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Neuromuscular electrical stimulation promoted plasticity of the human brain.

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Key points summary

- Neuromuscular electrical stimulation (NMES) delivered at levels sufficient to generate a fused contraction is capable of promoting restorative changes in a number of neurological disorders.
- With respect to lower levels of stimulation – at intensities close to motor threshold, the evidence that NMES promotes restorative neural adaptations is equivocal.
- Adjuvant techniques, such as voluntary contractions and mental imagery, may promote restorative responses to NMES delivered at intensities close to motor threshold.
- Such combined effects bear some of the hallmarks of associative neural plasticity.
- It appears likely that multiple brain pathways are involved in mediating the restorative effects brought about by NMES.

Abstract

The application of neuromuscular electrical stimulation (NMES) to paretic limbs has demonstrated utility for motor rehabilitation following brain injury. When NMES is delivered to a mixed peripheral nerve, typically both efferent and afferent fibres are recruited. Muscle contractions brought about by the excitation of motor neurons are often used to compensate for disability by assisting actions such as the formation of hand aperture, or by preventing others including foot drop. In this context, exogenous stimulation provides a direct substitute for endogenous neural drive. The goal of the present narrative review is to describe the means through which NMES may also promote sustained adaptations within central motor pathways, leading ultimately to increases in (intrinsic) functional capacity. There is an obvious practical motivation, in that detailed knowledge concerning the mechanisms of adaptation has the potential to inform neurorehabilitation practice. In addition, responses to NMES provide a means of studying CNS plasticity at a systems level in humans. We summarise the fundamental aspects of NMES, focusing on the forms that are employed most commonly in clinical and experimental practice. Specific attention is devoted to adjuvant techniques that further promote adaptive responses to NMES thereby offering the prospect of increased therapeutic potential. The emergent theme is that an association with centrally initiated neural activity, whether this is generated in the context of NMES triggered by efferent drive, or via indirect methods such as mental imagery, may in some circumstances promote the physiological changes that can be induced through peripheral electrical stimulation.

Background

Although historical antecedents are often ascribed to Galvani's *Commentarius*, published in the late 18th century, the practice of employing electricity to stimulate human nerves can be traced to ancient times (Finger & Piccolino, 2011). Murals depicting the Nile catfish Malopterurus electricus have been discovered in Egyptian tombs dating from the Vth dynasty (*ca*. 2750 B.C.). In extant records however it is not until 46 C.E. that the utilisation of the (saltwater) torpedo ray's electric discharge for electrotherapy is noted by the Roman physician Scribonius Largus. Writing some thirty years later, Dioscorides (see Gunther, 1934) provided perhaps the first explicit reference to the use of the torpedo's electric discharge for artificial muscle stimulation in relating a remedy for propalsus ani (Kellaway, 1946). The introduction of the Leyden jar in 1746 provided a platform for the modern progression of electrotherapy, with Benjamin Franklin observing in 1774 that muscle contractions could be brought about by exposure to static electricity (Isaacson, 2003). Subsequently, Faraday's application of the principle of magnetic induction provided a means of delivering electric current to the human body in a controlled fashion – for which the term "Faradization" was coined. Prominent among nineteenth century practitioners investigating the physiology of ''localized electrisation", Duchenne de Boulogne employed a Faradic stimulating machine to stimulate a wide range of muscles transcutaneously via a pair of "humid rheophore" electrodes (e.g. Clarac et al., 2009). Performing his studies in cat and monkey, Sherrington (1894) observed that a third to one half of the myelinated fibres of peripheral nerves failed to degenerate following section of their ventral (motor) spinal roots. As the application of maximal Faradic currents to these remaining fibres failed to elicit "motor reactions", he concluded that they must provide sensory innervation. The presence of both sensory and motor axons in the same ("mixed") nerve bundle, as revealed by Sherrington, is a key factor determining the physiological effects of contemporary forms of neuromuscular electrical stimulation (NMES).

The Greek name for the torpedo ray, *narkè*, meaning numbness, suggests the nature of the initial therapeutic applications of electrotherapy (Debru, 2006). Scribonius Largus for example records use of the torpedo's electric discharge as a treatment for the pain associated with intractable headache and gout (Kellaway, 1946). In the guise of "transcutaneous electrical nerve stimulation" (TENS), modern devices designed to achieve the same analgesic goals are now widely available. These typically generate high frequency (> 50 Hz) of trains of electrical stimulation, at current intensities that are insufficient to evoke overt motor responses. A

contemporaneous historical lineage for the therapeutic application of electrotherapy in motor rehabilitation can also be traced - from Dioscorides through Duchenne de Boulogne to the present day. Modes of electrical nerve stimulation used for this purpose (which tend to differ from those employed typically for pain relief - by using lower frequencies and higher intensities of stimulation) constitute the subject matter of the present review.

In a contemporary therapeutic context, applications of NMES in motor rehabilitation can be conceived of as being adaptive or restorative (Pomeroy *et al*., 2011). The term functional electrical stimulation (FES) refers typically to instances in which tetanic muscle contractions are induced to assist or reinstate movement, thereby enabling an otherwise quiescent limb to be engaged in goal-directed actions. This form of stimulation is deemed to be adaptive, as it provides direct compensation for the motor disability. In the period since Liberson and colleagues (1961) demonstrated that stimulation delivered to the common peroneal nerve reduced the degree of foot-drop during the swing phase of gait, numerous applications of FES have been developed successfully to assist movement of the upper and lower extremities (Prochazka, 2018). Yet NMES may also be used restoratively, with a view to promoting neural changes that lead ultimately to increased (intrinsic) functional capacity. This is the primary focus of the current review.

The delivery of electrical current to neuromuscular tissue (i.e. via a peripheral nerve or across a muscle belly) activates contractile muscle fibres indirectly by first depolarizing motor axons. As the sensory axons in the same mixed nerve bundle have lower activation thresholds, ascending afferent volleys are also generated at intensities of electrical stimulation that exceed the motor threshold (MT) (Dawson, 1956). These are followed by (secondary) reafference arising from the invoked muscle contraction. While the capacity of NMES to provide a direct substitute for (descending) endogenous neural drive to muscles in circumstances of CNS injury or disease can be readily appreciated, our goal is to address means through which the sensory-mediated consequences of NMES induce sustained “neuroplastic” modifications within central motor pathways.

Given an empirical literature that is characterised by extraordinary diversity with respect to the stimulation protocols that are employed (varying in relation to such features as stimulation frequency, intensity, duration, and temporal pattern), there is little consensus with respect to the cellular mechanisms engaged by NMES. Beyond providing insights in relation to the expression of CNS plasticity at a systems level in humans, there is an obvious practical motivation for seeking the elucidation of these processes. Detailed knowledge concerning the

mechanisms of adaptation clearly has the potential to inform the development of neurorehabilitation practice.

Scope of the review

While the intent of this narrative review is to examine general principles, the scope of the analysis is necessarily restricted – for the most part to the effects of transcutaneous (surface) electrical stimulation delivered using intensities at or above the threshold for a motor response. The emphasis is largely upon the upper limb, and upon supraspinal adaptations (cf. Bergquist et al., 2011). To the extent that specific clinical applications are considered, these will generally be drawn from the domain of stroke rehabilitation.

Evidently NMES exhibits the capacity to generate changes in the excitability of descending (e.g. corticospinal) projections from the cortex to the spinal cord (Chipchase et al., 2011a). It has generally been assumed that such changes in excitability reflect, at least in part, modifications in the organisation of the same brain networks that serve ultimately as a basis for the improvements in functional capacity that may be brought about by neuromuscular stimulation (Barker et al., 2012; Traversa et al., 1997; Vang et al., 1999). Although as we shall see, there are grounds to be cautious about such assumptions (Carson et al., 2016), we include a survey of studies that have characterised the neurophysiological effects of NMES in terms of corticospinal excitability. Most often these have been assessed through muscle responses evoked by transcranial magnetic stimulation (TMS) delivered over primary motor cortex (M1). We also consider instances in which the effects of NMES have been registered using various brain imaging methodologies. In the closing sections, we return to the issue of whether the neural pathways upon which NMES has the most readily detectable effects, are necessarily also those that play an instrumental role in mediating changes in functional capacity.

