From Karolinska Institutet, Department of Clinical Sciences,
Danderyd Hospital, Division of Rehabilitation Medicine
Stockholm, Sweden

COMPREHENSIVE EVALUATION OF SPASTICITY AND OTHER SENSORIMOTOR DYSFUNCTIONS AFTER LESIONS TO THE CENTRAL OR PERIPHERAL NERVOUS SYSTEM

Gaia Valentina Pennati

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-429-0

COMPREHENSIVE EVALUATION OF SPASTICITY AND OTHER SENSORIMOTOR DYSFUNCTIONS AFTER LESIONS TO THE CENTRAL OR PERIPHERAL NERVOUS SYSTEM

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Gaia Valentina Pennati

The thesis will be defended in public at The Lecture Hall, Danderyd Hospital, Stockholm, Sweden on December 15, 2021 at 9:00 AM.

Principal Supervisor:

Påvel G Lindberg
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital
Division of Rehabilitation Medicine
Institut de Psychiatrie et Neurosciences de Paris, Inserm U1266, Université de Paris, Paris, France

Co-supervisor(s):

Alison K Godbolt
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital
Division of Rehabilitation Medicine

Eva Melin
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital
Division of Rehabilitation Medicine

Susanne Palmcrantz
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital
Division of Rehabilitation Medicine

Opponent:

Anand D Pandyan
Bournemouth University
Faculty of Health and Social Sciences

Examination Board:

Magnus Andersson
Karolinska Institutet
Department of Clinical Neuroscience
Division of Neuro

Margit Alt Murphy
University of Gothenburg
Department of Clinical Neuroscience
Institute of Neuroscience and Physiology
Sahlgrenska Academy

Hélène Pessah
Lund University
Department of Clinical Sciences
Section IV, Neurology

ABSTRACT

Background: Understanding how sensorimotor impairments may contribute to changes in body structure and function, and also to activity and participation limitations is an important challenge in neurorehabilitation research, of high clinical relevance. Available assessment methods include mainly clinical scales, often with inadequate psychometric properties, such as the Modified Ashworth scale for assessment of spasticity. Novel tools, incorporating kinetic or kinematic aspects, are therefore needed to improve the diagnostic accuracy and management of sensorimotor impairments in neurological disorders.

Aim: The overall aim of this thesis was to improve methods of assessment of sensorimotor impairments after central or peripheral nervous system lesions by the use of standardized and valid objective measurement tools.

This thesis examined the validity and reliability of the novel NeuroFlexor foot module, a method designed to distinguish the contribution of reflex hyperexcitability from secondary changes of passive muscle properties to muscle tone. Moreover, it aimed to provide reference data of the NeuroFlexor method for the upper and lower extremities from a representative sample of healthy adult subjects and to establish cut-off values to differentiate the contributors to passive stretch resistance between patients in different phases after stroke and individuals with muscle-related effects of poliomyelitis infection.

Methods: A total of 93 patients (64 patients in different phases after stroke and 19 patients with prior polio) and 180 healthy subjects were examined with the NeuroFlexor hand and/or foot module. Neural, elastic and viscous components of passive movement resistance were quantified (in Newton, N) using a biomechanical model, during passive wrist extension and/or ankle flexion at controlled slow and fast velocities. In Study II the measured neural component, reflecting stretch reflex mediated resistance, was validated against electromyography activity of calf muscles recorded during NeuroFlexor assessment. A test-retest design with a two-way random effects model studied intra-rater reliability. Cut-off values for the NeuroFlexor components were established for the upper extremity (Study I) and lower extremity (Study II) by adding 3 SD to the mean. Additionally, specific limits were determined for the elastic component in the upper limb, which is significantly affected by age and gender. In the lower extremity, the pathological neural component was verified against electromyography amplitude using a Receiver Operating Characteristic (ROC) curve analysis. In Study III, the NeuroFlexor method in conjunction with electromyography evaluated the effectiveness of one session of electrical stimulation with the EXOPULSE Mollii suit at different stimulation frequencies on objective signs of spasticity. The response to passive muscle stretch with the NeuroFlexor instrument was characterized in patients in the sub-acute phase (Study I) or chronic phase (Study II) after stroke, and in subjects with prior paralytic poliomyelitis, with or without a diagnosis of progressive post-polio syndrome (Study IV). Finally, the Modified Ashworth scale of spasticity, the Medical Research Council scale, Jamar dynamometer and Biodex Multi-Joint System for muscle strength, the Fatigue Severity Scale and the

Multidimensional Fatigue Inventory (MFI-20) for the severity of fatigue, and the Visual Analogue Scale for pain were used as complementary tests of neurological impairment.

Results: The neural component measured with the NeuroFlexor foot module revealed a velocity dependent response correlating with the increase in electromyography amplitude ($p \leq 0.005$). Reliability was good for the neural component ($ICC_{2,1} \geq 0.899$) and high for the elastic component ($ICC_{2,1} \geq 0.909$). In the upper extremity, the cut-off value (mean + 3 SD) identified for the neural component was 3.4 N. In the lower limb, the neural component cut-off value (according to ROC analysis) for 40 degree stretch was 31.5 N and for 30 degree stretch was 18.9 N. Sixteen out of 39 patients (41%) early after stroke had a pathologically high neural component of the upper extremity and 11 out of 15 chronic stroke patients (73%) in the lower extremity. A limited correspondence between clinical evaluation of spasticity and NeuroFlexor measurement was observed.

The NeuroFlexor was sufficiently sensitive to detect variations in neural and mechanical contributions to the muscle resistance induced by the electrical stimulation with the EXOPULSE Mollii suit at different frequencies at the individual level. However, at group level no significant reduction in spasticity was observed during or immediately after 60 minutes of electrical stimulation at any frequency ($p > 0.35$), and there were no significant differences between OFF settings and active frequencies (20 and 30 Hz) of stimulation.

Both NeuroFlexor neural and mechanical components differed significantly in subjects with prior polio compared to healthy subjects ($p < 0.001$), with the elastic component contributing most to passive resistance. Low values of neural component were observed, especially in individuals with severe muscle atrophy. Finally, significant correlations were found between NeuroFlexor components, severity of fatigue and perceived pain ($p < 0.05$).

Conclusions: The NeuroFlexor may offer a clinically feasible and non-invasive way to objectively quantify post-stroke spasticity and polio-related neuromuscular alterations in the upper and lower extremities. The method may assess changes in spasticity after treatment with, for example, electrical stimulation, and elucidate potential associations between altered neural and passive muscle properties and clinical issues. Finally, it may guide new therapeutic approaches. However, further evaluation of the NeuroFlexor foot module is needed.

LIST OF SCIENTIFIC PAPERS

I. **Normative NeuroFlexor data for detection of spasticity after stroke: a cross-sectional study**
Pennati GV, Plantin J, Borg J, Lindberg PG.
J Neuroeng Rehabil. 2016 Mar 18;13:30. doi: 10.1186/s12984-016-0133-x.

II. **Validity, reliability and normative data of the NeuroFlexor method to measure spasticity in the lower limb**
Pennati GV, Carment L, Godbolt AK, Plantin J, Borg J, Lindberg PG.
Submitted and under review

III. **Effects of 60 Min Electrostimulation With the EXOPULSE Mollii Suit on Objective Signs of Spasticity**
Pennati GV, Bergling H, Carment L, Borg J, Lindberg PG, Palmcrantz S.
Front Neurol. 2021 Oct 15;12:706610. doi: 10.3389/fneur.2021.706610. eCollection 2021.

IV. **Objective measure of neuromuscular changes in patients with prior poliomyelitis**
Pennati GV, Melin E, Borg J, Lindberg PG.
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
CI	Confidence interval
EC	Elastic component
EMG	Electromyography
FES	Functional electrical stimulation
FMA-LE	Fugl-Meyer assessment for lower extremity
FMA-UE	Fugl-Meyer assessment for upper extremity
FSS	Fatigue Severity Scale
HZ	Hertz
ICC	Intraclass correlation coefficients
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile range
MAS	Modified Ashworth scale
MFI-20	Multidimensional Fatigue Inventor
MRC	Medical Research Council scale
MVC	Maximum voluntary contraction
N	Newton
NC	Neural component
NMES	Neuromuscular electrical stimulation
POLIO	Poliomyelitis
PPS	Post-polio syndrome
Rm-ANOVA	Repeated measures analysis of variance
ROC	Receiver Operating Characteristic
ROM	Range of motion
SD	Standard deviation
SRT	Stretch reflex threshold
TENS	Transcutaneous electrical nerve stimulation
TSRT	Tonic stretch reflex threshold
VAS	Visual Analog scale
VC	Viscous component

1 INTRODUCTION

1.1 INJURY TO THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM

Sensorimotor impairments may contribute to changes in body structure, activity limitations and participation restrictions in patients with injury to the central and/or peripheral nervous system (according to the International Classification of Functioning, Disability, ICF[1]). Clinical features of lesions to descending motor pathways at different levels differ markedly. Supraspinal lesions of various etiology (including stroke[2], trauma to the brain or spinal cord[3], cerebral palsy[4] and multiple sclerosis[5]) can cause increased muscle tone with exaggerated tendon reflexes.[6] Damage to the corticospinal tract at the level of the motor cortex or descending projectors is a leading cause of motor disabilities.[7-9] In contrast, damages to α motor neurons of the brainstem and spinal cord lead to muscle wasting (due to uncompensated denervation), fasciculations, weakness and paresis of muscles, and areflexia due to interruption of the efferent component of the sensory motor reflex arcs.[10]

1.2 SPASTICITY AFTER STROKE

Stroke is one of the leading causes of mortality and physical disability in adults in the world.[11,12] Approximately 16.9 million people experience a stroke each year worldwide, with a substantial difference in incidence rates between women and men (1.5 times higher in males).[13] In Sweden, approximately 25 700 individuals suffered from stroke in 2019.[14] Preliminary data for 2020 are available in the National Quality Register for Stroke Care in Sweden[15], which reports 19 997 medical care events for stroke registered in the year, an incident 5% lower than the previous year probably due to the Coronavirus pandemic negatively affecting the input to the national register at several hospitals. Based on the annual report 2019[14], approximately 20% of all strokes were recurrent, 13% were haemorrhagic and 87% ischemic in origin. The mean age of patients suffering a stroke was 75 years (73 years among men and 77 years among women). Less than 4 percent of the cases affected a person who was younger than 50 years.

Spasticity is a sensorimotor disorder that may develop after stroke and may impact the functional recovery of patients negatively.[16-19] The reported prevalence of spasticity following stroke is estimated between 20% and 25%[16,20-22] at 6 months, rising to 42.6%[23] in patients with more severe motor impairments referred to a department of rehabilitation medicine. It ranges from 17% to 38% at one year post stroke.[24-26] A recent systematic-review[27] revealed an overall incidence of spasticity in first-ever stroke patients of 25.3%, specifically 31.6% within 1 month, 21.8% in 1-3 months, 26.3% in 3-6 months, 24.2% beyond 6 months. The reported overall incidence of spasticity with concomitant paresis was higher: 39.5%, specifically 35.7% within 1 month, 34.6% in 1-3 months, 42.3% in 3-6 months, and 45.4% beyond 6 months. The variability in these estimated illustrates that the temporal development of spasticity is highly variable post-stroke[17]: onset of increased muscle tone has been observed within the first days up to 6 weeks after onset, whereas spasticity may peak at 1-3 months post-stroke.[19,20] Spontaneous reduction may occur in mild spasticity.[28]

Disabling spasticity[26], defined as spasticity causing disability as conceptualized according to the ICF, occurs in 9.4% of post-stroke patients, with an incidence increasing over time.[27]

Spasticity affects primarily the antigravity muscles, i.e. the flexor muscles of the upper limb (elbow in 79% of patients, wrist and fingers in 66%), and the extensor muscles in the lower limb (ankle in 66%).[20] The affected limbs achieve constraint postures or movement patterns: internal rotation and adduction of the shoulder coupled with elbow, wrist and fingers flexion, and adduction and extension of the knee with equinovarus foot.[29] The high focus on spasticity in stroke rehabilitation results from the evidence that spasticity may interfere with functional recovery and lead to secondary complications such as contractures, pain and weakness.[30-32] In the lower limb, spasticity of ankle plantarflexors and weakness of ankle dorsiflexors, together with other associated conditions such as pain, prolonged altered posture and limb non-use, may contribute to disordered gait.[33,34]

Severity of paresis, sensory impairments, poor functional status in the early phase post-stroke as well as corticospinal tract damage are predictors identified for the development of any and severe spasticity.[28,35-38] The optimal time for early prediction of any spasticity is estimated at 10 days post-stroke, while for severe spasticity at 4 weeks post-stroke.[39]

1.3 RECENT HISTORY OF SPASTICITY DEFINITIONS

In 1980, James Lance described spasticity as

> "*a disorder of the sensorimotor system characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motoneuron syndrome."*[40]

This definition, widely accepted, related spasticity specifically with abnormality of the stretch reflex circuit.[41]
In 2003, the North American Task Force for Childhood Motor Disorders redefined spasticity as

> "*a velocity dependent increase in hypertonia with a catch when a threshold is exceeded*".[42]

More recently, the European Thematic Network to Develop Standardized Measures of Spasticity (SPASM Consortium) suggested a broader and more clinically relevant characterization of spasticity as

> "*a disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles*".[43]

This latest definition did not focus anymore on the increased muscle tone exclusively rather than on the positive features arising after injury to the upper motor neuron (such as clonus, increased deep tendon reflexes, Babinski sign, exaggerated tonic stretch reflex, flexion or extension reflexes and co-contractions). Although relevant for clinical practice, it lacks

specificity. Moreover, it did not include one of the main characteristics of spasticity that is its velocity-dependence making it difficult to differentiate spasticity itself from other alterations in passive muscle properties and other confounding complications such as contracture.
A recent study proposed a new terminology to take into account all the factors that contribute to the clinically observed changes in muscle tone.[44] The new term "reversible muscle hypertonia" was defined as

> "*a focal, regional or generalized constant or posture- and/or activity- related state of skeletal muscle tension due to an upper motor neuron lesion that clinically manifests as resistance to passive muscle stretch, which may interfere with body functions, tasks and actions.*"

Finally, based on advancements in knowledge of the common pathophysiological process of post-stroke spasticity and related neuromuscular impairments[45], spasticity was defined by Sheng Li and colleagues as

> "*Spasticity is manifested as velocity- and muscle length–dependent increase in resistance to externally imposed muscle stretch. It results from hyperexcitable descending excitatory brainstem pathways and from the resultant exaggerated stretch reflex responses. Other related motor impairments, including abnormal synergies, inappropriate muscle activation, and anomalous muscle coactivation, coexist with spasticity and share similar pathophysiological origins*".[31]

Such diverse definitions of spasticity complicate comparisons of research in this area. At present, an accurate and internationally accepted definition of spasticity remains elusive[46] but it is fundamental both for assessment and management to properly distinguish between the neural (i.e., involving hyperexcitability of stretch reflex) and non-neural (i.e., soft tissue properties) contributions to increased muscle tone.

This thesis uses the term spasticity to describe the increased resistance to passive stretch in stroke, based on Lance's definition[47] and on its key points: "motor disorder", "velocity-dependent increase in tonic stretch-reflexes" and "resulting from hyperexcitability of the tonic stretch reflex".

1.4 PATHOPHYSIOLOGY OF SPASTICITY

To better understand the pathophysiology of spasticity and the different underlying mechanisms, it is useful to examine muscle responses to stretch. At velocities below the threshold of the stretch reflex, passive movement resistance is caused exclusively by the passive properties of the muscle, connective tissue, tendon and joint.[48,49] This resistance does not relate to the stretch velocity but depends on joint position and degree of stretch of the muscle.[48,50,51] Some authors called it *passive stiffness*.[52,53] A stretch reflex response can be evoked in healthy subjects at very high velocities (above 300 degree/s) or in neurological disorders, such as stroke, at lower velocities and it adds to the passive movement resistance, when stretches above a certain excitability threshold are applied.[48]

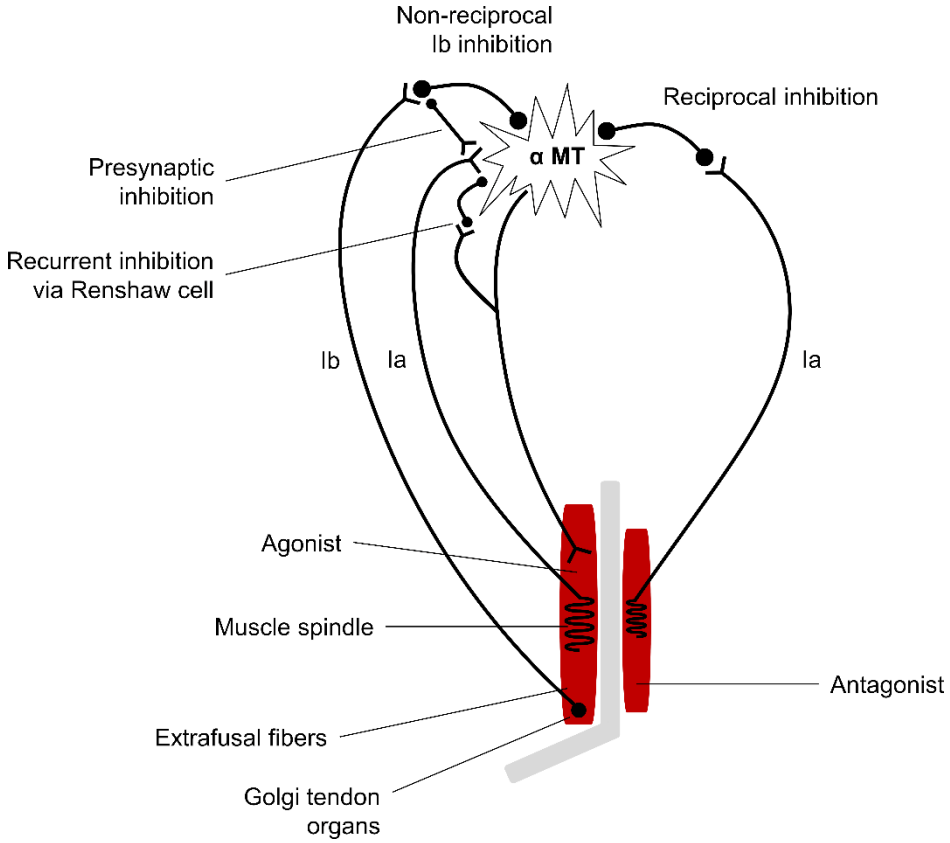
1.4.1 Brain, supraspinal and spinal mechanisms of spasticity

The pathophysiology of spasticity although well studied, has not been entirely clarified at present and several neural mechanisms seem to be involved. Findings regarding the relationship between the neuroanatomical location of the stroke lesion and spasticity are fairly contradictory. Damage to the insula, thalamus, basal ganglia and white matter tracts (internal capsule, corona radiata, external capsule, and superior longitudinal fasciculus) may increase the risk of developing severe spasticity in the upper extremity.[54-57] Additional neuroimaging findings highlighted the importance of putamen[58] as well as the supplementary motor area, cingulate cortex and secondary somatosensory cortex in the development of spasticity and related motor disorders after stroke[18]. By contrast, other studies did not indicate any lesioned region within the territory supplied by the middle cerebral artery as being responsible for the development of post-stroke spasticity.[59]

As a result of damage to the motor cortex, an imbalance in regulation of the descending inhibitory and facilitatory signals on spinal reflexes of supraspinal origin occurs. [55,60,61] Studies in animal models and with human imaging suggest the maladaptive role of the hyperexcitability of the brainstem reticular system and its descending reticulospinal tract in developing spasticity.[45,62] Moreover, damage to the insula may result in disorders of the vestibulospinal system, which may lead to hyperexcitability of the stretch reflex.[63,64]

At spinal level, the most credited hypothesis is that alterations in inhibitory mechanisms within spinal neural circuitry are the main contributors to the excitation of the stretch reflex and thus are mainly responsible for causing spasticity (Fig. 1).[60]

Figure 1. Role of spinal neuronal circuitry in spasticity



Representative schematic of the main spinal circuits involved in the development of spasticity: **i**. Ia afferent fibers originating from the muscle spindles have an excitatory monosynaptic connection with the motor neurons (α MT) innervating the homonymous muscle and **ii**. an inhibitory disynaptic reciprocal connection with the heteronymous motor neurons, providing the pathway for reciprocal inhibition; **iii**. Ia afferent fibers also connect with presynaptic inhibitory interneurons; **iv**. Ib fibers originating from the Golgi tendon organ connect with inhibitory interneurons, providing an inhibitory synapse onto the motor neurons innervating the homonymous muscle; **v**. recurrent inhibition of motor neurons through the activation of Renshaw cells, providing a negative feedback loop.

