stroke location or level of motor impairment. These data were not available in our population.

Figure 7 | Scatter plot of Activation Ratio versus Maximal Isometric Torque in post-stroke patients.

Dotted line: lowest values of AR and MIT in healthy volunteers (see minimum for healthy volunteers in Table 2). Patients with insufficient muscle activation are not represented in this figure. This figure illustrates the wide range of torque outputs for a given level of selective muscle activation. Lower torque in the agonist might indicate co-contraction of the antagonistic muscle, but only if it coincides with low selective muscle activation of that antagonist (lower left quadrant of upper right and lower left panel). Reversely, low torque combined with high selective muscle activation points more towards paresis of the agonist (lower right quadrant of upper left and lower right panel).



Bearing in mind that morphological changes (i.e. shortening of structures) may occur as early as four weeks post-stroke [45], the described neutral angle was chosen to minimize any influence of secondary biomechanical changes and to provide optimal conditions for the neural system in testing agonist and antagonist activity. Furthermore, an isometric task minimizes strain resulting from joint movement, allowing for isolated measurement of muscle activation.

AR were specifically developed in view of potential problems with normalization when comparing different muscles [28]. Issues with variance in quality, quantity and control of muscles as outlined in the introduction, are avoided by relating the activity of the same muscles in different tasks. Other drawbacks of EMG based methods that researchers should take into account [8,46] are e.g. crosstalk and elevated background EMG activity. Crosstalk might be increased by using two electrodes per muscle group, but only if the EMG-signal is relatively silent [47]. A small amount of crosstalk from other flexors besides FCR during flexion or other extensors besides ECR during extension would have negligible consequences for the results. Elevated background EMG activity, i.e. muscle EMG-activity at rest in post-stroke patients [48] could theoretically lead to unjustified exclusion of patients with insufficient voluntary muscle activation and falsely low AR by mechanism of a lower ratio of activity (in-phase) to rest (out-phase) EMG. However, as elevated background EMG in post-stroke patients was quantified at around 3% of maximal EMG during a maximal voluntary contraction task [48], we assume that this had no influence on our definition of insufficient voluntary muscle activation and was of no clinical relevance for AR.

Future work

Objective and reproducible data such as AR support a more substantiated analysis of clinical phenotypes. In this light the next step is to gather longitudinal information on selective muscle activation to follow functional recovery of stroke patients over time [49] and to monitor results of treatment. Combining AR data and kinematic data could give a valuable insight into the connection between loss of selective muscle activation around a single joint (e.g. co-contraction or co-activation) and multi joint synergistic movements. Moreover, to help prevent under- or overtreatment and to ensure that not only the affected muscle but also the aims of the patient on activity and participation level are treated, knowledge on the relation between selective muscle activation and functional outcome is essential in the future design of treatment paradigms for post-stroke patients.

CONCLUSION

Activation Ratios allow for reliable muscle specific quantification of selective muscle activation in participants with sufficient voluntary muscle activity. We observed significantly lower Activation Ratios in the group of post-stroke patients compared to the group of healthy participants, which indicate loss of selective muscle activation in post-stroke patients. Information on loss of selective muscle activation will allow clinicians to improve clinical decision making, follow patients over time and monitor results of treatment.

Acknowledgements

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Declaration of Interest

This study is part of EXPLICIT-stroke, which is funded by ZonMw (The Netherlands Organisation for Health Research and Development) grant 890000001, Vereniging van Revalidatieartsen, Revalidatiefonds and Revalidatie Nederland. The study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript and in the decision to submit the manuscript for publication.

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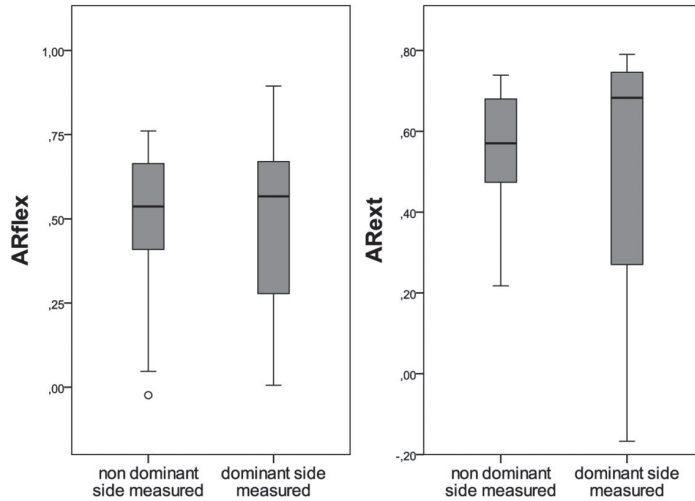
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Supplementary Figure S1 | Limb dominance.

Boxplot for both AR_{flex} and AR_{ext} of post-stroke patients, separately depicting dominant and non-dominant side. Before this study, we had no data on the effect of dominance of the affected limb on selectivity of muscle activation. Our method allowed to test this: In our patient group, approximately half of the patients were affected (and measured) at the dominant side (Main text Table 1). A t-test showed that there was no significant difference in muscle selectivity (AR) between post-stroke patients measured at the dominant side, compared to the non-dominant side.



Supplementary Figure S2 | Influence of variance on ICC and SEM.

Group differences in reliability and heteroscedasticity were graphically represented in Bland Altman plots (Figure 6). The ICC for the stroke group may well be underestimated. Separate calculation of ICC and SEM per group (healthy vs stroke) would increase the ICC for post-stroke patients, as ICC are the between-measurements variance expressed as a proportion of the total variance. Variance in the stroke group is large (as can be seen in Figure 4), leading to higher ICC's. Variance in the healthy group is smaller, leading to lower ICC. SEM's are almost unchanged when separately calculated per group (i.e. lower ICC but also lower standard deviation).

ICC and SEM per group are represented in this table. As can be inferred from the 95%CI of the ICC's there is no significant difference between the ICC of the 2 groups per parameter.

	Healthy volunteers ICC (95%CI)	Healthy volunteers SEM	Post-stroke patients ICC (95%CI)	Post stroke patients SEM
AR_{flex}	0.67 (0.23 – 0.88)	0.12	0.80 (0.58 – 0.92)	0.11
AR_{ext}	0.58 (0.06 – 0.84)	0.05	0.74 (0.48 – 0.88)	0.13

C h a p t e r

6

Early increase in active range of motion and a steady rest angle at the wrist are associated with better arm-hand function after stroke: a longitudinal study

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ABSTRACT

In stroke patients, pathophysiological mechanisms of functional recovery are largely unknown. The aims of this study were to quantify neural and non-neural contributors to endpoint wrist joint behavior under both passive and active task conditions, and to relate these neuromechanical parameters to the recovery of arm-hand function.

Methods

Wrist neuromechanical parameters (measured with haptic robotics and surface electromyography) and Action Research Arm Test (ARAT) were assessed prospectively in 36 stroke patients on 8 occasions during the first 6 months after stroke. At 6 months, maximum voluntary contraction, passive stiffness at rest angle and reflex modulation were related to ARAT by linear regression. Predictors of positive functional outcome (ARAT \geq 10) were determined by a repeated measures model.

Results

At 6 months after stroke, a lower maximum voluntary contraction and impaired reflex modulation were significantly related to poor functional outcome ($p < 0.001$ and $p = 0.047$). A steady rest angle and increasing active range of motion contributed most to prediction of positive functional outcome.

Conclusion

Longitudinally measured neuromechanical parameters relate to arm-hand function during the first 6 months after stroke and, as a reflection of pathophysiological dynamics of recovery, may assist clinicians in triage and assignment of optimally individualized therapy.

INTRODUCTION

Impairment in function of the upper extremity is common after stroke [1,2] and has a profound impact on activities and participation in daily life [1,3-5]. Despite an increased attention for measuring outcome on multiple levels of the International Classification of Functioning, Disability and Health (ICF), the relationship between pathophysiological mechanisms of recovery and functional outcome as measured with clinical scales, is still largely unknown [6-8]. Furthermore, the relationship between pathophysiological mechanisms of recovery and time after stroke is still uncharted territory, as longitudinal data in the acute phase after stroke are still scarce [9,10].