In the course of the review, specific attention is devoted to adjuvant techniques that further promote restorative responses to NMES. The emergent theme is that an association with centrally initiated neural activity, whether this is generated in the context of NMES triggered by efferent drive, or via indirect methods such as mental imagery, can in some circumstances be efficacious in promoting neural adaptations upon which changes in functional capacity may be based.

Exemplars

We do not seek to be comprehensive with respect to the characteristics of NMES that can be altered in either an experimental or a clinical context. Rather, the empirical literature is circumscribed with a view to emphasizing a limited number of key concepts. It being evident that the "dose" of NMES has a significant bearing on the changes in brain activity thus invoked, we consider both protocols in which the level of stimulation is just above motor threshold, and those in which it is of sufficient magnitude to elicit overt movement.

Stimulation at motor threshold intensity

Sensory axons in a mixed nerve bundle innervating skeletal muscle are typically depolarised at levels of electrical stimulation below those which are necessary to recruit motor axons (Panizza et al., 1989, 1992; Veale et al., 1973). At intensities of NMES at or above MT therefore, ascending afferent volleys will be generated directly by the depolarisation of sensory axons (e.g. Collins, 2007). Some degree of secondary reafference arising (indirectly) from the invoked muscle contraction will follow. While the nature and the extent of the reafference will in turn be determined by the characteristics of the joint movement thus induced (which will itself be influenced by the posture of the limb, degree of restraint and so on), a more general point is that the relationships between the intensity of stimulation and the level (and distribution) of brain activity arising from 1) the direct sensory afference and 2) the indirect secondary reafference, are unlikely to be the same. Indeed, both are context dependent and must be determined empirically. Their relative contributions notwithstanding, it is the sensory corollaries of NMES that provide the principal means by which sustained (central) neuroplastic adaptations are induced (Bergquist et al., 2011).

If the magnitude of a single electrical stimulus delivered transcutaneously to a peripheral nerve is set to approximately three times perceptual threshold, direct motor responses in the innervated muscles are typically observed (e.g. Litvak et al., 2007; McKay et al., 2002; Ridding et al., 2001). At such intensities, extended (up to two hours) sequences of stimulation are necessary to bring about sustained increases in the excitability of corticospinal projections to

the muscles in which the responses are evoked (see also Luft et al., 2002). For example, Ridding et al. (2000) delivered trains of pulses (10 Hz, 1 ms pulse width) to the ulnar nerve at the wrist, at a rate of one train per second, using a 50% duty cycle (i.e. one second on; one second off), for a period of 2 hours. The area of the scalp over which TMS elicited MEPs in the ulnar nerve innervated first dorsal interosseus (FDI) and abductor digiti minimi (ADM) muscles increased as a consequence of the intervention. Using precisely the same protocol, Kaelin-Lang et al., (2002) obtained increases in the amplitude of MEPs elicited in ADM (but not in FDI). As these were not accompanied by corresponding changes in the size of potentials evoked by stimulation by corticospinal axons at the level of the cervicomedullary junction, a cortical locus for the adaptation was inferred (see also Ridding et al., 2000). The capricious nature of the changes in corticospinal excitability induced using these stimulation durations and intensities is emphasised by the wide variation in response across individuals reported by Charlton et al. (2003), when FDI afferents were stimulated via the skin overlying the muscle, rather than via the nerve trunk at the wrist (using a protocol that was otherwise equivalent). Furthermore, if the frequency at which the trains are delivered and the total duration of the intervention is reduced, reliable elevations of MEP amplitude are not obtained (Uy & Ridding, 2003).

If however the effective dose (if not the specificity) of NMES is increased by delivering pulses simultaneously to both the radial and ulnar nerves, a progressive increase in the amplitude of potentials evoked in FDI occurs over the time course of the intervention (McKay et al., 2002). Furthermore, this dual stimulation technique increases reliably both the area of the scalp over which TMS elicited MEPs can be obtained in FDI (and other hand muscles), and the amplitude of the MEPs recorded following the cessation of NMES (Ridding et al., 2001). Indeed, when motor point stimulation is delivered simultaneously to FDI and ADM via the skin overlying the muscles, an intervention of one-hour duration is sufficient to induce reliable increases in corticospinal excitability (Schabrun & Ridding, 2007; cf. Charlton et al., 2003). As there are no accompanying changes in the size of responses elicited by cervicomedullary stimulation, a spinal locus for the adaptation appears to be precluded (Ridding et al., 2001).

Stimulation at supra-motor threshold intensities

FES typically comprises short bursts of electrical pulses delivered at a frequency above that necessary to yield a fused contraction (≈ 12 Hz) (Peckham & Knutson, 2005; Sheffler & Chae, 2007). The assumption that given an adequate dose of NMES, persistent elevations in the excitability of corticospinal projections can be induced, is supported by studies that have

employed stimulation at an intensity and frequency sufficient to induce tetanic motor responses (see Chipchase et al., 2011a for a review). While it is not possible to exclude the possibility that such supra-threshold intensity stimulation generates antidromic impulses that modify synapses in the ventral horn (Rushton, 2003), the consensus view is that the observed changes in corticospinal excitability are driven primarily by cortical reorganization (e.g. Luft et al., 2005).

For example, Schabrun et al. (2012) applied 30 minutes of NMES to the skin overlying the APB muscle at 30 Hz (4 s on: 6 s off) with six periods of stimulation being applied every minute. The intensity of stimulation was that which produced a mid-range abduction of the thumb. The amplitudes of MEPs evoked in APB following the intervention were substantially greater than those obtained prior to the stimulation. Corresponding effects have been reported when biceps brachii is the target of stimulation (Chipchase et al., 2011b). When NMES is applied to APB in this manner for periods of 20 or 40 minutes, the induced changes in corticospinal excitability are maintained for at least 20 minutes following the cessation of the intervention (Andrews et al., 2013).

While it is clear that increases in the dose of stimulation that is administered may be achieved by increases in the current/voltage of individual shocks, and/or by a higher frequency of delivery, it has been proposed (Chipchase et al., 2011b) that increases in corticospinal reactivity are generated reliably only by those forms of NMES giving rise to a motor response that mimics a voluntary muscle contraction. As noted previously, in addition to the initial ascending afferent volley induced directly by electrical stimulation of the nerve, such protocols encapsulate secondary reafference arising from the muscle contractions (Schabrun et al., 2012). The extent of the neural activity induced in M1 by such reafference can be substantially greater than that brought about directly by the ES-mediated depolarisation of the sensory axons (Shitara et al., 2013). De Kroon and colleagues (2005) in their review of the relationships between electrical stimulation characteristics and clinical outcomes, hypothesised that supra-motor stimulation is more likely than sub-motor stimulation to lead to improvements in motor control, as a consequence of muscle and joint afferent feedback, i.e. in addition to that derived from cutaneous afferents, which are also engaged at lower intensities of stimulation.

Indeed, repeated changes in muscle length brought about passively by mechanical joint rotation also induce both acute (Lewis et al., 2001) and chronic (Macé et al., 2008) increases in corticospinal excitability. Collectively, these observations suggest that the secondary mediation of Ia (muscle spindle) afferent projections to higher brain centres is instrumental in augmenting the direct depolarising effects of NMES. Although it has been proposed that cutaneous afferents

make a greater contribution than muscle spindle afferents to cortical potentials produced by electrical stimulation of mixed nerves in the upper limb (e.g. Allison et al., 1991; Halonen et al., 1988), it is the precise brain circuits that exhibit a change in state as a result of peripheral stimulation which is likely to assume particular functional significance. It is believed that Ia afferent input has its most direct effects upon both area 4 (primary motor cortex) (Jones & Porter, 1980) and area 3a (in primary somatosensory cortex) (Heath et al. 1976; Hore et al. 1976). Whereas, input from cutaneous receptors and low threshold mechanoreceptors first alters the excitability of neurons in areas 3b and 1 (Kaas & Pons, 1988). We thus turn our attention to the brain circuitry that is engaged by NMES, and to the impact of its parametric variation.

