Theoretical framework for the clinical applications of Mollii

An introductory review

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Contents

Introduction……2

Electrical stimulation by use of the Mollii method……2

Central paresis and the Upper Motor Neuron Syndrome……3

Spasticity……3

Assessment of spasticity……4

Electrical stimulation in the treatment of spasticity……4

Reciprocal inhibition……6

Mollii application for spasticity……7

Dystonia……8

Dystonic cerebral palsy……9

Mollii application for dystonia……9

Pain……10

Gait control theory of pain……11

Mollii application for pain……12

References……13

THEORETICAL FRAMEWORK FOR CLINICAL APPLICATIONS OF MOLLII

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Introduction

Sensory information from receptors of muscles and tendons (e.g. the head, trunk or limb position from proprioceptive sensors) and of the skin (from tactile, pressure, temperature and pain sensors) are essential for both voluntary and reflex mediated movements (1). There is a vast literature demonstrating that therapy aiming to modulate such sensory input after injury may reduce unwanted muscle activity, facilitate voluntary muscle activity and reduce pain that may interfere with motor function. This is the background of the Mollii concept. Experiences from clinical applications of Mollii indicate that the Mollii method may impact on both spasticity and other components of the Upper Motor Neuron Syndrome (UMNS), dystonic phenomena and pain. Studies to refine the application of Mollii are ongoing.

Electrical stimulation by use of the Mollii method

The Mollii method is an innovative approach for non-invasive, electrical stimulation that enables stimulation with multiple electrodes incorporated in a whole-body suit (Fig. 1). Mollii was primarily designed to reduce disabling spasticity and improve motor function in persons with a lesion in the central nervous system but may also reduce various forms of dystonia and pain. The suggested key mechanism of action to reduce spasticity, refers primarily to reciprocal inhibition elicited by stimulating the antagonist of a spastic muscle as further described below. However, other mechanisms related to a broad range of sensory input may play a role for effects both on spasticity, dystonia and on pain (see further below), which may occur in parallel in patients at focus. Thus, while some effects

Figure 1. The Mollii

of Mollii treatment are linked to a well-defined pathophysiologic mechanism allowing standardized design of the stimulation, other effects may depend on several complex and interacting mechanisms and therapeutic attempts are based on clinical experience and individually customized design.

Central paresis and the Upper Motor Neuron Syndrome

Central paresis refers to impaired central nervous system output directed to muscles when attempting to generate force or movement. Central paresis is caused by a lesion in the brain or spinal cord affecting the connections between the motor cortex in the brain and the lower motor neurons in the spinal cord. It is often associated with spasticity and other phenomena and then often referred to as the Upper Motor Neuron Syndrome (2).

The Upper Motor Neuron Syndrome (UMNS) is defined as a constellation of symptoms and signs of 1) involuntary muscle activity, such as spasticity, spastic co-contraction, associated movements and spastic dystonia, referred to as "positive components", and 2) impaired voluntary control of movements, such as reduced muscle strength, coordination of movements and dexterity, referred to as "negative components". The UMNS is often present in patients with stroke, cerebral palsy, traumatic brain injury, spinal cord injury and multiple sclerosis. Other signs at examination may be exaggerated cutaneous withdrawal (flexor, pain) reflexes and the Babinski sign.

Spasticity

Spasticity is commonly defined as a motor disorder characterized by a velocity dependent increase in the tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflexes as one component of the upper motor neuron (UMN) syndrome (3, 4).

In addition to spasticity per this strict definition, other "positive" components of the UMNS are often included in a broader definition of spasticity (5). Specifically, "spastic dystonia", which refers to abnormal positions, e.g. of the hand or foot, is a commonly recognized phenomenon in patients with moderate or severe paresis that is caused by ongoing, involuntary activation of a spastic muscle. It may be associated with pain and contracture and cause significant disability (6).

Assessment of spasticity

Most often spasticity is assessed by standardized passive stretch of the spastic muscles and quantified by use of the Ashworth scale (7). This scale is an ordinal scale, which has some documented reliability but also generally recognized limitations (8, 9). Notably, it does not allow separate evaluation of increased resistance due to spasticity or due to stiffness of tissues. Neurophysiological methods may be used to separate these components of increased resistance but are not easy to apply in clinical routine (10–12). A new method, the NeuroFlexor method (13–15), enables separation and quantification of genuine spasticity, i.e. the neural/reflex component, and of mechanical components, i.e. viscoelastic / soft tissue components of the resistance, and has been introduced in the evaluation of treatment with Mollii. When assessing muscle over activity in spastic paresis, it is important to consider the potential variation related to internal and external factors and to standardize the assessment with regard to time of day, stress level, external temperature and any nociceptive factor. Further, measurement of spasticity only at rest will not inform about its potential impact during movements.

