Full title: European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch

Running title: consensus on pathophysiological neuromuscular responses to passive muscle stretch

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Abstract

Background: To support clinical decision-making in central neurological disorders, physical examination is used to assess responses to passive muscle stretch. However, what exactly is being assessed is expressed and interpreted in different ways. A clear diagnostic framework is lacking. Therefore, the aim was to arrive at unambiguous terminology about the concepts and measurement around pathophysiological neuromuscular response to passive muscle stretch.

Methods: During two consensus meetings, 37 experts from 12 European countries filled online questionnaires based on a Delphi approach, followed by plenary discussion after rounds. Consensus was reached when agreement ≥75%.

Results: The term *hyper-resistance* should be used to describe the phenomenon of impaired neuromuscular response during passive stretch, instead of e.g. 'spasticity' or 'hypertonia'. From there, it is essential to distinguish *non-neural* (tissue-related) from *neural* (central nervous system related) contributions to hyper-resistance. Tissue contributions are elasticity, viscosity and muscle shortening. Neural contributions are velocity dependent *stretch hyperreflexia* and non-velocity dependent *involuntary background activation*. The term 'spasticity' should only be used next to stretch hyperreflexia, and 'stiffness' next to passive tissue contributions. When joint angle, moment and electromyography are recorded, components of hyper-resistance within the framework can be quantitatively assessed.

Conclusions: A conceptual framework of pathophysiological responses to passive muscle stretch was defined. This framework can be used in clinical assessment of hyper-resistance and will improve communication between clinicians. Components within the framework are defined by objective parameters from instrumented assessment. These parameters need experimental validation in order to develop treatment algorithms based on aetiology of the clinical phenomena.

Introduction

Impaired motor control is a consequence of most central nervous system movement disorders such as cerebral palsy (CP), stroke (CVA), spinal cord injury (SCI) or multiple sclerosis (MS). A common physical examination includes assessment of the resistance to passive muscle elongation. This examination is used to make judgments on the degree and nature of muscle hyper-resistance, to determine aetiology at the level of the muscular tissue and/or motor control, and to infer consequences for overall motor performance in functional tasks. It is considered important to a meaningful description of the clinical status of the patient and essential to inform decisions on the treatment options [1].

Although such physical examination is in widespread clinical use and yields clinically essential information, the concept of what is being assessed cannot be unambiguously phrased. This is expressed in the variety of typically used nomenclature for what is being assessed, e.g. hyper-resistance, spasticity, hypertonia, stiffness, (dynamic) contracture, or hypo-extensibility [2-11]. This is accompanied by a variety of interpretations, i.e. how these findings relate to presumed underlying pathophysiology. Therefore, in clinical practice, the concepts of pathophysiological neuromuscular response to passive muscle stretch must be considered implicit rather than explicit. The lack of a clear diagnostic conceptual framework obstructs effective communication between clinicians, and impedes construction of reliable treatment algorithms. Moreover, quantifying results of an assessment requires grading based on measurement instruments that, by definition, must rely on unambiguous conceptualization.

All in all, this diversity in clinical practices calls for a consensus on the conceptualization, interpretation and measurement of the pathophysiological neuromuscular responses to

imposed passive elongation, to fully exploit the potential of this diagnostic test in the context of treating patients with neurological diseases.

General physiological concepts

The aetiology of increased resistance to passive muscle stretch has both neurological and non-neurological components. The primary neurological component is generally accepted as being caused by supraspinal disregulation (disinhibition) of the spinal reflex loop, as a direct result of the neurological insult [12, 13]. This reflex loop evokes a *stretch reflex*, an essential mechanism of motor control that occurs when a muscle is lengthened rapidly and/or forcefully. Normally, stretch reflex activity is low when a muscle is passively lengthened. In the case of disinhibition due to a neurological insult, the stretch reflex is more readily elicited. This hyperactive reflex causes muscle contraction and therefore an opposing force to passive elongation. In fact, the complete pathophysiology of neural contributors is much more complex than this simplified description, as several mechanisms can be identified that give rise to involuntary muscle contractions resulting in increased resistance of muscles to their elongation. These mechanisms are referred to as excess, or positive motor symptoms, of the neurological disorder, as opposed to the deficit, or negative symptoms, that reflect the impairment to activate a muscle purposefully.

The non-neurological component of muscle hyper-resistance consists of secondary impairments that are thought to occur as a result of muscular adaptations to the neural dysregulation. For instance, muscles might shorten (muscle contractures) or stiffen due to intrinsic changes in the muscle tissue. In children these effects might be amplified as result of maladaptation to growth.

Definitions

Pathophysiological responses to passive muscle elongation have been defined and named. The use of the term '*spasticity'* has been used to refer to either an aetiology at spinal level or to a clinical expression at a joint level. Such wide usage of the term has led to its definition being subject to debate for a long time [6, 7]. One of the commonly used definitions of spasticity was provided by Lance in 1980: "*a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the upper motor neurone syndrome*" [3]. Clearly, Lance refers to the pathophysiological mechanisms. Sanger et al. (NIH task force, 2003) stayed closer to the clinical phenomena and defined spasticity as "*hypertonia in which one or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement, and/or 2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle*" [4]. Other features of neuromuscular impairments were defined by them as well, all under the umbrella term '*hypertonia'*. The definitions by Lance and by Sanger et al. are mutually compatible.

In 2005, the SPASM consortium introduced a new definition of spasticity using a motor control approach: "*disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles* " [8, 9]. This definition includes the entire range of signs and symptoms that are collectively described as excess features, and not exclusively the hyperactive stretch reflex.

Common clinical tests

Several physical examination tests have been constructed to assess spasticity or resistance in clinical practice, such as the (Modified) Ashworth Scale (MAS), the Tardieu Scale and the

Spasticity Test (SPAT, a simplification of the Tardieu Scale) [1, 14-25]. In these tests, passive muscle elongations are imposed at one or more velocities by the examiner. Perceived resistance during slow passive elongation is assumed to be related only to non-neural (changed mechanical response of the neuromuscular complex, i.e. stiffness (elasticity) and viscosity) components. In muscles with spasticity, high stretch velocities may additionally cause increased resistance and/or a catch, i.e. a stop in the movement due to the hyperactive stretch reflex [15, 26]. In contrast to the Tardieu Scale and the SPAT, the MAS does not use multiple velocities, and scores a single value, thereby not discriminating between neural and non-neural contributions [21].