Brain circuitry engaged by NMES

Somatosensory cortex

On the basis of findings derived using a variety of neuroimaging techniques, it has been surmised that electrical stimulation of peripheral afferents engages circuits in the primary somatosensory cortex (S1 – including Brodmann areas 3, 1, and 2) within the postcentral gyrus, the second somatosensory area (S2 – including parts of Brodmann areas 40 and 43) within the parietal operculum on the ceiling of the lateral sulcus, and the posterior parietal cortex (Korvenoja et al. 1999; Nihashi et al., 2005; Boakye et al. 2000). In relation to the complex cortical responses that are extracted from electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings, there is consensus that short-latency potentials occurring within the first 40 ms following stimulation of the median nerve (e.g. at the wrist) at intensities sufficient to elicit a muscle twitch, arise principally from contralateral (S1) (Allison et al., 1991). The presence of synchronised neuronal population activity in S2 (registered by MEG) during this period, while consistent with an influence of cortical afferents from S1, does not however preclude the possibility of mediation via additional parallel thalamocortical projections to S2 (Karhu & Tesche, 1999). With respect to the medium latency (> 40 ms) components, there is a distributed pattern of activation that includes not only S1, but also S2 bilaterally, and contralateral posterior parietal cortex (Hari et al. 1984; Allison et al. 1989a, 1989b, 1992; Forss et al. 1994). It is currently believed that cortico-cortical connections mediated by transcallosal projections play a major role in shaping the bilateral character of the

S2 response profile (Del Vecchio et al., 2019). These sources continue to be active simultaneously during a period 70–140 ms following the onset of stimulation (Mauguière et al., 1997). When a sequence of stimuli is administered, the offset of the sequence gives rise to a (P100 and N140) stimulus evoked potential (SEP) signature distinct from that associated with the individual stimuli (Yamashiro et al., 2008, 2009).

The functional magnetic resonance imaging (fMRI) derived blood oxygenation level-dependent (BOLD) response measured in contralateral S1 scales with the intensity of ES (at least up to MT) (Krause et al., 2001, see also Nelson et al., 2004). In contrast, bilateral activity evident in S2 and posterior parietal cortex does not appear to vary in this manner. A BOLD signal is however registered in S2 at lower levels of stimulation than in S1. This is augmented when attention is directed explicitly to the stimulation (Backes et al., 2000). In circumstances in which ES is applied in a range between the sensory threshold (ST) and 1.2 times MT, the amplitude of the N9, N20, and N20-P25 SEP components derived from EEG recordings increases in proportion to stimulation intensity (Gatica Tossi et al., 2013; cf. Lakhani et al., 2012). This effect remains present at 2.5 times MT (Urasaki et al., 1998). Components of the SEP recorded in S1 saturate at a level below the pain threshold (PT) (Parain & Delapierre, 1991), while the asymptote of the S2 response occurs at lower stimulation intensities than for the S1 response (Lin et al., 2003).

It is now broadly accepted that the initial (i.e. N20) EEG responses to NMES are dominated by cutaneous afferent input (Gandevia et al., 1990; Kunesch et al., 1995). The origin of the N20 response to cutaneous inputs is considered to be a deep tangential generator in area 3b (e.g. Desmedt & Ozaki, 1991; McLaughlin & Kelly, 1993). Whereas, it is probable that the source generator for cortical potentials invoked by muscle spindle afference is principally area 3a, although additional contributions from area 2 cannot be excluded (MacKinnon et al., 2000; Mima et al., 1996). This is consonant with evidence drawn from comparative studies that that the most significant input to area 3a is from muscle spindle afferents (Kaas, 1983). Thus surface electrical stimulation at intensities above motor threshold will give rise to cutaneous afferent mediated activity in area 3b of primary somatosensory cortex (S1), and also to activity in area 3a and area 2 (Wiesendanger & Miles, 1982), including that arising by virtue of muscle contraction induced reafference.

Cortico-cortical connections from somatosensory cortex to M1

Studies in cat indicate that stimulation of sensory cortex can induce long-lasting potentiation of synaptic potentials evoked in the motor cortex (Sakamoto et al., 1987). Detailed investigations in non-human primates (e.g. Jones et al., 1978; Pons and Kaas, 1986; Ghosh et al., 1987; Huerta and Pons, 1990) and in cat (Grant et al., 1975; Zarzecki et al., 1978; Waters et al., 1982; Burton and Kopf, 1984; Yumiya and Ghez, 1984; Porter and Sakamoto, 1988; Avendano et al., 1992; Schwark et al., 1993) have revealed extensive networks of cortico-cortical connections between SI and primary motor cortex (M1) (Burton & Fabri, 1995). Neurons that exhibit short-latency excitatory postsynaptic potentials (EPSPs) – indicative of direct input, in response to microstimulation of area 3a, are found in all laminae of the motor cortex, with the exception of layer I (Herman et al. 1985; Huerta & Pons, 1990; Porter et al., 1990). By comparison, only cells in the superficial layers of M1 (II and III) respond in this fashion to stimulation of area 2 (Kosar et al., 1985; Porter et al., 1990). It has thus been proposed that area 3a should be viewed as a relay to motor cortex (Jones & Porter, 1980), or even as a part of area 4 (Jones et al., 1978, cf. Kuehn et al., 2017). This intimacy of association provides a means through which muscle spindle input that is relayed through area 3a can exert a direct influence on pyramidal and multipolar neurons in deep (V and VI) layers of M1 (Porter et al., 1990). In contrast, while there are reciprocal connections between area 3b and area 1 in particular, and further projections to area 2 (which are ostensibly not reciprocated), projections from area 3b to M1 are sparse (Burton & Fabri, 1995; Darian-Smith et al., 1993), if indeed detectable (Jones et al., 1978).

Cerebello-thalamo-cortical and thalmo-cortical connections

Although the possibility of direct activation of the primary motor cortex via sensory afferents from the periphery (Padel & Relova, 1991) cannot be excluded, studies in non-human primates indicate that the ventral posterior complex of the thalamus - the major sensory thalamic relay, has relatively few direct projections to M1 (Darian-Smith & Darian- Smith, 1993; Huffman & Krubitzer, 2001a). In this regard, it is worth noting that while S1 areas 1, 2 and 3b are represented across the ventrobasal complex of the thalamus, area 3a has connectional relationships similar to those for area 4 (Jones et al., 1979). For example, area 3a receives projections from nuclei of the thalamus classically associated with the motor system, including indirect input from the cerebellum and basal ganglia via the ventral lateral (VL) nucleus (Huffman & Krubitzer, 2001b). Thalamic processing of somatosensory input extends beyond the relaying of primary afferent signals to the cortex. For example, at levels of ES above perceptual threshold (PT), thalamic SEPs can be elicited over intervals greater than 75 ms following the

peripheral shock, with the duration extending to 150 ms when the intensity is set to MT (Klostermann et al., 2009).

Through receipt of convergent inputs from both the sensorimotor cortex and the spinal cord, the interpositus nucleus of the cerebellum also exerts a modulating influence upon motor network responses to sensory stimulation via thalamic projections to premotor and primary motor cortices (Luft et al., 2005). Hemicerebellectomy blocks the modulation of cortical motor output associated with repetitive ES of the sciatic nerve in the rat (Ben Taib et al., 2005). It has also been proposed that the state of the motor cortex itself – acting via the intermediate cerebellum, may further serve to tune the gain of polysynaptic responses to peripheral stimulation (Manto et al., 2006). This is a possibility to which will return in the sections that follow.

Motor Network

In view of the patterns of connectivity outlined above, one might surmise that the electrical stimulation of peripheral afferents has clear potential to alter the state of circuits not only within somatosensory cortex, but also within the (classically defined) motor network. Although it does not provide a basis upon which to resolve the specific mediating pathways that are engaged, empirical support can now be drawn from human neuroimaging data. For the present purposes it will suffice to provide a brief, and necessarily partial, representation of the relevant findings. The picture that emerges is of a multi-stage hierarchical process in which various elements of the cortical motor network are consistently engaged (Avanzini et al., 2018).