Firstly, the excitation of Ia afferents originating in the muscle spindle, underlies the tendon jerk and thus contributes mainly to the excitation of the stretch reflex[65]. Other contributions include postsynaptic pathways (Ib inhibition[66], recurrent inhibition via motor axon collaterals and Renshaw cells[67], dysynaptic reciprocal Ia inhibition[68]) and presynaptic mechanisms (presynaptic Ia inhibition[69] and post-activation depression[70-72]).[73,74] It is likely that the different spinal mechanisms may have different roles in different patients, since unequal impairment of the two presynaptic mechanisms was even observed in patients after stroke.[75]

Finally, that reflex hyperexcitability develops after a variable period of time following the primary lesion suggests that neural plasticity occurs at the spinal and supraspinal level as well.[60] Axonal collateral sprouting with conversion of previously inhibitory synapses into excitatory ones, and denervation hypersensitivity due to receptors upregulation are possible causal factors of spasticity that have been investigated.[75]

1.4.2 Secondary changes in muscle and connective tissue

Secondary changes in mechanical properties of muscles can occur after central nervous system lesion.[76,77] Length-related changes in the muscle-tendon complex (result of loss of the number of sarcomeres in series along the myofibrils and increase of the proportion of connective tissue in the muscle), either caused by weakness or altered muscle contraction, lead to stiffness of soft tissue and ultimately to contractures with fixed shortening of tissues and reduced range of movement.[78,79] This in turn reduces the muscle compliance, enhances the activation of the muscle spindle and contributes to the increase in muscle tone.[80]

The temporal evaluation and causal relation between either spasticity or weakness and contracture development in the upper limb were investigated and findings showed that spasticity can cause contracture within the first few months after stroke. However, weakness is the main contributor to activity limitations.[81,82]

1.5 MEASUREMENT OF SPASTICITY

1.5.1 Clinical scales

Clinically, spasticity is often tested by manual evaluation of passive movement resistance without specific testing of stretch reflex responses. Measurements are mainly limited to clinical scales such as the Ashworth scale[83] and Tardieu scale[84] and their variations. These are easy to use and widely adopted in clinical practice but have limited validity and questionable reliability.[85-87] Moreover, at present there is no clear consensus regarding how clinically rate spasticity and especially whether attributing an increase in muscle resistance exclusively to a hyperactive stretch reflex is accurate. As discussed above, pathological changes in passive muscle properties, especially in elasticity, may also contribute to stretch resistance and thus confound the test result.

The modified Ashworth scale (MAS) is a six-point ordinal scale used to assess the perceived resistance encountered during passive muscle stretching. Its validity is questionable since the reflex responses in the stretched muscle are not discriminated from non-reflex muscle components, and because the velocity of passive movement is not taken into account.[83,88] Moreover, a reduced range of joint movement due to contractures might limit its reliability.[89]

The Tardieu scale may be a more appropriate measure of spasticity since it evaluates the velocity of passive movements, as well as the angle at which a catch or clonus is felt and potential tendon retraction.[90] Nevertheless, this scale may not reflect the neural origin of spasticity. Its validity and reliability are still limited and have been evaluated mostly in children with cerebral palsy.[18]

1.5.2 Electromyography and quantitative measures

Electrophysiological and biomechanical techniques may complement clinical scales by objectively quantifying the degree of spasticity in a more sensitive and reliable way.[91-93] Biomechanical evaluation of spasticity was introduced by Evert Knutsson in 1976[94] and since then various devices and techniques have been developed.[52,53,95-97]

Electromyography has been added and coupled with other methods (such as hand-held dynamometers[98,99]) to determine the reflex-mediated muscle activity and distinguish it from passive movement resistance.[48,100,101] The H-reflex (i.e., Hoffman reflex) and F-waves, as well as the increase in H/M or F/M ratio (i.e., ratio between H-reflex or F-waves and M-response, i.e., the maximal electrical stimulation of a motor nerve)[102], the co-contraction index[103,104] or the novel A-ApA index[105] (calculated with the root mean square of agonist muscle activity by the mean between the root mean square of agonistic and antagonistic muscle activations) are different measure to estimate spasticity based on electrophysiological assessment. Unfortunately, the involved technology seems often to be too demanding and time consuming for routine clinical use.

The tonic stretch reflex threshold (TSRT) indicates the minimal joint angle at which abnormal motoneuronal recruitment begins when the muscle is at rest and there is no motion, which distinguishes it from the stretch reflex threshold (SRT), i.e., the joint angle at which motoneuronal recruitment begins for a specific velocity of stretch.[106,107] SRT has been suggested to be a functionally relevant measure of upper and lower limb spasticity, but it is difficult to quantify in clinical practice. In the latest years, TSRT testing has been incorporated into a portable device to meet the needs of clinicians,[108-110] and inter-rater reliability, minimal detectable change and responsiveness of the method were determined.[111]

Continued research and optimization of similar devices are required to further understand and to quantify spasticity and other non-neural components of increased muscle tone. Moreover, it is important to provide normative data that can be used to define normal population-based neuromuscular characteristics and to describe the effects of age, gender and anthropometric variables on neural and mechanical properties of passive movement resistance.

1.5.3 NeuroFlexor method

The NeuroFlexor™ has been developed on the basis of a generally recognized need for more valid and accurate methods to measure spasticity, and could be used in clinical research as well as in guiding clinical interventions.[112] The biomechanical algorithm used in the device has been validated, and data on reliability and sensitivity to change of this method have been previously described.[113-117] The resistance opposing passive stretch is measured in Newton (N) and recorded during a very slow movement, where it is very unlikely that a stretch reflex response is elicited, and during rapid isokinetic movement with a velocity fast enough to ensure that a stretch reflex response is elicited. That make it possible to distinguish and quantify the different contributors to the resisting force: the force due to muscle contractions induced by stretch reflexes (i.e., spasticity) and the viscous-elastic mechanical components.

1.6 SPASTICITY MANAGEMENT

An accurate evaluation of spasticity is essential for both diagnosis and to optimize choice and timing of treatment. Spasticity management comprises physical therapy, pharmacological agents and surgical treatment.[2,18,118] Choice of treatment options depends, as stated above, on the underlying mechanisms that result in an increased resistance to passive movement.[19] Increased resistance that is considered to be predominantly neural in origin might respond to pharmacological medications, for example using intramuscular injection of botulinum toxin A[119] or to transcutaneous electrical nerve stimulation[120]. In contrast other methods, such as stretching techniques would be expected to be more effective if the resistance is predominantly due to increased elastic resistance in the muscles and connective tissue. It is important to consider that the indications for the spasticity treatment refer only to the case in which the condition is disabling.

There is now consistent evidence that focal spasticity and associated disabilities after stroke may be reduced by treatment with intramuscular injection of botulinum toxin combined with physiotherapy.[118] Botulinum toxin injection causes a reversible neuromuscular blockade, with late effect of both weakness and relaxation of overactive muscles in upper motor neuron lesions.[119] The muscles are as a result amenable to stretching and lengthening, with a final positive impact in passive range of motion and disability scores.[121] However, the effectiveness of botulinum toxin treatment on walking is still debated.[122]

Non-pharmacologic interventions such as splinting or orthosis and strength or task-oriented training programs may also reduce spasticity after stroke although more evidence is needed.[85,123] Regular stretching can reduce sarcomere shortening and improve the viscoelastic properties of the muscles and other musculoskeletal structures, and help to increase or preserve their extensibility as well as to reduce contracture, pain and spasticity.[124-126] At present, physical therapy represents the standard treatment for all patients with spasticity, however, further studies should investigate the scientific evidence of effectiveness of this method.[18]

1.6.1 Electrical stimulation and the EXOPULSE Mollii method

Electrical stimulation by use of surface electrodes is a non-invasive therapeutic method used in patients with upper motor neuron lesion to improve voluntary motor control by increasing muscle strength, reducing spasticity and pain and increasing passive range of motion.[127,128] Methods applied include transcutaneous electrical nerve stimulation (TENS), neuromuscular electrical stimulation (NMES) and functional electrical stimulation (FES) that refers to the process of combining the stimulation with a functional task. The mechanisms of TENS in spasticity reduction are hypothesized to be mediated by activation of large diameter sensory nerve afferents modulating abnormal interneuron activity in several spinal segments; continuous somatosensory stimulation causing insensitivity to prolonged central excitation, accompanied by lower corticomotor neuron excitability; stimulation of plasticity of the central nervous system and synaptic reorganization of sensory and motor cortices.[120,129] NMES depends instead on delivering electrical pulses through the skin to repeatedly activate muscles.

It was hypothesized that it induces improvements in spasticity by facilitating neuroplasticity of the brain as well as within spinal cord circuitries (e.g., Ib inhibition, recurrent inhibition from Renshaw cells, disynaptic reciprocal Ia inhibition, presynaptic inhibition of Ia terminals and post-activation depression).[130]

Electrical stimulation can be effective in improving spasticity-related outcome measures within the ICF domains[1] of body structure and function (e.g., clinical MAS) as well as activity (e.g., walking), especially if used as an adjunct to conventional therapy (e.g., intramuscular botulinum toxin) or another active intervention for improving function of affected limbs.[120,131-133]

Brain lesion location may influence the therapeutic effect of electrical stimulation. Motor function seems in fact to improve after electrical stimulation treatment in the absence of lesions in basal ganglia while high grade lesions of the periventricular white matter area can prevent any therapeutic effect.[134]

The EXOPULSE Mollii method is an innovative approach designed to reduce disabling spasticity and improve motor function, through the mechanism of reciprocal inhibition.[135] By applying electrical stimulation at low frequencies and low intensities, The EXOPULSE Mollii provides sensory input but does not directly elicit muscle contractions, similarly to TENS. Growing experiences from clinical use of Mollii and pilot studies in patients with stroke and cerebral palsy suggest certain benefits of this treatment.[136-139] However, the specific effect of the method on post-stroke spasticity remain unstudied.

1.7 POLIOMYELITIS, LATE EFFECTS OF POLIO AND POST-POLIO SYNDROME

There is still a need to better understand the neuromuscular changes resulting from damage to descending motor pathways at different levels, i.e. lesions to the upper motor neuron as well as to the lower motor neuron, such as in post-polio syndrome. Damage to α motor neurons does not result in spasticity development but is associated with extensive remodeling of muscle and connective tissue, worthy of further investigation.

Poliomyelitis is a viral disease affecting the anterior horn cells and leading to flaccid paralysis with residual neurological deficits over time. The term late effects of poliomyelitis describes impairments that arise in poliomyelitis survivors and resulting in deterioration of functions over the decades.[140] They are often consequences of biomechanical alterations due to musculoskeletal deformities of affected limbs, osteopenia or osteoporosis and residual weakness but are also impairments related to comorbidity or aging.[141] Progressive post-polio syndrome (PPS) refers specifically to a complex of symptoms (i.e., progressive muscle weakness, fatigue and pain) that may occur after a period of functional and neurological stability of many years following the initial episode of poliomyelitis, which affect function, activity, participation and quality of life of the patients.[140,142]

A total of 12-20 million people have polio sequelae worldwide with the risk of developing PPS according to Post-Polio Health International.[143] The prevalence of PPS ranges widely between 20 and 75%, with the highest percentage in individuals that had previously paralytic polio illness.[144] In Sweden, around 10 000 – 15 000 people are estimated to have progressive PPS and late effects of polio, making paralysis following poliomyelitis the most common neuromuscular disorder.[145]

1.8 LOSS OF STRENGTH, PAIN AND FATIGUE

The key clinical features of PPS are progressive and persistent new muscle weakness or muscle fatigability, general fatigue, pain and cold intolerance.[141]

Muscle strength declines slowly over the years in polio survivors with or without PPS, decreasing about 1-2.5 % annually after the age of 50.[146,147] The inter-individual variability is however, relatively high. The progressive muscle weakness is associated with change in physical mobility, as findings reported an average loss of 15% of quadriceps strength over 10 years was associated with about 6% of decline in walking capacity.[148] Gender might be a contributing factor to the progressive decline in muscle strength, with a higher rate of decline in males.[149] Nevertheless, clear prognostic factors have not yet been identified.

Fatigue is multidimensional in individuals with polio sequelae and usually reported as the most disabling symptom.[150] About 90% of individuals with PPS complains of fatigue mainly physical in origin. Mental fatigue (decreased mental endurance) can also occur. Stress, depression and reduced self-efficacy have been identified as important contributors (potentially

modifiable) to generalized and mental fatigue, while pain and limited physical activity contribute to physical fatigue.[140,150]

Pain occurs in more than 50% of patients with PPS and is associated with poor physical activity[151] and higher level of depression.[140,152] It is most common in females, young individuals or patients who have had a long stable period.[153] Muscle and joint pain is related to overload of muscles, tendons, and joints.[145] Biomechanical changes secondary to musculoskeletal deformities from the underlying poliomyelitis as well as other superimposed neurological conditions may also cause pain.[140,145]

1.9 PATHOPHYSIOLOGY OF POST-POLIO SYNDROME

In spite of the high prevalence, the exact pathophysiology of PPS is still unclear. An imbalance between multiple processes is hypothesized, including mechanisms of muscle denervation and reinnervation, loss of motor units secondary to overuse, morphological changes due to ageing process, reactivation of residual poliovirus, and mostly inflammatory and autoimmune processes.[154-157] Robust evidence suggests that inflammatory processes at the spinal cord level and in the skeletal muscle play a significant role in the pathophysiology,[156,158,159] and they may serve as a target for therapeutic approaches.[157,160] However, the relationship between inflammatory mediators and the clinical progression of PPS is still unclear, and developing a better understanding of post-polio pathophysiology is therefore necessary.

Finally, alteration of the muscular architecture refers mainly to the decreased number in motor units of increased size, due to the reinnervation mechanism after acute polio infection, often associated with fibrosis and steatosis of muscle fibers.[155,161,162]

1.10 DIAGNOSIS OF POST-POLIO SYNDROME

Post-polio syndrome is an exclusion diagnosis based on clinical criteria aimed at evaluating muscular atrophy and muscle dysfunction. The recommended criteria established by March of Dimes International Conference on Post-Polio Syndrome[163,164], include:

1. Prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness and atrophy of muscles on neurological examination, and signs of denervation on electromyography

2. A period of partial or complete functional recovery, followed by an interval (usually 15 years or more) of stable neurological function

3. Gradual or sudden onset of progressive and persistent new muscle weakness or abnormal fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain

4. Symptoms should persist for at least a year

5. Exclusion of other causes.

Currently, there is no cure for PPS and individual treatment includes physical rehabilitation, adaptive and orthotic equipment, and mobility aids to manage the symptoms and to improve quality of life of the patients.[142] However, improving knowledge of the pathophysiology of the underlying processes may help to open up for new treatment strategies and to potentially identify whether there are subgroups of patients who may benefit from selected medical intervention.

2 RESEARCH AIMS

The overall aim of this thesis project was to improve methods of assessment of sensorimotor impairments after central or peripheral nervous system lesions by the use of standardized and valid objective measurement tools. The analysis of resistance contributions to passive movement using a biomechanical model would lead to enhanced detection and accuracy of spasticity and passive muscle changes in neurological disorders, such as stroke and post-polio.

Specific aims for the four studies were:

Study I: To provide NeuroFlexor hand module normative data from healthy adult subjects and to define cut-off values for neural and mechanical contributions to resistance to passive muscle stretch. Secondly, to use these data to evaluate spasticity at the wrist and fingers in patients recovering from stroke.

Study II: To assess the validity and the reliability of the novel NeuroFlexor foot module to evaluate resistance to passive stretch of the foot. Secondly, to provide reference data from a representative sample of healthy adult subjects and to establish cut-off values for the active and passive components of the resisting force.

Study III: To examine the immediate response to the electrical stimulation provided by the EXOPULSE Mollii Suit with regard to reduction of objective signs of spasticity, measured with the NeuroFlexor instrument.

Study IV: To characterize the response to passive muscle stretch with the NeuroFlexor instrument in subjects with prior paralytic poliomyelitis, with or without a diagnosis of progressive post-polio syndrome. Secondly, to compare the mechanical properties of prior-polio muscles with the characteristics in a reference population, and to explore the potential correlation between the NeuroFlexor components, muscular fatigue and pain.

3 MATERIALS AND METHODS

An overview of the research questions, study design, study population and data collection, is illustrated in Table 1.

Table 1. Summary of research questions, study design, number of participants and methods of the four studies

Study	Research questions	Design	Participants	Principal methods
Study I	Are the NeuroFlexor components related to the anthropometric variables or age? Can use of normative data for the neural and non-neural components of the resisting force, obtained from a large cohort of healthy subjects, aid early detection of upper limb spasticity after stroke? Do MAS ratings correspond to pathological NC values?	Cross-sectional study	N= 107 healthy subjects and N= 39 sub-acute stroke patients	NeuroFlexor hand module MAS a- and pROM Jamar isometric dynamometer
Study II	What are the neuromuscular responses to passive stretch in a healthy population defined using the NeuroFlexor foot module? Can the NeuroFlexor foot module provide an accurate estimation of reflex and mechanical components of muscle resistance in the lower limb? Can this novel tool be a measurement method for clinical decision making?	Cross-sectional and test – retest design	N= 73 healthy subjects and N= 15 chronic stroke patients	NeuroFlexor foot module EMG MAS a- and pROM
Study III	Can the NeuroFlexor hand and foot modules measure immediate effects of 60 min of treatment with the EXOPULSE Mollii suit at different stimulation frequencies on spasticity? Do subjective perceptions during treatment with the EXOPULSE Mollii differ with stimulation at different frequencies?	Double-blind controlled, randomized, cross-over study	N= 20 chronic stroke patients	NeuroFlexor hand and foot modules EMG MAS a- and pROM Standardized questionnaire
Study IV	Which are the mechanical and reflex-related resistance components in a cohort of patients with prior-polio assessed with the NeuroFlexor hand and foot modules? Do the mechanical properties differ from normative data previously collected? Are the mechanical properties related to muscle atrophy, perceived fatigue and/or pain?	Exploratory observational study	N= 19 patients with prior polio	NeuroFlexor hand and foot modules a- and pROM Jamar isometric dynamometer Biodex dynamometer MRC FSS MFI-20 VAS

Abbreviation: a- and pROM: active and passive range of motion; EMG: surface electromyography; MAS: Modified Ashworth scale; MRC: Medical Research Council scale; FSS: Fatigue Severity Scale; MFI-20: Multidimensional Fatigue Inventory; VAS: Visual Analog Scale.

3.1 STUDY SETTINGS

Studies were carried out at the regional University Department of Rehabilitation Medicine at Danderyd Hospital, Stockholm, Sweden. The department provides qualified rehabilitation interventions by multi-professional teams to individuals living in the Stockholm region and in need of specialized rehabilitation interventions. Patients suffer an acquired brain injury, or congenital or acquired brain injury at a young age or residual conditions after poliomyelitis and long-term pain.

Inpatient rehabilitation is provided to adults of working age (18 – 70 years) in the sub-acute phase after acquired brain injury. Outpatient rehabilitation units are dedicated to provide rehabilitation interventions after the sub-acute phase or long-term.

Post-polio outpatient clinic offers comprehensive rehabilitation interventions to adult patients (> 18 years) with late effects of polio or post-polio syndrome, including physical and psychological problems and social issues.

3.2 RECRUITMENT

A total of 93 patients (74 patients in different phases after stroke and 19 patients with prior polio) and 180 healthy subjects were recruited between February 2015 and June 2021.

Stroke patients in Study I were extracted from the *ProHand study* cohort, a longitudinal study carried out at the Department of Rehabilitation Medicine, Danderyd Hospital, between March 2013 and September 2019 (ClinicalTrials.gov Identifier: NCT02878304). Eligible participants for Study II and IV were recruited from patients referred to the outpatient rehabilitation unit and post-polio unit at Danderyd Hospital, respectively. Finally, eligible participants for Study III were identified from primary health care units located in Stockholm, Sweden, by physiotherapists who informed the patient about the study and asked for consent for the study coordinator to make contact.

Healthy subjects were employees and students of Danderyd University Hospital, Stockholm, Sweden, or individuals interested in enrolling in a research study.

3.2.1 Study population

3.2.1.1 Study I

The participants in this first study comprised 107 healthy adult subjects (55 women and 52 men; 44.5 mean age ± 14.0 years, range 20 to 68 years) and 39 patients (13 women and 26 men; mean age 55.4 ± 8.3 years, range 33 to 69 years) in the sub-acute phase after stroke (i.e., mean time from onset to inclusion was 2 – 4 weeks).

3.2.1.2 Study II

Seventy-three healthy adult individuals (47 women and 26 men; 41.0 mean age ± 12.6 years, range 20 to 70 years) and fifteen patients (4 women and 11 men; 51.1 mean age ± 11.9 years, range 32 to 71 years) in the chronic phase after stroke (i.e., ≥ 6 months after onset) were included in Study II.