Although such physical examinations are commonly used in clinical practice, the resistance perceived by the examiner is difficult to relate to either a neural or non-neural origin [7, 27]. Moreover, the velocity of stretch as well as the level of activity of the muscle are uncontrolled [7, 16, 19, 23, 28]. Finally, the outcome of these tests is a numeric value scored by the examiner and based on subjective feeling and joint angle measurement with goniometry. Standardisation, reliability, sensitivity, quantification, and objectivity are lacking in these tests.

Instrumented tests

To unravel the neural and non-neural contributions to hyper-resistance during passive muscle elongation, instrumented assessments have been developed in several research settings [7, 16, 22, 24, 26-30]. These measurements employ electrophysiological signals (electromyography (EMG)) to assess the stretch reflex, in combination with joint movement (kinematics) and applied torques (net joint moment). In this way the resistance to muscle elongation can be objectified and the neural and non-neural aspects specifically discriminated, in order to arrive

194 at the correct treatment option, based on aetiology [28, 29]. Next to assessment of the stretch
195 reflex, the measurement of the Hoffman-reflex, using submaximal electric stimulation of the
196 nerve, is used to study the excitability of the Ia afferents [25, 31, 32].

197 Although there have been multiple efforts to arrive at clear concepts, and instruments are
198 developed to express objectivity, there is yet no unambiguous and generally accepted
199 conceptual frame work that incorporates a meaningful decomposition of perceived
200 phenomena with associated operationalization. Therefore, two consensus meetings were
201 organized with the aim (1) to arrive at unambiguous terminology about the concepts of, and
202 phenomena around, pathophysiological neuromuscular response to passive muscle stretch and
203 (2) to define requirements from a clinical perspective that enable the development of
204 instruments to quantitatively measure the defined concepts in clinical practice.

Methods

Thirty-seven participants from twelve European countries joined two consensus meetings, on 22-23 May 2014 in Amsterdam, the Netherlands and a follow-up meeting on 8 September 2015 in Heidelberg, Germany. Participants, from, but not restricted to, the network of the organizers (JN, JH, JB, LB, KD), were invited for the meetings based on their publications related to this field, and their experience in either treating or assessing spasticity in a clinical or research setting. Prior to the first meeting, participants were asked to fill in an online questionnaire (NETQ Internet Surveys, NetQuestionnaires Nederland BV, Utrecht, the Netherlands) about their background and experience with clinical spasticity assessment. Characteristics of the participants are presented in Table 1. During the meetings, a modified Delphi approach [33] was used to arrive at consensus about (1) terminology about the concepts of, and phenomena around, response to passive muscle stretch and (2) boundary conditions from clinical perspective to enable development of instruments to quantitatively measure the defined concepts in clinical practice.

Part 1

At the first meeting (31 participants), a schematic overview (Figure 1A) was presented to the participants. This overview was developed by the organizers of the consensus meetings (JH, JB, KD, LB, JN) based on careful review of the literature (as described in the Introduction) and their own experience in the field, with the aim to initiate the discussion on concepts and (new) terminology. Using this overview, a discussion was initiated on the terminology, concepts and phenomena around pathophysiological neuromuscular responses to passive muscle stretch. Thereafter, a Delphi questionnaire, consisting of 12 statements using a Likert

scale (i.e. strongly disagree, disagree, neutral, agree, strongly agree) (Table 2) was anonymously filled in by the participants (NETQ Internet Surveys, NetQuestionnaires Nederland BV, Utrecht, the Netherlands). The included domains were: terminology on the concepts, non-neural and neural contributions, and passive versus active impairment.

Subsequently, results of this first round were collated, presented to participants and discussed plenary. Consensus was reached when agreement was 75% or higher. Unclear questions from round 1 were rephrased and a second Delphi round of 8 statements was conducted (Table 3) on the same domains. Next, results of the second round were presented to the participants and discussed plenary to further reach consensus on those statements that were unclear or had limited agreement.

During the second meeting (26 participants), a summary of the results of the two Delphi rounds and the discussions of the first meeting was presented, followed by a plenary discussion for final agreement on conceptualization and terminology.

Part 2

To determine the requirements for instrumented measurement of the defined concepts in clinical and research practice, designs and data from previous instrumented setups developed in research settings were presented to the participants at the first meeting (such as described in the Introduction section of this paper). Subsequently, a Delphi round on concepts of measurement was carried out which included 75 questions or statements (Table 4) related to the following domains: pathology, muscles, in- and exclusion criteria, test time allowance, patient position, movement profile, theoretical importance of signals and sensors, practical feasibility of signals and sensors, feedback, outcome parameters, report, and training.

Questions were multiple choice or used the Likert scale. Results of the questionnaire were discussed plenary.

During the second meeting, a second Delphi round about concepts of measurements was conducted which included 18 rephrased statements that were unclear to the participants or had not reached consensus in round 1. The included domains were: protocol, feedback and report.

As instrumented measurement of spasticity in clinical settings is still fairly innovative, the aim of part 2 was not to reach full consensus on all questions but to get insight into important aspects for future development of a clinically-applicable instrumented spasticity assessment.

Results

Participant characteristics

Twenty-seven participants completed the online questionnaire about background, profession and experience with clinical spasticity assessment. Most responders were clinicians (86%) as well as researchers (86%), 71% of the responders clinically assessed patients with spasticity and 48% carried out clinical treatment of spasticity. Years of experience in assessing or treating spasticity ranged between 1 and 30 years, with a mean of 13 years and median of 15 years. The (modified) Tardieu scale was the most commonly used clinical test (57%) followed by the (modified) Ashworth scale (53%). Tests were mostly performed by physiotherapists (76%) or medical doctors (71%), most of the time before and after treatment (67% always before and after) and sometimes during consultations (62%). Most responders were unsatisfied with the current clinical tests (47%) or were neutral (33%). Of the participants using a form of instrumented assessment (81%), 24% were unsatisfied and 38% neutral.

Part 1: Conceptualization and terminology

Twenty-eight participants completed the first, and 30 participants completed the second Delphi round on the conceptualization of the pathophysiological neuromuscular responses to passive muscle stretch (Table 2 and 3).

In the initial plenary discussion following the presentation of the schematic overview (Figure 1A), the following was discussed: 1. *Increased resistance perceived by an examiner during physical examination*, i.e. passive muscle stretch, is, apart from the term spasticity, often termed *hypertonia*, which implies that the resistance results from involuntary muscle activation. 2. However, since hypertonia may also exist at rest (without muscle stretch), it

may not be equated to the resistance perceived during stretch. Therefore, the term *hyper-resistance* was suggested. 3. Although still the mostly commonly used term in clinical practice, it was also suggested to be careful with the term *spasticity*, since it may not cover all aspects of the perceived resistance.