When median nerve stimulation at motor threshold intensity (0.5 – 2.7 Hz; 0.2 – 0.3 ms pulse duration) is employed, elevated activity registered concurrently by fMRI (Spiegel et al. 1999) and by MEG (Kawamura et al., 1996) is evident in both contralateral S1 and M1. Similar protocols also yield an elevated BOLD response in supplementary motor area (SMA) (Manganotti et al., 2012). Notwithstanding the likelihood of prior disease and drug treatment related adaptations in brain organisation, recent reports of intracerebral recordings from epilepsy patients have provided hitherto unanticipated opportunities to resolve the spatiotemporal characteristics of motor network responses to peripheral nerve stimulation. These recordings indicate that in addition to enhanced gamma band power in areas 3a and 3b

(exceeding that of areas 1 and 2), 1Hz median nerve stimulation (0.2-ms pulse duration) at MT (and 20% below MT) gives rise to elevated activity in M1, and in large sectors of dorsal and ventral premotor cortex, and SMA (Avanzini et al., 2016). Further detailed analysis of the time course of these responses (Avanzini et al., 2018) indicates that M1 (BA4) exhibits an initial (peaks ≈ 30-40 ms) phasic response to median (and tibial) nerve stimulation that closely resembles those registered for areas 3a and 3b. Whereas, the responses recorded from premotor areas occur somewhat later. It is also notable that while median nerve stimulation just above MT gives rise to elevated gamma band activity (50–150 Hz) in ipsilateral PMd, no such response has been detected in ipsilateral M1 (Del Vecchio et al., 2019; see also Klingner et al., 2011).

There is an apparent dose-dependent character to the BOLD response to NMES observed for M1. For example, it appears to increase monotonically as the level of stimulation applied over the motor point of the quadriceps muscle is increased from sensory threshold to that eliciting a maximum motor response (Smith et al., 2003). Using functional levels of stimulation sufficient to bring about alternating flexion and extension of the wrist, Blickenstorfer et al. (2009) reported simultaneously registered BOLD activation peaks in regions defined as: contralateral primary motor cortex; primary somatosensory cortex and premotor cortex; the ipsilateral cerebellum; bilateral secondary somatosensory cortex; supplementary motor area and anterior cingulate cortex (see also Arienzo et al., 2006; Del Gratta et al., 2000; Joa et al., 2012). Patterned NMES (50 Hz with 200 μs pulses) sufficient to invoke finger flexion elevates the BOLD response in contralateral M1 and S1 and bilaterally in S2 (Iftime-Nielsen et al., 2012). A recent report suggests that 100s of 30Hz stimulation at intensities sufficient to generate wrist flexion (against gravity), gives rise to subsequent changes in EEG/EMG registered corticomuscular coherence (Xu et al., 2018).

It has also been shown that in some instances the physiological changes reflected in the BOLD response may be sustained. Two hours of median nerve stimulation (10 Hz trains, 50% duty cycle at 1 Hz, intensity just above MT) applied at the wrist, was observed (in the context of a thumb movement task) to bring about an increase in signal intensity and number of voxels activated M1, S1, and PMd, that persisted for up to 60 min after the stimulation had ended (Wu et al., 2005). Employing a protocol in which mesh-glove stimulation was applied at a level below sensory threshold for 30 minutes, Golaszewski et al. (2004) observed that the magnitude of the BOLD response registered in primary motor and primary somatosensory regions of both hemispheres during a finger-to-thumb tapping task, was greater than when the task was

performed in the absence of prior stimulation. The elevated activity registered for the contralateral primary motor region remained present two hours following the cessation of stimulation.

In general the spatial extent of the BOLD registered response (i.e. number of voxels) and the magnitude of the signal change (i.e. relative to rest) are larger for voluntary movement than those brought about by FES (Francis et al., 2009; Joa et al., 2012; Wegrzyk et al., 2017), although the particular regions of interest for which the greatest differences are obtained tend to vary somewhat across studies. In addition, S2 activation that is greater during FES than during voluntary contractions has been reported (Iftime-Nielsen et al., 2012; Christensen & Grey, 2013). At least with respect to ankle dorsiflexion, the spatial extent of the BOLD registered activity in M1, S1, S2, SMA, cingulate motor area (CMA), bilateral dorsal and ventral premotor areas and cerebellum VI is greater during FES generated movements, than during passive movements (Francis et al., 2009; see also Gandolla et al., 2014). The nature of the brain activation that characterizes combined NMES and voluntary or imagined movement is a matter to which we will return in the sections that follow.

Corticospinal projections

In circumstances in which the express intent has been to bring about changes in the state of the CNS (rather than produce overt movements) (see Bergquist et al., 2011), the effects of parametric variations in NMES upon the state of corticospinal projections have been investigated. When delivered in a 4 s ON and 6 s OFF cycle for 20 min at 30 Hz, median nerve stimulation applied at the wrist gave rise to increases in the amplitude of MEPs recorded in abductor pollicis brevis (APB) - when the intensity was 110% of MT, but not when it was 90% of MT (Sasaki et al., 2017). Applying 30 min of mesh-glove (MG) whole-hand stimulation, Golaszewski et al. (2012) noted 50Hz stimulation at sensory threshold, and 2Hz stimulation at motor threshold, gave rise to increases in corticospinal excitability extending to one hour following. Such changes were not obtained when 50Hz stimulation at a level below the sensory threshold, or 2Hz stimulation at sensory threshold were used. The outcomes of this specific form of intervention (i.e. using mesh glove stimulation), in which afferent fibres of multiple types, with widespread innervation zones, are likely to be involved, is not necessarily emblematic of those obtained when a single nerve is stimulated. Specifically, the magnitude of the change in corticospinal excitability depends on the stimulation frequency (for intensity ≈

MT). When applied at 100Hz and in the range of 20-50Hz, increases in corticospinal excitability (CSE) in excess of 50% are routinely observed. This is not generally the case for stimulation applied at 10Hz or less (Jaberzadeh et al., 2017).

If the intensity of peripheral nerve stimulation applied in humans is between 30% and 50% of that required to produce a maximum compound muscle action potential (M-max), MEPs evoked subsequently by TMS over M1 are facilitated at inter-stimulus intervals (ISIs) from 25 ms to 60 ms in abductor pollicis brevis (APB) - following median nerve stimulation at the wrist (Deletis et al., 1992). A similar outcome was noted (Komori et al., 1992) for the thenar muscle at ISIs between 50 and 80 ms when the peripheral shock was set to 10% of M-max. Devanne et al. (2009) reported than even when stimulation intensity is set just above motor threshold, median nerve stimulation (at the wrist) gives rise to marked facilitation of MEPs recorded in the APB, first dorsal interosseous (FDI), and extensor carpi radialis (ECR) muscles, when ISIs ranging from 40 to 80 ms are employed. At ISIs extending beyond 200 ms (and below 25 ms - around the latency of the N20 component of the somatosensory evoked potential) a diminution of MEP amplitude is generally obtained (e.g. Turco et al., 2018). It is of particular interest in the present context that after NMES is delivered over the ulnar nerve (100 Hz in a 20s on, 20s off duty cycle; intensity ~15% of that to elicit a maximum m-wave) for 40 min, short-latency afferent inhibition (SAI: ISI 18–25 ms) is markedly diminished. Whereas, for those ISIs (28–35 ms) at which there occurred potentiation of MEP amplitudes following a (single) conditioning peripheral nerve stimulus, the NMES intervention served to further increase the amplitude of the TMS evoked response (Mang et al., 2012). These findings are consistent with the possibility highlighted above, that the state of M1 (potentially acting via the intermediate cerebellum) may influence the gain of polysynaptic circuits that modulate the effects of peripheral stimulation (Manto et al., 2006)

It remains unclear at present whether sustained changes in corticospinal excitability brought about by prolonged NMES interventions are instrumentally related to changes in behaviour. Veldman et al. (2016) applied trains to the radial and median nerves (proximal to the elbow) consisting of five square wave pulses at 10 Hz (pulse width, 1 ms) 50% duty cycle, at intensities just below MT. In three separate interventions the stimulation was applied for either 20, 40 or 60 minutes. Changes in the performance of a visuomotor tracking task (post intervention relative to baseline) were compared to a fourth group of participants who did not receive stimulation. Although some improvements in task completion, and in measures of CSE were observed over the course of the following week, there was no evidence that these

outcomes were related. A more general issue (to which we will return) is thereby illustrated. Variations in CSE – as revealed by TMS, are not necessarily indicative of the functional adaptations (in this case brought about by NMES) that mediate improvements in performance (Carson et al., 2016).