In translational research, the connection between pathophysiological changes and functional outcome is typically addressed by relating neural imaging techniques (e.g. functional MRI, transcranial magnetic stimulation) and movement analysis (e.g. kinematics) to clinical scales [11] on the ICF-levels of impairment (e.g. Fugl Meyer Assessment), activity (e.g. Action Research Arm Test (ARAT), Motor Activity Log) and participation (e.g. Health Related Quality of Life). Neuromechanics [12] may contribute to this framework of assessments by providing a quantitative high resolution assessment of neural and non-neural contributors to endpoint joint behavior under passive and active conditions and as a reaction to external mechanical perturbations [13-15] by use of biomechanical and neurophysiological techniques [6,16]. Measuring neuromechanical parameters around a single joint excludes interference of compensatory movements as seen in multi-joint tasks. Previous studies in stroke indicate a large contribution of paresis, stiffness and a decreased ability to modulate reflexes in a changing environment to poor functional outcome [6,14,16-20]. To further explore this, a longitudinal study was conducted. We hypothesize that a poor functional outcome (less than 10 points on ARAT at 6 months after stroke [11]) is associated with a more pronounced paresis, a higher degree of stiffness and absence of reflex modulation at 6 months post stroke. Furthermore, using our earlier described comprehensive neuromechanical assessment protocol [21], we systematically describe the course of passive, active and reflexive parameters at the wrist joint during the first 6 months after stroke and, with this information, identify neuromechanical predictors of functional outcome.

METHODS

Participants

This study was conducted as an observational study within the EXplaining PLasticITY after stroke trial (EXPLICIT-stroke, Dutch Trial register NTR1424, part B3). EXPLICIT-stroke is a multicenter research program, consisting of a randomized clinical trial on the effects of early rehabilitation intervention on arm-hand function after stroke and a longitudinal survey into the dynamics of post-stroke recovery [11]. Participants were assessed for eligibility within one week after stroke according to the following criteria: first-ever ischemic stroke in area of middle cerebral artery; impairment of the arm (National Institutes of Health Stroke Severity (NIHSS) item 5a or 5b score 1 – 4); age 18 to 80 years; able to travel to Leiden University Medical Center (LUMC) or University Medical Center Utrecht (UMCU).

Participants were excluded in case of previous upper extremity orthopedic limitations on affected side; insufficient communication (Utrecht Communication Observation item 19: score less than 4 points) [22]; and/or severe cognitive impairment (Mini Mental State Examination: score 22 points or less) [23]. Participants were then stratified into 2 prognostic groups according to National Institutes of Health Stroke Severity (NIHSS) item 5a or 5b; group F with a favorable prognosis (score 1 – 2) and group U with an unfavorable prognosis (score 3 – 4). The study was approved by the Medical Ethical Committees of the LUMC and UMCU. Written informed consent was given by all participants in the first week after stroke. All participants started with inpatient rehabilitation and were discharged home as soon as this was safe. This was followed by ambulant/outpatient rehabilitation according to usual care. In addition to usual care, the intervention therapies of the main trial were applied according to stratification (favorable prognosis: modified Constrained Induced Movement Therapy; unfavorable prognosis: electromyography-triggered Neuromuscular Stimulation) and randomization. Participants were compensated for travel expenses.

Measurement set up and protocol

Measurements consisted of a neuromechanical assessment protocol and the ARAT, which were administered on eight occasions at fixed time points within the first 6 months after stroke: weekly in the first 5 weeks after stroke and subsequently at 8, 12 and 26 weeks after stroke. The neuromechanical assessment protocol was performed at the department of Rehabilitation at the LUMC and UMCU. A haptic robot (Wristalyzer^a) delivered precise torque or position perturbations to a handle^b via a vertically positioned servomotor^a. Muscle activity of m. flexor carpi radialis and m. extensor carpi radialis brevis and longus was recorded by a surface EMG-system^c. Participants were seated upright in front of a screen, with their hand fixed to the handle. The handle had an ellipsoidal shape to prevent finger flexion (Figure 1). The arm and elbow were stabilized in an arm rest. The motor axis was aligned with the rotation axis of the wrist joint, therefore rotation of the motor was directly

coupled to flexion/extension movement of the wrist. Participants were provided with visual feedback on torque, angle or EMG-level, depending on the task instruction.

Each test within the measurement protocol was aimed at quantification of either non-neural contributors (passive parameters) or neural contributors (active and reflexive parameters) to movement disorder after stroke. Passive parameters were measured at low velocity to minimize muscle activation and stretch reflexes, and included a task instruction to “do nothing”. Measurement of active parameters included task instructions to “move/push/hold”, i.e. exert a voluntary torque or complete a prescribed movement trajectory. Reflexive parameters were measured at higher wrist rotation velocities, to elicit reflexes, with either passive or active task instructions [24]. Measurements took 45 minutes.

Observers of neuromechanical parameters (HK and AK) and ARAT (RN) were blinded for each other’s outcome.

Data analysis

Data were retrieved and processed with customized software written in Matlab 2007b^d. The following neuromechanical parameters were extracted [24]:

Passive parameters:

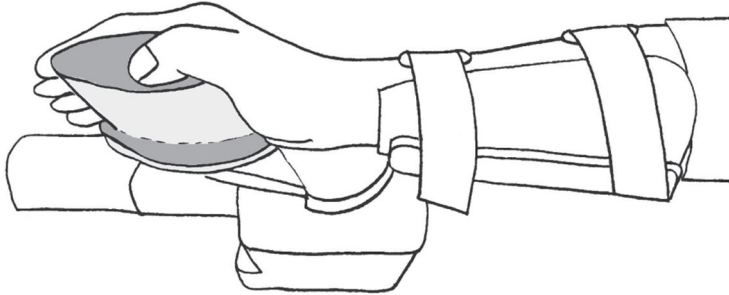
- *Passive Range of Motion* (P_{ROM}): range between maximal flexion and extension wrist angles during a slow sinusoidal passive movement with a maximal torque of 2 Nm.
- *Rest Angle* (P_{RA}): angle within passive range of motion where the angle-torque curve crosses 0 Nm, during a slow, position controlled, passive movement.
- *Stiffness in Rest* (P_{λ}): resistance to passive movement during a slow, position controlled, passive movement through passive range of motion. The average negative tangent of the angle-torque curve over 0.2 rad around P_{RA} was calculated.

Active parameters:

- *Active Range of Motion* (A_{ROM}): range between maximal flexion and extension wrist angles obtained during a voluntary movement through range of motion without external resistance.
- *Maximal Voluntary Contraction* (A_{MVC}): maximal isometric torque generated by participants in direction of flexion ($A_{MVC\ flex}$) and extension ($A_{MVC\ ext}$). The handle of the haptic robot was fixed at the Rest Angle (P_{RA}).
- *Control over Joint Torque* (A_{CJT}): ability of participant to achieve steadily increasing target torque in direction of flexion ($A_{CJT\ flex}$) and extension ($A_{CJT\ ext}$). The handle of the haptic robot was fixed at P_{RA} .

Figure 1 | Illustration of Wristalyzer handle and arm-rest.

For a better view of the hand position, the hand straps are not represented in this illustration.



Reflexive parameters:

- *Reflexive Loop Time* (R_{lt}): time from start of ramp and hold perturbation to short latency reflex onset. Participants were asked either to relax (“do nothing”) ($R_{lt\ pas}$) or to deliver 10% of maximum EMG-activity as measured during A_{MVC} ($R_{lt\ act}$). Perturbations consisted of position controlled angular displacements over 0.14 rad at a velocity of 2 rad/s.
- *Reflex Magnitude* (R_{AUC}): area under EMG-time curve in window of 0.02 – 0.05s after perturbation. Participants were asked either to relax (“do nothing”) ($R_{AUC\ pas}$) or to deliver 10% of maximum EMG-activity as measured during A_{MVC} ($R_{AUC\ act}$). Perturbations consisted of position controlled angular displacements over 0.14 rad at a velocity of 2 rad/s. EMG was normalized, rectified and low pass filtered (80Hz Butterworth).
- *Reflexive Contribution to Joint Resistance* (R_{kv}): participants were asked to resist fast multisine force perturbations (“hold position”). Velocity dependent reflex gain was computed using system identification methods [25].
- *Reflex Modulation due to Environmental Changes* ($R_{m\ env}$): participants were asked to resist fast multisine force perturbations (“hold position”) in a damped environment (i.e. a viscous environment was simulated by the haptic robot). Velocity dependent reflex gain in this altered environment was computed [17].

Parameter changes over time were separately analyzed for three groups of participants, defined on both initial prognosis: group F with a favorable prognosis (NIHSS item 5 score 1-2) and group U with an unfavorable prognosis (NIHSS item 5 score 3 – 4); and functional outcome post stroke: ARAT \geq or $<$ 10 points at 26 weeks [11]. This led to the following groups: favorable prognosis-positive functional outcome (F_{positive}); unfavorable prognosis-positive functional outcome (U_{positive}) and unfavorable prognosis-poor functional outcome (U_{poor}).