3.2.1.3 Study III

A sample of 20 chronic stroke patients (i.e., ≥ 12 months after onset) was included in Study III (7 women and 13 men; 58.8 mean age ± 13.1 years, range 28 to 79 years).

3.2.1.4 Study IV

A total of 19 patients (10 women and 9 men; 51.7 mean age ± 19.0 years, range 20 to 77 years) with history of paralytic poliomyelitis, with or without diagnosis of progressive PPS, were recruited in Study IV. In addition, normative data based on the healthy individuals included in Study I and Study II were used for comparative purposes.

3.2.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for all studies are summarized in Table 2. Eligible patients who regularly received botulinum toxin injections could be included in Study II and III only if their latest treatment was at least 3 months before the study assessment and no new treatment was scheduled during the study period. Patients with ongoing pharmacological treatment for management of spasticity (e.g., with Baclofen), could participate in Study III only if the treatment regimen had been stable for at least 3 months.

Healthy subjects were volunteers with no history of neurological or rheumatologic disease.

Table 2. Inclusion and exclusion criteria

		Study I	Study II	Study III	Study IV
Inclusion criteria	First ever stroke	X	X	X	
	Hemiplegia of upper and/or lower extremity	X		X	
	Clinical diagnosis of spasticity	X	X	X	
	Limited activity in the upper extremity			X	
	Limited ability to walk			X	
	History of paralytic poliomyelitis				X
Exclusion criteria	Presence of any other neurological or rheumatologic disorder	X	X	X	X
	Cerebellar lesions	X			
	Presence of any other severe concomitant disease, uncontrolled epilepsy or blood pressure;			X	
	Major surgery during the last year			X	
	Limited range of motion of wrist and/or ankle	X	X	X	X
	No objective sign of spasticity according to NeuroFlexor hand module measure			X	
	Any implanted medical devices	X	X	X	X
	Pregnancy	X	X	X	X
	BMI > 35			X	
	Inability to understand oral and written information	X	X	X	X

3.3 INTERVENTION

The EXOPULSE Mollii method (Figure 2) was developed by the Exoneural Network AB (Danderyd, Sweden) and represents an innovative approach for non-invasive and self-administered electrical stimulation. It was designed to reduce disabling spasticity and improve motor function.

Figure 2. The EXOPULSE Mollii suit

The figure has been reproduced with permission from Exoneural Network AB

The EXOLPULSE Mollii suit (Class IIa for medical device CE marking) consists of a tight-fitting jacket and trousers incorporating 58 electrodes positioned to potentially stimulate a total of 40 muscles throughout the body. Only a subset of the electrodes were activated for each participant of Study III. Choice of electrodes was based upon an initial clinical evaluation of the degree of spasticity performed by a physiotherapist, in order to apply the electrical stimulus specifically to the antagonists of muscles identified as spastic for each individual.

The electrical stimulation delivered through the EXOPULSE Mollii was applied at two active frequencies (20 and 30 Hz) and an "OFF" setting in a randomized order, every second day. Twenty Hz was chosen as this was the frequency commonly adopted in clinical practice at the time of the study, and 30 Hz represented the maximum frequency anticipated by the suit. The "OFF" setting was a sham inactive stimulation at 0 Hz.

For further details, please refer to Scientific paper III.

3.3.1 Randomization

In Study II, the order in which the assessments with the NeuroFlexor foot module were performed at the different isokinetic velocities, was randomized to minimize order effects by using a random number generator. The three sequences were: (a). 5, 120, 180, 240 deg/s; (b). 120, 5, 240, 180 deg/s, and (c). 240, 120, 180, 5 deg/s.

In Study III, the randomization of the order in which the frequencies of the electrical stimulation delivered through EXOPULSE Mollii suit were tested on patients, was performed using a block design, by a physiotherapist not otherwise involved in the study.

3.4 DATA COLLECTION

In Study I, II and III testing was performed in a single session. A health status questionnaire was administered and anthropometric measurements such as height, body weight, hand and/or foot length, and forearm and/or calf circumference recorded. All assessments were performed by the same medical doctor experienced in stroke rehabilitation. The evaluation took 2 – 2.5 hours in most cases.

In Study III, a physiotherapist and a medical doctor blinded to the frequency of stimulation conducted the clinical assessments before, during, and after each intervention session on day 1, 2, and 3. Evaluations took 1 – 1.5 hours in most cases.

A list of assessment methods used in Study I – IV, is presented in Table 3 according to the International Classification of Functioning, Disability, and Health domains of body structure and function (ICF).[1]

Table 3. Assessments of body function, activity and participation limitations adopted in the four studies

ICF-domain	Assessment methods	Targeted Functioning	Study I	Study II	Study III	Study IV
Body function	NeuroFlexor method	Neural and mechanical components	X	X	X	X
	Surface electromyography	Reflex muscle activity		X	X	
	Goniometer	Active and passive range of motion	X	X	X	X
	Jamari isometric dynamometer	Maximum voluntary contraction (MVC) during power grip	X		X	
	Biodex dynamometer	Maximal isometric ankle dorsiflexion				X
	Modified Ashworth scale (MAS)	Spasticity	X	X	X	
	Medical Research Council scale (MRC)	Muscle strength				X
	Visual Analog Scale (VAS)	Pain				X
	Fugl-Meyer scale for upper (FMA–UE) and/or lower extremity (FMA–LE)	Sensorimotor function including voluntary and passive movement, tactile sensibility to light touch, proprioception and pain	X		X *	
Body function, activity and participation	Fatigue Severity Scale (FSS)	Fatigue				X
	Multidimensional Fatigue Inventory (MFI-20)	Fatigue				X
Body function, activity	Standardized questionnaire	Subjective Perceptions of the use of the EXOLPULSE Mollii suit			X	

* Method used to assess patient characteristics.

3.4.1 NeuroFlexor method

The NeuroFlexor™ method (Aggero MedTech AB, Älta, Sweden) allows to quantify the relative contributors to the passive movement resistance during wrist extension or ankle dorsiflexion, i.e., the neural component and passive muscle components reflecting changes in mechanical properties such as viscosity and elasticity.

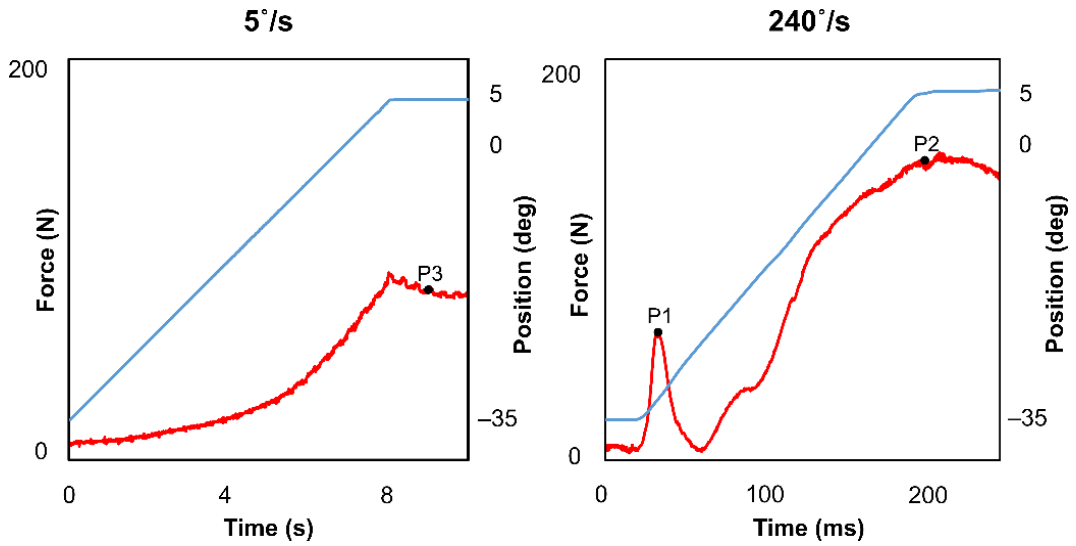
Figure 3. NeuroFlexor hand module

The figure has been reproduced with permission from Aggero MedTech AB

The method was developed using Koo and Mak's neuromusculoskeletal model[165], which simulates the resistance of the muscles and connective tissue opposing a constant angular velocity on elbow extension.

To allow calculation of the different contributors, resistance is recorded by the NeuroFlexor instrument both at a very slow movement (5 deg/s), during which it is very unlikely that a stretch reflex response is elicited, and also during rapid isokinetic stretch with a movement velocity fast (236 or 240 deg/s) enough to ensure that a stretch reflex response is elicited, as shown in Figure 4.

Figure 4. NeuroFlexor force traces



Resistance profiles (N, newton) during slow and fast velocity movements in a stroke patient. Blue traces show the angle of ankle movement (from plantarflexion to dorsiflexion). Red traces show resisting force. Three time points are: P3 1 s after slow passive stretch; P1 and P2 during the fast movement. Measured value of neural component was 63.99 N, elastic component 71.98 N and viscous component 2.93 N.

Elastic component (EC) is the length-dependent resisting force that increases as muscles and tendons are stretched. EC is expressed such that high EC reflects lower elasticity of tissues. It is recorded 1 s after the onset of the slow stretch movement (at P3).

Viscous component (VC) is the velocity-dependent resisting force produced by friction from neighbouring tissues, for example sliding muscle fibres. VC is highest during the initial acceleration and continues at a lower level during the remaining muscle stretch. It is thus composed by an early viscosity recorded at the first amplitude peak during acceleration phase (P1), and a late viscosity measured at the end of the movement (P2), which is equal to approximately 20% of the initial viscosity.

Neural component (NC) is the active force produced by muscle contractions induced by stretch reflexes. NC is estimated at the maximal stretch at the end of the movement (P2) by subtracting EC and VC from the total force, measured in Newton (N).

The biomechanical model was initially applied to the NeuroFlexor hand module, and data on the validity, reliability and sensitivity to anti-spastic treatment change of this method have been previously described.[112,114,117]

3.4.1.1 Acceleration profiles

Inertia is one of the contributors to the total resistance calculated by the biomechanical algorithm incorporated in the NeuroFlexor instrument as $IC = m\ X\ a$, where m is the mass of the hand or foot in kg, and a is the acceleration in m/s^2. The mass is estimated in the model as percentage of the total body weight, i.e., 0.6% for the hand and 1.3% for the foot. The acceleration of the NeuroFlexor hand module was previously determined and increased consistently with stretch velocity.[112] A series of experiments performed both in healthy subjects

and post stroke patients, determined the rate of acceleration (in deg/s^2) of the NeuroFlexor foot module for different stretch velocities, as presented in Table 4.

Table 4. Rate of acceleration of the NeuroFlexor foot module

NeuroFlexor hand module		**NeuroFlexor foot module**	
Stretch velocity	**Linear Acceleration**	**Stretch velocity**	**Acceleration**
71 deg/s	9.50 m/s^2	120 deg/s	5.42 deg/s^2
142 deg/s	11.80 m/s^2	180 deg/s	9.42 deg/s^2
236 deg/s	21.00 m/s^2	240 deg/s	16.13 deg/s^2

3.4.1.2 Procedure

A series of pilot tests were conducted both in healthy subjects and post stroke patients in order to optimize the NeuroFlexor foot module assessment protocol, and to investigate the effect of various knee and ankle joint positions on the resisting force.

Firstly, the knee joint was set at 90, 60, 45 and 30 degrees from the maximal knee extension to examine the relative contribution of the gastrocnemius and soleus muscles to the passive stretch response. As a biarticular muscle, the fascicle length of medial gastrocnemius muscle both increases with the dorsiflexion of ankle and decrease with the flexion of knee, and thus may influence the elastic contributor to the resistance.[166] Assessments with the higher degrees of knee flexion turned out to be not feasible due to excessive level of resistance developed in the lower extremity.

The ankle joint was set at a starting angle of 50, 40 and 35 degrees of plantarflexion to a final angle of 0, 5 and 10 degrees of dorsiflexion. The choice of the ankle range of movement was based on the concept that an angle of 5 / 10 degrees of ankle dorsiflexion is required to achieve foot clearance during the swing phase of gait. It was hypothesized that at least a sub-sample of patients could achieve this range of passive movement. The final assessment procedure defined for the lower extremity, is reported below.

The measurement with the NeuroFlexor hand module followed a previously developed standardized protocol.[114] The participants were seated comfortably, with the shoulder in a slightly abducted position and the elbow in 90 degrees of flexion, the forearm in pronation and the hand placed on the device platform. Passive extension movement of the wrist were completed at two isokinetic velocities, slow (5 deg/s) and fast (236 deg/s), from a starting wrist angle of 20 degrees of palmar flexion to 30 degrees of extension, for a total range of movement of 50 degrees.

The assessment with the NeuroFlexor foot module was conducted similarly with the participants in sitting position and instructed to relax. Passive dorsiflexion movement of the ankle were performed at 5 deg/s and 240 deg/s, from 35 degrees of plantarflexion to 5 degree of dorsiflexion (or -5 degrees in case of limited range of motion).

Dedicated software (NeuroFlexor Scientific, Release 1.0.0) calculated the value of NC, EC and VC by averaging the resisting forces of the latest four slow and nine fast passive movements

(the first movements of both velocities were excluded to limit contamination by startle response).

3.4.2 Surface electromyography

Surface electromyography (EMG) of the flexor carpi radialis, gastrocnemius, and soleus muscles recordings were synchronized with the NeuroFlexor assessment in order to measure the response evoked by stretching of the muscle at controlled velocities. The EMG signal amplitude reflects the muscle over-activity caused by the velocity-dependent exaggeration of the stretch reflex, which is consistent with the definition of spasticity by Lance.[47]

Disposable Ag/AgCl surface electrodes were placed in a belly-tendon montage aligned with the muscle fibers using the SENIAM electrode placement guidelines.[167]

3.4.3 Clinical measures

3.4.3.1 Passive and active range of motion

A goniometer was used to measure passive and active range of motion (ROM) of the wrist and/or ankle in order to evaluate any limitation in joint movement related to changes occurring in soft tissue, and moreover, to minimize the risk of discomfort or injury during NeuroFlexor assessment.

3.4.3.2 Jamari isometric dynamometer and Biodex dynamometer

Jamar isometric dynamometer (Digital Hand Dynamometer, Saeham, South Korea) was used to measure the maximum voluntary contraction (MVC) during power grip. The Biodex® Multi-Joint System 3 PRO dynamometer (Biodex Medical, Shirley, New York, USA) was used to assessed the maximal isometric ankle dorsiflexion (peak torque). Measurements of these lower limb muscles is important since weakness affects often the ankle dorsiflexor muscles in individuals after prior polio, increasing walking difficulties and reducing balance with impact on daily activities and participation.[168,169] Three maximal isometric measurements of the flexor muscles of the hand and of the dorsiflexor muscles were performed, and the mean value from the three attempts was recorded.

For further details regarding the procedure of Biodex measurements, please see Scientific paper IV.

3.4.3.3 Modified Ashworth scale

Modified Ashworth scale[83] (MAS) assesses clinical ratings of resistance to manual stretch on a six-point ordinal scale. The scale varies from 0, which represents no spasticity, and 4, in presence of muscle rigid in flexion or extension. The modified version of the scale presents an addition grade (1+, i.e., “Slight increase in muscle tone, manifested as a catch, followed by minimal resistance through the remainder (less than half) of the range of motion”) compared to the original version, and was developed since patients present usually low level of spasticity.

For analysis and interpretation of the data, the grades were converted as: 1+ to 2, 2 to 3, 3 to 4 and 4 to 5.

In spite of its limitations[170,171], the scale is widely applied in clinical practice and research, and therefore was used for comparison with previous studies.

3.4.3.4 Medical Research Council scale

Medical Research Council scale[172] (MRC) assesses the muscle strength in the upper and lower extremities, and was used to assess shoulder abductors, elbow flexors and wrist extensors, and hip flexors, knee extensors and foot dorsiflexors, respectively, grading from 0 for no movement observed, to 5 in case of normal muscle contraction against resistance, for a total score of 60.

3.4.3.5 Fugl-Meyer scale

Fugl-Meyer assessment for upper (FMA-UE) and lower extremity[173] (FMA-LE) measures sensorimotor functions including voluntary and passive movement, tactile sensibility to light touch and proprioception, and pain during passive range of motion. The maximum scores are 126 and 86 points, respectively, with a lower score indicating more severe impairment. The scale is a reliable and valid instrument for measuring upper and lower limb impairment after stroke.[174-176]

3.4.3.6 Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS)[177,178] is a 9-statements self-administered questionnaire rating the severity of fatigue, and its effect on patient's activities and participation. Each statement is scored from 1 to 7. The sum of the 9 scores (ranging from 9 to 63) is then divided by 9 to obtain the final score, with a higher final score corresponding to more severe fatigue which affects the patient's activities more negatively. A final score of 4 or higher is indicative of a moderate to a high level of fatigue. The scale was originally designed to rate fatigue in multiple sclerosis or systemic lupus erythematosus, but it is nowadays a valid and reliable tool used in different patient populations.[178-180]

3.4.3.7 Multidimensional Fatigue Inventory (MFI-20)

The Multidimensional Fatigue Inventory (MFI-20)[181] is a 20-item self-administered questionnaire that assesses five different fatigue dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Each item is scored from 1 to 4, yielding a total fatigue score from 20 to 100. Higher finale score indicates a higher level of fatigue, with a value > 60 defining severe fatigue. The Swedish version of MFI-20 is a valid and reliable instrument for measuring fatigue in different patient populations.[182]

3.4.3.8 Visual Analog scale

Visual Analog Scale (VAS) assesses the intensity of pain on a 10 cm line, ranging from 0= no pain, to 10= worst imaginable pain.[183]

3.4.3.9 Study specific questionnaire

Participants of Study III were interviewed regarding their perception of the effects of EXOPULSE Mollii, using a standardized semi-structure questionnaire developed by our study group. The patients were asked to respond to the questions "*How did you feel putting the Mollii suit on?*", "*How do you feel wearing the Mollii suit under stimulation?*", "*Do you experience any positive effects or negative effects or discomfort?*"

The patients were also asked to rate the effort of putting the suit on and any discomfort during the stimulation session, from 1 (no effort / no discomfort) to 10 (maximum imaginable effort / discomfort).

3.5 DATA ANALYSIS

EMG data were acquired in Study II and III using Spike2 software (Version 7.12; CED) and analysed off-line using custom-written programs in MATLAB R2021a (The MathWorks, Inc., Natick, Massachusetts, USA). A detailed description of the analysis procedure is reported in the corresponding papers. Briefly, the EMG signals were amplified, sampled at 1 kHz and rectified. The root mean square of the EMG signal, with a 50 ms sliding window, was computed to generate the EMG amplitude during the whole NeuroFlexor passive movement.

3.6 STATISTICAL ANALYSIS

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0, 26.0 and 27.0 (Armonk, NY: IBM Corp). *P* value of < 0.05 was considered to be significant.

An overview of the statistical methods adopted in each paper is presented in Table 5.
Descriptive statistics (mean ± standard deviation (SD), median and interquartile range (IQR), minimum and maximum values, 95% confidence interval (CI), frequency and percentage) were used to present baseline characteristics and outcomes, after assessing normality using Shapiro-Wilk's test and graphically with boxplots, histograms and Q-Q plots. A natural log transformation was applied to allow further analyses of skewed data.

Table 5. Statistical methods used in the four studies

Statistical methods		**Study I**	**Study II**	**Study III**	**Study IV**
Analysis of difference within and between group(s)	Mann-Whitney *U* test	X	X		X
	Independent t Test				X
	Pared t Test		X		
	One way ANOVA	X			X
	Repeated measures ANOVA		X	X	
	Two-way repeated measures ANOVA			X	
	Friedman test		X		
Analysis of association	Pearson's correlation	X			
	Spearman's rank correlation	X	X	X	X
	Linear regression	X			
Analysis of variability	Intraclass correlation coefficient		X		

In Study I and II, cut-off scores for NeuroFlexor hand and foot module components were calculated by adding 3 SD to the mean. This conservative approach ensured that almost all healthy subjects fall within the cut-off score and therefore that a measured value above the limit could be considered pathological. Additionally, age and gender specific reference limits for upper extremity were established using prediction reference limits (99 % CI) obtained from linear regression. For the lower extremity, a Receiver Operating Characteristic (ROC) curve analysis was used to validate cut-off values for neural component in function of limits of normality (as mean + 2 SD) of the stretch induced EMG amplitudes.