In light of the assumption that contractions of an intensity sufficient to mimic some features of those brought about by voluntary activation are necessary to causes reliable changes in CSE (Chipchase et al., 2011a), it may appear paradoxical that FES (primarily lower limb) protocols bring about immediate effects that are of lesser magnitude than those associated with 20-50Hz or 100Hz stimulation delivered closer to MT (Jaberzadeh et al., 2017). Nonetheless, it is also the case (i.e. as with intensity ≈ MT) that supra-motor threshold stimulation is more effective at increasing CSE when delivered 30Hz than at 10Hz (Chipchase et al., 2011b). It has been reported that while 20 min and 40 min of stimulation (30Hz) at intensities sufficient to generate a "voluntary-like" contraction in APB increased CSE, this was not the case for 60 min of stimulation (Andrews et al., 2013). Although perhaps counterintuitive, a similar but less pronounced non-monotonic effect of duration is however also present for MT level stimulation (Jaberzadeh et al., 2017). In other words, there comes a point at which increasing the intensity or duration of stimulation brings about no further gains, at least in terms of the excitability of corticospinal projections to the target muscles.

There exist forms of NMES (typically delivered over the muscle belly) that have been developed with the express aim of preventing skeletal-muscle weakness, for example during acute critical illness. They are sufficient to generate high levels of force (and thus sometimes designated electrostimulation strength training (EST)). Usually utilizing frequencies between 35 and 100 Hz, the stimulation can be applied for up to an hour daily, over periods ranging between one and six weeks (Maffiuletti et al., 2011, 2013). There are comprehensive reviews dealing with the nature of the central and peripheral adaptations that may mediate the observed increases in functional capacity that can be accrued by these methods (e.g. Hortobágyi & Maffiuletti, 2011). The present aim is not to recapitulate these analyses. It is however pertinent to highlight one of the key observations to emerge in the course of this research. As noted in preceding sections, bilateral alterations in the state of brain circuits that constitute the classical motor network in both hemispheres are frequently observed following unilateral NMES. It is therefore particularly salient that these NMES variants can increase the force generating capacity of homologous muscles in the limb opposite to the one in receipt of

stimulation (Cabric et al., 1987; Hortobágyi et al., 1999; Huang et al., 2007; Kadri et al., 2017; Zhou et al., 2002).

In recent studies conducted with the aim of determining the mechanistic basis of such effects, there has been an understandable initial focus upon the degree to which less "intense" forms of unilateral NMES might bring about bilateral changes in CSE. Veldman et al. (2015) applied trains consisting of five square wave pulses delivered to the radial and median nerves of the right arm (above the elbow) at 10 Hz (pulse width, 1 ms) 50% duty cycle, using an intensity equal to twice the perceptual threshold (i.e. presumed to be below MT) in five blocks of 5 min duration. They noted increases in the amplitude of MEPs recorded in both right and left extensor carpi radialis (ECR) following the intervention, which were accompanied by improvements in the performance of a visuomotor tracking task (i.e. for both limbs). There was however no evidence of a statistical association between these measures (see also Summers et al., 2017). Using a largely equivalent stimulation protocol, Veldman et al. (2018) also observed improvements in the performance of the opposite limb, in this case during a retention test conducted two days following the intervention. And as in the preceding study study, electrophysiological measures (in this case EEG derived) of directional oscillatory coupling (representing "corticocortical connectivity") - between posterior parietal and primary somatosensory cortex to the primary motor cortex, did not vary in accordance with the changes in behaviour.

A reflection on the brain circuitry engaged by NMES

It is evident that there exist variants of NMES that provide a means of altering the state of elements within an extended brain network (encompassing not only classically defined somatosensory and motor areas), and the excitability of circuits with projections to the spinal cord (e.g. Schabrun et al., 2012). That which remains to be determined are the causal relations between the changes in brain state that can be registered by modern neuroimaging and electrophysiological techniques, and alterations in functional capacity that can in some circumstances be brought about by NMES. In recent years there has perhaps been an undue haste to infer that intervention induced changes in corticospinal excitability are indicative of the neural adaptations that mediate sustained changes in behaviour (Carson et al., 2016). Indeed, well powered individual studies (e.g. Ruddy et al., 2016) and several meta-analyses (e.g.

Berghuis et al., 2017; Manca et al., 2018; Veldman et al., 2014) have failed to demonstrate an association between changes in CSE and improvements in motor performance. There is consequently a growing recognition that in our empirical investigations we must devote greater attention to paths and structures other than the ones that can be assayed easily by such techniques as TMS (Veldman et al., 2016), or conventional brain imaging analysis approaches. For example, a case can be made for considering the individual differences in functional or structural brain connectivity associated with variations in the expression of performance changes (e.g. Ruddy et al., 2017) that follow the administration of NMES. This would be in contrast to simply registering brain regions or pathways that exhibit a change in state following stimulation.

Adjuvant techniques

The production of voluntary movement has two essential components: central efferent drive that is initiated at the level of the cortex; and consequentially muscle contractions that displace joints and thus give rise to afference. Electrical stimulation of peripheral nerves provides a means of producing muscular contractions without the initial central drive by direct depolarization of motor axons located below the stimulating electrodes. It has been noted previously that the effectiveness (both adaptive and restorative) of NMES may be enhanced through the use of specific protocols (e.g. pulse width/frequency combinations) that promote synaptic recruitment of spinal motoneurons by the electrically evoked sensory volley (e.g. Collins, 2007). The adaptive benefits are readily appreciated. For example, afference mediated (i.e. synaptic) recruitment of spinal motoneurons is likely to occur in normal physiological order, and thus preferentially include fatigue- resistant motor units. The restorative benefits, while perhaps less obvious, are however also potentially significant. In this regard, emphasis has been placed on a capacity for the repeated evocation of sensory volleys by NMES to induce increased activity in spinal and supraspinal circuits, and in turn bring about acute and chronic neuroplastic adaptations that are sufficient to enhance function (e.g. Bergquist et al., 2011). While in this scheme the accent is on the cumulative effects of stimulus repetition per se, there are further possibilities.

In recent years, there has been particular interest in associative forms of neural plasticity, such as those in which the repeated coincidence of experimentally induced activity in both sensory circuits (by peripheral nerve stimulation) and motor circuits (by TMS applied over M1) gives rise to sustained changes in corticospinal excitability (e.g. Stefan et al., 2000). In terms of the phenomenology of the induced effects, there is notionally a resemblance to Hebbian plasticity

(Hebb, 1949), whereby a presynaptic input onto a postsynaptic neuron is strengthened as a consequence of both the pre- and postsynaptic neurons being active simultaneously. In seeking to provide a more mechanistic account of this paired associative stimulation (PAS), it has been proposed that it shares key features with spike timing-dependent plasticity (STDP) (Müller-Dahlhaus et al. 2010) – as this has been elaborated in animal models and reduced (e.g. slice) preparations. In STDP, the polarity of the induced change in synaptic efficacy is determined by the sequence of pre- and postsynaptic neuronal activity (for reviews see Dan & Poo, 2004; Markram, Gerstner & Sjostrom, 2011). In prototypical representations of STDP (e.g. Song et al., 2000), potentiation occurs if a presynaptic neuron fires no more than 50 ms in advance of the postsynaptic neuron (Feldman, 2000). Depression arises if postsynaptic spikes precede presynaptic action potentials – (or transpire without activity in the presynaptic neuron) (Bi and Poo 1998; Cooke & Bliss, 2006; Levy & Steward, 1983). There is also held to be a sharp transition from a weakening of synaptic efficacy (long term depression (LTD)) to strengthening of synaptic efficacy (long term potentiation (LTP)) at time differences in the vicinity (within 5 ms) of zero (Feldman, 2012).