During the first Delphi round (Table 2), it was concluded that the term 'hyper-resistance' is preferred over the terms 'hypertonia' and 'spasticity' to describe the phenomenon of impaired neuromuscular response during passive stretch. Hyper-resistance is therefore defined as increased resistance perceived during passive muscle stretch.

It was agreed that it is essential to distinguish non-neural (tissue-related) from neural (CNS related) contributions to hyper-resistance. It was proposed that the different contributions could be described by three subgroups: muscle tissue properties (non-neural), hyperstretch reflex (neural and induced by motion) and involuntary activation (neural) (Figure 1B). Muscle tissue properties consist of muscle stiffness (elasticity) and viscosity. Participants remarked that joint stiffness and viscosity are not only the result of muscle tissue properties, but are also influenced by the ligaments and surrounding tissue. However, hyper-resistance reflects neuromuscular unit function only when no bony and ligament response is assumed (second Delphi round, Table 3).

During the first Delphi round (Table 2) consensus was reached that it is essential to distinguish hyperstretch reflex and other muscle activity within the neural (CNS related) contributions to hyper-resistance. Clonus and clasp-knife are specific manifestations of the exaggerated stretch reflex. In the discussion prior to the first Delphi round it was suggested that hyper-resistance is the net effect of the agonist and antagonist muscles, and co-contraction might be present during examination. Therefore, co-contraction should be considered as part of the involuntary activation subgroup. In the second Delphi round (Table 3), the majority of the participants agreed that hyper-resistance reflects the neuromuscular unit

function of an agonist muscle group only when no effects of antagonistic muscle(s) (shortening) is assumed.

In the discussion prior to the second Delphi round, three alternatives were proposed for terminology of the two neural contribution subgroups to hyper-resistance, i.e. "hyperstretch reflex" and "involuntary activation" (Figure 1B). In the second Delphi round (Table 3), consensus was reached that the *neural contributions to hyper-resistance* must be distinguished in *"velocity dependent involuntary activation"* and *"non-velocity dependent involuntary activation"*. Also the terms *"stretch hyperreflexia"* and *"involuntary background activation"* were considered to be appropriate as alternative terms to distinguish different neural contributions (Figure 1B) and further used in the final discussions in combination with the terms *"(non-)velocity dependent"* (Figure 1C). Participants showed less preference for the terms "stretch reflex involuntary activation" and "non-stretch reflex involuntary activation".

In the final discussions of the conceptualization phase (following the two Delphi rounds), the characteristics of subgroups of hyper-resistance were further specified (Figure 1C).

(Muscle) tissue properties (non-neural) contain elasticity, viscosity and shortening. The neural contributions are subdivided into stretch hyperreflexia (velocity dependent) and involuntary background activation (non-velocity dependent). Postural reflexes, non-selective activation, tonic reflexes and fixed background tone are all part of the involuntary background activation.

The word 'spasticity' is not part of the conceptual framework, since almost all participants (strongly) agreed that the term 'spasticity' should be used with care and only when clearly defined (Table 3). Also, participants agreed that the term refers to involuntary, stretch-velocity induced muscle activity as part of the neural contributions to hyper-resistance (definition according to Lance and Sanger et al. [3, 4]) (Table 2 and 3). Therefore, within the

framework, spasticity refers to velocity dependent stretch hyperreflexia as part of hyper-resistance, and should only be used next to the term ‘stretch hyperreflexia’.

Also, the term ‘stiffness’ is not part of the conceptual framework. It is mechanically defined as the linear relation between joint angle and joint moment (i.e. elasticity), however in practice, the term ‘stiffness’ is often used in a broader perspective to refer to various (muscle) tissue properties. In this case, it should only be used next to the term (muscle) tissue related contributions to hyper-resistance.

Finally, it was discussed whether passive measurement is representative of the problems occurring during active, functional tasks. Hyper-resistance (ICF body functions and structures level, WHO 2001 [34]) only partly determines any impaired muscle function during performance of activities (ICF activity level) (Table 2). Further research should compare the hyper-resistance measured during passive and active movements.

Part 2: Requirements for instrumented measurement of hyper-resistance

Twenty-eight participants completed the first questionnaire, and 19 participants completed the second questionnaire about concepts of measurement. Outcomes (Tables 4 and 5) showed that an instrumented assessment of hyper-resistance must be applicable to children (>3years) and adults with cerebral palsy, stroke, SCI and MS. The main muscle groups that need to be assessed are (lower limb) medial and lateral gastrocnemius, soleus, rectus femoris, hamstrings (semimembranosus and semitendinosus) and to a lesser extent hip adductors, as well as (upper limb) elbow and wrist flexors. It is required that patients must be in a comfortable position that promotes muscle relaxation during the test.

The test procedure must start from the minimum end of the range of motion (corresponding to the shortest muscle length) to the maximum end of the range of motion (corresponding to the

longest muscle length). The assessment is not applicable to joints with fixed deformities or muscle contractures that limit the range of motion in the direction of movement to less than 10 degrees. At least two different stretch velocities are required (slow and fast), the number of stretches must be kept to a minimum and a rest period is necessary between repetitions. It is important to hold the end of the stretch for a minimum amount of time in order to capture differences in type of catch (e.g. 2-5 sec.). Feedback on the achieved stretch velocity, muscle activity (agonist and antagonist), range of motion in direction of movement and force applied in main direction of movement are essential.

From the first Delphi round (Table 4), requirements for outcome parameters of instrumented assessment concerning neural contributions (either available in a report or in raw data that can be processed post-hoc) are: amount of reflex activity measured by EMG (i.e. mean amplitude over a certain period), timing of EMG activation, duration of EMG activity and increase in EMG amplitude due to velocity and due to position separately. Essential non-neural based parameters are start and end joint angle, joint range of motion (ROM) and angle of catch (AOC) [28], as well as maximal angular velocity. A clinical report of instrumented assessment should contain at least discrete values of the recommended outcome parameters and comparisons of the data with typically developing/healthy subjects, as well as pre- or post-treatment comparisons.

Following on this, in the second Delphi round (Table 5), it was agreed that for a slow stretch, the following five outcome parameters would be sufficient in a report: ROM, maximal angular velocity, average root mean square EMG, stretch reflex threshold (i.e. joint angle at which EMG onset is first detected) and average work. Eighteen percent of the participants also indicated that stiffness (i.e. elasticity: the linear relation between joint angle and joint moment) might be a valuable outcome parameter for a slow stretch. For a fast stretch, six outcome parameters should be included: maximal angular velocity, average root mean square

EMG, stretch reflex threshold, average work, AOC and intensity of catch. As a difference between slow and fast stretch three outcome parameters should be included: difference between ROM and AOC, difference in average root mean square EMG, difference in work.