By time, both negative and positive signs of the UMNS may induce significant changes in muscle composition with shortening of muscles and limitation of the range of motion (16). Then joints may become completely immobile and movements painful. Spasticity and soft tissue changes may interact in a way that enhances spasticity. Further, soft tissue changes may cause increased resistance to passive stretch that mimics the resistance due to spasticity and thus interfere with the evaluation of spasticity.

Electrical stimulation in the treatment of spasticity

Electrical stimulation by use of surface electrodes is a non-invasive therapeutic method used in patients with upper motor neuron lesion with the aim of improving voluntary motor control by increasing muscle strength, reducing spasticity and pain and increasing passive range of motion (17, 18).

Methods applied include neuromuscular electrical stimulation (NMES), transcutaneous electrical nerve stimulation (TENS) and functional electrical stimulation (FES). The term FES refers to the process of combining the stimulation with a functional task. There is

significant evidence in the literature that electrical stimulation triggered or in addition to voluntary activated movements may be more effective than non-triggered stimulation in improving motor recovery by adding a cognitive component (19, 20).

In clinical practice, electrical stimulation can be applied directly to paretic muscles to improve function or over antagonist muscles to reduce spasticity of the corresponding agonist muscles by reciprocal inhibition (see further below) in subjects with central nervous system lesions. Suggested mechanisms by which electrical stimulation may reduce spasticity include enhancement of spinal inhibitory signaling (by disynaptic reciprocal Ia inhibition and presynaptic Ia inhibition of alpha motor neurons) from the stimulated muscle groups or nerve to the reciprocal muscle groups or nerve (21). The effects on spinal reflexes have been shown to be frequency-dependent. Moreover, neuroplasticity changes within circuits of the spinal cord may be induced and play a role for the therapeutic effects of electrical stimulation (22).

The literature reports a wide variety of therapeutic strategies in terms of stimulation parameters, including frequency, intensity/amplitude, duty cycle, pulse width/duration and pattern as well as methods for stimulation and duration of treatment. The application of different stimulation settings evokes diverse responses (17, 19). Stimulation at low current intensity generates a sensory input without any motor response and it is often used for treatment of pain and spasticity, while a stimulation at a current intensity high enough to exceed motor threshold evokes muscle contractions and may improve muscle function.

Notably, increasing current intensity increases the force of muscle contraction but also the risk of side effects like pain and skin irritation. No specific recommendations for the electrical stimulation parameters exist but the application should be customized for the therapeutic goals (17). Frequency refers to the number of pulses per second during stimulation and varies in the range of 20–50 Hz for motor stimulation and 1.7–100 Hz for sub-motor stimulation. A biphasic waveform is preferred in motor stimulation while mono- or bi-phasic stimuli has been applied for sub-motor stimulation. Pulse duration varies in the range of 0.2–0.5 ms for motor stimulation and 0.1–0.3 ms for sub-motor stimulation. Cycling pulses are usually described by the ratio between on and off; ratios of 1:1 – 1:10 are used in clinical applications. Finally, the effect of an electrical current on the underlying tissue is highly related to electrode size. Electrodes of 5 x 5 to 5 x 9 cm are adequate depending on the muscle size while a diameter of 2.5–3 cm is suitable to stimulate a nerve directly. Further, placement of the electrodes and conductivity of the skin-electrode interface must be considered.

The Mollii method uses low frequencies and low intensities that evokes sensory input but does not directly elicit muscle contractions.

The selection of stimulation parameters influence the perception/comfort of the stimulation as well as safety. Further, electrical stimulation may induce neuromuscular fatigue by alteration of the normal motor unit recruitment order (18). Good compliance of the patient is therefore essential for successful treatment and requires optimizing stimulation parameters.