In the sections that follow, we use the conceptual framework of associative plasticity to consider the impact of adjuvant techniques upon responses to NMES. The argument is made that an association of NMES generated afference with centrally initiated neural activity, such as that which occurs if the stimulation is triggered by efferent drive, or is delivered following instructions to engage in mental imagery, may promote neural adaptations upon which changes in functional capacity may be based. In doing so, we first make the critical point that the induction of associative effects that can be observed at a systems level in humans does not require adherence to the defining characteristics of STDP. In particular, associative effects are expressed when the relative timing of the activity induced in sensory and motor circuits is not precisely circumscribed.

Extending the concept of associative stimulation

There are a number of recent and comprehensive reviews of paired associative stimulation (e.g. Carson & Kennedy, 2013; Suppa et al., 2017). It is not our intent to reprise their

contents. There are nonetheless important points that can be gleaned from these reviews, and from empirical findings that have appeared subsequently. Foremost among these is the observation variants of PAS in which the timing of the contributory elements is not strictly confined – for example when extended trains of peripheral nerve stimuli are used (e.g., Carson et al., 2013; Carson & Rankin, 2018; McNickle & Carson, 2015; Ridding & Taylor, 2001; Shulga et al., 2016; Tolmacheva et al., 2019), produce elevations in CSE that are comparable to, if not greater than, those obtained when the inter-stimulus interval (ISI) separating the peripheral and cortical events is precisely circumscribed. The associative nature of the effects are however emphasised by the fact that in these studies the NMES alone (typically at an intensity ≈ MT) does not bring about changes in CSE. The conclusion that the relative timing need not be either precise or restricted is further emphasised by reports that the nerve stimulation component of PAS can be replaced by movement generated afference, without loss of generality (Edwards et al., 2014; see also McNickle & Carson, 2015). In this vein, cortical microstimulation experiments in freely behaving non-human primates reveal that changes in synaptic strength between stimulated sites in precentral and/or postcentral cortex can be brought about without adherence to STDP rules (Seeman et al., 2017). These recent findings also serve to emphasise that which should perhaps be apparent on a priori grounds alone – when applied in vivo, there are multiple pathways via which the corollaries of (i.e. peripheral) stimulation may reach and influence the cortex (Carson & Kennedy, 2013), and as a consequence relative timing is likely to be only one of many factors that govern the induction of neuroplastic adaptations (Feldman, 2012).

It is in this light that the outcomes yielded by associative stimulation protocols can be more easily reconciled with the results of studies demonstrating that the combined effects of NMES and forms of exogenous cortical stimulation other than TMS are greater than those of each stimulation modality alone. Rizzo et al. (2014) described a protocol in which NMES (500 μs pulse duration, at 5 Hz, for 5 min - 1500 stimuli, intensity ≈ 2 × ST) was delivered to the median nerve simultaneously with transcranial direct current stimulation (tDCS). When the cortical electrode montage was such that the anode was positioned on the scalp over M1 contralateral to the site of peripheral nerve stimulation, the elevation in CSE recorded following the cessation of the intervention was markedly greater than that induced by tDCS alone (NMES + sham tDCS did not alter CSE). In addition, the duration of the elevation in CSE brought about by the combined stimulation persisted for at least one hour (considerably longer than following anodal tDCS alone). Employing an NMES variant in which 1 ms pulses (intensity ≈ MT) were applied simultaneously to the FDI and ABP motor points (at frequencies between 0.35–6.7 Hz ≈ 6345

pairs) for a period of 30 minutes, and anodal tDCS delivered for the final 25 minutes, Hoseini et al. (2016) observed subsequent improvements in performance of the Purdue pegboard test (used to assess dexterity) that were not seen following either NMES + sham tDCS or anodal tDCS + sham NMES. For cases in which tDCS is applied (i.e. continuously) over an extended period during which NMES is also delivered at various intervals, there exists no discrete timing relationship between peripheral and cortical stimulation events. Yet associative effects are nonetheless obtained. Although not in accordance with STDP based models of associative plasticity, this general pattern of findings is however consistent with recent analyses showing that not only the phase, but also the power of the cortical oscillatory beta cycle (e.g 16-17 Hz) at the moment stimulation is delivered, influences the increase in CSE caused by TMS (Khademi et al., 2019). There is a more general point. Since a single relative timing relationship between the corollaries of cortical and peripheral stimulation is not a prerequisite for the induction of associative effects, when NMES is paired with endogenously generated elevations in motor network excitability, similar neuroplastic adaptations are likely to occur. There is now a considerable body of evidence to support this conjecture, and to suggest that that the adaptations may be functionally significant.

Augmenting NMES at motor threshold intensity

For the present purposes, we consider two endogenous means of altering the state of the motor network: voluntary contractions and mental imagery. With a view to confining the limits of the discussion, "cognitive" factors such as the focus of attention, which are believed to have an influence on the efficacy of associative stimulation protocols (e.g. Stefan et al., 2004), will not be treated in any detail.

It has for some time been appreciated that when NMES is applied in the context of voluntary contractions, the consequential changes in the state of efferent projections from the brain to the spinal cord are greater than those achieved through NMES alone (de Kroon et al, 2005). Although the majority of empirical studies conducted in this domain have employed levels of stimulation sufficient to evoke overt motor responses, it can also be shown that these features emerge when much lower intensities of NMES are used. For example, Taylor and colleagues (2012) delivered biphasic pulses (50 Hz; 200 μs pulse duration; intensity ≈ MT; 50% duty cycle for 6 s) over the wrist extensors (ECR and extensor carpi ulnaris (ECR)) at the onset of 60

isometric wrist extension contractions (to 15% MVC) – triggered when the surface EMG recorded from the target muscles exceeded 25 μV. In a control condition NMES was delivered in isolation. An elevation of CSE was observed following EMG triggered delivery of NMES, but not following NMES alone. Similar findings have been obtained for the lower limb, when NMES is delivered either over the tibialis anterior (TA) muscle or to the (common peroneal) nerve during ballistic dorsiflexions of the ankle (Jochumsen et al., 2016). In this regard, it is notable that the acute augmentation of CSE appears to be greater when NMES is combined with shortening contractions, than with isometric contractions (Saito et al., 2014).

Of greater practical relevance are the changes in functional capacity that arise from the combination of NMES and voluntary contractions. Carvalho et al. (2018) conducted a double-blind, sham-controlled, randomized trial engaging healthy adults, in which median nerve stimulation (random frequency ranges (1–4 Hz, 8–12 Hz, and 60–90 Hz) and intensity levels (2–6 mA)) at the wrist was applied during 20 minutes practice of a serial reaction time task (SRTT) requiring keypress responses. This was followed by a similar "consolidation" session of 30 minutes duration. It was noted that explicit recall of the learned sequence improved following both initial training and consolidation. No such improvements were obtained for either a group that received "off line" NMES, or a group that was given sham stimulation.

That the origin of the neuroplastic effects of combined voluntary contraction and NMES is likely to be predominantly supraspinal rather than spinal, at least when relatively low levels of electrical stimulation are employed, is indicated by a series of studies in which the delivery of NMES has been in the context of motor imagery tasks performed by the recipient. Employing a task in which the participants were asked to imagine that they were squeezing and relaxing a ball (motor imagery), while watching a video of the action (observation) (during which time the ball was held "passively"), Yasui et al. (2019) applied NMES (trains of 20 pulses at 10-Hz; 1ms pulse duration; intensity ≈ 90% MT; 50% duty cycle of 2 s on, 3s off) during four blocks of 5 minutes duration. A cumulative increase in the amplitude of MEPs recorded from FDI was obtained in this condition, but not for NMES alone (or imagery/observation alone). Corresponding effects that are sustained for at least 30 minutes following cessation of combined NMES/motor imagery have also been reported for the lower limb (Takahashi et al., 2019). In a small-scale study (without a control group), Okuyama et al. (2018) observed increases in upper extremity function in ten chronic stroke survivors, following an intervention (10 trials per day for 10 days) in which stimulation (≈ MT of the extensor digitorum communis (EDC)) of the

radial nerve - innervating wrist and finger extensors, was combined with motor imagery/observation.