Statistical analysis

Parameters were inspected for normality of distribution. The relation between stiffness (Stiffness in Rest = P_k) at 26 weeks and positive functional outcome (i.e. ARAT ≥ 10 at 26 weeks) was described by linear regression. The same applied for paresis (Maximal Voluntary Contraction = $A_{MVC\ flex}$) and reflex modulation (Reflex Modulation due to Environmental Changes = R_{m_env}).

Changes over time and between groups were visually inspected and screened per parameter by a generalized estimating equation with the outcome group (F-_{positive}, U-_{positive}, U-_{poor}) as a between participants factor and time as a within participants factor, and the interaction of time with outcome included in the model. Post-hoc testing per week was then performed by ANOVA and Tukey (or Dennett when parameters were not equally distributed per group as tested with Levene's test).

To determine predictors of a positive functional outcome on the ARAT, a multivariate repeated measures model was fitted by means of a generalized estimating equation. Within this model, the stratified group (F- or U-group) was modeled as a factor, and time (i.e. # weeks after stroke) was modeled as a within participants factor. Descriptive parameters (age, affected hand and gender) and outcome parameters (P_{ROM} , P_k , P_{RA} , A_{ROM} , A_{MVC} , A_{CJT} , R_{It} , R_{AUC} , R_{kv} , R_{m_env}) were added stepwise. Statistics were performed in SPSS Statistics 20^e.

RESULTS

Out of an eligible cohort of 68 patients, 36 participants were included between April 1th 2009 and March 1th 2012: 15 participants were stratified into the F-group and 21 participants were stratified into the U-group. A description of the study population is presented in Table 1. Due to medical factors associated with stroke (e.g. fatigue, co-morbidity) and logistic difficulties inherent to a multicenter trial (e.g. transport of participants between facilities), 41 out of 288 scheduled visits were cancelled. Sixty visits were missed because of late enrollment; participants were enrolled in EXPLICIT-stroke, but could not participate in part B3 yet, due to location or co-morbidity. An additional 20 visits were cancelled on account of loss to follow up. With an average of 4.7 visits per participant (SD 1.9) in the F-group and 4.6 (SD 1.9) in the U-group, participation in both groups was comparable ($p = 0.941$, 95% confidence interval -1.2 to 1.3 visits) (Figure 2 Flow Diagram).

All 15 participants in the group with an initial favorable prognosis (F-group) achieved a positive functional outcome of an ARAT score of 10 points or higher at 26 weeks (F-_{positive}). In the group with an initial unfavorable prognosis (U-group), 12 participants (57%) achieved an ARAT of 10 or higher (U-_{positive}) and 9 participants did not (43%) (U-_{poor}).

Table 1 | Descriptive data of the study population.

Overall descriptive data and separate descriptives per group. Groups based on prognosis (NIHSS score item 5) and functional outcome (Action Research Arm Test): F_{positive} : favorable prognosis-positive functional outcome; U_{positive} : unfavorable prognosis-positive functional outcome, and U_{poor} : unfavorable prognosis-poor functional outcome. All variables presented as n (%), unless otherwise indicated. IQR: interquartile range.

	Overall	F_{positive}	U_{positive}	U_{poor}
Participants	36	15	12	9
Age, years (mean, (SD))	59.8 (10.6)	60.7 (8.2)	59.6 (14.6)	58.6 (8.6)
Gender (male)	27 (75)	12 (80)	8 (67)	7 (78)
Hand preference: right hand	30 (83)	13 (87)	11 (91)	7 (78)
Affected hand: right hand	12 (33)	3 (20)	5 (42)	4 (44)
Affected hand = preferred hand	10 (28)	4 (27)	4 (33)	2 (22)
ARAT week 1 (median [IQR])		9 [6 – 31]	0 [0 – 0]	0 [0 – 0]
ARAT week 26 (median [IQR])		40 [38 – 57]	39 [31 – 53]	0 [0 – 3]

Functional outcome related to stiffness, paresis and reflex modulation

At week 26, P_k was not significantly related to functional outcome ($p = 0.940$; Standard Error of the Estimate (SE) 0.055) (Figure 3 top panel). $A_{\text{MVC flex}}$ at 26 weeks did have a significant relation with functional outcome (Figure 3 middle panel): participants that did not reach 10 points on the ARAT at 26 weeks produced less torque compared to participants with an ARAT score ≥ 10 points at 26 weeks ($p < 0.001$; SE 0.391). $R_{\text{m env}}$ at 26 weeks had a less outspoken, but still significant relation with functional outcome ($p = 0.047$; SE 0.005). In participants that did not reach 10 points on the ARAT, the ability for reflex modulation was diminished (Figure 3 lower panel).

Longitudinal changes

In the first 6 months after stroke, P_{ROM} , P_{RA} , A_{ROM} , $A_{\text{MVC flex}}$, $A_{\text{MVC ext}}$, $A_{\text{CJT flex}}$, $A_{\text{CJT ext}}$ and $R_{\text{AU Cact flex}}$ had a significant change in outcome over time and/or between groups as tested with the generalized estimating equation and post-hoc test with ANOVA and Tukey or Dennett. The time course of these parameters is illustrated in Figure 4 and Table 2.

In the F_{positive} group, passive parameters did not change over time. Active parameters recuperated most before week 4. On average, maximal voluntary contraction (A_{MVC}) and control over joint torque (A_{CJT}) at week 26 did not recover to values measured in healthy volunteers [21]. Reflexive parameters demonstrated small reflex magnitudes and an ability to modulate reflexes in a changing environment.

The U_{positive} group showed no change in passive parameters except for a reduction in passive range of motion (P_{ROM}). Active parameters recuperated, but at a later moment in time than observed in the F_{positive} group. The ability to modulate reflexes in a changing environment ($R_{\text{m env}}$) did not change over time.

The U_{-poor} group had a marked shift in rest angle (P_{RA}) towards flexion as early as the first week after stroke (this could only be quantified from week 8 onwards because of small groups/missing values), little or no improvement in active parameters, higher reflex magnitudes (R_{AUC}) and a diminished ability to modulate reflexes in a changing environment (R_{m_env}). A marked increase in A_{ROM} in the F_{-positive} and U_{-positive} group was observed before week 4, while an increase in A_{ROM} in the U_{-poor} group was not observed until week 8. The increase in Maximal Voluntary Contraction ($A_{MVC\ flex}$) in the U-group started at 5 weeks. Improvement in Control over Joint Torque ($A_{CJT\ flex}$) in the U-group started at 5 weeks or later.

Figure 2 | Flow Diagram.

Progress of participants through our observational study. Flow diagram based on CONSORT statement [26]. F-group = favorable prognosis, U-group = unfavorable prognosis.

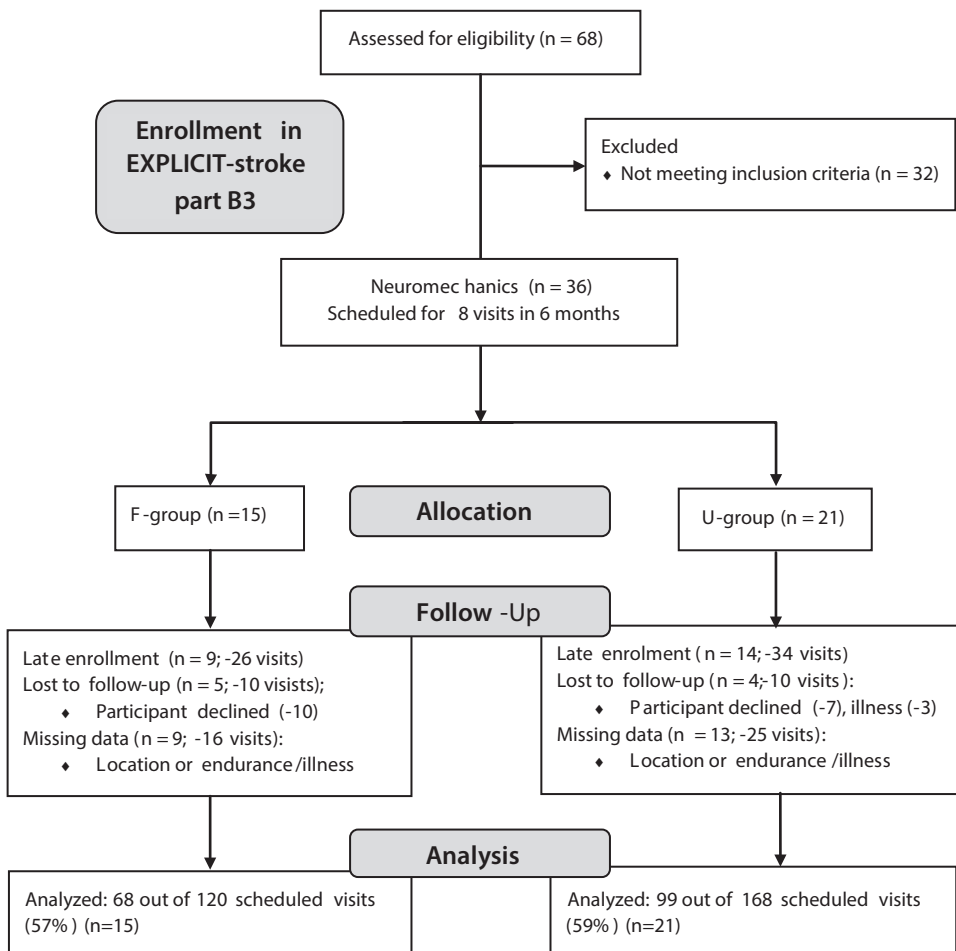


Figure 3 | Stiffness in Rest, paresis and reflex modulation related to ARAT at 26 weeks post stroke: scatter plot.