Reciprocal inhibition

Movements over a joint are controlled by opposing sets of muscles, e.g. extensors and flexors, which must work in synchrony to generate smooth movements. Reciprocal inhibition refers to the deactivation of an antagonist muscle in response to Ia sensory input from a contracting agonist and is mediated by Ia inhibitory interneurons in the spinal cord (Fig. 2). Thus, when an agonist muscle is active, the opposing (antagonistic) muscle group is inhibited to prevent it from working against the contraction of the agonist muscle. Reciprocal inhibition plays a fundamental role for the normal performance of movements and may be utilized to reduce spasticity as well as other unwanted muscle over activity and to improve voluntary muscle activation and movement control.

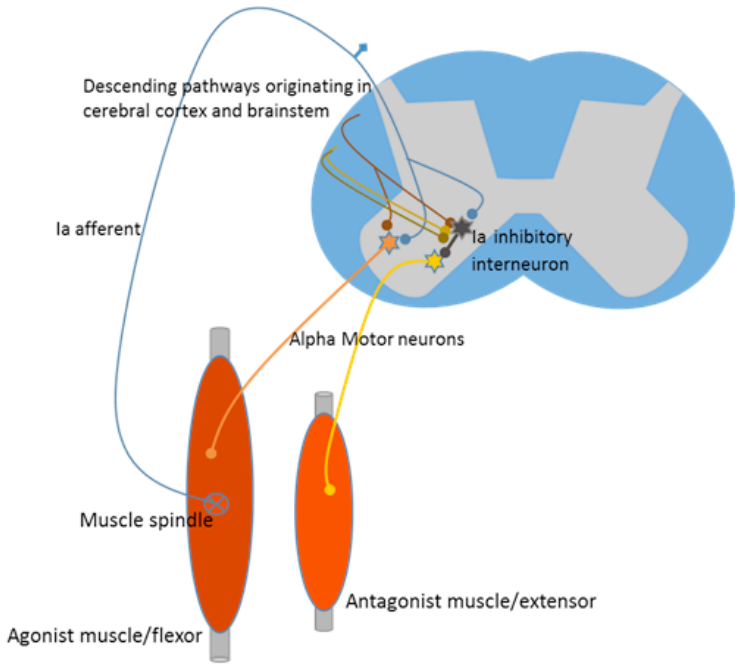

Figure 2. Reciprocal inhibition. When a muscle (e.g. an elbow flexor) is stretched, this evokes sensory input from muscle spindles passing in afferent nerve fibers (large diameter sensory fibers, called Ia afferents) that have direct contact with lower motoneurons in the spinal cord and elicits impulses in efferent nerve fibers which activates the same muscle and cause a reflex muscle contraction (the stretch reflex). In parallel, the sensory input also inhibits antagonist muscles (in this case elbow extensor muscle) by activation of spinal interneurons in the same spinal segment - reciprocal inhibition. This mechanism may be utilized to reduce spasticity in e.g. an elbow flexor muscle by electrical stimulation of afferent nerve fibers of the opposing elbow extensor muscle that activates inhibitory Ia interneurons and reduce the excitability of the flexor muscle motor neuron. Illustration adapted from Principles of Neural Science, Fifth Edition (Fig 35-5, p. 798), by Kandel ER, et al. 2013.

Mollii application for spasticity

The principle mechanism targeted in the Mollii approach for treatment of spasticity is the activation of the disynaptic reciprocal Ia inhibitory pathway illustrated in Fig. 3. Relaxation of the agonist muscle is achieved by the electrical stimulation of the antagonist, thus enhancing contraction of the agonist and voluntary movements.