A repeated measures analysis of variance (rm-ANOVA) was employed in Study II in order to examine the difference in neural component quantified at three different stretch velocities both in the stroke patients and healthy subjects. A non-parametric Friedman test confirmed the differences in stroke patients' NC depending on stretch velocities. Rm-ANOVA evaluated also the potential spontaneous fluctuations in spasticity (i.e., difference in neural component and NeuroFlexor total resistance) over the course of Study III. Two-way repeated measures ANOVAs were conducted instead to examine the effects of stimulation delivered through EXOPULSE Mollii at the different stimulation frequencies (OFF settings, 20 and 30 Hz). Finally, one-way ANOVA using Tukey post hoc tests investigated group differences in NeuroFlexor components in Study IV.

Gender differences were evaluated with Mann-Whitney *U* test in all the studies. The test also compared the NeuroFlexor hand and foot module components quantified in healthy subjects with the values measured in patients after stroke (Study I and II) or with prior polio (Study IV). Independent t Test was conducted for normally distributed data.

Pearson's correlation or Spearman's rank correlation, when data were not normally distributed, were conducted to test for relationships between age, participants' anthropometric data and NeuroFlexor variables in all studies. In addition, correlation tests investigated relationships between EMG signal and NC as well as between the clinically scored muscle tone according to MAS and the NeuroFlexor neural component (Study II and III). In Study IV, the correlation analysis explored the relationship between the NeuroFlexor components and perceived fatigue and pain. Corrections for multiple comparisons were done using Bonferroni corrections, to rule out false positives.

Finally, a test-retest design over an interval of 10 minutes was used to assess intra-rater reliability of the NeuroFlexor foot module (Study II). A two-way random effects model single measure was used to generate an intraclass correlation coefficient model 2.1 ($ICC_{2,1}$) with 95% CI, rated based on Currier's reliability level.[184] A paired t-test was then used to assess any systematic bias between the two sessions.

3.7 ETHICAL CONSIDERATION

All studies adhered to the declaration of Helsinki and were reviewed and approved by the Swedish Ethical Review Authority, with diary numbers: 2014-77-32 (Study I), 2016/2213-31/2 (Study II), 2017/935-31 (Study III) and 2019-02604 (Study IV).

Study III was registered as a clinical trial at https://clinicaltrials.gov/ct2/show/NCT04076878, identifier: NCT04076878.

The rights, safety and well-being of all participants were preserved by obtaining written informed consent to participate after written and oral information about the specific study, and by maintaining confidentiality. Patients and healthy individuals were informed that they may terminate participation at any time without explanation, and that this would not have any impact on their further contacts with the health care system. All collected data were protected by the Swedish Public Access to Information and Secrecy Act and were stored in coded records, with the key only available to the investigators.
None of the study procedures were associated with any significant risk of serious adverse event. The major measurement tool, the NeuroFlexor method, is CE certified[185]. The EXOPULSE Mollii suit is CE certified and commonly used by patients for the treatment of spasticity and pain. Electrical stimulation may interfere with monitoring equipment and should not be placed close to transdermal drug delivery systems. For this reason, any implanted electrical device was an exclusion criterion in Study III.

4 RESULTS

The main findings of Studies I – IV are reported in summary form in this chapter. For further details of the results, please refer to the corresponding scientific paper in the appendix.

4.1 NORMATIVE DATA AND CUT-OFF VALUES

Study I and II provided normative data for NeuroFlexor hand and foot modules from two large cohorts of healthy subjects (N= 107 and N=73, respectively). Age, gender and anthropometric measurements effects on the NeuroFlexor components of the upper and lower extremities were described.

Age correlated inversely with EC measured in the upper extremity ($r = -0.30$, $p = 0.01$). In the lower limb, there was no significant correlation between age and any NeuroFlexor component ($p > 0.22$). In both extremities, there was no gender differences for NC and VC. However, males had a statistically significantly higher EC compared to females both in the upper and lower extremity ($F = 12$, $p = 0.001$ and $U = 216$, $p < 0.001$, respectively).

Elasticity represented the major contributor to the resistance to passive movement both in in the upper and lower extremity. Values of mean ± SD or median (IQR) of NeuroFlexor components are reported (in Newton, N) in Table 6.

Table 6. NeuroFlexor hand and foot modules components (Newton, N)

	NeuroFlexor hand module	**NeuroFlexor foot module**	
		30° of ankle movement	**40° of ankle movement**
Neural component	0.8 ± 0.9	7.30 (6.41)	13.37 (7.97)
Elastic component	2.7 ± 1.1	28.13 (15.31)	47.13 (26.16)
Viscous component	0.3 ± 0.3	3.53 (1.24)	3.57 (1.29)

Mean ± SD or median (IQR).

Cut-off values for detection of spasticity in the upper and lower extremities were established by adding 3 SD to the mean, and reported in Table 7. In the lower limb, two limits were calculated respectively for the two range of muscle stretch, 30 and 40 degrees.

Table 7. Cut-off values for components of NeuroFlexor hand and foot modules (according to mean + 3SD)

	NeuroFlexor hand module	**NeuroFlexor foot module**	
		30° of ankle movement	**40° of ankle movement**
Neural component	3.4	21.80	32.97
Elastic component	6.0	59.60	99.98
Viscous component	1.1	6.49	6.33

Additionally, specific limits of normality for the upper extremity were obtained from a linear regression model with 99 % CI limits, and are here presented for the only component which is affected by age and gender, that is elasticity.

Table 7. Reference limits for elasticity measured with the NeuroFlexor hand module obtained from a linear regression analysis (99 % CI) related to age and gender (N, newton)

	30 years	**40 years**	**50 years**	**60 years**	**70 years**
Elastic component					
All population	5.8	5.6	5.3	5.1	4.9
Male	6.6	6.2	5.8	5.4	5.1
Female	4.8	4.7	4.7	4.6	4.5

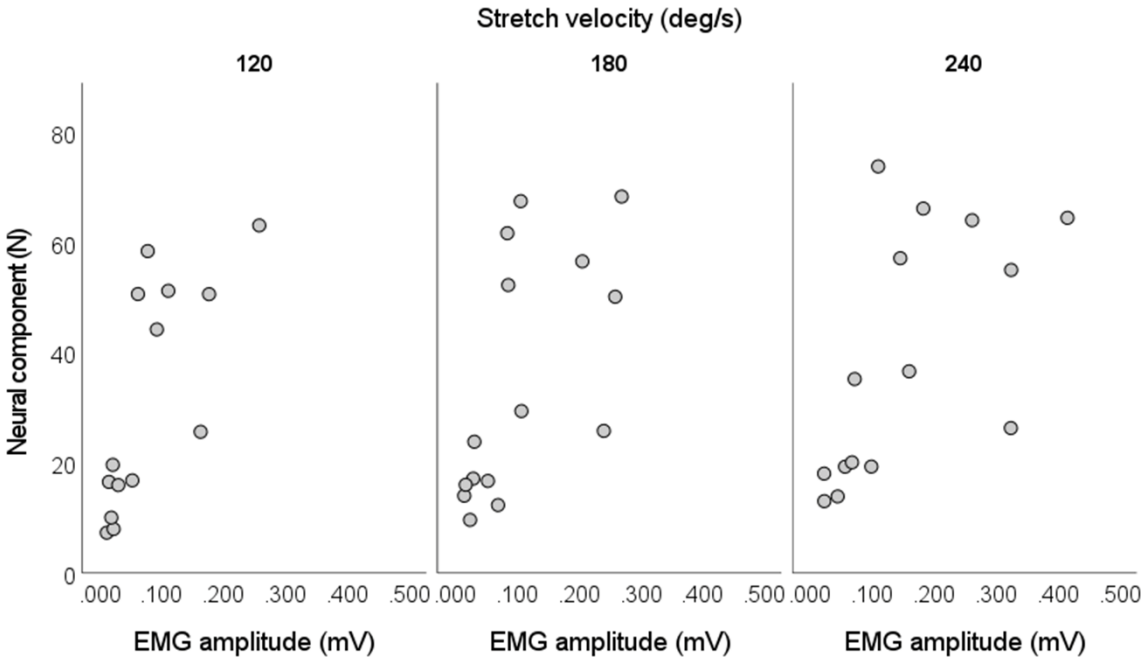
In the lower extremity, a Receiver Operating Characteristic (ROC) curve analysis was used to determine cut-off value for NC, by discriminating between pathologic and non-pathologic amplitude of the EMG signal recorded during the NeuroFlexor assessment. The cut-off value identified for 30 degree stretch was 18.94 N, and 31.46 N for 40 degree stretch.

4.2 VALIDITY OF THE NEUROFLEXOR FOOT MODULE

Evidence of validity of the NeuroFlexor foot module was provided in Study II in two ways. Firstly, the velocity dependence of the neural component was investigated by performing passive dorsiflexions of the ankle at different controlled velocities. NC differed significantly between velocities, both in stroke patients [$F(1.3, 17.3) = 7.82$, $p = 0.008$] and a sub-group (n= 18) of healthy subjects [$F(1.3, 22.7) = 16.30$, $p < 0.001$]. While NC increased significantly across all velocities in healthy subjects, the increase in NC was significant only for passive movements at 120 deg/s, or 180 deg/s, compared to 240 deg/s in stroke patients.

Secondly, NC correlated significantly with the EMG response to soleus muscle stretches at all velocities ($p < 0.001$), as shown in Figure 5. NC correlated also with EMG amplitude of gastrocnemius muscle at 120 deg/s stretch ($p = 0.005$). Notably, no EMG responses were visually detected during passive stretches at 5 deg/s and no significant correlation was found between EC and EMG amplitude.

Figure 5. Scatterplot of NeuroFlexor neural component and electromyography response



Correlation between neural component and EMG amplitude of soleus muscle at different velocities of muscle stretch: $r_s = 0.82$, $p < 0.001$ at 120 deg/s; $r_s = 0.76$, $p < 0.001$ at 180 deg/s and $r_s = 0.76$, $p < 0.001$ at 240 deg/s.

4.3 RELIABILITY OF THE NEUROFLEXOR FOOT MODULE

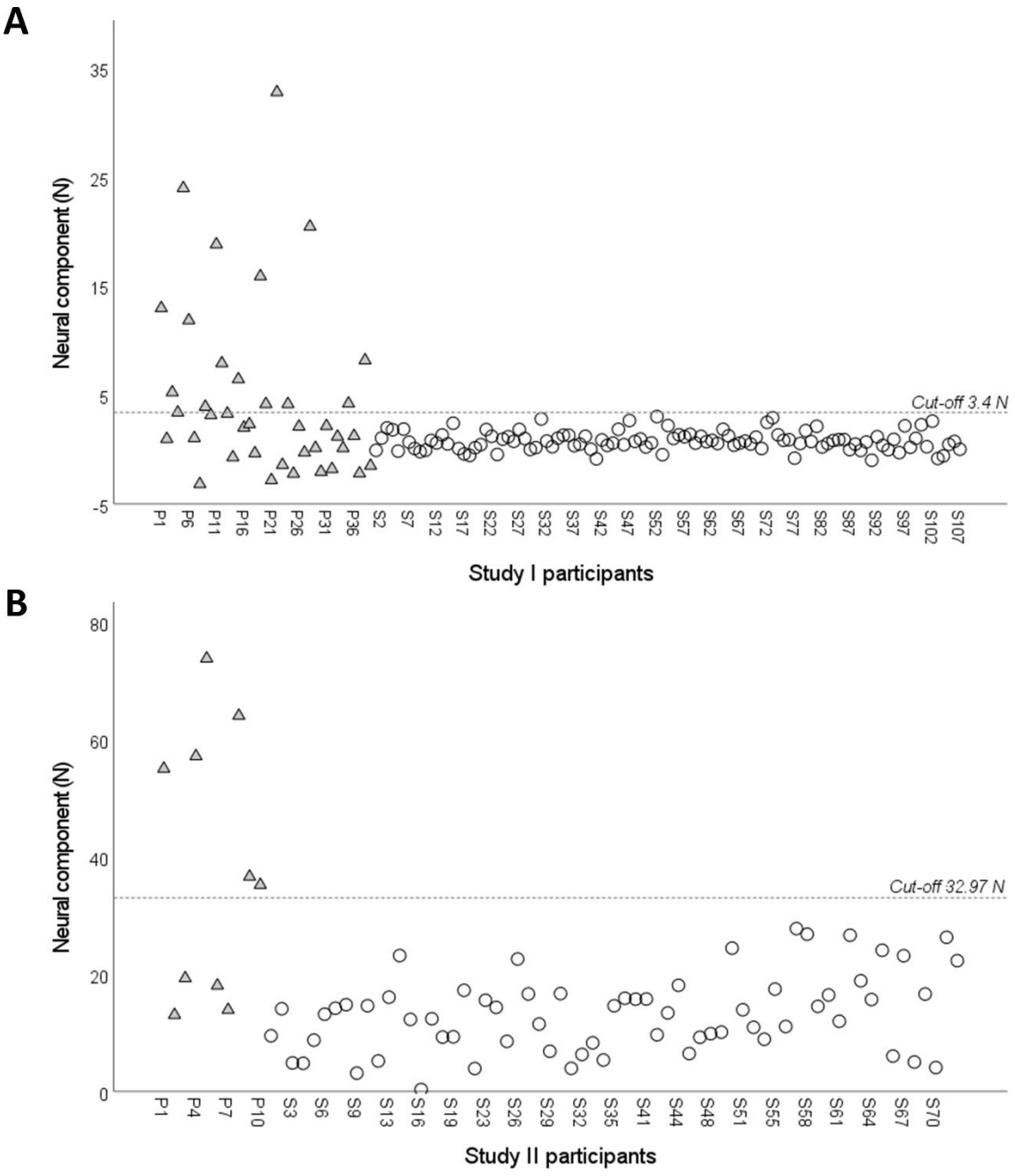
Study II also explored the intra-rater reliability of the measurements with the NeuroFlexor foot module. Reliability was good for NC within rater ($ICC_{2,1} \geq 0.899$, 95% CI 0.70 – 0.97), high for EC ($ICC_{2,1} \geq 0.909$, 95% CI 0.72 – 0.97) and fair for VC ($ICC_{2,1} \geq 0.702$, 95% CI 0.24 – 0.90).

4.4 APPLICATION OF THE NEUROFLEXOR METHOD

4.4.1 Diagnosis of spasticity

Healthy population-based cut-off values established in Study I and Study II proved useful for detection of pathologically high neural and mechanical components of the resistance produced during passive stretch of upper and lower extremities in stroke patients. Sixteen stroke patients had NC values at or above the upper extremity cut-off value of 3.4 N (mean + 3SD) and six out of 10 stroke patients presented pathological NC above the cut-off limit of 32.97 (mean + 3SD) in the lower extremity (Fig. 6). The ROC curve analysis for NC, gave the same results.

Figure 6. Scatterplot of the neural component in Newton (N) measured in stroke patients (triangles) and healthy subjects (circles) with A. the NeuroFlexor hand module and B. the NeuroFlexor foot module



Stroke patients presented higher NC compared to healthy subjects, measured both in upper ($U = 1487.5$, $p = 0.008$) and lower extremity ($U = 19.00$, $p < 0.001$). However, while NC represented the main contributor to the total resistance of stroke patients' upper limb, EC was the component contributing the most in the lower extremity.

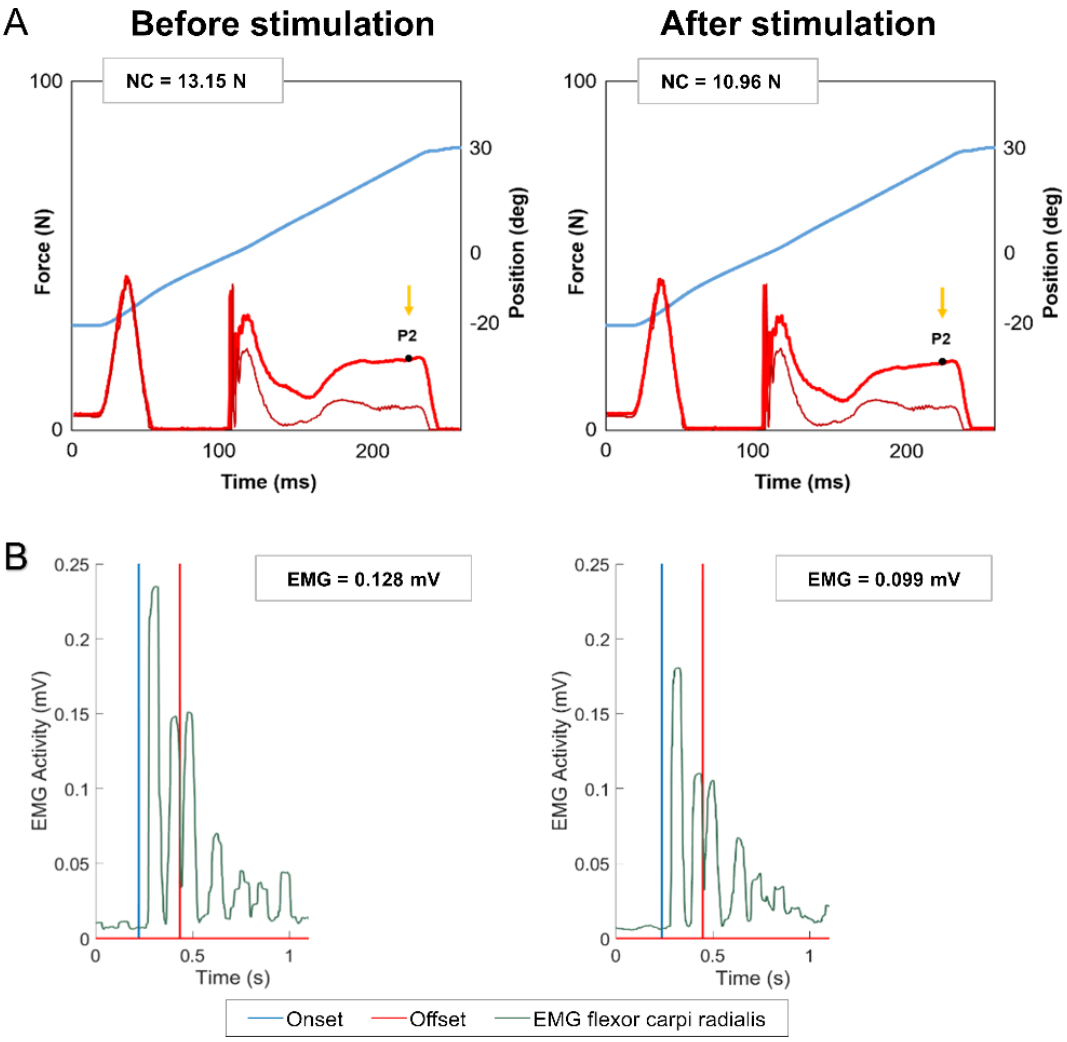
4.4.2 Effects of electrical stimulation

Study III explored the feasibility of using the NeuroFlexor instrument to assess and compare the immediate effects of the EXOPULSE Mollii on objective signs of spasticity at different frequencies of stimulation.

At the group level, no significant effect was detected on NC measured in the upper and lower extremity ($p = 0.352$ and $p = 0.803$, respectively), or on EMG amplitude recorded on the flexor carpi radialis, gastrocnemius, and soleus muscles ($p = 0.381$, $p = 0.644$, and $p = 0.625$, respectively). However, the variability in response to the electrical stimulation delivered through the EXOPULSE Mollii was high at the individual level, especially in patients who presented severe spasticity (i.e., NC $\geq$ 8 N[36]) at baseline. Fifty percent of patients presented in fact a decrease of NC greater than 1 N (i.e., beyond the margin of measurement error of the NeuroFlexor instrument) in the upper extremity, and 80% in the lower extremity, after 60 minutes of stimulation at 20 and/or 30 Hz, compared with before.

Figure 7 provides an example of reduction of NC accompanied by a reduction of EMG amplitude of the flexor carpi radialis in a stroke patient, after one session of electrical stimulation with EXOPULSE Mollii at 30 Hz.

Figure 7. Example of NeuroFlexor force trace and electromyography signal before and after stimulation with EXOPULSE Mollii



(A) NeuroFlexor hand module resistance profile during the fast velocity movement, before and after 60 min of electrical stimulation with EXOPULSE Mollii at 30 Hz. Blue trace shows the angle of wrist movement, from 20° of palmar flexion to 30° of extension. Bright red trace shows resisting force to the passive stretch and the ticker dark red line shows resistance profile when the device ran without hand. Arrow shows the late resistance toward the end of the movement (P2 time point). Values of neural component (NC) are reported in Newton, N. **(B)** Electromyography (EMG) signal of the flexor carpi radialis recorded synchronized with the NeuroFlexor assessment from onset (i.e., 20° of flexion) until full extension of wrist (offset, i.e., 30°). The amplitude of EMG signal is reported in mV. After stimulation, a decreased NC was accompanied by a reduced EMG amplitude (i.e., smaller burst in EMG signal in green). Published with permission of *Frontiers in Neurology*.