A compelling case that these effects are associative in nature can be made on the basis of reports that they can be obtained when the delivery of NMES is triggered by EEG-registered movement-related cortical potentials (MRCP) – generated when individuals follow an instruction to imagine the "kinaesthetics" of ballistic movements. Deploying an intervention of this type, Niazi et al. (2012) triggered stimulation (1ms pulse duration; intensity ≈ MT) of the common peroneal nerve (CPN) upon detection of the initial negative phase of the MRCP, as 50 self-paced imagined movements were performed. The intervention gave rise to increases in the excitability of corticospinal projections to TA. No such changes were induced by NMES alone or by motor imagery alone (see also Mrachacz-Kersting et al., 2017). Comparable results are obtained if the timing of the NMES is yoked (using an estimate of the contingent negative variation (CNV)) to the onset of a cued imagined movement (Mrachacz-Kersting et al., 2012). In a recent investigation using MRCP-triggered NMES (equivalent to the Niazi et al., 2012 protocol), increases in CSE persisting for one hour were registered (Olsen et al., 2018; see also Jochumsen et al., 2018). In addition to giving rise to increases in CSE in both chronic (Mrachacz-Kersting et al., 2016) and sub-acute (Mrachacz-Kersting et al., 2019) stroke survivors, imagery-related MRCP triggered NMES appears capable of promoting positive changes in motor function. As far as we are aware however, it has not been established that any changes in CSE brought about by these techniques are instrumentally related to improvements in performance.

Given the very large number of brain imaging studies that have been conducted, there are several meta-analyses (e.g. Grezes and Decety, 2001; Caspers et al., 2010; Molenberghs et al., 2012; Hetu et al., 2013; Hardwick et al., 2018) that provide a basis upon which to survey the brain regions engaged during voluntary movement, action observation and motor imagery. As has been highlighted recently however (Savaki & Raos, 2019), by and large these meta-analyses are based upon studies in which the three task contexts have been investigated independently of one another. On the basis of these analyses it appears reasonable to draw the conclusion that voluntary movement, action observation and motor imagery all give rise to consistent activation of a brain network encompassing premotor, parietal, and somatosensory areas (e.g. Hardwick et al., 2018). In the present context, we follow the lead of Savaki and Raos (2019) in suggesting that there is additional information to be gained by giving particular weight to the small number of studies in which fMRI has been used to assay the whole brain when all three variants of the

same "motor" task, have been performed by the same group of participants. In a recent study in which there were no a priori constraints upon regions of interest (ROIs) deemed to be of interest, Simos et al. (2017) determined that during both motor imagery and execution of a geometric tracing task performed by the *right* index finger, BOLD activity in the following regions surpassed the assigned threshold: bilateral dorsal and ventral premotor cortex, left supplementary motor cortex (SMA-proper), bilateral BA 7 in the superior and BA 40 in the inferior parietal cortex, bilateral BA 8 in the middle frontal gyrus (MFG), bilateral BA 22 in the posterior part of superior temporal gyrus (pSTG) including the temporo-parietal junction (TPj), bilateral BA 37 in the posterior part of the middle temporal gyrus (pMTG) including the extrastriate body area (EBA), the left extrastriate visual BA 19 in the cuneus, the right lingual gyrus (LG) and the left middle occipital gyrus (MOG), left BA 7 in the posterior precuneus and right BA 37 in the fusiform gyrus. The left secondary somatosensory cortex (SII) was also deemed engaged in both tasks. As might be anticipated, while the upper limb representations of the primary motor and somatosensory cortical areas (2/3) exhibited bilateral activity, the magnitude of the BOLD response was larger during execution than during imagery. In contrast, during motor imagery there was relative greater BOLD response magnitude bilaterally in prefrontal, premotor and parieto-temporal cortices. In a related investigation in which the technique of multi-voxel pattern analysis (MVPA) was used in conjunction with a priori selection of ROIs (excluding MI and SI), Filimon et al. (2015) reported that during both execution and motor imagery of reaching to visual targets, the BOLD response is registered across both ventral and dorsal premotor, and parietal areas.

It is readily apparent therefore that during both the execution of (upper limb) movements and motor imagery there is a high degree of overlap with those brain regions that are believed to exhibit increased activity in response to NMES (see preceding sections). As such, and the consequential changes in CSE that have been observed in some cases notwithstanding, it cannot be assumed that the M1 or S1 is the principal locus of the associative interactions that occur when NMES is delivered during either motor imagery tasks or during voluntary contractions. Indeed, it is clear that there are many potential loci. At present there is no empirical basis upon which to resolve the various possibilities. It is important to emphasise that during all motor tasks, the notionally "active" (i.e. in a BOLD registration context) brain regions constitute a network of functional connections (e.g. Simos et al., 2017), such that the task-relevant contribution of any specific region of interest cannot sensibly be considered in isolation (e.g. Anderson, 2008). In closing this section, it should also be noted that there have been very few randomised clinical trials (with appropriate blinding) in which the combined effects – on

function, of either voluntary contractions or motor imagery and NMES at motor threshold intensity have been evaluated.

Augmenting NMES at supra-motor threshold intensities

Empirical studies, in which the focus has been upon the combined effects of voluntary contractions and NMES delivered at intensities sufficient to generate functional levels of muscle tension (i.e. FES), have typically been undertaken in a clinical context. In many such instances the focus has been upon the promotion of movement capacity in stroke survivors. In light of the relatively large number of investigations of this kind that have been undertaken, several systematic reviews have been compiled. Although initial summaries of this nature (e.g. de Kroon et al., 2005) tended to suggest that clinical outcomes obtained for FES triggered by voluntary contraction (e.g. via EMG registration) were superior to those following FES alone, it was not generally the case that cumulative effect size estimates were obtained. In a more recent analysis that was restricted to the outcomes of randomized controlled trials (RCTs) engaging chronic stroke survivors, Yang et al. (2019) reported that the changes in function (as assessed by the Fugl–Meyer test) and activity (e.g. as assessed by the Action Research Arm Test) arising from "cyclic" FES (not triggered by voluntary contraction) and EMG-triggered FES could not be distinguished in terms of their quantified effects (although both were superior to control). In their systematic reviews, both Monte-Silva et al. (2019) and Nascimento et al. (2014) arrived at a same conclusion. In the single RCT of which we are aware (Wilson et al., 2016), that compared their relative efficacy in acute stroke survivors (< 6 months post-stroke), the improvements in Fugl-Meyer scores and the Arm Motor Ability Test, registered following an eight weeks intervention period did not differ between administrations of "cyclic" FES and EMG-triggered FES.

It is particularly notable therefore that when the delivery of stimulation at levels sufficient to produce joint displacement is triggered by contractions of the *opposite* (i.e. non-impaired) limb, improvements in clinical outcomes greater than those induced by NMES alone have been obtained in several trials. Knutson et al. (2016) employed with chronic stroke survivors a method whereby opening of the ipsilesional hand (monitored using an instrumented glove) modulated the intensity of stimulation applied to the finger (and wrist) extensors of the paretic hand, such that both hands opened synchronously. Fugl-Meyer scores and performance of the

Arm Motor Ability Test exhibited by following a 12 weeks intervention (≈10 hours of stimulation per week), were greater than those exhibited by patients who received cyclic FES (see also Knutson et al., 2012). In the context of a trial of three weeks duration (5 sessions per week; 20 min per session) engaging acute (≤3 post) stroke survivors, Shen et al. (2015) implemented a protocol whereby a wrist extension movement executed by the non-impaired limb triggered the delivery of stimulation (50 Hz; 200 μs pulse duration; intensity – up to that sufficient to produce full range wrist extension) to the impaired limb. In the NMES group, matched levels of stimulation were applied. Although both groups exhibited clinically relevant improvements in capacity (Fugl-Meyer assessment (FMA), the Hong Kong version of functional test for the hemiplegic upper extremity (FTHUE-HK) and active range of motion (AROM)), the magnitude of these changes was substantially greater in the group for whom NMES was triggered by movement of the opposite limb. In a more recent trial using the same methodology that engaged individuals within 15 days of stroke, the combination of routine rehabilitation with NMES triggered by movement of the ipsilesional limb, gave rise to better outcomes than routine rehabilitation combined with matched levels of electrical stimulation (Zheng et al., 2019).