By these requirements, the three components in the conceptual framework of the pathophysiological neuromuscular responses to passive muscle stretch (muscle tissue properties, stretch hyperreflexia and involuntary background activation) could be linked to instrumented measurement of the joint angle, net joint moment and EMG to quantify the components of hyper-resistance (Figure 1C).

Discussion

A conceptual framework of the pathophysiological neuromuscular responses to passive muscle stretch was defined. This framework enables unambiguous terminology and a clear definition of the contributions to the clinical phenomenon of hyper-resistance that can be used in clinical practice and instrumented assessment. This will optimize communication between clinicians, improve diagnostics and objectify treatment outcomes.

In summary, the participants concluded that the term ‘hyper-resistance’ should be used to describe the phenomenon of the pathophysiological neuromuscular responses to passive muscle stretch, instead of spasticity or hypertonia. Furthermore, it was considered essential to distinguish non-neural (tissue-related) from neural (central nervous system related) contributions to hyper-resistance. Tissue properties consist of elasticity, viscosity and muscle shortening. The neural contributions are two-fold: velocity dependent stretch hyperreflexia and non-velocity dependent involuntary background activation. The term ‘spasticity’ should be used with care, only when clearly defined, next to the term ‘stretch hyperreflexia’. The same holds for the term ‘stiffness’, that should only be used next to tissue related contributions to hyper-resistance.

The components of hyper-resistance in the framework can be quantitatively assessed using instrumented measurement of the joint angle, net joint moment and EMG during slow and fast passive muscle stretch. Instruments like gyroscopes, accelerometers, force sensors and EMG sensors can be used to obtain these signals [16, 26-28, 30]. A list of outcome parameters to be derived from these signals was determined.

Clinical implications

The framework and the related requirements for instrumented assessment as defined by the consensus describe and measure the pathophysiological neuromuscular responses to passive muscle stretch. Some aspects of the defined parameters have already been validated in various patient groups, compared to clinical scores and assessed pre-post treatment [22]. Further experimental validation of the proposed parameters to measure hyper-resistance, could be used to advance treatment algorithms that are based on aetiology of the clinical phenomena. In clinical practice however, physical examination is only one part of the clinical routine, reflecting only some aspects of the 'body functions and structures' level of the ICF , upon which clinicians base their diagnoses and prognoses of treatment plans [34]. As such, clinical decision-making in relevant patient groups is not solely based on passive tests, but also involves clinical gait analyses [35] and assessment of the 'activity' and 'participation' domains of the ICF.

In the online questionnaire filled in prior to the first consensus meeting, 47% of the participants indicated to be unsatisfied with the current clinical tests (Table 1). Furthermore, 24% of the responders were unsatisfied with the currently available instrumented assessments. These findings might be related to experience with the commonly used Ashworth scale which is not standardized, not reliable, not discriminative and poorly related to reflex muscle activity [21]. Dissatisfaction with instrumented assessment might be related to too complex instruments that are not suitable for clinical use (like robotic systems), or too simple measures that are not precise or do not measure multiple parameters (like goniometry) [16]. Also, instrumented measurements can be time consuming which may limit its use in clinical practice. These factors stress the fact that clear terminology on the concepts of the pathophysiological responses is needed, as well as development of instrumented measurement that is meaningful towards these concepts and easily applicable in clinical practice. To further

assess clinical and research applicability, it is essential to formally investigate the clinical feasibility, patient and assessor usability and friendliness of any developed instruments.

Low correlations between clinical scales like the Ashworth and instrumented assessments have been reported [18, 21, 23]. The new framework helps explain these findings, and may lead to recommendations for use of existing clinical scales or development of new scales. Assessment of the sensitivity of parameters, measured with an instrument, to different treatments, might lead to classification of treatments based on the three components of the framework, e.g. botulinum toxin type-A, baclofen and selective dorsal rhizotomy (related to neural contributions) or orthopaedic surgery, casts or splints (related to non-neural contributions) [36].

The defined requirements on instrumented measurement also provide some guidelines for the assessment of patients such as patient position, ROM, muscle stretch velocities and use of outcome parameters needed for clinical decision-making (related to the framework). The posture of the patient influences the muscle length [10, 37], and should therefore be standardized. Some studies also already described standardized postures and movements for some clinical hyper-resistance tests [15, 16, 38, 39]. With regard to stretch velocity and interpretation of outcome parameters, it needs to be realized that in some cases it might be difficult to differentiate the neural and non-neural components of hyper-resistance, for example if a fast velocity cannot be obtained due to altered muscle properties (shortening, elasticity) or high background activation.

It was not the aim of the consensus meeting to develop a new definition of 'spasticity' to be used in clinical and research practice. However, agreement was reached that the term 'spasticity' should refer to stretch reflex activity, in according to Lance's and Sanger's definitions (Tables 2 and 3). More importantly, the consensus stated to use the term 'spasticity' with care Avoiding the word 'spasticity' may not be easy in clinical practice, as it

464 is still widely used. Therefore, it is advised to only use the term when clearly defined, and
465 next to the term 'stretch hyperreflexia' (Figure 1C).

466

467 *Further directions*

468 Some components in the proposed framework need further clarification. The non-velocity
469 dependent, involuntary background activation that can sometimes be observed during slow
470 passive muscle stretch, might also be influenced by other phenomena [10]. Also, if patients
471 are not able to completely relax during the testing; assist or oppose an imposed movement; or
472 experience pain during the movement, it might be difficult to discriminate this muscular
473 activation from pathological involuntary background activation. Therefore, it should be a
474 future aim to develop methods that can distinguish underlying factors in background muscle
475 activation.

476 Different requirements for detecting the different non-neural and neural contributions to
477 hyper-resistance were proposed. Two stretch velocities were advised (slow and fast).
478 However, it is yet not defined what velocity and movement profile should be applied. In
479 physical examination the movement profile is determined by constraints of human
480 performance of the examiner, as opposed to motorized tests in which a particular movement
481 profile can be imposed [40-43]. However, a motorized test is less feasible in clinical practice
482 and constant velocities do not represent natural movement profiles [44]. To standardize the
483 movement profile in manual testing feedback on achieved stretch velocity, range and direction
484 of movement can be provided. This might be different for each muscle, per age range and
485 patient population, as a consequence of muscle length, initial position, muscle volume and
486 weight of the body segment. For future research it is advised to establish further guidelines on
487 movement velocity, either in ranges or thresholds.