4.4.3 Mechanical and stretch reflex resistance after prior-polio

Study IV characterized the different contributors to the resisting force produced during passive wrist extension and ankle dorsiflexion in patients with prior poliomyelitis, with or without diagnosis of PPS.

Both neural and elastic components turned out to be affected, both in the affected and non (or less severely) affected limbs, defined based on evidence of prior poliomyelitis, such as denervation or re-innervation, in EMG examinations previously performed. EC measured in

the upper extremity was significantly lower in both sides compared to the healthy control group [$F(2, 128) = 10.587$, $p < 0.001$ and $p < 0.003$ for post-hoc tests].

In the lower extremity, all NeuroFlexor components differed between groups, NC: $F(2, 85) = 9.661$, $p < 0.001$; EC: $F(2, 85) = 7.654$, $p < 0.001$; VC: $F(2, 85) = 11.738$, $p < 0.001$. NC was significantly lower in the affected lower extremity compared to the contralateral side and the healthy subjects' extremity ($p \leq 0.001$). EC and VC were significantly higher in prior polio patients' extremities compared to the healthy control group ($p \leq 0.040$).

Table 9 confronts the NeuroFlexor components measured in healthy subjects, in patients with prior polio and after stroke (in sub-acute and in chronic phase for the upper and lower extremity, respectively).

Table 8. Comparison of the NeuroFlexor components (in Newton, N) between groups

Variables		Healthy subjects	Prior polio patients		Stroke patients
			Affected side	Non / Less severely affected side	Affected side
Upper extremity	**Neural component**	0.74 (0.98)	0.57 (1.25)	0.42 (0.45)	2.15 (6.80)
	Elastic component	2.69 (1.34)	1.55 (1.46)	1.69 (1.61)	3.51 (1.78)
	Viscous component	0.25 (0.31)	0.26 (0.71)	0.24 (0.55)	1.26 (0.92)
Lower extremity	**Neural component**	7.30 (6.41)	0.75 (9.39)	8.29 (12.78)	35.88 (45.13)
	Elastic component	28.13 (15.31)	29.65 (38.78)	46.28 (11.49)	72.32 (37.65)
	Viscous component	3.53 (1.24)	2.20 (1.07)	2.61 (0.59)	3.12 (2.06)

Median (IQR). Values in lower extremity assessed with 30 degree stretch.

The study investigated also the difference in NeuroFlexor components between subjects with and without diagnosis of progressive PPS. Patient with progressive PPS had significantly higher EC of the affected lower extremity, compared to patients without progressive PPS ($U = 8.50$, $p = 0.019$). No other difference in the upper or lower extremities was detected.

4.5 CORRELATION OF NEUROFLEXOR COMPONENTS WITH CLINICAL OUTCOMES

The NeuroFlexor components and total resistance were compared with clinical measures of spasticity, pain and fatigue across the four studies.

In Study I, eight stroke patients were rated as MAS score ≥ 1 in wrist and/or finger flexors, five of which with NC below the normal limit. On the contrary, 10 patients with pathologically high NC did not present clinical sign of spasticity according to MAS. There was a low positive correlation between objective sign (NC) and clinical assessment (MAS) of spasticity of stroke

patients' upper extremity ($r_s = 0.36$, $p = 0.024$). Moreover, total resistance correlated significantly with MAS ($r_s = 0.41$, $p = 0.010$).

In Study II, all stroke patients had a positive clinical MAS ratings in the gastrocnemius muscle (mean 2.47 ± SD 0.92) and soleus muscle (2.47 ± 0 .99). The NeuroFlexor foot module NC strongly correlated with MAS in the gastrocnemius muscle ($r_s = 0.58$, $p = 0.022$) and soleus muscle ($r_s = 0.64$, $p = 0.010$). Total resistance did not significantly correlate with MAS, but high values of total resistance were generally measured in patients with high MAS scores.
Finally, in Study IV, MAS showed no change during or immediately after a stimulation session with EXOPULSE Mollii ($p > 0.40$), similarly to NC.

Pain intensity was rated according to FMA–UE and FMA–LE in Study III [median 24.00 (IQR 2) and 20.00 (1.00), respectively], and assessed on VAS scale in Study IV, where 53% of the patients with prior polio graded a positive score [2.00 (5.00)]. VAS score correlated with NC measured in the non or less severely affected arm of the entire population ($r_s = 0.72$, $p = 0.009$) and inversely with EC measured in the upper and lower extremities of the sub-group of patients with diagnosis of progressive PPS ($p \leq 0.035$).

Finally, both neural and mechanical components of the NeuroFlexor hand and foot modules correlated significantly with different aspects of fatigue scored according to FSS [median 5.22 (IQR 1.67)], and MFI-20 [58 (22)] in patients after prior polio (Study IV). The main associations between NeuroFlexor components and fatigue are reported in Table 10, both at level of the group-as-a-whole and specifically in the sub-group of patients with diagnosis of progressive PPS.

Table 9. Relation between NeuroFlexor components and fatigue in patients with prior polio

Variables		Prior polio patients (N= 19)						Patients with progressive PPS (n= 13)					
		Affected side			Non/Less severely affected side			Affected side			Non/Less severely affected side		
		NC	EC	VC	NC	EC	VC	NC	EC	VC	NC	EC	VC
Upper extremity	FSS	0.77**	-0.62*	-0.69*	0.38	-0.17	-0.31	0.83*	-0.67	-0.91**	0.83*	-0.28	-0.58
	MFI-20	0.48	-0.29	-0.60*	0.56	-0.13	-0.66*	0.71*	-0.57	-0.80*	0.98**	-0.41	-0.83*
	Physical fatigue	0.22	-0.30	-0.39	0.34	-0.04	-0.47	0.46	-0.72*	-0.58	0.84**	-0.33	-0.62
	Mental fatigue	0.41	-0.24	-0.55	0.65*	-0.13	-0.73**	0.81*	-0.42	-0.83**	0.85**	-0.10	-0.73*
Lower extremity	FSS	0.29	0.19	0.21	0.53**	0.03	-0.29	0.21	-0.21	-0.04	0.64*	0.00	-0.73**
	MFI-20	0.13	-0.23	0.03	0.37	0.24	-0.54*	0.32	-0.35	-0.10	0.48	-0.05	-0.70**
	Physical fatigue	0.16	-0.28	-0.09	0.17	0.29	-0.51*	0.42	-0.40	-0.23	0.32	0.04	-0.64*
	Mental fatigue	-0.07	-0.01	0.04	0.59**	0.28	-0.62**	0.10	0.12	0.05	0.76**	0.15	-0.74

Physical fatigue: MFI-20, physical fatigue sub-scale. Mental fatigue: MFI-20, mental fatigue sub-scale.
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

5 DISCUSSION

An accurate evaluation of spasticity, distinguishing the contribution of reflex hyperexcitability from secondary changes of passive muscle properties to increased muscle tone accompanying a central paresis, is essential for improved diagnosis as well as to better design and evaluate specific treatments. An accurate characterization of reflex and passive muscle properties after a peripheral paresis, such as after poliomyelitis infection, may elucidate potential associations between altered passive muscle properties and clinical issues and guide new therapeutic approaches.

Therefore, this thesis examined the validity, reliability and normative data of the NeuroFlexor method for the upper and lower extremities, and how the neural and mechanical contributors to passive resistance differ between healthy subjects, patients in different phases after stroke and individuals with muscle-related effects of polio.
In the following sections, the main findings from the individual studies and the pathophysiological insights thus gained, are discussed.

5.1 MEASUREMENT CHARACTERISTICS

5.1.1 Evidence of validity

Validity is defined as the degree to which an instrument measures accurately what it is designed to measure[186], and thus represents the truthfulness of the findings[187]. Five different sources of validity evidence are specified: evidence based on test content, internal structure, response processes, relations to other variables, and testing consequences.[188]
Study II provides preliminary validity evidence based on test content and based on relations to other variables, of the neural and mechanical viscous-elastic components of the resisting force to a passive movement produced by the novel NeuroFlexor foot module.

NeuroFlexor neural component is defined as the force attributed to a hyperactive stretch reflex[112], in agreement with Lance's definition of spasticity.[47] Based on this definition, the first evidence of content validity, i.e., the extent to which the content of a test is congruent with the test purposes[189], relied on the velocity dependence of NC during a rapid passive stretch movement.
The second evidence concerned whether the measured output, i.e., NC, behaves in predictable patterns and correlates with previous established measure considered gold standard, which is the quantitative surface electromyography signals of calf muscles recorded during NeuroFlexor assessment. Results showed strong correspondence between NC and EMG data across different stretch velocities, both in stroke patients and in healthy subjects. Notably, the neuromuscular response to passive movements at predefined isokinetic velocities was quantified as the amplitude of EMG signal and not as a measure of the tonic stretch reflex threshold[190], which precludes, by definition, to determine the speed at which a passive stretch response is elicited.

Finally, despite the known limitations of the scale suggesting caution, the clinically measured muscle tone according to MAS correlated strongly with NC obtained at the highest stretch velocity. Findings are consistent with a recent study[115] showing similarity between the NeuroFlexor method and another biomechanical model, the EMG-based Wristalyzer, and thus provided additional evidence of validity.

Even though, considered together, these findings corroborate evidence of the validity of the NeuroFlexor foot module as a new method for spasticity measurement in the lower limb, an inhibition of stretch reflexes with local nerve block would have been a valuable addition. An examination of changes in NC and in EMG amplitude before and after a local nerve block achieved by intraneural injection of anaesthetics to the posterior tibial nerve might be worth further investigation.[191]

The viscous and elastic components are the mechanical contributors to resistance to passive stretch and mainly reflect secondary changes in the muscle and tendon tissue properties. More specifically, EC represents the length dependent force due to alteration both in the composition of the muscle[192,193] and in the muscle architecture including the fascicle length[194,195]. Validity evidence based on test content for EC was provided by an increase of the values with increasing stretch angle (from 30 to 40 degrees of total range of movement) and by the lack of EMG response visually detected during stretches at velocity less than the stretch-reflex threshold.

The viscous component is the velocity-dependent force due to friction from neighbouring tissues, like for example between muscle fibers or between the muscle-tendon unit and the surrounding connective tissue.[196] Velocity dependence of VC was the first evidence of validity based on test content. To note that VC contributed very little to the total resisting force produced in the lower extremity, both in stroke patients and in the healthy subjects.[197] Considering that VC according to its definition, should be proportional to the muscle size, it might be possible that the biomechanical model for estimation of VC, which was initially developed for the upper extremity, needs further validation when incorporated in the foot module, and that the percentage of late viscosity measured at the end of fast movement may be higher in the lower limb.

Once again, a nerve block test would have provided an additional confirmation if EC and VC had not changed during and after the block, indicating independence of these mechanical components from the stretch reflex.

Future studies might also investigate the sensitivity of the NeuroFlexor foot module to measure the change in the neural and mechanical components after the well-defined treatment with Botulinum toxin.[198]

5.1.2 Evidence of reliability

Reliability refers to the consistency of a measurement method, and specifically the intra-rater reliability is defined as consistency over time.[199] Study II demonstrated evidence of intra-rater reliability of the NeuroFlexor foot module through a test-retest design, with a 10 minutes interval between the sessions. Findings showed high intraclass correlation coefficients (ICC) for NC, very high for EC and slightly lower for VC. Interpretation of ICC was based on Currier's suggestion[184].

Ten minutes interval was long enough to guarantee that no carry-over effects occurred due to repetitive muscle stretches, but at the same time that the neural component would not be affected by the intrinsic fluctuations of spasticity. It has been hypothesized that oscillation of spasticity may be due to the time of the day[200] and internal or external factors such as outdoor cold, fatigue or stress[201].

No repeatability coefficient[202], as an expression of the smallest real difference between measurements, was calculated and might deserve further investigation before the NeuroFlexor instrument could be adopted to measure long-term or post-treatment outcomes.

5.1.3 Methodological consideration

The NeuroFlexor foot module assessment protocol was developed in healthy subjects and successively optimized to investigate patients with neuromuscular alterations and thus with potential limitation in joint movement. This has allowed minimization of the risk of discomfort or injury. Nevertheless, the procedure is quite error-prone and could lead to erroneous evaluation of all NeuroFlexor components if not performed with accuracy. The patient's position and relaxation, the angle of the knee joint, the foot placement according to the NeuroFlexor force sensors as well as the correspondence between ankle joint and the axis of rotation of the apparatus, are all essential to ensure similar biomechanical contributions at each assessment and thus to obtain reliable data. Similarly to the hand module[112], a series of tests showed that an incorrect displacement of the centre of mass of known weight (1 kg) of 0.5 cm relative to the rotational axis of the NeuroFlexor foot module, generated a measurement error of 1 N for NC. Therefore, a variation of NC higher than 1 N was considered a true value beyond the margin of measurement error of the biomechanical model in Study III.

5.2 DIFFERENTIATION OF CENTRAL AND PERIPHERAL NERVE SYSTEM PATHOLOGIES

Study I and II provided normative data of NeuroFlexor hand and foot modules from two large cohorts of healthy subjects, allowing to estimate the effect of age, gender and anthropometric measurements on the NeuroFlexor components measured in the upper and lower extremities. Age did not influence NC either in arm or the lower limb, in accordance with previous neurophysiological findings which reported the absence of any age-related decrease in motoneuronal excitability or changes in tonic stretch reflex.[203-205] To note, participants were under 70 years of age. Gender difference was however observed with respect to EC in both

extremities, where greater muscle mass in males compared to females was consistent with higher values for elasticity.

Comparison between NeuroFlexor components measured in healthy subjects compared to stroke patients highlighted the predominant role of NC in pathologically high resistance produced by passive stretching of the arm, in line with hyperactivity of elicited stretch reflexes.[77,82,206] However, EC represented the major contributors of the resisting force measured in the lower extremity of both healthy subjects and stroke patients. It should be noted that individuals in Study II were in a chronic phase after stroke (i.e., > 6 months) compared to patients in Study I who were evaluated in an earlier phase (mean time 2-4 weeks after onset). Additionally, the greater mass of the triceps surae muscles compared to the forearm muscles, likely due to their postural role, may influence the relative contributor of EC to the total resistance.

Finally, optimal cut-off values were determined for NeuroFlexor components, both for upper and lower extremities with different approaches. The mean + 3 SD approach provided more conservative limits. Pathologically high neural component (above the cut-off value of 3.4 N) allowed detection of spasticity in the upper limb after stroke in studies included[207] or not[36,139] in this thesis. The perfect correspondence between pathologically high EMG amplitude (i.e., > mean + 2 SD of healthy subjects) and NC beyond the limits of normality defined by ROC analysis, suggests that the novel NeuroFlexor foot module can objectively assess spasticity in the lower extremity.

Spasticity of upper extremity was detected with the NeuroFlexor hand module in 41% of the participants of Study I, an occurrence higher than reported in literature[27] (i.e., about 20-25% early after stroke). Discrepancy might be due to both the relatively young age of the participants who might develop more severe spasticity, and that the patients referred to a rehabilitation unit for intensive care and thus had probably more severe sensorimotor impairments than participants in other studies of unselected samples.[23] Clinically, 28% of patients were rated positive using the Modified Ashworth scale, and both false positives and false negatives were observed in MAS ratings compared to NC. A better correspondence between clinical evaluation of spasticity and neuromechanical measurement was observed in Study II. Seventy-tree percent of the chronic stroke patients had a pathologically high neural component in the lower extremity while the totality had a positive MAS rating in the gastrocnemius and soleus muscles. MAS has been shown to be more suitable at later stage after stroke, when the patients present more severe increased resistance to passive movement[89,112], and that may explain the difference observed.

Both neural and passive components were altered in patients with a history of poliomyelitis. Elastic component contributed most to passive movement resistance in patients with prior polio, especially in patients presenting progressive PPS[208] (i.e., with slowly progressive weakness, fatigue and/or pain). However, alterations in EC differed between extremities, with the upper extremity showing lower EC compared to the healthy subjects while lower extremity higher elasticity. Neural component instead was lower in the polio-affected lower extremity compared to the contralateral side and the healthy subjects, especially when measured in

muscles with severe atrophy. It is reasonable to relate the decrease in NC, which is a stretch reflex response, with the lower motor neuron loss occurring in prior paralytic poliomyelitis.[209] These findings lend further support to the validity of the NeuroFlexor method.

Although Study IV is preliminary and caution is needed in drawing conclusions, these findings suggest that the NeuroFlexor method can aid to characterize polio-related neuromuscular alterations. If confirmed by larger studies, neural and elastic components could reflect disruption in muscle architecture both in quantity (atrophy due to loss of motor units) and quality (gradual steatosis and fibrosis of muscle tissue).[161,162,210] Abnormalities of the NeuroFlexor components measured in the non or less-severely affected lower extremity was in line with previous findings[211,212], and might be beneficial to planning of long-term rehabilitation strategies, especially in prior-polio patients with subclinical involvement of the limb.

The association between neuromuscular changes, fatigue and pain experienced by polio patients has long been of great interest and has not been fully clarified. Study IV investigated whether the characteristics defined by the NeuroFlexor hand and foot modules might be contributing factors to these symptoms. Fifteen participants in the study experienced general fatigue and ten patients suffered from pain both of muscular origin and joint-related, a prevalence in line with previous findings.[213] Severe fatigue rated by Fatigue Severity scale and pain co-occurred in 53% of patients. Correlations of varying degrees between fatigue and both neural and mechanical components concerned both the affected and the non or less affected extremities underlining the role of the strongest side and its compensatory mechanisms and potential overuse, in the perception of general and physical fatigue. Notable, NC correlated significantly with FSS score both in the upper and lower affected extremities ($p < 0.05$), which allows one to hypothesize a relation between less atrophic and thus more active musculature and the severity of fatigue perceived. In addition, higher values for elasticity measured in the affected lower limb corresponded to more severe physical fatigue ($p = 0.005$), and both EC and VC in the unaffected or less severely affected arm correlated strongly with physical fatigue [r_s= 0.60, p= 0.039 and r_s= 0.73, p= 0.007 (data not shown), respectively], an association between viscosity and muscle fatigue previously suggested.[214,215]

5.3 NEUROFLEXOR RESPONSIVENESS TO ELECTRICAL STIMULATION

Study III explored the feasibility of the NeuroFlexor instrument to investigate and compare the instant response to the electrical stimulation anticipated by the EXOPULSE Mollii suit at different frequencies, with regard to the reduction of objective signs of spasticity in patients with chronic stroke (> 12 months after onset). The study was part of a series of studies within a European consortium aiming to explore the clinical effects of the EXOPULSE Mollii suit in patients with stroke (Danderyd Hospital, Stockholm, Sweden), cerebral palsy (Hvidovre Hospital, Copenhagen, Denmark) and spinal cord injury (Medical University, Vienna, Austria).

No significant reduction in spasticity during or immediate after 60 minutes of electrical stimulation at any frequency was observed at the group level ($p > 0.35$), and there were no significant differences between OFF settings and active frequencies (20 and 30 Hz) of

stimulation. A parallel pattern between NeuroFlexor neural component and EMG amplitudes was detected in both extremities, and confirmed by a significant correlation before and/or after stimulation at different active frequencies ($p \leq 0.02$). Nevertheless, the NeuroFlexor proved to be sufficiently sensitive to detect variations in neural and mechanical contributions to the muscle resistance at the individual level. The individual response was in fact highly variable, especially among patients with severe spasticity in the upper extremities, defined as NC > 8 N[36]. It was therefore speculated that the EXOPULSE Mollii method might be more effective for severe spasticity, with potential implications for both future research and clinical practice. Moreover, it was hypothesized a dose-effect model of the stimulation with EXOPULSE Mollii on spasticity and that as such a single session of stimulation may have provided insufficient stimulation to relieve spasticity. Previous studies demonstrated the effects of repeated applications of EXOPULSE Mollii in home-settings in reducing spasticity in chronic stroke patients[139] and in children and young adults with cerebral palsy[138,216,217], and thus support this hypothesis. A higher number of stimulation sessions should be considered in the future for a more reliable analysis of the effectiveness of the EXOPULSE Mollii suit.

The low number of participants (N= 20 evaluated with the NeuroFlexor hand module and n= 10 properly tested with the foot module) represented the main limitation of this explorative study and precluded any further consideration. It should be addressed in further studies.

6 CONCLUSIONS

The different contributors to the resisting force opposing a passive movement produced by the novel NeuroFlexor were significantly disordered in stroke patients and in subjects with prior paralytic poliomyelitis.

The neural component, which is the force produced by muscle contractions induced by stretch reflexes, correlated significantly both with the electromyography response to muscle stretch and the clinical evaluation of spasticity using the Modified Ashworth scale in patients in sub-acute and chronic phases after stroke. Elastic and viscous components reflect mainly secondary changes in the muscle and tendon tissue properties. They were altered both in stroke patients and in subjects with prior-polio, and correlated with the perception of fatigue and pain.