Top panel: P_k = Stiffness in Rest; Middle panel: A_{MVC} = Maximal Voluntary Contraction; Lower panel: $R_{m,env}$ = Reflex Modulation due to Environmental Changes. Black dots: $F_{positive}$ group, Grey squares: $U_{positive}$ group, White triangles: U_{poor} group. ARAT = Action Research Arm Test.

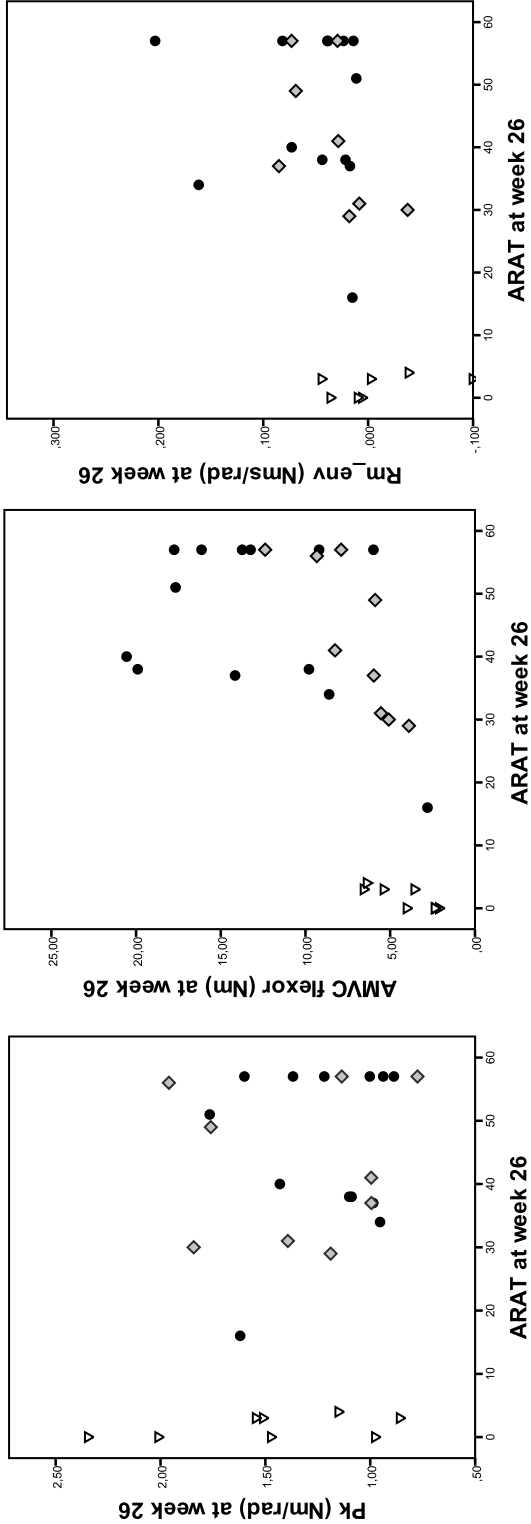


Figure 4 | Passive, active and reflexive parameters from week 1 to week 26 after stroke.

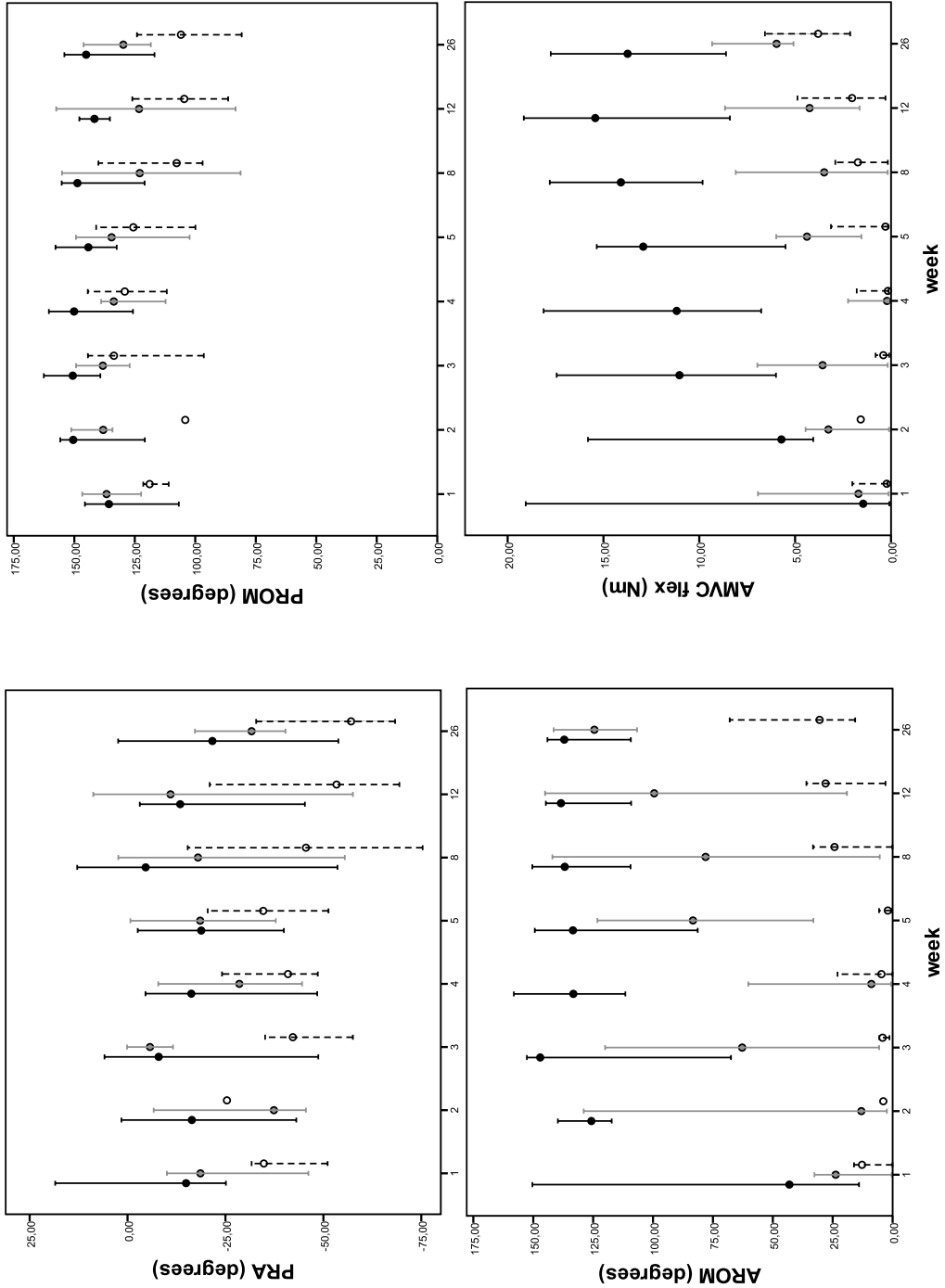


Table 2 | Analysis of changes over time and between groups per parameter.