Previous research suggested that reflex activity is both length and velocity dependent [10, 37, 38]. The effect of muscle length might possibly be established using the slow passive movement, taking into account the delay between the trigger and the electrical response and the delay between the electrical and mechanical response of specific muscles [26, 45]. For example, the delay between maximal joint angular velocity and stretch reflex threshold might be an additional valuable outcome parameter in instrumented assessment. Furthermore, as mentioned before, the posture of the patient influences the muscle length [10, 37], and should therefore be standardized.

Clinical research will most certainly benefit from the recommended framework and instrumented assessment. Is ensures the use of similar terminology and standardization in measurement, leading to data comparison and data pooling and, with that, a framework to investigate many clinically relevant research questions. This in turn will support clinicians by providing detailed information on the underlying pathology and effectiveness of treatment.

Further, instrumentation and standardization of performance of passive muscle stretch in clinical practice will enable pre-post intervention comparisons and may optimize precision diagnostics and patient-specific treatment. This requires experimental validation of the proposed outcome parameters obtained from instrumented measured joint angles, joint moments and EMG, which is subject of further study.

Limitations of the study

Since both researchers and non-physicians were invited to participate in the consensus, not all participants personally treat spasticity in daily clinical practice (48% does, Table 1). However, all participants are experienced in either assessing or measuring hyper-resistance in a clinical (71%) or research setting (81%). Furthermore, 86% of the participants were clinicians responsible either for clinical decision-making, executing the physical examinations

or working as part of a multi-disciplinary team that treats spasticity. Since the consensus was focussed on concepts of assessment and measurement, the participants very well represent the professionals in the field related to this topic. As we believe that close collaboration between clinicians and (applied) researchers is key to a better understanding of the complex phenomena, and hence better treatment in the future, we consider the heterogenetic composition an asset of the study.

The first schematic overview presented was developed by the organizers of the consensus meetings, as were the first round of Delphi questionnaires. This might have introduced bias. However, the aim of the first overview and the first generation of statements (based on careful review of the literature and own experience) was to discuss, to rephrase the statements and to reach consensus. The Delphi method [33] is specifically designed to work in this way.

Conclusion

A conceptual framework of the pathophysiological neuromuscular responses to passive muscle stretch was defined, based on European consensus meetings with experts in the field. The neutral term hyper-resistance should be used to describe the phenomenon of impaired neuromuscular responses during passive stretch. It is essential to distinguish non-neural from neural contributions to hyper-resistance. This framework can be used to standardize and objectify the clinical assessment of hyper-resistance and will improve communication between clinicians and researchers. Components within the framework are defined by objective parameters that can be derived from instrumented assessment. These parameters need experimental validation after which they can be used as part of the development of treatment algorithms that are based on the aetiology of the clinical phenomena.

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540

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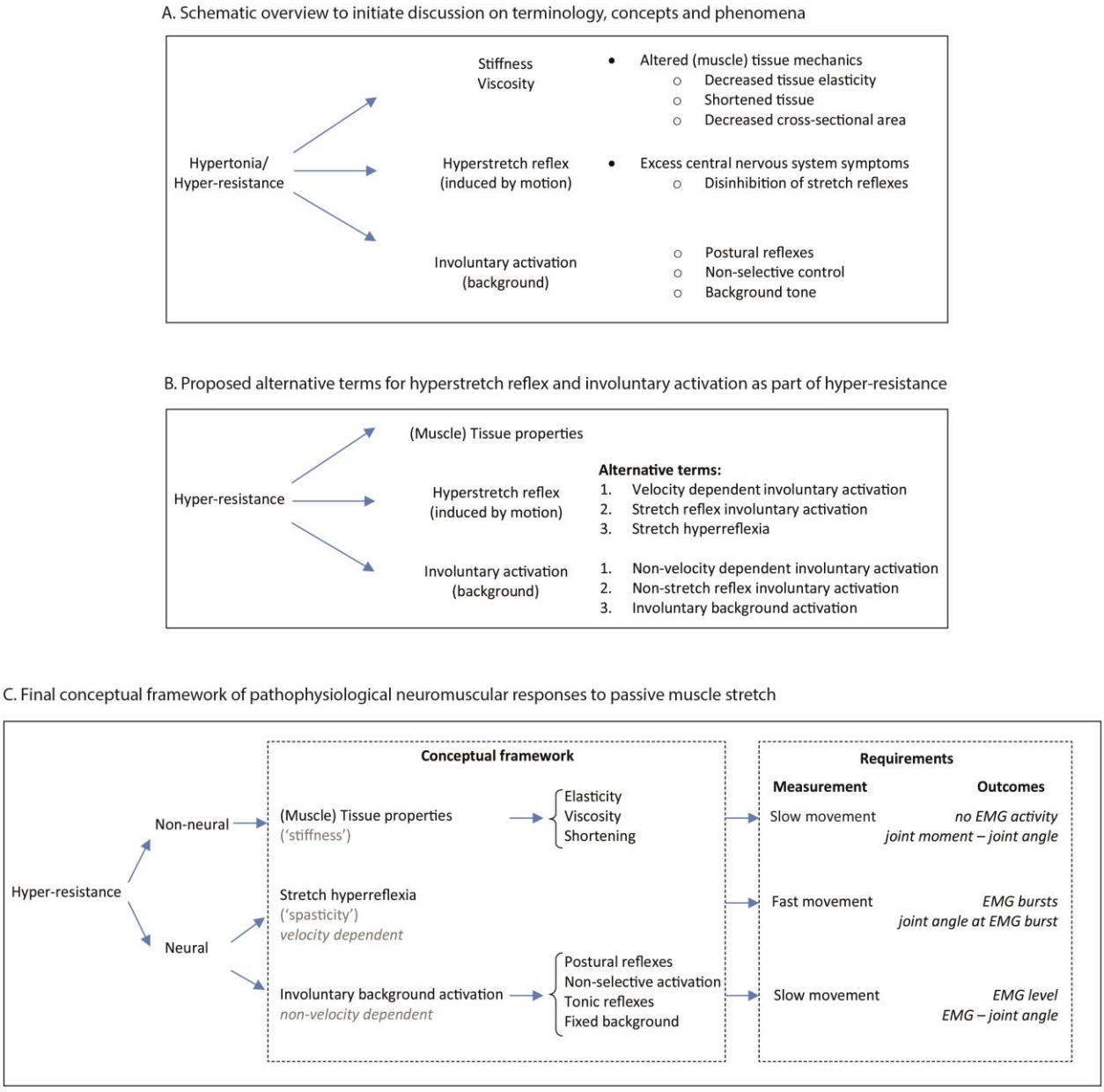
548

549 **Figure**

550



551 **Figure 1. (A)** Schematic overview to discuss terminology in concepts of and phenomena
552 around pathophysiological neuromuscular response to passive muscle stretch; **(B)** Alternative
553 terms for hyperstretch reflex and involuntary activation as part of hyper-resistance; **(C)** Final
554 conceptual framework of pathophysiological neuromuscular responses to passive muscle
555 stretch.