NeuroFlexor has shown to be a valid and reliable method to assess spasticity and changes in muscle and connective tissue. It may be an instrument of potential interest for longitudinal follow-up and evaluation of treatment interventions for different categories of patients.

To conclude, this thesis project has added new knowledge about the relative contributors to resistance encountered during passive stretching in patients with post-stroke spasticity and in subjects after peripheral paresis following poliomyelitis infection.

7 CLINICAL IMPLICATIONS AND FUTURE RESEARCH PERSPECTIVES

An accurate evaluation of spasticity, distinguishing the contribution of reflex hyperexcitability from secondary changes of passive muscle properties to increased muscle tone, is essential for a proper diagnosis and to design and evaluate treatment approach.

The NeuroFlexor method is CE marked and has now been used in clinical research. Further applications of interest comprise early detection of spasticity after stroke as well as other central nervous system disorders and more precise evaluation of post-treatment outcome after injection of Botulinum toxin in patients with clinical signs of spasticity. Botulinum toxin has proved to be effective in the management of post-stroke spasticity but multiple injections over time seem to be linked to a slight decrease of the effect and the need to escalate the dose administered per treatment session. It is hypothesized that this may be due to the onset of contractures or be an adverse effect of the same Botulinum toxin on passive muscle properties, i.e., increase of collagen content in the muscle following injections.[218] The possibility to assess both the neural spasticity and other mechanical components of passive resistance accurately with the NeuroFlexor method may help to elucidate the role of secondary alterations in muscle and tendon tissue in the waning of the effect over time.

The role of long-term soft tissue alterations are relevant also in disorders associated with a peripheral paresis, such as the post-polio syndrome. There are no specific treatments for the progressive post-polio syndrome; symptomatic management includes physical therapy, rehabilitation strategies and orthotic interventions. Both neural and mechanical components of passive resistance are altered in both extremities of subjects with previous paralytic poliomyelitis. The NeuroFlexor may be a non-invasive instrument feasible in clinical practice for monitoring muscle function over time and for potentially helping quantify the rate of decline in post-polio syndrome. Future studies may address sub-clinical neuromuscular characteristics in the less severely affected muscles of patients with progressive post-polio syndrome, and determine their potential role in the perception of fatigue and pain. This may eventually help to delineate new therapeutic interventions.

Finally, the evidence provided in this thesis project and in previous studies[112,114] supports the validity and reliability of the NeuroFlexor hand and foot modules. Nevertheless, future research is required to strengthen the validity of the foot module. For example, the study of the effect of reduction in the neural component of local nerve block is worth further investigation. The adjunction of ultrasound to the assessment with the NeuroFlexor, may also provide further information regarding the muscle architecture, and elucidate the mechanism behind the mechanical contribution to increased muscle tone.

8 SVENSK SAMMANFATTNING

Spasticitet är en motorisk funktionsnedsättning, som ofta uppstår efter stroke liksom efter andra skador i centrala nervsystemet. Spasticitet kännetecknas av ökat motstånd mot passiv sträckning och stelhet i försvagade muskler på grund av ökad reflexaktivitet. Det kan påverka individens förmåga att utföra viljemässiga rörelser och orsaka problem i dagliga aktiviteter. Spasticitet mäts idag kliniskt när undersökaren passivt sträcker en muskel. Den kliniska metoden är dock bristfällig eftersom det är omöjligt att skilja stelhet till följd av ökad reflexaktivitet, från stelhet till följd av andra komplikationer i musklerna, som kan utvecklas över tid i försvagade muskler. Också egenskaperhos i patienter med skador i perifera nervsystemet, som till exempel efter tidigare poliomyelit kan egenskaperna i försvagade muskler ändra över tid. Det finns ingen kurativ behandling för patienter med tidigare poliomyelit och det behövs känsliga mätinstrument för uppföljning och för ökad förståelse av förändrade muskelegenskaper som skulle kunna leda till en nya behandlings- och rehabiliteringsstrategier.

Målet med detta avhandlingsprojekt var att tilllämpa och utvärdera NeuroFlexormetoden, som har utvecklats för att kvantifiera och särskilja reflex- och muskelkomponenter av motståndet vid passiv sträckning av en muskel. Genom att kvantifiera dessa faktorer kan man få mer säker information om spasticitetet respektive muskelvävnadsförändringar än den kliniska undersökningen medger. I studierna utvärderades aspekter på NeuroFlexormetodens tillförlitlighet vid mätning i nedre extremiteten. Vidare jämfördes Neuroflexordata från patienter med kvarstående svaghet efter tidigare stroke respektive poliomyelit med data från friska personer. Slutligen undersöktes effekten på spasticitet av en ny elektrostimuleringsmetod.

I studierna undersöktes totalt 74 personer med stroke, 19 personer med tidigare poliomyelit och 180 friska kontrollpersoner. Upprepade mätningar visade god mätstabilitet (reliabilitet) och samtidig undersökning av reflexaktivitet med elektromyografi visade god korrelation, vilket ger stöd för att Neuroflexormetoden verkligen mäter spasticitet. Vidare sågs att Neuroflexordata korrelerade med klinisk bedömning av spasticitet efter stoke respektive med muskelatrofi, muskeltrötthet och smärta efter poliomyelit. Vid undersökning före och efter ett behandlingstillfälle med elektrisk stimulering visade Neuroflexormetoden skillnader hos patienter med tecken på svår spasticitet men ingen statistiskt säker skillnad.

Studierna har ökat kunskapen om neuromuskulära förändringar efter stroke respektive poliomyelit och ger stöd för planering av behandlingsstudier. På sikt kan resultaten bidra till förbättrad behandling av spasticitet och muskelstelhet efter stroke och andra tillstånd, som är förenade med liknande problem, och till utveckling av nya rehabiliteringsstrategier för patienter med tidigare poliomyelit.

9 ACKNOWLEDGEMENTS

Many people have helped and guided me throughout the years. To all of you, I am forever grateful!

I would like to express my sincere gratitude to the patients and control subjects for their kind participation. Without their willingness and patience, none of this would have ever happened.

I especially would like to thank Påvel Lindberg, my main supervisor. His acuity, knowledge and enthusiasm have been an inspiration to me. I am so grateful for our frequent discussions which reduced the distance Stockholm Paris to zero. Thanks for making me feel independent but never alone, for knowing exactly when to correct me and to support my ideas.

Alison Godbolt, my co-supervisor, for sharing her broad knowledge and always giving me new perspectives. Many thanks for all the ideas and work efforts.

Eva Melin, my co-supervisor, for being ever so supportive and confident. Thanks for the exciting discussions in the research field and clinical practice.

Susanne Palmcrantz, my co-supervisor. I am grateful since the first day she stepped in with her positive energy. Thanks for always bringing hope and inspiration, for providing immensely valuable guidance and support.

My profound thanks to Professor Jörgen Borg, for welcoming me to Sweden eight years ago and being aware of my ambitions. His broad knowledge and long experience have always helped me, and his words have brought me strength when I needed it the most.

To past and present members of my research group at Danderyd Hospital, many thanks for fruitful discussions and lots of laughter, and for always celebrating our accomplishments. Jeanette Plantin for opening her home to me and for keeping a watchful eye on me. Hanna Bergling, my co-author and desk mate for her positive attitude. I miss you! Anneli Wall for all good times enjoying a cup of strong coffee. Maria Pettersson, Beatrice Felixson and Disa Sommerfeld for all reflections and advice.

I would also like to thank:

The research group at INSERM in Paris: Loïc Carment, Maxime Teremetz, Lucile Dupin, Marion Verneau, Marc Maier, Quentin Le Boterff and Anaelle Alouit for meaningful and creative discussions, and especially for the precious memories we have made all over the world.

Fellow PhD students at the Division of Rehabilitation Medicine, for all good times: Ann-Christine Persson, Christina Sargénius Landahl, Christian Oldenburg, Gabriella Markovic, Giedré Matusevičienė, Märta Berthold, Natascha Ekdahl. Marika Möller and Monika Löfgren for providing a place of learning, of debate and of exchanges of best advice. Helena Hybbinette for her kindness, and Katarina Skough Vreede for so kindly sharing her knowledge.

The physiotherapists at the Outpatient Rehabilitation unit at Danderyd Hospital, especially Pär Lindholm, Lotta Melander and Sofia Hartell for invaluable support throughout the years.

Johan Gäverth and Anders Fagergren for generously sharing knowledge on NeuroFlexor method and biomechanics. Thanks for giving time to me and saying yes to requests for help.

Aggero MedTech AB, especially Fredrik Lundqvist, Annika Rydgård, Dag Fredriksen and Mimi Westerlund for pleasant and successful cooperation, for having enabled access to the EXOPULSE Mollii suit and for sharing expertise in the method.

Ruoli Wang at the Royal Institute of Technology, and Olga Tarassova, Bonnie Östergren and Toni Arndt at The Swedish School of Sport and Health Sciences for exchanging experiences and knowledge, and for welcoming me in the Biomechanics and Motor Control Laboratory.

Co-workers at the Post-polio outpatient clinic at Danderyd Hospital whom I have had the pleasure to work with during the latest year. Thanks for contributing to my knowledge and for giving me a lot of laughs during these months.

I would like to express my gratitude to Promobilia Foundation, Stroke-Riksförbundet, NEURO, The Swedish Research Council (Vetenskapsrådet), Eurostars (a joint programme between EUREKA and the European Commission) and The Swedish Association for Survivors of Accident and Injury (RTP) for generous financial support to this research.

I am grateful to the University Department of Rehabilitation Medicine at Danderyd Hospital for giving me the opportunity to work on this research project. To Christian Andersén and Kristian Borg for encouragement throughout the years. To Charikleia Pappas, Kjell Kullander, Carin Persson, Catharina Nygren Deboussard, Marita Bengtsson and Vera Häglund for introducing me to the clinical practice. A special thanks also to Karola Ollas, Agneta Tamwelius and Anne Åvall. To Mikael Gewers for his kind attention to coffee and lunch breaks. To Karolina Krakau, Kajsa Söderhielm and the late Kanoknart (Kano) Yingcharoen for care and wisdom.

My sincere thanks to the Department of Clinical Sciences at Karolinska Institutet Danderyd Hospital (KIDS) for giving me the opportunity to become a PhD student. To Nina Ringart, Siw Svensson, Åsa Misic and Malin Wirf for their assistance and advice.

To all my friends outside of the Academia, thanks for being like an extended family.

To my parents Tiziana and Vincenzo for always believing in me and for letting me go my own way. Grazie! To my sisters Stefania and Alessandra and their big or small but still precious families, you have always been there for me and I love you!

A heartfelt thanks go to Davide, who not fully understood what I've been doing all these years but who firmly believes that one day I will be given the Nobel Prize. Unlikely but never stop looking up and reaching for the stars!

Svea, my most precious gift. Stay curious, and keep exploring the world.

10 REFERENCES

1. Rosenbaum P, Stewart D. The World Health Organization International Classification of Functioning, Disability, and Health: a model to guide clinical thinking, practice and research in the field of cerebral palsy. *Seminars in pediatric neurology*. Mar 2004;11(1):5-10.

2. Sommerfeld DK, Gripenstedt U, Welmer AK. Spasticity after stroke: an overview of prevalence, test instruments, and treatments. *American journal of physical medicine & rehabilitation*. Sep 2012;91(9):814-20. doi:10.1097/PHM.0b013e31825f13a3

3. Adams MM, Hicks AL. Spasticity after spinal cord injury. *Spinal cord*. Oct 2005;43(10):577-86. doi:10.1038/sj.sc.3101757

4. Morgan P, McGinley JL. Cerebral palsy. *Handbook of clinical neurology*. 2018;159:323-336. doi:10.1016/b978-0-444-63916-5.00020-3

5. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Multiple sclerosis (Houndmills, Basingstoke, England)*. Oct 2004;10(5):589-95. doi:10.1191/1352458504ms1085oa

6. Emos MC, Agarwal S. Neuroanatomy, Upper Motor Neuron Lesion. *StatPearls*. StatPearls Publishing; 2021 Jan.

7. Javed K, Reddy V, Lui F. Neuroanatomy, Lateral Corticospinal Tract. *StatPearls*. StatPearls Publishing; 2021 Jan.

8. Van Wittenberghe IC, Peterson DC. Corticospinal Tract Lesion. *StatPearls*. StatPearls Publishing; 2021 Jan.

9. Mayer NH, Esquenazi A. Muscle overactivity and movement dysfunction in the upper motoneuron syndrome. *Physical medicine and rehabilitation clinics of North America*. Nov 2003;14(4):855-83, vii-viii.

10. Javed K, Daly DT. Neuroanatomy, Lower Motor Neuron Lesion. *StatPearls*. StatPearls Publishing; 2021 Jan.

11. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet (London, England)*. May 10 2008;371(9624):1612-23. doi:10.1016/s0140-6736(08)60694-7

12. Organisation WH. Global Health Estimates: Life expectancy and leading causes of death and disability in 2019. 2021. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates

13. Béjot Y, Daubail B, Giroud M. Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. *Rev Neurol (Paris)*. Jan 2016;172(1):59-68. doi:10.1016/j.neurol.2015.07.013

14. Socialstyrelsen. Statistik om stroke 2019. 2020-12-02. 2021. https://www.socialstyrelsen.se/statistik-och-data/statistik/statistikamnen/stroke/

15. Riksstroke. Stroke och TIA. Årsrapport från Riksstroke för 2020 års data (The Swedish National Registry for Quality Assessment of Acute Stroke Care, Report Year 2020). https://www.riksstroke.org/sve/forskning-statistik-och-verksamhetsutveckling/rapporter/arsrapporter/

16. Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke*. Jan 2004;35(1):134-9. doi:10.1161/01.Str.0000105386.05173.5e

17. Ward AB. A literature review of the pathophysiology and onset of post-stroke spasticity. *European journal of neurology*. Jan 2012;19(1):21-7. doi:10.1111/j.1468-1331.2011.03448.x

18. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: physiology, assessment and treatment. *Brain injury*. 2013;27(10):1093-105. doi:10.3109/02699052.2013.804202

19. Kuo C-L, Hu G-C. Post-stroke Spasticity: A Review of Epidemiology, Pathophysiology, and Treatments. *International Journal of Gerontology*. 2018/12/01/ 2018;12(4):280-284. doi:https://doi.org/10.1016/j.ijge.2018.05.005

20. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. *Journal of neurology*. Jul 2010;257(7):1067-72. doi:10.1007/s00415-010-5463-1

21. Lundstrom E, Smits A, Terent A, Borg J. Time-course and determinants of spasticity during the first six months following first-ever stroke. *Journal of rehabilitation medicine*. Apr 2010;42(4):296-301. doi:10.2340/16501977-0509

22. Urban PP, Wolf T, Uebele M, et al. Occurence and clinical predictors of spasticity after ischemic stroke. *Stroke*. Sep 2010;41(9):2016-20. doi:10.1161/strokeaha.110.581991

23. Ryu JS, Lee JW, Lee SI, Chun MH. Factors predictive of spasticity and their effects on motor recovery and functional outcomes in stroke patients. *Topics in stroke rehabilitation*. Sep-Oct 2010;17(5):380-8. doi:10.1310/tsr1705-380

24. Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK. Prevalence of spasticity post stroke. *Clinical rehabilitation*. Aug 2002;16(5):515-22. doi:10.1191/0269215502cr512oa

25. Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK, Watkins CL. Predicting spasticity after stroke in those surviving to 12 months. *Clinical rehabilitation*. Jun 2004;18(4):438-43. doi:10.1191/0269215504cr727oa

26. Lundstrom E, Terent A, Borg J. Prevalence of disabling spasticity 1 year after first-ever stroke. *European journal of neurology*. Jun 2008;15(6):533-9. doi:10.1111/j.1468-1331.2008.02114.x

27. Zeng H, Chen J, Guo Y, Tan S. Prevalence and Risk Factors for Spasticity After Stroke: A Systematic Review and Meta-Analysis. Systematic Review. *Frontiers in Neurology*. 2021-January-20 2021;11(1884)doi:10.3389/fneur.2020.616097

28. Sunnerhagen KS, Opheim A, Alt Murphy M. Onset, time course and prediction of spasticity after stroke or traumatic brain injury. *Annals of physical and rehabilitation medicine*. May 16 2018;doi:10.1016/j.rehab.2018.04.004

29. Hefter H, Jost WH, Reissig A, Zakine B, Bakheit AM, Wissel J. Classification of posture in poststroke upper limb spasticity: a potential decision tool for botulinum toxin A treatment? *International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation*. Sep 2012;35(3):227-33. doi:10.1097/MRR.0b013e328353e3d4

30. Barnes MP. An overview of the clinical management of spasticity. In: Johnson GR, Barnes MP, eds. *Upper Motor Neurone Syndrome and Spasticity: Clinical Management and Neurophysiology*. 2 ed. Cambridge University Press; 2008:1-8.

31. Li S, Francisco GE, Rymer WZ. A New Definition of Poststroke Spasticity and the Interference of Spasticity With Motor Recovery From Acute to Chronic Stages. *Neurorehabil*

Neural Repair. Jul 2021;35(7):601-610. 15459683211011214. doi:10.1177/15459683211011214

32. Lackritz H, Parmet Y, Frenkel-Toledo S, et al. Effect of post-stroke spasticity on voluntary movement of the upper limb. *Journal of neuroengineering and rehabilitation*. 2021/05/13 2021;18(1):81. doi:10.1186/s12984-021-00876-6

33. Arene N, Hidler J. Understanding motor impairment in the paretic lower limb after a stroke: a review of the literature. *Topics in stroke rehabilitation*. Sep-Oct 2009;16(5):346-56. doi:10.1310/tsr1605-346

34. Tao W, Yan D, Li JH, Shi ZH. Gait improvement by low-dose botulinum toxin A injection treatment of the lower limbs in subacute stroke patients. *Journal of physical therapy science*. Mar 2015;27(3):759-62. doi:10.1589/jpts.27.759

35. Sunnerhagen KS. Predictors of Spasticity After Stroke. *Current Physical Medicine and Rehabilitation Reports*. 2016/09/01 2016;4(3):182-185. doi:10.1007/s40141-016-0128-3

36. Plantin J, Pennati GV, Roca P, et al. Quantitative Assessment of Hand Spasticity After Stroke: Imaging Correlates and Impact on Motor Recovery. *Frontiers in neurology*. 2019;10:836-836. doi:10.3389/fneur.2019.00836

37. Glaess-Leistner S, Ri SJ, Audebert HJ, Wissel J. Early clinical predictors of post stroke spasticity. *Topics in stroke rehabilitation*. 2021/10/03 2021;28(7):508-518. doi:10.1080/10749357.2020.1843845

38. Bavikatte G, Subramanian G, Ashford S, Allison R, Hicklin D. Early Identification, Intervention and Management of Post-stroke Spasticity: Expert Consensus Recommendations. *J Cent Nerv Syst Dis*. 2021;13:11795735211036576-11795735211036576. doi:10.1177/11795735211036576

39. Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Early prediction of long-term upper limb spasticity after stroke: part of the SALGOT study. *Neurology*. 2015;85(10):873-880. doi:10.1212/WNL.0000000000001908

40. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koella WP, eds. *Spasticity, disordered motor control*. Year Book Medical Publishers; 1980:485–494.

41. Katz RT, Rymer WZ. Spastic hypertonia: mechanisms and measurement. *Arch Phys Med Rehabil*. Feb 1989;70(2):144-55.

42. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics*. Jan 2003;111(1):e89-97.

43. Pandyan AD, Gregoric M, Barnes MP, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. *Disabil Rehabil*. Jan 7-21 2005;27(1-2):2-6.

44. Bakheit AM, Fheodoroff K, Molteni F. Spasticity or reversible muscle hypertonia? *Journal of rehabilitation medicine*. May 2011;43(6):556-7. doi:10.2340/16501977-0817

45. Li S, Chen Y-T, Francisco GE, Zhou P, Rymer WZ. A Unifying Pathophysiological Account for Post-stroke Spasticity and Disordered Motor Control. Perspective. *Frontiers in Neurology*. 2019-May-10 2019;10(468)doi:10.3389/fneur.2019.00468

46. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clinical rehabilitation*. Jul 2009;23(7):651-8. doi:10.1177/0269215508101747

47. Lance JW. What is spasticity? *Lancet (London, England)*. Mar 10 1990;335(8689):606.

48. Lorentzen J, Grey MJ, Crone C, Mazevet D, Biering-Sorensen F, Nielsen JB. Distinguishing active from passive components of ankle plantar flexor stiffness in stroke, spinal cord injury and multiple sclerosis. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. Nov 2010;121(11):1939-51. doi:10.1016/j.clinph.2010.02.167

49. Mirbagheri MM, Rymer W, Tsao C, Settle K. *Evolution of Reflexive and Muscular Mechanical Properties in Stroke-Induced Spasticity*. vol 4. 2005:4393-5.