Group and time effect and the interaction between group and time as tested with a generalized estimating equation. Group was modelled as a between participants factor and time (i.e. # weeks after stroke) as a within participants factor; p-values of the Wald Chi Square are represented. Post-hoc analysis by ANOVA and Tukey (or Dennett when parameters were not equally distributed per group as tested with Levene's test). P_{RA} = Rest Angle, P_{ROM} = Passive Range of Motion, P_k = Stiffness in Rest, A_{ROM} = Active Range of Motion, A_{MVC} = Maximal Voluntary Contraction, A_{CTJ} = Control over Joint Torque, R_{lt} = Reflexive Loop Time, R_{AUC} = Reflex Magnitude, R_{kv} = Reflexive Contribution to Joint Resistance, R_{m_env} = Reflex Modulation due to Environmental Changes. F = F-positive group, U+ = U-positive group, U- = U-poor group.(continues on next page)

Parameter	Generalized estimating equation			Post hoc analysis				
	Group	Time	Interaction	Week 4	Week 5	Week 8	Week 12	Week26
P_{RA}	< 0.001	0,217	< 0.001	n.s.	n.s.	U-/F 0.041	U-/F 0.043	U-/F 0.007 U-/U+ 0.037
P_{ROM}	< 0.001	< 0.001	< 0.001	n.s.	U-/F 0.028	U-/F 0.003	U-/F 0.001 U+/F 0.044	U-/F 0.001 U-/U+ 0.012
P_k	0.525	0.487	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.
A_{ROM}	< 0.001	< 0.001	< 0.001	U-/F <0.001 U+/F <0.001	U-/F <0.001 U-/U+ <0.001 U+/F 0.020	U-/F <0.001 U-/U+ <0.001 U+/F <0.001	U-/F <0.001 U-/U+ <0.001 U+/F 0.010	U-/F <0.001 U-/U+ <0.001
$A_{MVC\ flex}$	< 0.001	< 0.001	0.015	U-/F 0.005 U+/F 0.005	U-/F <0.001 U+/F 0.004	U-/F <0.001 U+/F <0.001	U-/F <0.001 U+/F <0.001	U-/F <0.001 U-/U+ 0.039 U+/F 0.010
$A_{MVC\ ext}$	< 0.001	< 0.001	< 0.001	U-/F 0.005 U+/F 0.005	U-/F <0.001 U-/U+ 0.001 U+/F <0.001	U-/F <0.001 U-/U+ 0.007 U+/F <0.001	U-/F <0.001 U-/U+ 0.035 U+/F 0.001	U-/F <0.001 U-/U+ 0.001 U+/F 0.021
$A_{CTJ\ flex}$	< 0.001	< 0.001	0.001	U-/F 0.006 U+/F 0.006	U-/F <0.001 U+/F 0.011	U-/F <0.001 U+/F <0.001	U-/F <0.001 U+/F 0.001	U-/F <0.001 U+/F 0.026
$A_{CTJ\ ext}$	< 0.001	< 0.001	< 0.001	U-/F 0.003 U+/F 0.003	U-/F <0.001 U+/F <0.001	U-/F <0.001 U+/F 0.001	U-/F 0.001 U+/F 0.050	U-/F <0.001
$R_{lt\ flex\ pas}$	0.765	< 0.001	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{lt\ ext\ pas}$	0.141	< 0.001	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{lt\ flex\ act}$	0.660	0.001	0.002	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{lt\ ext\ act}$	0.577	< 0.001	0.097	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{AUC\ flex\ act}$	< 0.001	< 0.001	< 0.001	n.s.	U-/F <0.001 U+/F <0.001	n.s.	n.s.	U-/F 0.012
$R_{AUC\ ext\ act}$	0.501	< 0.001	0.105	n.s.	n.s.	n.s.	n.s.	n.s.
R_{kv}	0.199	0.076	0.009	n.s.	n.s.	n.s.	n.s.	n.s.
R_{m_env}	0.828	< 0.001	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.

A catch or clonus during measurements of reflexive parameters with the haptic robot was observed in 1 out of 12 participants in the U-positive group (8%) and 4 out of 9 participants in the U-poor group (44%), the earliest at week 5.

Prediction of positive functional outcome

In the repeated measures model, descriptive parameters (age, affected hand and gender) were not influential. Co-linearity was observed between the active parameters A_{ROM} , A_{MVC} and A_{CJT} . Of these parameters, A_{ROM} was included in the model as most influential. R_{AUC} was identified as a confounder for P_k , and therefore kept in the model, although not reaching significance. Therefore, the definitive model included passive parameters P_k and P_{RA} ; active parameter A_{ROM} ; and reflexive parameters R_{m_env} and R_{AUC} . Quasi Likelihood under Independence Model Criterion (QIC) of the definitive model was 50 (in a smaller-is-better format). Adding more parameters worsened the QIC, while not altering beta-coefficients and p-values of parameters mentioned above.

From this model it can be concluded that a steady P_{RA} and an increasing A_{ROM} were the best predictors of reaching a score of 10 points or higher at the ARAT at 26 weeks after stroke (p 0.039 and $p < 0.001$ respectively), but only when outcomes of the reflexive parameters R_{m_env} and R_{AUC} were included in the model. See Table 3 for model parameters and confidence intervals.

Table 3 | Repeated measures model.

To identify predictors of a positive functional outcome (ARAT ≥ 10 (per week)), a multivariate repeated measures model was fitted by means of a generalized estimating equation. Within this model, the stratified group (F- or U-group) was modeled as a between participants factor, and time (i.e. # weeks after stroke) was modeled as a within participants factor. Parameters were added stepwise.

F-group = favorable prognosis, U-group = unfavorable prognosis. P_{RA} = Rest Angle, A_{ROM} = Active Range of Motion, R_{AUC} = Reflex Magnitude, R_{m_env} = Reflex Modulation due to Environmental Changes. * significant $p < 0.05$ †F is set to zero because this is the reference category, i.e. functional outcome of U-group is compared to F-group. Wrist flexion angles were defined as negative angles.

Parameter	Beta	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	p-value
(Intercept)	0.293	1.3829	-2.418	3.003	0.045	1	0.832
F- group	0 [†]						
U- group	-3.378	1.8903	-7.083	0.327	3.192	1	0.074
P_{RA}	0.040	0.0194	0.002	0.078	4.257	1	0.039*
A_{ROM}	0.046	0.0131	0.021	0.072	12.510	1	0.000*
R_{AUC}	-0.657	4.2594	-9.006	7.691	0.024	1	0.877
R_{m_env}	1.369	3.3986	-5.292	8.030	0.162	1	0.687
(Scale)	1						

DISCUSSION

As hypothesized, paresis and diminished ability to modulate reflexes (quantified by reduced A_{MVC} and lower R_{m_env}) were significantly related to poor functional outcome (ARAT less than 10 points at 26 weeks after stroke). Stiffness (P_k at rest angle), was not significantly related to poor outcome.

Repeated measurements with a neuromechanical assessment protocol in this cohort of acute stroke patients showed changes in two out of three passive parameters, changes in active parameters even before week 4, and small to no changes in reflexive parameters.

A steady rest angle (P_{RA}) and an increasing active range of motion (A_{ROM}) were the best predictors for functional outcome at 26 weeks after stroke (ARAT \geq 10 points).

Clinical implications

In this study, changes in tissue properties in the U-group with a poor functional outcome (U_{-poor} group) were represented by a shift in rest angle (P_{RA}) and passive range of motion (P_{ROM}), and not by a change in stiffness in rest (P_k). Apparently, when objectively measuring these separate properties under standardized measurement conditions, shortening of elastic structures is represented by a shift in operating point (rest angle) and a limitation in the movement trajectory (passive range of motion). This is supplementary to previous findings [27,28].

Functional recovery in the group with an initial unfavorable prognosis is first heralded by an increase in active range of motion. It should be noted that recovery in time can differ between patients and it may take at least 5 – 8 weeks for an increase in active range of motion to become apparent in patients with an initial unfavorable prognosis. This is in accordance with earlier published research [9,10]. A marked shift in rest angle towards flexion is apparent from the start in the group with an initial unfavorable prognosis. These combined outcomes lead to the recommendation of regular (e.g. weekly) measurements of A_{ROM} , P_{ROM} and rest angle in the first 8 weeks after stroke, ideally in a standardized environment.

Strengths and limitations

Studies on longitudinal assessment in the acute phase after stroke are scarce. We comprehensively and prospectively assessed neuromechanics by means of passive, active and reflexive parameters at fixed time points after stroke with a validated neuromechanical assessment protocol [21] and related them to functional outcome in a stratified cohort of stroke patients in the early phase after stroke. Despite all efforts to complete all visits, missing data were unavoidable and occurred predominantly in the early phase after stroke. Due to the stratification based on early prediction of outcome the effects of selection bias were limited.