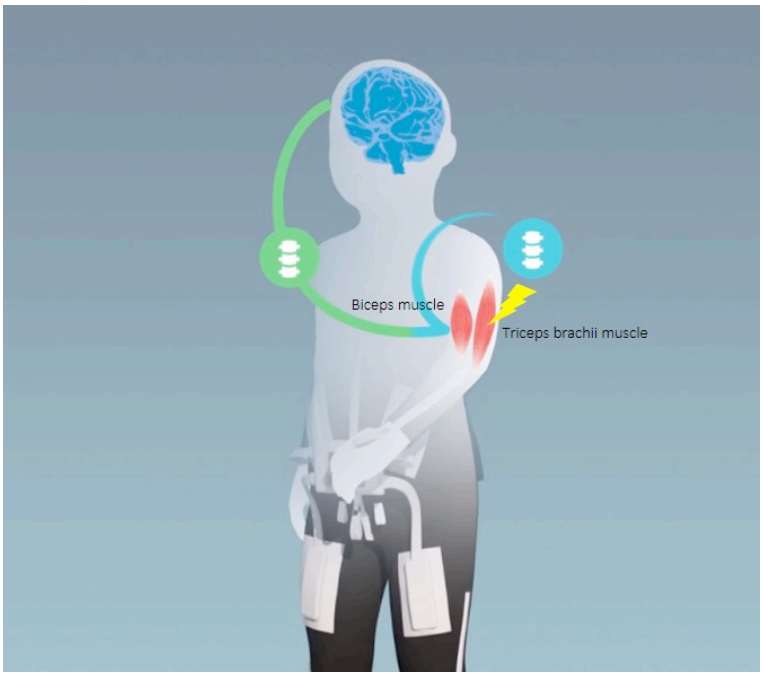

Figure 3. Example of a spastic/dystonic flexor position of the arm. Electrical stimulation is applied on the antagonist (triceps brachii muscle) of the biceps muscle to reciprocal relax the spastic agonist elbow flexor. A similar approach for therapeutic electrical stimulation can be applied in all limbs and body parts where spasticity is present. Video frame adapted from Stora Designpriset: Inerventions Mollii suit, available from: https://vimeo.com/126102361.

Dystonia

Dystonia is a disabling disorder characterized by sustained or intermittent muscle contractions causing involuntary movements and/or abnormal postures (23, 24). Dystonia can be classified clinically according to age of onset, body distribution, temporal pattern and associated features (23). Anatomically, it can be focal (one body part involved, e.g. one hand), segmental (two or more contiguous body parts), multifocal (two or more non-contiguous body parts) or generalized. Dystonia can be also isolated, combined with another movement disorder or associated to other neurological or systemic manifestations (defined as complex dystonia). The term focal dystonia may refer both to specific independent movement diseases, e.g. cervical dystonia or torticollis (a focal dystonia involving neck muscles), and to focal dystonic signs present in other disorders, such as the spastic dystonia of the hand or foot arising after stroke.

The etiological classification of dystonia considers instead the evidence of nervous system pathology, whether dystonia is inherited or acquired, and whether the underlying cause is unknown (idiopathic) or not. The term primary dystonia refers to cases with no degenerative or

structural lesions to the nervous system while secondary dystonia resulted from a broad range of causes including genetic mutations, perinatal brain injury (dystonic cerebral palsy), vascular or traumatic brain injury, infections and as a reaction to certain drugs.

The neural mechanism underlying dystonia involves many regions of the central nervous system. The basal ganglia play a key role in many movement disorders and although the role of sensory function in dystonia is far from fully understood, proprioceptive sensory input plays a crucial part in the generation and coordination of movements (25).

Dystonic cerebral palsy

Dystonia in cerebral palsy (CP) presents with varying patterns of abnormal posture and involuntary movements (26). Dystonic CP is the second most common type of cerebral palsy after the spastic forms, presenting in one out of six patients with CP (27, 28). Even if typically related to disturbed function in basal ganglia networks, the pathophysiology of this movement disorder is still largely unknown and the rehabilitation strategies are typically multidisciplinary, including oral drugs and neuromodulation interventions.

Mollii application for dystonia

Treatment trials with Mollii may be relevant for both focal, segmental and general dystonia although controlled clinical trials are needed. Clinical experiences suggest that Mollii may reduce dystonic symptoms and maintenance of optimal body posture. The sensory input provided by both electrical stimulation and the dress itself may also have an impact on proprioceptive awareness, which is essential not only for motor control in dynamic activity but also for maintaining position and balance control. Coordination of movements (e.g. that muscular activity around the shoulder joint is coordinated with muscular activity around the elbow to perform a successful reaching movement) may also be disturbed by concomitant presence of ataxia, and be reduced by Mollii treatment, see Figure 4.