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Table 1. Characteristics participants

Participants characteristics (N=27)						
Gender	*Male*	*Female*				
	57%	43%				
Countries	Netherlands, Belgium, Poland, Norway, Sweden, United Kingdom, Switzerland, Germany, Greece, France, Spain, Austria					
Background	*Clinical, responsible for clinical decision-making*	*Clinical, executing physical examinations*	*Researcher*	*Technician*	*Other*	
	43%	43%	86%	5%	10%	
Profession	medical doctors; physiotherapists; clinical scientists; (paediatric) orthopaedic surgeons; (paediatric) physiatrist; coordinator gait and exercise laboratory; biomedical engineers; mechanical engineers; PhD students; assistant professors; professors					
Do you clinically assess patients with spasticity?	*Yes*	*No*				
	71%	29%				
Do you clinically treat patients with spasticity?	*Yes*	*No*				
	48%	52%				
Years of experience in assessing/treating spasticity	13±8y (mean±sd, range 1-30y, median 15y)					
Treated/assessed patient groups	cerebral palsy children en adults; stroke; multiple sclerosis; spinal cord injury; traumatic brain injury; neurometabolic disease; neurodegenerative disease; encephalitis hypoxia					
Upper or lower limbs	*Upper*	*Lower*	*Both*			
	5%	32%	58%			
Used clinical tests	*(modified) Ashworth Scale*	*(modified) Tardieu Scale*	*Spasticity Test (SPAT)*	*Duncan-Ely test (rectus femoris)*	*Other*	
	53%	57%	29%	33%	14%	
Performance of tests by	*Doctors*	*Physiotherapists*	*Laboratory clinicians*	*Other*		
	71%	76%	33%	10%		
How often are tests performed?		*During consultations*	*Before treatment*	*After treatment*		
	Always	38%	67%	67%		
	Sometimes	62%	33%	33%		
	Never	0%	0%	0%		
Satisfaction clinical tests	*Very satisfied*	*Satisfied*	*Neutral*	*Unsatisfied*	*Very unsatisfied*	*Not applicable*
	0%	19%	33%	33%	14%	0%
Research on assessment/treatment of spasticity in the past	*Yes*	*No*				
	76%	24%				
Currently doing research	*Yes*	*No*				
	81%	19%				
Use of instrumented assessments in clinic	Goniometry; electromyography; inertial sensors; force sensors; motor driven tests / robotic assessment; camera systems; electrophysiology (H/M reflexes); muscle strength tests					
Satisfaction instrumented tests	*Very satisfied*	*Satisfied*	*Neutral*	*Unsatisfied*	*Very unsatisfied*	*Not applicable*
	0%	19%	38%	19%	5%	19%

Table 2. First Delphi Round Concepts around pathophysiological neuromuscular response to passive muscle stretch (consensus ≥75% agreement)

Delphi round 1. Concepts around response to passive muscle stretch (N=28)					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
Terminology					
The term hyper-resistance is preferred over hypertonia to describe the phenomenon of impaired neuromuscular function during passive examination					
	0	7	18	46	29
The term hypertonia is preferred over hyper-resistance to describe the phenomenon of impaired neuromuscular function during passive examination					
	18	61	14	4	4
Non-neural contributions					
It is essential to distinguish non-neural (tissue-related) from neural (central nervous system (CNS) related) contributions to hypertonia/hyper-resistance					
	0	0	0	29	71
Non-neural contributions to hypertonia/hyper-resistance reflect muscle tissue properties					
	0	18	18	43	21
Muscle tissue properties consist of muscle stiffness (elasticity) and viscosity					
	4	11	4	54	29
Neural contributions and terminology					
It is essential to distinguish stretch reflex and other musde activity in the neural (CNS related) contributions to hypertonia/hyper-resistance					
	0	4	7	50	39
The term spasticity is used to describe stretch reflex activity of the neural (CNS related) contributions to hypertonia/hyper-resistance (definition according to Lance and Sanger)					
	7	7	7	50	29
Clonus and clasp-knife are manifestations of the exaggerated stretch reflex					
	0	11	4	64	21
Passive versus active impairment					
Hypertonia/hyper-resistance (ICF body functions and structures level) only partly determines any impaired musde function during performance of activities (ICF activity level)					
	0	0	4	29	68

Table 3. Second Delphi Round Concepts around pathophysiological neuromuscular response to passive muscle stretch (consensus ≥75% agreement)

Delphi round 2. Concepts around response to passive muscle stretch (N=30)						
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*	
Terminology						
The term spasticity should be used only when clearly defined						
	0	7	7	43	43	
By default, the term spasticity refers to involuntary stretch velocity induced muscle activity as a part of hyper-resistance						
	3	13	3	60	20	
Non-neural contributions						
Hyper-resistance (i.e. increased perceived resistance during passive stretch) reflects neuromuscular unit function only when no bony and ligament response is assumed						
	0	10	10	63	17	
Neural contributions and terminology						
Hyper-resistance (i.e. increased perceived resistance during passive stretch) reflects neuromuscular unit function of an agonistic musde group only when no effects of antagonistic (shortening) muscles is assumed						
	0	13	10	60	17	
The neural contributions to hyper-resistance must distinguish "velocity dependent involuntary activation" and "non-velocity dependent involuntary activation"						***Consensus*** *preference order*
	0	13	7	43	37	1
The neural contributions to hyper-resistance must distinguish "stretch reflex involuntary activation" and "non-stretch reflex involuntary activation"						
	0	23	17	43	17	3
The neural contributions to hyper-resistance must distinguish "stretch hyperreflexia" and "involuntary background activation"						
	0	13	13	60	13	2

Table 4. First Delphi round Concepts of Measurement (consensus ≥75% agreement)