50. Mirbagheri MM, Tsao C, Rymer WZ. Natural history of neuromuscular properties after stroke: a longitudinal study. *Journal of neurology, neurosurgery, and psychiatry*. Nov 2009;80(11):1212-7. doi:10.1136/jnnp.2008.155739

51. de Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *Journal of neuroengineering and rehabilitation*. Jul 27 2010;7:35. doi:10.1186/1743-0003-7-35

52. Toft E, Espersen GT, Kalund S, Sinkjaer T, Hornemann BC. Passive tension of the ankle before and after stretching. *The American journal of sports medicine*. Jul-Aug 1989;17(4):489-94. doi:10.1177/036354658901700407

53. Toft E, Sinkjaer T, Andreassen S. Mechanical and electromyographic responses to stretch of the human anterior tibial muscle at different levels of contraction. *Exp Brain Res*. 1989;74(1):213-9.

54. Picelli A, Tamburin S, Gajofatto F, et al. Association between Severe Upper Limb Spasticity and Brain Lesion Location in Stroke Patients %J BioMed Research International. 2014;2014:6. 162754. doi:10.1155/2014/162754

55. Li S. Spasticity, Motor Recovery, and Neural Plasticity after Stroke. *Front Neurol*. 2017;8:120. doi:10.3389/fneur.2017.00120

56. Jin Y, Zhao Y. Post-stroke Upper Limb Spasticity Incidence for Different Cerebral Infarction Site. *Open medicine (Warsaw, Poland)*. 2018;13:227-231. doi:10.1515/med-2018-0035

57. Lee KB, Hong BY, Kim JS, et al. Which brain lesions produce spasticity? An observational study on 45 stroke patients. *PLoS One*. 2019;14(1):e0210038. doi:10.1371/journal.pone.0210038

58. Cheung DK, Climans SA, Black SE, Gao F, Szilagyi GM, Mochizuki G. Lesion Characteristics of Individuals With Upper Limb Spasticity After Stroke. *Neurorehabil Neural Repair*. Jan 2016;30(1):63-70. doi:10.1177/1545968315585357

59. Volny O, Justanova M, Cimflova P, et al. 24-Hour Alberta Stroke Program Early CT Score Assessment in Post-Stroke Spasticity Development in Patients with a First Documented Anterior Circulation Ischemic Stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. Jan 2018;27(1):240-245. doi:10.1016/j.jstrokecerebrovasdis.2017.08.033

60. Mukherjee A, Chakravarty A. Spasticity mechanisms - for the clinician. *Frontiers in neurology*. 2010;1:149-149. doi:10.3389/fneur.2010.00149

61. Karbasforoushan H, Cohen-Adad J, Dewald JPA. Brainstem and spinal cord MRI identifies altered sensorimotor pathways post-stroke. *Nat Commun*. 2019;10(1):3524-3524. doi:10.1038/s41467-019-11244-3

62. Li S, Francisco GE. New insights into the pathophysiology of post-stroke spasticity. *Frontiers in human neuroscience*. 2015;9:192. doi:10.3389/fnhum.2015.00192

63. Miller DM, Klein CS, Suresh NL, Rymer WZ. Asymmetries in vestibular evoked myogenic potentials in chronic stroke survivors with spastic hypertonia: Evidence for a vestibulospinal role. *Clin Neurophysiol*. 2014/10/01/ 2014;125(10):2070-2078. doi:https://doi.org/10.1016/j.clinph.2014.01.035

64. McCall AA, Miller DM, Yates BJ. Descending Influences on Vestibulospinal and Vestibulosympathetic Reflexes. *Frontiers in neurology*. 2017;8:112-112. doi:10.3389/fneur.2017.00112

65. Hultborn H. Changes in neuronal properties and spinal reflexes during development of spasticity following spinal cord lesions and stroke: studies in animal models and patients. *Journal of rehabilitation medicine*. May 2003;(41 Suppl):46-55.

66. Delwaide PJ, Oliver E. Short-latency autogenic inhibition (IB inhibition) in human spasticity. *Journal of neurology, neurosurgery, and psychiatry*. Dec 1988;51(12):1546-50.

67. Mazzocchio R, Rossi A. Involvement of spinal recurrent inhibition in spasticity. Further insight into the regulation of Renshaw cell activity. *Brain : a journal of neurology*. Jun 1997;120 (Pt 6):991-1003.

68. Crone C, Petersen NT, Gimenez-Roldan S, Lungholt B, Nyborg K, Nielsen JB. Reduced reciprocal inhibition is seen only in spastic limbs in patients with neurolathyrism. *Exp Brain Res*. Jul 2007;181(1):193-7. doi:10.1007/s00221-007-0993-1

69. Kagamihara Y, Masakado Y. Excitability of spinal inhibitory circuits in patients with spasticity. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society*. Apr 2005;22(2):136-47.

70. Nielsen J, Petersen N, Crone C. Changes in transmission across synapses of Ia afferents in spastic patients. *Brain : a journal of neurology*. Aug 1995;118 (Pt 4):995-1004.

71. Masakado Y, Kagamihara Y, Takahashi O, Akaboshi K, Muraoka Y, Ushiba J. Post-activation depression of the soleus H-reflex in stroke patients. *Electromyography and clinical neurophysiology*. Mar 2005;45(2):115-22.

72. Grey MJ, Klinge K, Crone C, et al. Post-activation depression of soleus stretch reflexes in healthy and spastic humans. *Exp Brain Res*. Feb 2008;185(2):189-97. doi:10.1007/s00221-007-1142-6

73. Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke. *Neurology*. Jan 15 2013;80(3 Suppl 2):S20-6. doi:10.1212/WNL.0b013e31827624a7

74. Nielsen JB, Crone C, Hultborn H. The spinal pathophysiology of spasticity--from a basic science point of view. *Acta physiologica (Oxford, England)*. Feb 2007;189(2):171-80. doi:10.1111/j.1748-1716.2006.01652.x

75. Lamy JC, Wargon I, Mazevet D, Ghanim Z, Pradat-Diehl P, Katz R. Impaired efficacy of spinal presynaptic mechanisms in spastic stroke patients. *Brain : a journal of neurology*. Mar 2009;132(Pt 3):734-48. doi:10.1093/brain/awn310

76. Sheean G, McGuire JR. Spastic hypertonia and movement disorders: pathophysiology, clinical presentation, and quantification. *PM & R : the journal of injury, function, and rehabilitation*. Sep 2009;1(9):827-33. doi:10.1016/j.pmrj.2009.08.002

77. Trompetto C, Marinelli L, Mori L, et al. Pathophysiology of spasticity: implications for neurorehabilitation. *BioMed research international*. 2014;2014:354906. doi:10.1155/2014/354906

78. O'Dwyer NJ, Ada L. Reflex hyperexcitability and muscle contracture in relation to spastic hypertonia. *Current opinion in neurology*. Dec 1996;9(6):451-5.

79. Wood KS, Daluiski A. Management of Joint Contractures in the Spastic Upper Extremity. *Hand clinics*. Nov 2018;34(4):517-528. doi:10.1016/j.hcl.2018.06.011

80. Gracies JM. Pathophysiology of spastic paresis. II: Emergence of muscle overactivity. *Muscle Nerve*. May 2005;31(5):552-71. doi:10.1002/mus.20285

81. Ada L, O'Dwyer N, O'Neill E. Relation between spasticity, weakness and contracture of the elbow flexors and upper limb activity after stroke: an observational study. *Disabil Rehabil*. Jul 15-30 2006;28(13-14):891-7. doi:10.1080/09638280500535165

82. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle Nerve*. May 2005;31(5):535-51. doi:10.1002/mus.20284

83. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. Feb 1987;67(2):206-7.

84. Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. *Clinical rehabilitation*. Feb 2006;20(2):173-82. doi:10.1191/0269215506cr922oa

85. Alibiglou L, Rymer WZ, Harvey RL, Mirbagheri MM. The relation between Ashworth scores and neuromechanical measurements of spasticity following stroke. *Journal of neuroengineering and rehabilitation*. Jul 15 2008;5:18. doi:10.1186/1743-0003-5-18

86. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *Journal of neurology, neurosurgery, and psychiatry*. Jan 2010;81(1):46-52. doi:10.1136/jnnp.2009.177071

87. Abolhasani H, Ansari NN, Naghdi S, Mansouri K, Ghotbi N, Hasson S. Comparing the validity of the Modified Modified Ashworth Scale (MMAS) and the Modified Tardieu Scale (MTS) in the assessment of wrist flexor spasticity in patients with stroke: protocol for a neurophysiological study. *BMJ open*. 2012;2(6)doi:10.1136/bmjopen-2012-001394

88. Gracies J-M, Burke K, Clegg NJ, et al. Reliability of the Tardieu Scale for assessing spasticity in children with cerebral palsy. 2010;91(3):421-428.

89. Mehrholz J, Major Y, Meißner D, Sandi-Gahun S, Koch R, Pohl MJCr. The influence of contractures and variation in measurement stretching velocity on the reliability of the Modified Ashworth Scale in patients with severe brain injury. 2005;19(1):63-72.

90. Haugh A, Pandyan A, Johnson GJD, rehabilitation. A systematic review of the Tardieu Scale for the measurement of spasticity. 2006;28(15):899-907.

91. Balci BP. Spasticity Measurement. *Noro Psikiyatr Ars*. 2018;55(Suppl 1):S49-s53. doi:10.29399/npa.23339

92. Luo Z, Lo WLA, Bian R, Wong S, Li L. Advanced quantitative estimation methods for spasticity: a literature review. *The Journal of international medical research*. Mar 2020;48(3):300060519888425. doi:10.1177/0300060519888425

93. Cha Y, Arami A. Quantitative Modeling of Spasticity for Clinical Assessment, Treatment and Rehabilitation. *Sensors*. 2020;20(18):5046.

94. Knutsson E, Mårtensson A. Action of dantrolene sodium in spasticity with low dependence on fusimotor drive. *Journal of the Neurological Sciences*. 1976/10/01/ 1976;29(2):195-212. doi:https://doi.org/10.1016/0022-510X(76)90171-4

95. Sinkjaer T. Muscle, reflex and central components in the control of the ankle joint in healthy and spastic man. *Acta neurologica Scandinavica Supplementum*. 1997;170:1-28.

96. Wood DE, Burridge JH, van Wijck FM, et al. Biomechanical approaches applied to the lower and upper limb for the measurement of spasticity: a systematic review of the literature. *Disabil Rehabil*. Jan 7-21 2005;27(1-2):19-32. doi:10.1080/09638280400014683

97. Pilla A, Trigili E, McKinney Z, et al. Robotic Rehabilitation and Multimodal Instrumented Assessment of Post-stroke Elbow Motor Functions-A Randomized Controlled Trial Protocol. *Front Neurol*. 2020;11:587293. doi:10.3389/fneur.2020.587293

98. Barden HL, Nott MT, Baguley IJ, Heard R, Chapparo C. Test-retest reliability of computerised hand dynamometry in adults with acquired brain injury. *Australian occupational therapy journal*. Aug 2012;59(4):319-27. doi:10.1111/j.1440-1630.2012.01016.x

99. van der Krogt H, Klomp A, de Groot JH, et al. Comprehensive neuromechanical assessment in stroke patients: reliability and responsiveness of a protocol to measure neural and non-neural wrist properties. *Journal of neuroengineering and rehabilitation*. Mar 13 2015;12:28. doi:10.1186/s12984-015-0021-9

100. Kim KS, Seo JH, Song CG. Portable measurement system for the objective evaluation of the spasticity of hemiplegic patients based on the tonic stretch reflex threshold. *Med Eng Phys*. Jan 2011;33(1):62-9. doi:10.1016/j.medengphy.2010.09.002

101. Lee HM, Chen JJ, Ju MS, Lin CC, Poon PP. Validation of portable muscle tone measurement device for quantifying velocity-dependent properties in elbow spasticity. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology*. Oct 2004;14(5):577-89. doi:10.1016/j.jelekin.2004.02.002

102. Çakır T, Evcik FD, Subaşı V, Demirdal ÜS, Kavuncu V. Investigation of the H reflexes, F waves and sympathetic skin response with electromyography (EMG) in patients with stroke and the determination of the relationship with functional capacity. *Acta Neurologica Belgica*. 2015/09/01 2015;115(3):295-301. doi:10.1007/s13760-014-0397-5

103. Falconer K, Winter DA. Quantitative assessment of co-contraction at the ankle joint in walking. *Electromyography and clinical neurophysiology*. Mar-Apr 1985;25(2-3):135-49.

104. Rudolph KS, Axe MJ, Snyder-Mackler L. Dynamic stability after ACL injury: who can hop? *Knee Surgery, Sports Traumatology, Arthroscopy*. 2000/09/01 2000;8(5):262-269. doi:10.1007/s001670000130

105. Lei W, Xin G, Peng F, et al. A new EMG-based index towards the assessment of elbow spasticity for post-stroke patients. *Annu Int Conf IEEE Eng Med Biol Soc*. Jul 2017;2017:3640-3643. doi:10.1109/embc.2017.8037646

106. Calota A, Feldman AG, Levin MF. Spasticity measurement based on tonic stretch reflex threshold in stroke using a portable device. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. Oct 2008;119(10):2329-37. doi:10.1016/j.clinph.2008.07.215

107. Blanchette AK, Mullick AA, Moin-Darbari K, Levin MF. Tonic Stretch Reflex Threshold as a Measure of Ankle Plantar-Flexor Spasticity After Stroke. *Phys Ther*. May 2016;96(5):687-95. doi:10.2522/ptj.20140243

108. Silva MB, Silva AN, Naves EL, Palomari ET, Soares AB. An improved approach for measuring the tonic stretch reflex response of spastic muscles. *Computers in biology and medicine*. Jan 1 2017;80:166-174. doi:10.1016/j.compbiomed.2016.12.001

109. Levin MF, Solomon JM, Shah A, Blanchette AK, Feldman AG. Activation of elbow extensors during passive stretch of flexors in patients with post-stroke spasticity. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. Oct 2018;129(10):2065-2074. doi:10.1016/j.clinph.2018.07.007

110. Marques IA, Silva MB, Silva AN, Luiz LMD, Soares AB, Naves ELM. Measurement of post-stroke spasticity based on tonic stretch reflex threshold: implications of stretch velocity for clinical practice. *Disabil Rehabil*. Jan 2019;41(2):219-225. doi:10.1080/09638288.2017.1381183

111. Frenkel-Toledo S, Solomon JM, Shah A, et al. Tonic stretch reflex threshold as a measure of spasticity after stroke: Reliability, minimal detectable change and responsiveness. *Clin Neurophysiol*. 2021/06/01/ 2021;132(6):1226-1233. doi:https://doi.org/10.1016/j.clinph.2021.02.390

112. Lindberg PG, Gaverth J, Islam M, Fagergren A, Borg J, Forssberg H. Validation of a New Biomechanical Model to Measure Muscle Tone in Spastic Muscles. Article. *Neurorehabil Neural Repair*. Sep 2011;25(7):617-625. doi:10.1177/1545968311403494

113. Gaverth J, Eliasson AC, Kullander K, Borg J, Lindberg PG, Forssberg H. Sensitivity Of The Neuroflexor Method To Measure Change In Spasticity After Treatment With Botulinum Toxin A In Wrist And Finger Muscles. Article. *Journal of rehabilitation medicine*. Jul 2014;46(7):629-634. doi:10.2340/16501977-1824

114. Gaverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-Retest And Inter-Rater Reliability Of A Method To Measure Wrist And Finger Spasticity. Article. *Journal of rehabilitation medicine*. Jul 2013;45(7):630-636. doi:10.2340/16501977-1160

115. Andringa A, van Wegen E, van de Port I, Kwakkel G, Meskers C. Measurement Properties of the NeuroFlexor Device for Quantifying Neural and Non-neural Components of Wrist Hyper-Resistance in Chronic Stroke. Original Research. *Frontiers in Neurology*. 2019-July-03 2019;10(730)doi:10.3389/fneur.2019.00730

116. Wang R, Herman P, Ekeberg Ö, Gäverth J, Fagergren A, Forssberg H. Neural and non-neural related properties in the spastic wrist flexors: An optimization study. *Med Eng Phys*. Sep 2017;47:198-209. doi:10.1016/j.medengphy.2017.06.023

117. Gaverth J, Eliasson AC, Kullander K, Borg J, Lindberg PG, Forssberg H. Sensitivity of the NeuroFlexor method to measure change in spasticity after treatment with botulinum toxin A in wrist and finger muscles. *Journal of rehabilitation medicine*. Jul 2014;46(7):629-34. doi:10.2340/16501977-1824

118. Ward AB. Spasticity treatment with botulinum toxins. *Journal of neural transmission (Vienna, Austria : 1996)*. 2008;115(4):607-16. doi:10.1007/s00702-007-0833-2

119. Ward AB, Wissel J, Borg J, et al. Functional goal achievement in post-stroke spasticity patients: the BOTOX(R) Economic Spasticity Trial (BEST). *Journal of rehabilitation medicine*. Jun 2014;46(6):504-13. doi:10.2340/16501977-1817

120. Mills PB, Dossa F. Transcutaneous Electrical Nerve Stimulation for Management of Limb Spasticity: A Systematic Review. *American journal of physical medicine & rehabilitation*. Apr 2016;95(4):309-18. doi:10.1097/phm.0000000000000437

121. Moeini-Naghani I, Hashemi-Zonouz T, Jabbari B. Botulinum Toxin Treatment of Spasticity in Adults and Children. Article. *Semin Neurol*. Feb 2016;36(1):64-72. doi:10.1055/s-0036-1571847

122. Gupta AD, Chu WH, Howell S, et al. A systematic review: efficacy of botulinum toxin in walking and quality of life in post-stroke lower limb spasticity. *Systematic reviews*. Jan 5 2018;7(1):1. doi:10.1186/s13643-017-0670-9

123. Sunnerhagen KS, Olver J, Francisco GEJN. Assessing and treating functional impairment in poststroke spasticity. 2013;80(3 Supplement 2):S35-S44.

124. Harvey L, Herbert R, Crosbie JJPRI. Does stretching induce lasting increases in joint ROM? A systematic review. 2002;7(1):1-13.

125. Bovend'Eerdt TJ, Newman M, Barker K, et al. The effects of stretching in spasticity: a systematic review. 2008;89(7):1395-1406.

126. Coroian F, Jourdan C, Bakhti K, et al. Upper Limb Isokinetic Strengthening Versus Passive Mobilization in Patients With Chronic Stroke: A Randomized Controlled Trial. *Arch Phys Med Rehabil*. Feb 2018;99(2):321-328. doi:10.1016/j.apmr.2017.08.490

127. Kwong PWH, Ng GYF, Chung RCK, Ng SSM. Transcutaneous electrical nerve stimulation improves walking capacity and reduces spasticity in stroke survivors: a systematic review and meta-analysis. *Clinical rehabilitation*. Sep 2018;32(9):1203-1219. doi:10.1177/0269215517745349

128. Marcolino MAZ, Hauck M, Stein C, Schardong J, Pagnussat AdS, Plentz RDM. Effects of transcutaneous electrical nerve stimulation alone or as additional therapy on chronic post-stroke spasticity: systematic review and meta-analysis of randomized controlled trials. *Disability and Rehabilitation*. 2020/02/27 2020;42(5):623-635. doi:10.1080/09638288.2018.1503736

129. Mahmood A, Veluswamy SK, Hombali A, Mullick A, N M, Solomon JM. Effect of Transcutaneous Electrical Nerve Stimulation on Spasticity in Adults With Stroke: A Systematic Review and Meta-analysis. *Arch Phys Med Rehabil*. Nov 16 2018;doi:10.1016/j.apmr.2018.10.016

130. Motta-Oishi AA, Magalhaes FH, Micolis de Azevedo F. Neuromuscular electrical stimulation for stroke rehabilitation: is spinal plasticity a possible mechanism associated with diminished spasticity? *Medical hypotheses*. Nov 2013;81(5):784-8. doi:10.1016/j.mehy.2013.08.013

131. Schuhfried O, Crevenna R, Fialka-Moser V, Paternostro-Sluga T. Non-invasive neuromuscular electrical stimulation in patients with central nervous system lesions: an educational review. *Journal of rehabilitation medicine*. Feb 2012;44(2):99-105. doi:10.2340/16501977-0941

132. Stein C, Fritsch CG, Robinson C, Sbruzzi G, Plentz RD. Effects of Electrical Stimulation in Spastic Muscles After Stroke: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Stroke*. Aug 2015;46(8):2197-205. doi:10.1161/strokeaha.115.009633

133. Lin S, Sun Q, Wang H, Xie G. Influence of transcutaneous electrical nerve stimulation on spasticity, balance, and walking speed in stroke patients: A systematic review and meta-analysis. *Journal of rehabilitation medicine*. Jan 10 2018;50(1):3-7. doi:10.2340/16501977-2266

134. Sonde L, Bronge L, Kalimo H, Viitanen M. Can the site of brain lesion predict improved motor function after low-TENS treatment on the post-stroke paretic arm? *Clinical rehabilitation*. Oct 2001;15(5):545-51. doi:10.1191/026921501680425261

135. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ. *Principles of neural science*. McGraw-Hill, Health Professions Division; 2012.