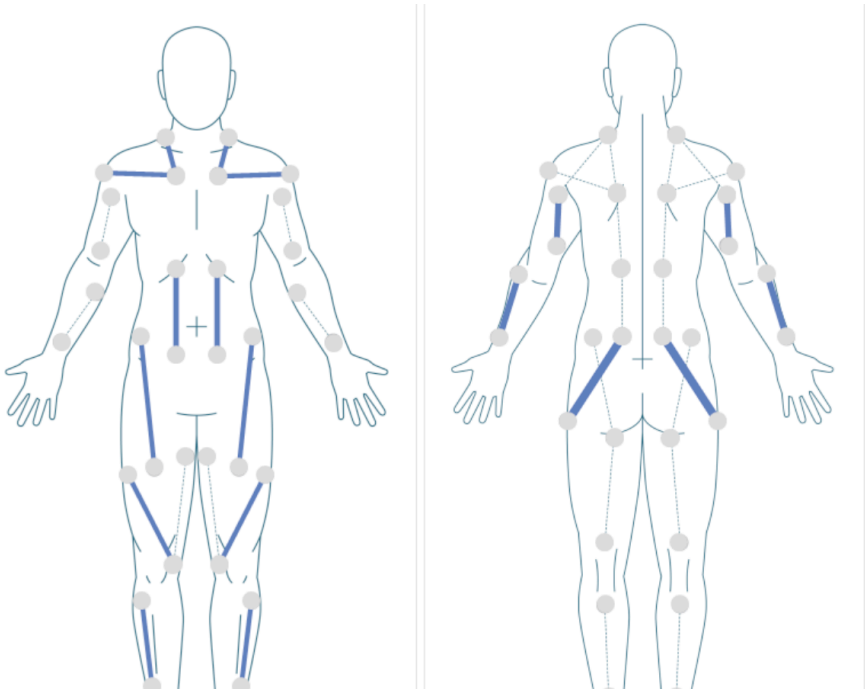

Figure 4. Example of favorable Mollii settings for dystonic symptoms. A large interindividual heterogeneity in the clinical presentation must be considered for an appropriate electrical stimulation (e.g. in mixed cerebral palsy (CP) that occurs when an individual exhibits traits of spastic, athetoid and ataxic CP, and accounts for 10% of CP cases total).

Pain

Pain of both neuropathic and nociceptive origin is a common symptom in patients with a lesion in the central nervous system and may contribute to reduced quality of life (29, 30). Neuropathic pain is caused by damage to or dysfunction of the nervous system, while nociceptive pain is caused by damage to non-neural tissue either musculoskeletal due to bone, joint, muscle trauma or inflammation, mechanical instability or muscle spasm.

Transcutaneous electrical nerve stimulation (TENS) is a commonly used nonpharmacological and noninvasive treatment for pain of various etiologies (31–33). TENS may reduce pain through both central and peripheral mechanisms. In the central nervous system, the activation of opioid, GABA, serotonin, and muscarinic receptors induced by TENS may reduce pain related dorsal horn neuron activity (34). In peripheral nerves, opioid and α-2 noradrenergic receptors are involved in TENS-induced analgesia at the site of stimulation.

Factors that play a role for the analgesic effect of TENS include stimulation frequency and intensity and electrode placement. TENS can be applied with low frequencies (<

10 Hz) or high (> 50 Hz). As pointed out above, the Mollii method uses low frequencies and low intensities that evokes sensory input but does not directly elicit muscle contractions. "Sensory intensity" may be perceived as a clear tingling sensation without pain or motor contraction. Different frequencies activate different opioid receptors to produce analgesia and have been shown to provide analgesic effect specifically when applied at a strong, nonpainful intensity. Specifically, low-frequency TENS activates μ-opioid receptors in the spinal cord and the brainstem leading to a decreased sensation of pain. Spinal serotonin concentrations are also increased during and immediately after treatment with low-frequency TENS (35, 36). Stimulation sites are not crucial to get this effect while number of electrodes applied are important for spinal serotonin increase. Increase in beta endorphin and met-enkephalin is also been reported with low-frequency electrical stimulation.

Gate control theory of pain

Based on the axonal diameter and the conduction velocity, nerve fibers can be classified into three types: A (with subgroups), B and C (37). Aβ-fibers are larger and have higher conduction velocity when compared with A-delta fibers and C fibers, and conduct afferent nerve impulses related to sensation for touch and pressure to the central nervous system. A-delta fibers and C fibers instead conduct pain signals. A-delta fibers are faster than C fibers and conduct afferent nerve impulses that evoke sharp pain while the slower C fibers conduct nerve impulses that evoke diffuse pain.