Delphi round 1. Requirements instrumented measurement of hyper-resistance (N=28)					
Pathologies					
An instrumented assessment should be applicable to the following pathologies					
Cerebral Palsy	*Stroke*	*Spinal Cord Injury*	*Multiple Sclerosis*	*Other*	
100%	96%	89%	82%	25%	
Muscles					
Which lower limbs muscle groups are important to assess?					
Medial gastrocnemius	*Soleus*	*Rectus femoris*	*Lateral Gastrocnemius*	*Semimembranosus*	*Semitendinosus*
100%	93%	98%	86%	79%	79%
Hip adductors	*Biceps femoris*	*Tibialis Posterior*	*Gracilis*	*Illiopsoas*	*Other*
71%	57%	57%	54%	46%	11%
Which upper limbs muscle groups are important to assess?					
Elbow flexors	*Wrist flexors*	*Elbow extensors*	*Wrist extensors*	*Elbow pronators*	*Shoulder adductors*
89%	82%	68%	57%	54%	46%
Shoulder anti-flexors	*Shoulder retro-flexors*	*Elbow supinators*	*Other*		
36%	32%	32%	25%		
Patient in/exclusion criteria					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
An instrumented assessment must be applicable to children (>3yrs) and to adults					
	0	0	0	61	39
An instrumented assessment is not applicable to joints with fixed deformities or muscle contractures that limit the range of motion in the direction of movement to less than 10 degrees					
	0	11	11	54	25
Test time allowance					
	15 minutes [%]	*30 minutes [%]*	*45 minutes [%]*	*60 minutes [%]*	
An instrumented assessment may take up to "…" to test an upper limb or lower limb					
	32	61	4	4	
An instrumented assessment may take up to "…" to process the data from an upper or lower limb assessment					
	43	36	4	18	
Patient position					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
During an instrumented assessment, the patient must be in a comfortable position that promotes muscle relaxation					
	0	0	0	21	79
Movement profile					
The test procedure must start from the extreme of the joint range of motion, corresponding to the shortest muscle length					
	0	14	11	36	39
A movement through the full range of motion is required					
	0	14	4	50	32
At least two different stretch velocities (slow and fast) are required					
	4	0	0	21	75
Feedback on the achieved stretch velocity is required					
	0	7	11	43	39
The number of stretch repetitions must be kept to a minimum					
	0	14	0	57	29
A rest period is required between stretch repetitions					
	0	7	7	57	29
Signals and sensors – theoretical importance and practical feasibility					
It is important / feasible to measure a neurophysiological signal during an instrumented assessment					
Important	0	0	11	21	68
Feasible	0	0	11	50	39
It is important / feasible to measure joint angles and angular velocity during an instrumented assessment					
Important	0	0	0	21	79
Feasible	0	4	0	39	57

It is important / feasible to measure a net joint moment during an instrumented assessment					
Important	0	0	11	57	32
Feasible	0	0	21	61	18
Neurophysiological signals must be / can be collected from as many superficial muscles acting about the joint as possible (agonists and antagonist)					
Feasible	0	21	4	43	32
All sensors placed on the patient must be / can be wireless					
Feasible	0	0	7	50	43
Sensors that can measure different signals simultaneously must be used / are feasible (e.g. combination of electromyography and joint angles)					
Feasible	0	11	11	39	39
All sensors placed on the patient must be / can be smaller than a matchbox					
Feasible	0	7	4	46	43
Feedback during assessment					
Velocity of stretch					
	0	0	14	29	57
Muscle activity (agonist)					
	0	7	18	32	43
Muscle activity (antagonist)					
	0	14	7	54	25
How should the feedback during acquisition be provided?					
Graphical representation	*Real-time feedback*	*Immediately after performance*	*Actual values*	*Binominal performance rating (e.g. good/bad)*	*Ordinal performance rating (e.g. score 1-5)*	*Other*
79%	61%	57%	57%	36%	25%	14%
Outcome parameters - neural					
	Yes [%]	*No [%]*	*I don't know [%]*		
Amount of electromyographic (EMG) reflex activity (i.e. mean amplitude over a particular period)					
	93	4	4		
Timing of reflex activity (joint angle threshold, joint angular velocity threshold)					
	89	7	4		
EMG amplitude (mean or max) increase due to velocity (e.g. slow versus fast velocity stretches)					
	93	7	0		
EMG amplitude (mean or max) increase due to joint position (e.g. start versus end range of motion during a slow stretch					
	82	14	4		
Duration of EMG activity					
	79	11	11		
Outcome parameters - non-neural					
Start joint angle					
	79	11	11		
End joint angle					
	86	11	4		
Joint range of motion					
	89	11	0		
Angle of catch					
	89	4	7		
Maximum angular velocity					
	75	21	4		
Decomposition of the neural and non-neural components of the resistance during passive stretch is required					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
	0	0	0	32	68
Report of instrumented assessment					
Outcome parameters (discrete values)					
	0	0	7	39	54
Comparison with typically developing / healthy subjects					
	0	4	4	46	46
Pre- to post-treatment comparison					
	0	0	0	36	64

Table 5. Second Delphi round Concepts of Measurement (consensus ≥75% agreement)

Delphi round 2. Requirements instrumented measurement of hyper-resistance (N=19)

Protocol

	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
It is important to assess the hip adductors for spasticity. The test will be carried out as in a clinical examination					
	0	5	16	58	21
Depending on the duration of muscle activation due to stretch hyperreflexia, different phenomena can occur at joint level, e.g. a sudden catch and release, or a catch with no release. In order to capture these differences, it might be important to hold the end of the stretch for a minimum amount of time					
	0	0	0	63	37
How long should the end of the stretch be held for? (in seconds) (open question)					
<2 sec [%]	*2 sec [%]*	*3 sec [%]*	*5 sec[%]*	*>9 sec [%]*	*other [%]*
16	21	32	16	11	5

Feedback

Feedback during assessment is important for …					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
Range of motion in direction of movement					
	0	5	5	79	11
Force applied in main direction of movement					
	0	5	11	68	16

Report

The following outcome parameters for slow stretch are sufficient for the report:
- ROM: range of motion in [deg]
- Vmax: Maximal angular velocity in [deg/s]
- Average RMS EMG: average root mean square EMG in [uV]
- Stretch reflex threshold: joint angle [deg] at which EMG onset is first detected
- Average work in [J]

	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
	0	5	16	74	5

The following parameter(s) from a slow stretch need(s) to be added to the report (open question)

Mean angular velocity [%]	*Stiffness [%]*	*Maximal acceleration [%]*	*Passive and active ROM [%]*	*Torque/angle and torque /angular velocity curves [%]*	*None [%]*	*Other [%]*
12	18	12	6	6	47	12