136. Ertzgaard P, Alwin J, Sorbo A, Lindgren M, Sandsjo L. Evaluation of a self-administered transcutaneous electrical stimulation concept for the treatment of spasticity: a randomized placebo-controlled trial. Article. *Eur J Phys Rehabil Med*. Aug 2018;54(4):507-517. doi:10.23736/s1973-9087.17.04791-8

137. Nordstrom B, Prellwitz M. A pilot study of children and parents experiences of the use of a new assistive device, the electro suit Mollii. *Assistive Technology*. 2019:1-8. doi:10.1080/10400435.2019.1579267

138. Hedin H, Wong C, Sjödén A. The effects of using an electrodress (Mollii®) to reduce spasticity and enhance functioning in children with cerebral palsy: a pilot study. *European Journal of Physiotherapy*. 2020:1-10. doi:10.1080/21679169.2020.1807602

139. Palmcrantz S, Pennati GV, Bergling H, Borg J. Feasibility and potential effects of using the electro-dress Mollii on spasticity and functioning in chronic stroke. *Journal of neuroengineering and rehabilitation*. Aug 10 2020;17(1):109. doi:10.1186/s12984-020-00740-z

140. Lo JK, Robinson LR. Postpolio syndrome and the late effects of poliomyelitis. Part 1. pathogenesis, biomechanical considerations, diagnosis, and investigations. *Muscle Nerve*. Dec 2018;58(6):751-759. doi:10.1002/mus.26168

141. Dalakas MC. The post-polio syndrome as an evolved clinical entity. Definition and clinical description. *Ann N Y Acad Sci*. May 25 1995;753:68-80.

142. Lo JK, Robinson LR. Post-polio syndrome and the late effects of poliomyelitis: Part 2. treatment, management, and prognosis. *Muscle Nerve*. Dec 2018;58(6):760-769. doi:10.1002/mus.26167

143. Post-Polio Health International. http://www.post-polio.org/edu/pabout.html

144. Khadilkar SV, Yadav RS, Patel BA. Post-polio Syndrome. *Neuromuscular Disorders, A Comprehensive Review with Illustrative Cases*. Springer Singapore; 2018:chap 8.

145. Gonzalez H, Olsson T, Borg K. Management of postpolio syndrome. *The Lancet Neurology*. Jun 2010;9(6):634-42. doi:10.1016/s1474-4422(10)70095-8

146. Harbo T, Brincks J, Andersen H. Maximal isokinetic and isometric muscle strength of major muscle groups related to age, body mass, height, and sex in 178 healthy subjects. *European journal of applied physiology*. Jan 2012;112(1):267-75. doi:10.1007/s00421-011-1975-3

147. Stolwijk-Swuste JM, Beelen A, Lankhorst GJ, Nollet F. The course of functional status and muscle strength in patients with late-onset sequelae of poliomyelitis: a systematic review. *Arch Phys Med Rehabil*. Aug 2005;86(8):1693-701. doi:10.1016/j.apmr.2004.12.022

148. Bickerstaffe A, Beelen A, Nollet F. Change in physical mobility over 10 years in post-polio syndrome. *Neuromuscular disorders : NMD*. Mar 2015;25(3):225-30. doi:10.1016/j.nmd.2014.11.015

149. Flansbjer UB, Brogardh C, Horstmann V, Lexell J. Men With Late Effects of Polio Decline More Than Women in Lower Limb Muscle Strength: A 4-Year Longitudinal Study.

PM & R : the journal of injury, function, and rehabilitation. Nov 2015;7(11):1127-1136. doi:10.1016/j.pmrj.2015.05.005

150. Trojan DA, Arnold DL, Shapiro S, et al. Fatigue in Post-poliomyelitis Syndrome: Association With Disease-Related, Behavioral, and Psychosocial Factors. *Pm&R*. 2009/05/01/ 2009;1(5):442-449. doi:https://doi.org/10.1016/j.pmrj.2009.03.003

151. Werhagen L, Borg K. Impact of pain on quality of life in patients with post-polio syndrome. *Journal of rehabilitation medicine*. Feb 2013;45(2):161-3. doi:10.2340/16501977-1096

152. Stoelb BL, Carter GT, Abresch RT, Purekal S, McDonald CM, Jensen MP. Pain in persons with postpolio syndrome: frequency, intensity, and impact. *Arch Phys Med Rehabil*. Oct 2008;89(10):1933-40. doi:10.1016/j.apmr.2008.03.018

153. Widar M, Ahlstrom G. Pain in persons with post-polio. The Swedish version of the Multidimensional Pain Inventory (MPI). *Scandinavian journal of caring sciences*. 1999;13(1):33-40.

154. Borg K. Post-polio muscle dysfunction 29th ENMC workshop 14-16 October 1994, Naarden, the Netherlands. *Neuromuscular disorders : NMD*. Jan 1996;6(1):75-80.

155. Grimby G, Stalberg E, Sandberg A, Sunnerhagen KS. An 8-year longitudinal study of muscle strength, muscle fiber size, and dynamic electromyogram in individuals with late polio. *Muscle Nerve*. Nov 1998;21(11):1428-37.

156. Gonzalez H, Ottervald J, Nilsson KC, et al. Identification of novel candidate protein biomarkers for the post-polio syndrome - implications for diagnosis, neurodegeneration and neuroinflammation. *Journal of proteomics*. Jan 30 2009;71(6):670-81. doi:10.1016/j.jprot.2008.11.014

157. Melin E, Lindroos E, Lundberg IE, Borg K, Korotkova M. Elevated expression of prostaglandin E2 synthetic pathway in skeletal muscle of prior polio patients. *Journal of rehabilitation medicine*. Jan 2014;46(1):67-72. doi:10.2340/16501977-1230

158. Gonzalez H, Khademi M, Andersson M, Wallstrom E, Borg K, Olsson T. Prior poliomyelitis-evidence of cytokine production in the central nervous system. *J Neurol Sci*. Dec 15 2002;205(1):9-13.

159. Gonzalez H, Khademi M, Andersson M, et al. Prior poliomyelitis-IVIg treatment reduces proinflammatory cytokine production. *Journal of neuroimmunology*. May 2004;150(1-2):139-44. doi:10.1016/j.jneuroim.2004.01.010

160. Gonzalez H, Sunnerhagen KS, Sjoberg I, Kaponides G, Olsson T, Borg K. Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial. *The Lancet Neurology*. Jun 2006;5(6):493-500. doi:10.1016/s1474-4422(06)70447-1

161. Bickerstaffe A, Beelen A, Zwarts MJ, Nollet F, van Dijk JP. Quantitative muscle ultrasound and quadriceps strength in patients with post-polio syndrome. *Muscle Nerve*. Jan 2015;51(1):24-9. doi:10.1002/mus.24272

162. Maeda K, Joko M. Segmental muscular atrophy in a patient with post polio syndrome. *Internal medicine (Tokyo, Japan)*. 2007;46(2):75-6.

163. Farbu E, Gilhus NE, Barnes MP, et al. EFNS guideline on diagnosis and management of post-polio syndrome. Report of an EFNS task force. *European journal of neurology*. Aug 2006;13(8):795-801. doi:10.1111/j.1468-1331.2006.01385.x

164. March of Dimes. Post-polio syndrome: Identifying best practices in diagnosis and care. March of Dimes Birth Defects Foundation White Plains, NY; 2001.

165. Koo TK, Mak AF. A neuromusculoskeletal model to simulate the constant angular velocity elbow extension test of spasticity. *Med Eng Phys*. Jan 2006;28(1):60-9. doi:10.1016/j.medengphy.2005.03.012

166. Arampatzis A, Karamanidis K, Stafilidis S, Morey-Klapsing G, DeMonte G, Brüggemann GP. Effect of different ankle- and knee-joint positions on gastrocnemius medialis fascicle length and EMG activity during isometric plantar flexion. *Journal of biomechanics*. 2006;39(10):1891-902. doi:10.1016/j.jbiomech.2005.05.010

167. Hermens HJ, Freriks B. Recommendations for sensor locations on individual muscles. The SENIAM project (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles). Accessed 1 August, 2017, 2017. http://seniam.org/sensor_location.htm

168. Lygren H, Jones K, Grenstad T, Dreyer V, Farbu E, Rekand T. Perceived disability, fatigue, pain and measured isometric muscle strength in patients with post-polio symptoms. *Physiother Res Int*. Mar 2007;12(1):39-49. doi:10.1002/pri.352

169. Flansbjer U-B, Drake A, Lexell J. Reproducibility of ankle dorsiflexor muscle strength measurements in individuals with post-polio syndrome. *Isokinetics and exercise science*. 01/10 2011;19:55-61. doi:10.3233/IES-2011-0397

170. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clinical rehabilitation*. Oct 1999;13(5):373-83. doi:10.1191/026921599677595404

171. Ward AB. Assessment of muscle tone. *Age Ageing*. Sep 2000;29(5):385-6. doi:10.1093/ageing/29.5.385

172. Compston A. Aids to the Investigation of Peripheral Nerve Injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with Aids to the Examination of the Peripheral Nervous System. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. *Brain : a journal of neurology*. 2010;133(10):2838-2844. doi:10.1093/brain/awq270

173. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scandinavian journal of rehabilitation medicine*. 1975;7(1):13-31.

174. Hernández ED, Galeano CP, Barbosa NE, et al. Intra- and inter-rater reliability of Fugl-Meyer Assessment of Upper Extremity in stroke. *Journal of rehabilitation medicine*. Oct 4 2019;51(9):652-659. doi:10.2340/16501977-2590

175. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties. *Neurorehabil Neural Repair*. 2002;16(3):232-240. doi:10.1177/154596802401105171

176. Duncan Millar J, van Wijck F, Pollock A, Ali M. Outcome measures in post-stroke arm rehabilitation trials: do existing measures capture outcomes that are important to stroke survivors, carers, and clinicians? *Clinical rehabilitation*. 2019/04/01 2019;33(4):737-749. doi:10.1177/0269215518823248

177. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. Oct 1989;46(10):1121-3. doi:10.1001/archneur.1989.00520460115022

178. Lexell J, Jonasson SB, Brogardh C. Psychometric Properties of Three Fatigue Rating Scales in Individuals With Late Effects of Polio. *Ann Rehabil Med*. 2018;42(5):702-712. doi:10.5535/arm.2018.42.5.702

179. Johansson S, Kottorp A, Lee KA, Gay CL, Lerdal A. Can the Fatigue Severity Scale 7-item version be used across different patient populations as a generic fatigue measure--a comparative study using a Rasch model approach. *Health Qual Life Outcomes*. Feb 22 2014;12:24. doi:10.1186/1477-7525-12-24

180. Burger H, Franchignoni F, Puzic N, Giordano A. Psychometric properties of the Fatigue Severity Scale in polio survivors. *International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation*. Dec 2010;33(4):290-7. doi:10.1097/MRR.0b013e32833d6efb

181. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. Apr 1995;39(3):315-25. doi:10.1016/0022-3999(94)00125-o

182. Hagelin CL, Wengström Y, Runesdotter S, Fürst CJ. The psychometric properties of the Swedish Multidimensional Fatigue Inventory MFI-20 in four different populations. *Acta Oncol*. 2007;46(1):97-104. doi:10.1080/02841860601009430

183. Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: Which to use? *Am J Emerg Med*. Apr 2018;36(4):707-714. doi:10.1016/j.ajem.2018.01.008

184. Currier DP. *Elements of Research in Physical Therapy*. 3rd ed. Williams & Wilkins; 1990.

185. Bentley D. CE marking--what does it really mean? *J Tissue Viability*. Jan 1999;9(1):11-5. doi:10.1016/s0965-206x(99)80004-7

186. Blumberg BCDRSPS. *Business research methods*. McGraw-Hill; 2005.

187. Altheide DL, Johnson JM. Criteria for assessing interpretive validity in qualitative research. *Handbook of qualitative research*. Sage Publications, Inc; 1994:485-499.

188. Association AER, Association AP, Education NCoMi. *Standards for educational and psychological testing*. American Educational Research Association; 1999.

189. Sireci S, Faulkner-Bond M. Validity evidence based on test content. *Psicothema*. 02/01 2014;26:100-7. doi:10.7334/psicothema2013.256

190. Latash ML, Levin MF, Scholz JP, Schöner G. Motor control theories and their applications. *Medicina (Kaunas)*. 2010;46(6):382-92.

191. Arendzen JH, van Duijn H, Beckmann MK, Harlaar J, Vogelaar TW, Prevo AJ. Diagnostic blocks of the tibial nerve in spastic hemiparesis. Effects on clinical, electrophysiological and gait parameters. *Scandinavian journal of rehabilitation medicine*. 1992;24(2):75-81.

192. Lieber RL, Runesson E, Einarsson F, Fridén J. Inferior mechanical properties of spastic muscle bundles due to hypertrophic but compromised extracellular matrix material. *Muscle Nerve*. 2003;28(4):464-471. doi:https://doi.org/10.1002/mus.10446

193. Lieber RL, Ward SR. Cellular Mechanisms of Tissue Fibrosis. 4. Structural and functional consequences of skeletal muscle fibrosis. *American Journal of Physiology-Cell Physiology*. 2013;305(3):C241-C252. doi:10.1152/ajpcell.00173.2013

194. Gao F, Grant TH, Roth EJ, Zhang L-Q. Changes in Passive Mechanical Properties of the Gastrocnemius Muscle at the Muscle Fascicle and Joint Levels in Stroke Survivors. *Arch Phys Med Rehabil*. 2009;90(5):819-826. doi:10.1016/j.apmr.2008.11.004

195. Leng Y, Wang Z, Bian R, et al. Alterations of Elastic Property of Spastic Muscle With Its Joint Resistance Evaluated From Shear Wave Elastography and Biomechanical Model. Original Research. *Frontiers in Neurology*. 2019-July-10 2019;10(736)doi:10.3389/fneur.2019.00736

196. Stecco C, Pirri C, Fede C, Yucesoy C, Caro R, Stecco A. Fascial or Muscle Stretching? A Narrative Review. *Applied Sciences*. 12/30 2020;11:307. doi:10.3390/app11010307

197. Tian M, Hoang PD, Gandevia SC, Herbert RD, Bilston LE. Viscous elements have little impact on measured passive length–tension properties of human gastrocnemius muscle–tendon units in vivo. *Journal of biomechanics*. 2011/04/29/ 2011;44(7):1334-1339. doi:https://doi.org/10.1016/j.jbiomech.2011.01.005

198. Dong Y, Wu T, Hu X, Wang T. Efficacy and safety of botulinum toxin type A for upper limb spasticity after stroke or traumatic brain injury: a systematic review with meta-analysis and trial sequential analysis. *Eur J Phys Rehabil Med*. Apr 2017;53(2):256-267. doi:10.23736/s1973-9087.16.04329-x

199. Drost EA. Validity and reliability in social science research. *Education Research and perspectives*. 2011;38(1):105-123.

200. Bhimani RH, Peden-McAlpine C, Gaugler J, Anderson LC. Spasticity over time during acute rehabilitation: a study of patient and clinician scores. *Applied Nursing Research*. 2016/05/01/ 2016;30:16-23. doi:https://doi.org/10.1016/j.apnr.2015.08.007

201. Cheung J, Rancourt A, Di Poce S, et al. Patient-identified factors that influence spasticity in people with stroke and multiple sclerosis receiving botulinum toxin injection treatments. *Physiother Can*. Spring 2015;67(2):157-166. doi:10.3138/ptc.2014-07

202. Vaz S, Falkmer T, Passmore AE, Parsons R, Andreou P. The case for using the repeatability coefficient when calculating test-retest reliability. *PLoS One*. 2013;8(9):e73990-e73990. doi:10.1371/journal.pone.0073990

203. Lin FM, Sabbahi M. The aging effects on the EMG and mechanical responses of the human wrist flexor stretch reflexes. *Electromyography and clinical neurophysiology*. Sep 1998;38(6):323-31.

204. Chung SG, Van Rey EM, Bai Z, Rogers MW, Roth EJ, Zhang LQ. Aging-related neuromuscular changes characterized by tendon reflex system properties. *Arch Phys Med Rehabil*. Feb 2005;86(2):318-27. doi:10.1016/j.apmr.2004.04.048

205. Klass M, Baudry S, Duchateau J. Modulation of reflex responses in activated ankle dorsiflexors differs in healthy young and elderly subjects. *European journal of applied physiology*. Aug 2011;111(8):1909-16. doi:10.1007/s00421-010-1815-x

206. Chakravarty A, Mukherjee A. Spasticity Mechanisms – for the Clinician. Review. *Frontiers in Neurology*. 2010-December-17 2010;1(149)doi:10.3389/fneur.2010.00149

207. Pennati GV, Plantin J, Borg J, Lindberg PG. Normative NeuroFlexor data for detection of spasticity after stroke: a cross-sectional study. *Journal of neuroengineering and rehabilitation*. Mar 18 2016;13:30. doi:10.1186/s12984-016-0133-x

208. Dimes Mo. Post-polio syndrome: Identifying best practices in diagnosis and care. White Plains, NY: March of Dimes Birth Defects Foundation; 2001.

209. McComas AJ, Quartly C, Griggs RC. Early and late losses of motor units after poliomyelitis. *Brain : a journal of neurology*. Aug 1997;120:1415-1421. doi:10.1093/brain/120.8.1415

210. Li Hi Shing S, Chipika RH, Finegan E, Murray D, Hardiman O, Bede P. Post-polio Syndrome: More Than Just a Lower Motor Neuron Disease. Mini Review. *Frontiers in Neurology*. 2019-July-16 2019;10(773)doi:10.3389/fneur.2019.00773

211. Luciano CA, Sivakumar K, Spector SA, Dalakas MC. Electrophysiologic and histologic studies in clinically unaffected muscles of patients with prior paralytic poliomyelitis. *Muscle Nerve*. Nov 1996;19(11):1413-20. doi:10.1002/(sici)1097-4598(199611)19:11<1413::Aid-mus5>3.0.Co;2-f

212. Fidancı H, Öztürk İ, Köylüoğlu A, Buturak Ş, Arlier Z. Pattern of muscle involvement according to needle electromyography findings in clinically unaffected extremities of polio survivors with lower extremity weaknesses. *Journal of Surgery and Medicine*. 09/03 2019;3doi:10.28982/josam.612567

213. Dencker A, Sunnerhagen KS, Taft C, Lundgren-Nilsson Å. Multidimensional fatigue inventory and post-polio syndrome - a Rasch analysis. *Health Qual Life Outcomes*. Feb 12 2015;13:20. doi:10.1186/s12955-015-0213-9

214. Zhang L-Q, Rymer WZ. Reflex and Intrinsic Changes Induced by Fatigue of Human Elbow Extensor Muscles. *J Neurophysiol*. 2001;86(3):1086-1094. doi:10.1152/jn.2001.86.3.1086

215. Chalchat E, Gennisson J-L, Peñailillo L, et al. Changes in the Viscoelastic Properties of the Vastus Lateralis Muscle With Fatigue. Original Research. *Frontiers in Physiology*. 2020-April-24 2020;11(307)doi:10.3389/fphys.2020.00307

216. Wong C, Torabi TP, Mortensen K, Michelsen J. The Mollii-suit®—A novel method using reciprocal inhibition in children with cerebral palsy, gross motor function classification system IV-V: A 6-month prospective study. *Toxicon*. 2018/12/01/ 2018;156:S116. doi:https://doi.org/10.1016/j.toxicon.2018.11.279

217. Flodström C, Viklund Axelsson S-A, Nordström B. A pilot study of the impact of the electro-suit Mollii® on body functions, activity, and participation in children with cerebral palsy. *Assistive Technology*. 2020:1-7. doi:10.1080/10400435.2020.1837288

218. Binder-Markey BI, Murray WM, Dewald JPA. Passive Properties of the Wrist and Fingers Following Chronic Hemiparetic Stroke: Interlimb Comparisons in Persons With and Without a Clinical Treatment History That Includes Botulinum Neurotoxin. *Frontiers in neurology*. 2021;12:687624-687624. doi:10.3389/fneur.2021.687624