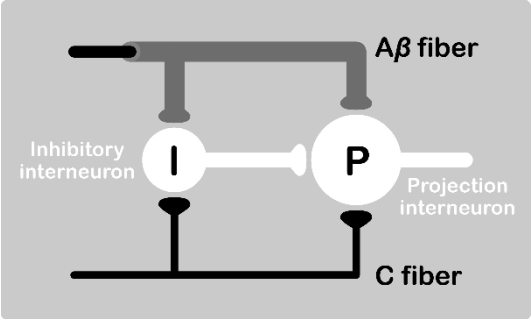

Figure 5. Gate control theory of pain

According to the gate control theory of pain postulated by Melzack and Wall in 1965 (38), a "gate" function consisting of excitatory and inhibitory synapses in the dorsal horn of the spinal cord, can regulate the transmission of pain stimuli via ascending spinal tracts to the brain. This gate could be opened by nociceptive stimuli conducted in pain afferents and could be closed by non-noxious stimuli (e.g. touch, pressure and electrical currents) that excite low threshold large diameter peripheral afferents. Therefore, low level electrical stimulation that selectively activates non-noxious, afferent nerve fibers (Aβ-fibers), may stop transmission of pain impulses to the brain and thus reduce pain.

Even though further studies have demonstrated that tactile-nociceptive interactions in the spinal cord is not the only mechanism involved in the processing of nociceptive signaling (which also include the brain stem and higher levels), the model has inspired new treatment approaches such as TENS (39).

Mollii application for pain

Programming of Mollii should primarily be designed to target whatever movement disorder is present but, as outlined above, adding other sites of active electrodes to approach pain may be considered. Thus, lower intensity stimulation that will not interfere with the activation/deactivation of motor symptoms, may be added at multiple sites if pain is a major factor.

References

1. Bolognini N, Russo C, Edwards DJ. The sensory side of post-stroke motor rehabilitation. Restor Neurol Neurosci. 2016 Apr 11;34(4):571-86. doi: 10.3233/RNN-150606.
2. Barnes MP and Johnson GR, Eds. Upper motor neurone syndrome and spasticity clinical management and neurophysiology (2nd Edition). Cambridge: Cambridge University Press; 2008.
3. Lance JW. Spasticity: disordered motor control. In: Feldman RG, Young RR, Koella WP, editors. Symposium Synopsis. 4th ed. Chicago: Year Book Medical Publishers; 1980: p. 485-94.
4. van den Noort JC. European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch. Eur J Neurol. 2017 Jul;24(7):981-e38. doi: 10.1111/ene.13322. Epub 2017 May 29
5. Pandyan AD, Gregoric M, Barnes MP, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disability and Rehabilitation 2005; 27: 2–6.
6. Brainin M, Norrving B, Sunnerhagen KS, et al. Poststroke chronic disease management: towards improved identification and interventions for poststroke spasticity-related complications. Int J Stroke. 2011 Feb;6(1):42-6. doi: 10.1111/j.1747-4949.2010.00539.x.
7. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67(2):206-7.
8. Pandyan AD, Price CI, Rodgers H, Barnes MP, Johnson GR. Biomechanical examination of a commonly used measure of spasticity. Clinical Biomechanics 2001; 16:859–865.
9. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. J Neurol Neurosurg Psychiatry. 2010;81(1):46-52. doi: 10.1136/jnnp.2009.177071.
10. 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. 2006 Jul 15-30;28(13-14):891-7.
11. Malhotra S, Pandyan AD, Rosewilliam S, Roffe C, Hermens H. Spasticity and contractures at the wrist after stroke: time course of development and their association with functional recovery of the upper limb. Clin Rehabil. 2011 Feb;25(2):184-91. doi: 10.1177/0269215510381620. Epub 2010 Oct 4.

12. Mirbagheri MM, Lilaonitkul T, Rymer WZ. Prediction of natural history of neuromuscular properties after stroke using Fugl-Meyer scores at 1 month. Neurorehabil Neural Repair. 2011 Jun;25(5):458-68. doi: 10.1177/1545968310390222. Epub 2011 Feb 8.

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

14. Gäverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. J Rehabil Med. 2013;45(7):630-6. doi: 10.2340/16501977-1160.

15. Gäverth 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. J Rehabil Med. 2014;46(7):629-34. doi: 10.2340/16501977-1824.

16. Sheng Li and Gerard E. Francisco. New insights into the pathophysiology of post-stroke spasticity. Front Hum Neurosci. 2015; 9: 192. Published online 2015 Apr 10. doi: 10.3389/fnhum.2015.00192.