The following outcome parameters for fast stretch are sufficient for the report:
- Vmax: Maximal angular velocity in [deg/s]
- Average RMS EMG: average root mean square EMG in [uV]
- Stretch reflex threshold: joint angle [deg] at which EMG onset is first detected
- Average work in [J]
- Angle of catch (AOC) in [deg]
- Intensity of catch in [W]

	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
	0	0	11	74	16

The following parameters for fast stretch can be skipped from the report

Vmax [%]	*RMS EMG [%]*	*Stretch reflex threshold [%]*	*Average work [%]*	*AOC [%]*	*AOC intensity [%]*	*None [%]*
0	0	0	5	0	16	84

The following parameter(s) from a fast stretch need(s) to be added to the report (open question)

Viscosity [%]	*Stiffness (elasticity) [%]*	*Torque/angle curve [%]*	*Mean angular velocity [%]*	*Velocity curve [%]*	*Antagonist activity [%]*	*Maximal acceleration [%]*	*None [%]*	*Other [%]*
5	5	5	15	5	5	5	50	5

The following outcome parameters for fast vs. slow stretch are sufficient for the report:
- Difference between ROM and AOC in [deg]
- Difference in Average RMS EMG in [uV]
- Difference in Work in [J]

	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
	0	*5*	*11*	*79*	*5*

The following parameters for fast vs. slow stretch can be skipped from the report

	ROM – AOC [%]	*RMS EMG [%]*	*Work [%]*	*None [%]*	

	0	*0*	*0*	*100*	
The following parameter(s) from a fast vs. slow stretch need(s) to be added to the report (open question) Difference in …					
	Maximal acceleration [%]	*Stiffness (elasticity) [%]*	*Velocity [%]*	*None [%]*	*Other [%]*
	5	*11*	*5*	*68*	*11*

Appendix. Results of Delphi rounds with no consensus (<75% agreement)

Delphi round 1. Concepts around response to passive muscle stretch (N=28)					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
Terminology					
Impaired neuromuscular function during passive examination refers to the increased resistance felt during passive stretch					
	11	14	11	39	25
The term hypertonia/hyper-resistance is used to describe impaired neuromuscular function for agonist and antagonist separately (i.e. not at joint level)					
	7	25	29	21	18
Neural contributions and terminology					
The term spasticity includes both stretch reflex and other muscle activity in the neural (CNS related) contributions to hypertonia/hyper-resistance (definition according to SPASM)					
	14	29	18	25	14
Delphi round 2. Concepts around response to passive muscle stretch (N=30)					
Terminology					
Use of the term spasticity must be avoided because it is 'loaded' and too broad					
	7	13	17	37	27

Delphi round 1. Requirements instrumented measurement of hyper-resistance (N=28)					
Patient in/exclusion criteria					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
An instrumented assessment must be applicable only to patients who are able to understand and perform the test procedure					
	18	25	7	25	25
An instrumented assessment is not applicable to patients with predominantly dyskinetic and ataxic tone abnormalities					
	0	18	21	29	32
Patient position					
An instrumented assessment must be carried out before other testing procedures (e.g. gait analysis)					
	4	18	43	32	4
Movement profile					
A movement through a limited range of motion is required					
	18	46	21	11	4
A sinusoidal movement is required					
	25	36	25	11	4
The end range of motion position must be held for a minimum period of time (e.g. 3 seconds)					
	4	14	14	50	18
It is more important to *measure* stretch velocity than to *control* it					
	1	18	11	46	21
Signals and sensors – theoretical importance and practical feasibility					
Joint kinematics should be / can be measured from at least 2 joints simultaneously					
Important	0	43	25	18	14
Feasible	0	11	29	39	21
Neurophysiological signals must be / can be collected from as many superficial muscles acting about the joint as possible (agonists and antagonist)					
Important	0	32	0	43	25

All sensors placed on the patient must be / can be wireless					
Important	4	11	18	39	29
Sensors that can measure different signals simultaneously must be used / are feasible (e.g. combination of electromyography and joint angles)					
Important	0	7	39	25	29
All sensors placed on the patient must be / can be smaller than a matchbox					
Important	0	14	18	43	25
Feedback during assessment					
Range of motion in direction of movement					
	0	7	32	14	46
Force applied in main direction of movement					
	0	18	14	25	43
Movement out of the desired plane of motion					
	0	4	32	43	21
Outcome parameters - neural					
	Yes [%]	*No [%]*	*I don't know [%]*		
Amount of EMG reflex activity (i.e. maximum amplitude)					
	64	29	7		
Outcome parameters - non-neural					
Intensity of catch (i.e. power)					
	64	18	18		
Mean angular velocity					
	43	32	25		
Maximum acceleration					
	46	39	14		
Maximum deceleration					
	32	46	21		
Joint torque (net joint moment) at a common angle					
	54	25	21		
The integral of torque with respect to time					
	36	32	32		
The integral of torque with respect to joint angle (work)					
	68	14	18		
The integral of torque with respect to velocity					
	29	36	36		
The derivative of torque with respect to time					
	18	39	43		
The derivative of torque with respect to joint angle (resistance)					
	46	25	29		
Report of instrumented assessment					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
Raw data					
	0	18	11	25	46
Continuous waveforms					
	0	7	25	46	21
Comparison to a representative patient group					
	0	18	14	36	32
Training					

	2 full days [%]	*1 full day [%]*	*Half a day [%]*	*2 hours [%]*	*No training [%]*
How much training must be acquired to learn the testing procedure of an instrumented assessment?					
	0	18	39	29	14
How much training must be acquired to learn how to interpret the data?					
	7	18	18	39	18
Delphi round 2. Requirements instrumented measurement of hyper-resistance (N=19)					
Protocol					
	Strongly disagree [%]	*Disagree [%]*	*Neutral [%]*	*Agree [%]*	*Strongly agree [%]*
An instrumented assessment should be applicable only to patients who are able to remain sufficiently relaxed during the critical moments of the test procedure					
	5	42	5	26	21
Instrumented spasticity assessment (ISA) data has not yet been collected on patients with predominantly dyskinetic and ataxic tone abnormalities. While it would be interesting in research setting to use ISA to assess dyskinesia and ataxia, at this stage, ISA is not yet validated for patients with predominantly dyskinetic and ataxic tone abnormalities					
	5	5	16	53	21
The timing of ISA should be considered in relation to time of day, previous activities and other testing procedures (e.g. gait analysis). This is especially the case when comparing pre- post-treatment					
	5	5	21	32	37
Report					
The following parameters for slow stretch can be skipped from the report					
ROM [%]	*Vmax [%]*	*RMS EMG [%]*	*Stretch reflex threshold [%]*	*Average work [%]*	*None [%]*
0	0	0	16	26	58