Division in passive and active parameters was based on task instructions. This facilitates clinical assessment and interpretation of parameters, yet does not absolutely discriminate between tissue properties and motor unit recruitment [28,29], as involuntary motor unit recruitment may also be present at rest when measuring passive parameters (e.g. elevated baseline activation). Also, reflex magnitude measurement was calculated relative to the baseline EMG of the participant. Some underestimation of stretch reflex activation might therefore be expected [29]. Possible variance in EMG caused by daily fluctuations in reflex thresholds may introduce additional variance in reflexive parameters. Sophisticated system identification techniques are required to further discriminate neural and non-neural contributors to movement disorder after stroke, e.g. to discern baseline activity from reflexive activity [29,30].

CONCLUSION

In this observational study, longitudinally measured neuromechanical parameters were combined with data on arm-hand function after stroke. Paresis (i.e. low maximal voluntary contraction) and a diminished ability to modulate reflexes are associated with poor functional outcome at 6 months after stroke. Changes in tissue properties were represented by a shift in wrist rest angle towards flexion and a decline in passive range of motion, rather than by passive stiffness measured around the rest angle. Passive, active and reflexive neuromechanical parameters significantly changed over time and showed group effects based on favorable/unfavorable prognosis versus positive/poor functional outcome 6 months after stroke. An increase in active range of motion and a steady rest angle contributed most to prediction of functional outcome at 6 months after stroke. These neuromechanical parameters show potential as biomarkers for prediction of arm-hand function after stroke and may contribute to the translation of neural repair at the level of body function and structures to recovery on the level of activities and participation.

Abbreviations

ARAT: Action Research Arm Test;

EMG: Electromyography;

EXPLICIT-stroke: the EXplaining PLasticITY after stroke trial;

ICF: International Classification of Functioning, Disability and Health (WHO, Geneva 2001);

LUMC: Leiden University Medical Center;

QIC: Quasi Likelihood under Independence Model Criterion;

UMCU: University Medical Center Utrecht;

SE: Standard Error.

Suppliers

- a. Haptic wrist manipulator “Wristalyzer” containing a Parker SMH100 series servo motor: Moog FCS, PO Box 187, 2150 AD Nieuw-Vennep, the Netherlands.
- b. Handle production: Meester techniek, Dorus Rijkersweg 23, 2315 WC Leiden, the Netherlands
- c. Bagnoli 8 channel surface electromyography acquisition equipment and surface EMG sensors: Delsys Inc. P.O. Box 15734 Boston, MA, 02215, USA.
- d. Mathworks, 3 Apple Hill Drive, Natick, MA 01760-2098, USA.
- e. SPSS Statistics 20: IBM, 1 New Orchard Rd. Armonk, NY, 10504-1783, USA.

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Conflicts of interest

None

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C h a p t e r

7

Discussion

The aim of this thesis was to explore the neuromechanics of recovery of arm-hand function after stroke by assessing neural and non-neural contributors to movement disorders in the acute and chronic phase after stroke. Key questions were: How and to what extent does endpoint wrist joint behavior, as measured with neuromechanical parameters, change in the first 6 months after stroke? And how do those changes relate to functional outcome? For this purpose, an assessment protocol with valid and sensitive parameters had to be developed, based on clear pathophysiological concepts. With the assessment protocol, a prospective study with repeated measurements of neuromechanical parameters in the first 6 months after stroke was conducted.

Developing a neuromechanical assessment protocol

A literature review revealed a number of initiatives to quantify and objectify movement disorders after stroke. In 19 out of the 37 articles describing the use of biomechanical and/or EMG outcome measures to analyze post-stroke movement disorder, the authors strived to separate neural contributors (motor control and stretch reflexes) from non-neural contributors (tissue properties). The most frequently used pathophysiological constructs were spasticity, muscle tone and muscle overactivity. However, definitions of these constructs were not uniform and the distinction between neural and non-neural contributors to movement disorders after stroke was not commonplace yet. Only 6 of the articles measured biomechanical and electromyographical outcome measures simultaneously, while applying the active and passive tasks and multiple movement velocities necessary to separate neural and non-neural contributors to movement disorders after stroke (chapter 2).

The overview of pathophysiological constructs and required measurement conditions generated a methodology to assess endpoint joint behavior around a single axis. This methodology was translated into a comprehensive assessment protocol to quantify endpoint wrist joint behavior i.e. motor control, stretch reflex properties and tissue properties during flexion-extension movement under different task instructions and with different external perturbations, resulting in passive, active and reflexive neuromechanical parameters (chapter 3).

The neuromechanical parameters were responsive to clinical status, i.e. results demonstrated differences between a cohort of healthy participants and a cohort of chronic stroke patients. Test-retest reliability was assessed: passive and active parameters could be assessed with excellent reliability. The passive parameter rest angle and all but one of the reflexive parameters had fair to good reliability (chapter 4).

Evaluation of selective muscle activation by means of Activation Ratios (AR) of flexor carpi radialis (FCR) and extensor carpi radialis communis (ECR) was supported by high measurement reliability in participants with any voluntary muscle activation. AR were significantly lower in chronic stroke patients compared to healthy participants, indicating loss of selective muscle activation in the chronic stroke patients. Based on the ability for

voluntary muscle activation and selective muscle activation, three clinical phenotypes were confirmed, i.e. patients with flaccid paresis and therefore insufficient voluntary muscle activation to determine selective muscle activation; patients with some loss of selective muscle activation; and patients with selective muscle activation comparable to healthy volunteers, despite not reaching maximum voluntary torque comparable to healthy volunteers (chapter 5).

Neuromechanical parameters in the first 6 months after stroke

In the longitudinal study, neuromechanical parameters were repeatedly assessed with the comprehensive assessment protocol in the first 6 months after stroke in the two groups stratified within the EXPLICIT-stroke trial according to the finger extension algorithm [1]. In the group of patients with an initial favorable prognosis for recovery of arm-hand function, passive parameters did not change over time, while active parameters recuperated most before week 5. However, on average, maximal voluntary contraction and control over joint torque at week 26 did not recover to values measured in healthy volunteers. Reflexive parameters demonstrated small reflex magnitudes and an ability to modulate reflexes in a changing environment.

In patients with an initial unfavorable prognosis for recovery of arm-hand function, two subgroups could be distinguished: those with a positive functional outcome (≥ 10 points on the Action Research Arm Test (ARAT) at 6 months) and those with a poor functional outcome (ARAT < 10 points) [2]. In the group with an initial unfavorable prognosis and a positive functional outcome, there was no change in passive parameters except for a reduction in passive range of motion. Active parameters recuperated, but at a later moment in time than observed in the group with an initial favorable prognosis. The ability to modulate reflexes in a changing environment did not change over time. In patients with an initial unfavorable prognosis and a poor functional outcome, there was a marked shift in rest angle towards flexion as early as the first week after stroke, little or no improvement in active parameters, higher reflex magnitudes and a diminished ability to modulate reflexes in a changing environment. Moreover, if there was any increase in function, it was not observed until week 5-8. A catch or clonus during measurements of reflexive parameters was only observed in the groups with an initial unfavorable prognosis, in 8% of participants with a positive functional outcome and in 44% of participants with a poor functional outcome, the earliest at week 5 (chapter 6).

The relation between neuromechanical parameters and functional outcome

All participants with an initial favorable prognosis for recovery of arm-hand function after stroke reached a positive functional outcome of ARAT ≥ 10 points at 26 weeks. Within the group of patients with an unfavorable prognosis for functional outcome, 57% reached a positive functional outcome at 26 weeks. A diminished ability for maximal voluntary

contraction and a diminished ability to modulate reflexes at 26 weeks were significantly related to poor outcome. Stiffness (as measured around the rest angle) at 26 weeks was not significantly related to poor outcome. However, structural changes in tissue properties were represented by a changed rest angle towards wrist flexion and a diminished passive range of motion. Prediction of functional outcome on activity level was mostly determined by an increase in active range of motion and a stable rest angle (chapter 6).

Clinical implications

The precision diagnostics provided by a neuromechanical assessment protocol could support clinical decision making. To enhance prediction of recovery of arm-hand function after stroke and better represent endpoint joint behavior [3,4], neuromechanical parameters could be added to the current set of biomarkers of stroke recovery [5]. Furthermore, implementation of the use of neuromechanical parameters such as selective muscle activation, rest angle and active range of motion in future intervention trials concerning e.g. botulinum toxin, surgery or robot therapy will support both stratifying the patients most likely to benefit from an intervention and evaluating the results of a given therapy in a more objective manner. Moreover, neuromechanical parameters allow for a connection to be made between pathophysiology and treatment goals within the framework of the International Classification of Functioning, Disability and Health (ICF) [6].