17. 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. J Rehabil Med. 2012 Feb;44(2):99-105.

18. Doucet BM, Lam A, Griffin L. Neuromuscular Electrical Stimulation for Skeletal Muscle Function. The Yale Journal of Biology and Medicine. 2012;85(2):201-215.

19. de Kroon JR, Ijzerman MJ, Chae J, Lankhorst GJ, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. J Rehabil Med. 2005 Mar;37(2):65-74.

20. Mills PB, Dossa F. Transcutaneous Electrical Nerve Stimulation for Management of Limb Spasticity: A Systematic Review. Am J Phys Med Rehabil. 2016 Apr;95(4):309-18.

21. Koyama S, Tanabe S, Takeda K, Sakurai H, Kanada Y. Modulation of spinal inhibitory reflexes depends on the frequency of transcutaneous electrical nerve stimulation in spastic stroke survivors. Somatosens Mot Res. 2016 Mar;33(1):8-15.

22. Motta-Oishi AA, Magalhães FH, Mícolis de Azevedo F. Neuromuscular electrical stimulation for stroke rehabilitation: is spinal plasticity a possible mechanism associated with diminished spasticity? Med Hypotheses. 2013 Nov;81(5):784-8.

23. Klein C, Lohmann K, Marras C, et al. Hereditary Dystonia Overview. 2003 Oct 28 [Updated 2017 Jun 22]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK1155/

24. Pana A, Saggu BM. Dystonia. [Updated 2017 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2017 Jun-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448144/

25. Patel N, Jankovic J, Hallett M. Sensory aspects of movement disorders. Lancet Neurol. 2014 Jan;13(1):100-12. doi: 10.1016/S1474-4422(13)70213-8.

26. Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol. 2005 Aug;47(8):571-6.

27. Monbaliu E, Himmelmann K, Lin JP, et al. Clinical presentation and management of dyskinetic cerebral palsy. Lancet Neurol. 2017 Sep;16(9):741-749. doi: 10.1016/S1474-4422(17)30252-1.

28. Rice J, Skuza P, Baker F, Russo R and Fehlings D. Identification and measurement of dystonia in cerebral palsy. Dev Med Child Neurol. 2017 Aug 8. doi: 10.1111/dmcn.13502.

29. Hagen EM, Rekand T. Management of Neuropathic Pain Associated with Spinal Cord Injury. Pain and Therapy. 2015;4(1):51-65. doi:10.1007/s40122-015-0033-y.

30. Harrison RA, Field TS. Post stroke pain: identification, assessment, and therapy. Cerebrovasc Dis. 2015;39(3-4):190-201. doi: 10.1159/000375397. Epub 2015 Mar 5.

31. Binder A, Baron R. Utility of transcutaneous electrical nerve stimulation in neurologic pain disorders. Neurology. 2010 Jan 12;74(2):104-5.

32. Johnson MI, Paley CA, Howe TE, Sluka KA. Transcutaneous electrical nerve stimulation for acute pain. Cochrane Database Syst Rev. 2015 Jun 15;(6):CD006142.

33. Johnson MI, Jones G. Transcutaneous electrical nerve stimulation: current status of evidence. Pain Manag. 2017 Jan;7(1):1-4.

34. Vance CG, Dailey DL, Rakel BA, Sluka KA. Using TENS for pain control: the state of the evidence. Pain Manag. 2014 May;4(3):197-209.

35. Sluka KA, Lisi TL, Westlund KN. Increased Release of Serotonin in the Spinal Cord During Low, But Not High, Frequency Transcutaneous Electric Nerve Stimulation in Rats With Joint Inflammation. Arch Phys Med Rehabil. 2006 Aug; 87(8): 1137–1140.

36. DeSantana JM, Walsh DM, Vance C, Rakel BA, Sluka KA. Effectiveness of Transcutaneous Electrical Nerve Stimulation for Treatment of Hyperalgesia and Pain. Curr Rheumatol Rep. 2008 Dec; 10(6): 492–499.

37. Standring S. Gray's Anatomy E-Book: The Anatomical Basis of Clinical Practice. (Forty-first edition). New York : Elsevier Limited, 2016.

38. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150 (3699):971–9.

39. Treede RD. Gait control mechanisms in the nociceptive system. Pain. 2016 Jun;157(6):1199-204.