To achieve an improvement in activities or participation, it is sometimes, but not always, necessary to intervene at the level of body functions and structures first. This decision should be based on clear patient-related information concerning which pathophysiological entity is most constraining for arm-hand function at that moment in time and in the context of a prediction model. For example, to optimize the period in which neural repair is possible and prevent secondary complications, neuromechanical parameters such as rest angle and/or active range of motion could be monitored systematically in the first months after stroke and treatment adapted accordingly. In the group of patients with a favorable prognosis for recovery of arm-hand function, active task oriented training can start right away, while in patients with an unfavorable prognosis, the focus should be on passive movement to prevent contractures until there is an increase in active range of motion (which can take up to 5-8 weeks after stroke). If there is no improvement in active function after 5-8 weeks, compensation strategies should be considered [7] and efforts to prevent contractures can be monitored by repeated assessment of rest angle.

Methodological considerations

The neuromechanical assessment protocol aimed to identify neural and non-neural contributors to movement disorders by differences in task and measurement conditions. For example: the protocol was designed to minimize the effects of neural contributors during non-neural tasks and vice versa. However, this might not yet give a complete reflection

of endpoint joint behavior, as system behavior under active task conditions involves a combination of both neural and non-neural contributors. The same goes for passive conditions, where neural contributors may be present through increased baseline activation [8]. Further development of System Identification and Parameter Estimation techniques might help to differentiate even better between neural and non-neural contributors to movement disorders after stroke, e.g. further differentiation between passive and reflexive stiffness [9].

The studies in this thesis refer to wrist function, a single axis joint function. This could do injustice to arm-hand function in general when not connected to outcome measures on the level of activity or participation. On the other hand, the limitation in freedom of movement gives us a unique insight in function without synergies and compensatory trunk movement. Stratification of patient groups makes it more difficult to generalize the results to the stroke population as a whole; however, as stratification contributes to an increased homogeneity within the subgroup and an increased heterogeneity between subgroups, interpretation of the results in our study is greatly ameliorated by stratification according to the finger extension algorithm [10,11].

Future work

As the comprehensive neuromechanical assessment protocol is only used in a research setting so far, future work should include implementation of the protocol in daily practice. Further research into e.g. the amount of training needed for caregivers to apply the protocol and the applicability of the protocol in the general stroke population could help remove the behavioral and economical barriers often seen in implementation of robot-assisted assessments [12]. Interpretation of the results could be enhanced by developing a flowchart containing distinctive neuromechanical parameters for different patient categories and treatment questions. To assemble such a flowchart, systematic measurement of neuromechanical parameters should be incorporated in intervention trials, to answer e.g. the following questions:

- Can a shift in rest angle be prevented? For example by passive (possibly robot assisted) movement, splinting, oral spasmolytics or botulinum toxin?
- If a shift in rest angle is prevented, does this help in recovery of arm-hand function?
- In the presence of selective muscle activation and a suboptimal maximal voluntary contraction, is an exercise program aimed at strength beneficial in recovery of arm-hand function?
- Does botulinum toxin have an effect on active range of motion or on arm-hand function in terms of activity or participation if there is no selective muscle activation?
- How can additional therapy (e.g. splinting, passive movement) maximize the possible effect of botulinum toxin on passive range of motion and/or stiffness? Can additional therapy help to prevent a relapse once the effect of botulinum toxin wanes?

- If there is no selective muscle activation in a transposed muscle, is surgery aimed at creating a functional joint beneficial?
- Are neural contributors to movement disorders after stroke a risk for pressure sores or even losing the desired position of the joint after surgery to stabilize a joint?
- Which stretch reflex properties help in selecting patients for surgery aimed at interruption of the stretch reflex loop?

These examples may seem very plain, but objective and reproducible assessment of neural and non-neural contributors to movement disorders after stroke are not commonplace yet. Neuromechanical parameters should be used in prediction models and as biomarkers to support clinical decision making in recovery of arm-hand function after stroke, for example by improving the time-window and selection of patients. Thus, rehabilitation strategies can be optimized.

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C h a p t e r

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**Nederlandse samenvatting
(Summary)**

Een cerebrovasculair accident of een beroerte wordt door de Wereldgezondheidsorganisatie gedefinieerd als "een onderbreking van de bloedtoevoer naar de hersenen, meestal omdat een bloedvat scheurt of wordt geblokkeerd door een stolsel. Dit blokkeert de toevoer van zuurstof en voedingsstoffen en veroorzaakt schade aan het hersenweefsel". De effecten van een beroerte hangen af van welk deel van de hersenen betrokken is en hoe ernstig de schade is. Slechts 10% van de patiënten met een beroerte heeft een volledig functioneel herstel en 15 % overlijdt aan de gevolgen van de beroerte. Tussen de 32% en 60% van de patiënten ervaart een blijvende beperking van de arm-handfunctie, met als gevolg beperkingen in activiteiten van het dagelijks leven of in participatie in de samenleving, zoals sociale activiteiten, sport of werk.

Interventies gericht op het herstel van de arm-handfunctie zijn ofwel gericht op herstel van hersenweefsel en -functie of op compensatiemethoden en het voorkomen van secundaire complicaties zoals contracturen. Therapieën zijn vaak duur en tijdrovend voor zowel patiënten als therapeuten. De doelmatigheid van therapieën kan worden verbeterd door het selecteren van het juiste moment en de juiste patiënt voor een bepaalde interventie. Voorspellingsmodellen en biomarkers kunnen de klinische besluitvorming op dit gebied ondersteunen. Maar de huidige voorspellingsmodellen en biomarkers maken nog onvoldoende gebruik van informatie over factoren die de uiteindelijke beweging van een gewricht bepalen, zoals weefseleigenschappen, de controle over aanspanning van spieren en reflexeigenschappen. Klinisch wordt de uiteindelijke beweging van een gewricht meestal beschreven in termen als parese en spasticiteit en gemeten door lichamelijk onderzoek.

Bewegingsstoornissen na een beroerte zijn het resultaat van een complexe interactie tussen neurale ontregeling en veranderingen in weefseleigenschappen, leidend tot een herkenbaar beeld van spierzwakte (parese), spier-overactiviteit en contracturen. Parese wordt bepaald door verminderde vrijwillige aanspanning van spieren. Overactiviteit wordt bepaald door toegenomen onvrijwillige aanspanning van spieren. Contracturen worden gekenmerkt door veranderde weefseleigenschappen en een veranderde positie van het gewricht. Met behulp van neuromechanica wordt een kwantitatieve beschrijving mogelijk van de factoren die de uiteindelijke beweging van een gewricht bepalen, onder passieve en actieve omstandigheden en als reactie op externe mechanische verstoringen. Door het toepassen van verschillende meetcondities en taken kunnen weefseleigenschappen, controle over aanspanning van spieren en reflexeigenschappen apart gemeten worden. Het toepassen van verschillende meetcondities en taken en een reproduceerbare, objectieve vastlegging van de resultaten wordt mogelijk gemaakt door biomechanische technieken (die gebruik maken van haptische robots, meetinstrumenten met krachttransducers en elektrogoniometers) in combinatie met elektromyografie.

Het doel van het onderzoek in dit proefschrift was het beschrijven van de veranderingen in neuromechanica bij het herstel van arm-handfunctie na een beroerte, door het in kaart brengen van weefseleigenschappen, controle over aanspanning van spieren en

reflexeigenschappen in de acute en chronische fase na een beroerte. Hoofdvragen waren: Hoe en in welke mate veranderen de factoren die de uiteindelijke beweging van het polsgewricht bepalen, beschreven in neuromechanische parameters, in de eerste zes maanden na een beroerte? En hoe verhouden deze veranderingen zich tot de functionele uitkomst? Voor dit doel moest een meetprotocol met valide en nauwkeurige parameters worden ontwikkeld, gebaseerd op eenduidige pathofysiologische concepten. Op basis van dit protocol werd een prospectieve studie uitgevoerd, waarin patiënten de eerste zes maanden na een beroerte werden gevolgd en de neuromechanische parameters werden gemeten. De studies in dit proefschrift werden uitgevoerd in het kader van de Explaining PLasticity trial (EXPLICIT-stroke). Dit multicenter onderzoeksprogramma bestond uit een gerandomiseerde klinische studie naar de effecten van vroege therapie op de armhandfunctie na een beroerte en een longitudinaal onderzoek naar de dynamiek van herstel na een beroerte.

Eerst werd door middel van literatuuronderzoek de kloof tussen de dagelijkse praktijk (lichamelijk onderzoek) en de mogelijkheden van biomechanische en elektrofysiologische technieken in kaart gebracht. Dat resulteerde in een overzicht van regelmatig gebruikte pathofysiologische concepten en biomechanische en elektromyografische uitkomstmaten van bewegingsstoornissen na een beroerte (hoofdstuk 2).

Het overzicht van pathofysiologische concepten en vereiste meetcondities genereerde een methode om de bewegingen van een gewricht rond een enkele as te beoordelen. Deze methode werd vertaald in een uitgebreid meetprotocol om de factoren te kwantificeren die de uiteindelijke beweging van het polsgewricht bepalen. Weefseigenschappen, controle over aanspanning van spieren en reflexeigenschappen werden bepaald tijdens flexie-extensiebewegingen van de pols onder verschillende taakinstructies en met verschillende externe verstoringen, resulterend in passieve, actieve en reflexieve neuromechanische parameters (hoofdstuk 3).

Test-hertestbetrouwbaarheid van het nieuw ontwikkelde protocol werd beoordeeld en er werd berekend of er verschillen aangetoond konden worden tussen een groep patiënten in de chronische fase na een beroerte met een verminderde arm-handfunctie en een groep gezonde deelnemers. De neuromechanische parameters verschilden tussen de gezonde deelnemers en de patiënten in de chronische fase na een beroerte. De test-hertestbetrouwbaarheid van passieve en actieve parameters was uitstekend. De rusthoek en bijna alle reflexieve parameters (op één na) hadden een redelijke tot goede test-hertestbetrouwbaarheid (hoofdstuk 4).

De invloed van co-contractie en parese op de arm-handfunctie werd onderzocht door het vaststellen van stoornissen in selectieve spieractivatie. Het meten van selectieve spieractivatie door middel van activatieratio's (AR) van m. flexor carpi radialis (FCR) en m. extensor carpi radialis (ECR) had een hoge betrouwbaarheid. De AR waren significant lager bij patiënten in de chronische fase na een beroerte in vergelijking met gezonde deelnemers,

wat wijst op verlies van selectieve spieractivatie bij patiënten in de chronische fase na een beroerte. Op basis van vrijwillige aanspanning van de spieren en selectieve spieractivatie werden drie klinische fenotypes onderscheiden: patiënten met slappe parese en derhalve onvoldoende vrijwillige aanspanning om selectieve spieractivatie te bepalen, patiënten met enig verlies van selectieve spieractivatie, en patiënten met selectieve spieractivatie vergelijkbaar met gezonde vrijwilligers, ondanks het niet bereiken van een maximaal vrijwillige kracht die vergelijkbaar is met gezonde vrijwilligers (hoofdstuk 5).

Uiteindelijk werden veranderingen in neuromechanische parameters longitudinaal gemeten in het prospectieve cohort van de EXPLICIT-studie. In de groep patiënten met een aanvankelijk gunstige prognose voor herstel van arm-handfunctie, veranderden de passieve parameters niet in de loop van de tijd, terwijl actieve parameters het meest herstelden vóór week 5. De maximale vrijwillige kracht en controle van de krachtsopbouw herstelden zich echter niet naar waarden zoals gemeten bij gezonde vrijwilligers. De reflexieve parameters lieten relatief lage reflexen zien en een vermogen om reflexen te moduleren in een veranderende testomgeving. Bij patiënten met een aanvankelijk ongunstige prognose voor het herstel van de arm-handfunctie, konden twee subgroepen worden onderscheiden: die met een positieve functionele uitkomst (≥ 10 punten op de Action Research Arm Test (ARAT) na zes maanden) en die met een slechte functionele uitkomst (ARAT <10 punten). In de groep met een aanvankelijk ongunstige prognose en een positieve functionele uitkomst was er geen verandering in de passieve parameters over de tijd, behalve een vermindering van de passieve range of motion. De actieve parameters herstelden, maar op een later tijdstip dan waargenomen in de groep met een aanvankelijk gunstige prognose. Het vermogen om reflexen te moduleren in een veranderende omgeving veranderde niet in de loop van de tijd. Bij patiënten met een aanvankelijk ongunstige prognose en een slechte functionele uitkomst, was er al in de eerste week na een beroerte een duidelijke verschuiving van de rusthoek in de richting van flexie. Daarnaast was er weinig of geen verbetering van de actieve parameters, waren er hogere reflexen en was er een verminderd vermogen om reflexen te moduleren in een veranderende omgeving. Bovendien werd de toename in functie, als deze er al was, pas waargenomen vanaf week 5-8. Een catch of clonus tijdens het meten van de reflexieve parameters werd alleen waargenomen in de groepen met een initiële ongunstige prognose, bij 8% van de deelnemers met een positieve functionele uitkomst en bij 44% van de deelnemers met een slechte functionele uitkomst, op zijn vroegst in week 5 (hoofdstuk 6).

Alle deelnemers met een aanvankelijk gunstige prognose voor het herstel van de arm-handfunctie na een beroerte bereikten een positieve functionele uitkomst van ARAT ≥ 10 punten na 26 weken. Binnen de groep patiënten met een ongunstige prognose voor functionele uitkomst, bereikte 57% een positieve functionele uitkomst na 26 weken. Een verminderde maximale vrijwillige kracht en een verminderd vermogen om reflexen te moduleren na 26 weken waren significant gerelateerd aan een slechte uitkomst. Stijfheid

(gemeten rond de rusthoek) na 26 weken was niet significant gerelateerd aan een slechte uitkomst. Structurele veranderingen in weefseigenschappen waren wel zichtbaar door een veranderde rusthoek (meer polsflexie) en een verminderd passieve range of motion. Voorspelling van een positieve functionele uitkomst op activiteitsniveau werd grotendeels bepaald door een toename in de actieve range of motion en een stabiele rusthoek (hoofdstuk 6).

In de algemene discussie komen de diverse aspecten van het meten van stoornissen in armhandfunctie na een beroerte aan bod, inclusief klinische implicaties, methodologische overwegingen en aanbevelingen voor toekomstig werk (hoofdstuk 7).

CONCLUSIE

Objectieve en reproduceerbare beoordeling van de factoren die de uiteindelijke beweging van een gewricht bepalen na een beroerte is nog geen gemeengoed. Neuromechanische parameters zouden gebruikt kunnen worden in voorspellingsmodellen en als biomarkers om klinische besluitvorming bij het herstel van de arm-handfunctie na een beroerte te ondersteunen, bijvoorbeeld door het verbeteren van de selectie van patiënten en van het juiste moment voor een bepaalde therapie. Hiermee kunnen behandelstrategieën in de revalidatiegeneeskunde worden geoptimaliseerd.

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Curriculum Vitae

Johanna Mathilda van der Krogt werd op 24 december 1977 geboren in Voorschoten. Zij voltooide in 1996 cum laude het gymnasium aan het Adelbert College in Wassenaar. In 1997 behaalde zij haar propedeuse Gezondheidswetenschappen aan de Universiteit van Maastricht. Van 1997 t/m 2003 studeerde zij Geneeskunde aan de Universiteit Leiden, waar zij in 2003 haar artsexamen behaalde. Van 2003 t/m 2005 werkte zij in het Leids Universitair Medisch Centrum op het Centrum Eerste Hulp en de afdeling Heelkunde-Traumatologie als arts-assistent niet in opleiding (ANIOS). Van 2005 t/m 2007 werkte zij als ANIOS op de afdeling Intensive Care van het MC Haaglanden locatie Westeinde.

In 2007 begon Hanneke aan de opleiding revalidatiegeneeskunde en haar promotietraject als arts in opleiding tot medisch specialist en klinisch onderzoeker (AIOS KO) bij de Revalidatiegeneeskunde in het LUMC en het Rijnlands Revalidatiecentrum. In 2014 behaalde zij haar registratie als revalidatiearts. Tijdens het laatste jaar van de opleiding verbleef zij vier maanden in Australië voor een keuzestage dwarslaesierevalidatie bij het Princess Alexandra Hospital in Brisbane en het Royal North Shore Hospital in Sydney, met een klein uitstapje naar het Royal Rehabilitation Centre in Sydney.

Sinds 2014 is Hanneke werkzaam als revalidatiearts in het Rijnlands Revalidatiecentrum met een detachering naar het Leids Universitair Medisch Centrum, met als aandachtsgebied revalidatie van amputatiepatiënten, multitraumapatiënten, dwarslaesiepatiënten, patiënten met perifere zenuwletsels en patiënten met gewrichtsklachten.

Zij woont in Leiden met haar echtgenoot en zoon.

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