The contrasting effects (relative to FES alone) of FES triggered by voluntary engagement of the same limb, and of FES triggered by movement of the opposite limb, might also be considered in light of the following. Systematic reviews of randomized or quasi-RCTs examining the effects of electrical stimulation delivered at intensities close to sensory threshold (e.g. TENS) on motor recovery following a stroke suggest that clinical outcomes are superior when it is combined with voluntary movement (e.g. Ikuno et al., 2012; Laufer et al., 2011). Taken together, these findings suggest that the functional impact of combining NMES with voluntary contraction depends on the intensity of the electrical stimulation. When it is insufficient to generate muscle contractions, additive effects are obtained. In contrast, when FES intensities are employed, the combined effects are comparable to those induced by FES alone. There are at least two possible accounts of this phenomenon. The first is that there is a ceiling effect. That is, if the effects of FES alone on the state of the motor network approach asymptotic levels, there may be little scope for endogenous activity generated in the context of voluntary contractions to promote additional restorative changes. The additive effects of contractions performed by the opposite limb however suggest that this explanation is insufficient. As described above, in both acute and chronic stroke survivors, when the delivery of FES is triggered by contractions of the ipsilesional limb, the benefits in term of clinical outcomes are greater than those brought about by FES alone. Similarly, when NMES at functional intensities is delivered during mental imagery

(triggered by very low "incidental" levels of EMG), improvements in function achieved by chronic stroke survivors are greater than those achieved using FES alone (Hong et al., 2012; You & Lee, 2013; cf. Park, 2019). There is no ceiling effect. An alternative possibility is that when voluntary contractions are combined with, or initiate (e.g. EMG-triggered FES), NMES delivered at intensities sufficient to produce joint displacement, there is a mismatch between the anticipated consequences of the efferent drive and the afferent feedback that arises from the combined effects of the voluntary contraction and stimulation driven recruitment of motoneurons (e.g. Iftime-Nielsen et al., 2012). As a corollary, the degree of any such "mismatch" is likely to depend not only on the intensity of the stimulation, but also on the degree to which the pattern of its application mimics natural muscle synergies. For example, it is known that in the context of tasks in which a large number of degrees of freedom (muscular and biomechnical) must be coordinated such as the formation of a grasp, if electrical stimulation (of the intrinsic and extrinsic flexor muscles) is imposed upon a voluntary contraction, maximal grip force diminishes (Boisgontier et al., 2010). In other tasks in which a relatively small number of muscles actuate a single joint (e.g. Barker et al., 2008, 2017), the discrepancy may be smaller. The assumption is that, to the degree to which a mismatch is present, further augmentation of the effects of NMES through associative mechanisms is precluded.

There have been relatively few studies in which imaging techniques have been used to compare patterns of brain activity arising when FES is delivered both in isolation, and in combination with voluntary contractions. Employing the method of near-infrared spectroscopy (NIRS) with healthy adults, Lin et al., (2016) reported that when NMES was delivered at a level sufficient to augment force output during isometric knee extension contractions, the O2 demand in the contralateral premotor cortices and SMA was greater than the sum of that observed during NMES alone and during voluntary movement alone. Oxy-Hb increases in "sensory-motor cortex" (relative to rest) of greater magnitude during EMG-triggered FES than for voluntary contractions alone (and FES alone) have also been reported for chronic stroke survivors (Hara et al., 2013). There are two further studies (of which we are aware) in which fMRI has been employed during upper limb movements (for the lower limb see Gandolla et al., 2014). Joa et al. (2012) reported that FES combined with voluntary wrist extension gave rise to a greater BOLD signal in ipsilateral cerebellum, contralateral MI ("primary central gyrus"), and SI ("post central gyrus") than during FES alone. Christensen and Grey (2013) noted that a larger BOLD response was registered during combined FES and voluntary (finger flexion-extension) movements than during voluntary movements alone in the following brain regions: superior temporal gyrus; supramarginal gyrus; insula; rolandic operculum and angular gyrus. There were no regions for

which a larger BOLD response was obtained during voluntary movements alone. Of particular interest in the present context is the observation that following administration of an ischaemic nerve block that removed sensory feedback (but preserved the capacity for voluntary movement), there were no differences in BOLD response between the two conditions (i.e. voluntary movement with and without FES). This pattern of outcomes supports the conjecture that the additional brain activity otherwise evident during combined voluntary movement and FES (i.e. compared to voluntary movement) is related to the integration of afferent feedback (i.e. relative to that anticipated on the basis of the efferent command). Gandolla et al. (2014) present a somewhat similar line of argument.

For completeness, we highlight briefly the finding that for both healthy adults and survivors of stroke, the excitability of corticospinal projections to muscles in receipt of FES is greater when it is combined with, or triggered by, voluntary contraction than when it is delivered in isolation (Barsi et al., 2008; Khaslavskaia & Sinkjaer, 2005; McGie et al., 2015; Stein et al., 2013). Although these data were not obtained in the context of the clinical trials described above, they do serve to emphasise an important point. Two variants of an intervention that can be distinguished clearly in terms of the changes in corticospinal excitability to which they give rise do not necessarily lead to different treatment outcomes when they are deployed over multiple sessions in a rehabilitation setting.

A reflection on the augmentation of NMES at supra-motor threshold intensities

There was a period during which it was widely assumed that NMES at supra-motor threshold intensities in combination with voluntary contractions – particularly when there was a contingent relation (as in EMG-triggered FES), gave rise to outcomes superior to those that could be achieved by NMES alone. In such circumstances it was natural to seek explanatory constructs. For example, De Kroon et al. (2005), in what was then a comprehensive review of the available data, hypothesised that there may be an additional cognitive element present in EMG-triggered NMES that is not a feature of NMES alone. In was suggested that an additional investment of mental resources and attention improves performance. Any explanation of this type should apply in equal measure to instances in which the effects of NMES delivered at lower (e.g. ≈ MT) intensities are accentuated by simultaneous voluntary contractions. The inconvenient truth is however that there is currently little by way of systematic evidence to

indicate that EMG (or movement) triggered FES is more efficacious than cyclic FES (which is not yoked to voluntary movement).

Clarac et al. (2009, page 367) remark that Wundt (1863) was among the first to note explicitly that passive movements and active movements differ in respect of their perceptual consequences. More particularly, they are distinguished by the relationship between efferent impulses and the referent response. Duchenne de Boulogne also promoted the concept of an "efferent sense" of central origin, which precedes a muscle contraction and is necessarily distinguishable from the sensation that arises as a result of the contraction (Clarac et al., 2009). On the basis of electrophysiological recordings obtained using modern methodologies, Lebedev et al. (1994) established that during self-initiated movement, activity in the primary somatosensory cortex becomes evident before the initiation of motor output. This was interpreted as preparation for receipt of the imminent changes in afferent inflow that will result from the movement (see also Nelson, 1996; Nelson et al., 1991). fMRI-based investigations in healthy volunteers further reveal that during active but not passive movement, a BOLD response in the Brodmann Area 2 subregion of S1 that is closely associated with that registered in premotor and supplementary motor areas, the parietal cortex and the cerebellum, in the absence of common mediation by area 3b (Cui et al., 2014). These and similar observations have been taken as evidence in support of the construct of efference copy – conceived of by von Holst and Mittelstaedt (1950) as the internal copy of an outgoing, action-producing "command" generated by the motor system. In an extension of the concept, it is proposed that the CNS instantiates forward internal models that utilise efference copy in order to anticipate the sensory consequences of an action (e.g. Miall & Wolpert, 1996).

The conventional contemporary line of thinking is that brain computer interfaces (BCI) that instantiate closed-loop control (i.e. brain-efference-change in muscle length/joint displacement-afference-brain) offer concordance between the efference copy and sensory consequences of an action. It is furthermore assumed that (repeated) concomitance of voluntarily generated brain activity, and movement-related afference (even if generated by artificial means) can promote neuroplastic adaptation and in some cases restoration of function (e.g. Jackson & Zimmermann, 2012). A key requirement in this regard is that there is a persistent causal relationship between the initiating endogenous neural activity (e.g. descending drive leading to recruitment of motoneurons – as registered by EMG) and the consequential endogenous neural activity (e.g. afference generated by EMG triggered FES). A further necessity is temporal congruency. That is, the delay between the initiating and consequential neural activity must be consistent with the

natural latency between the efference copy of a motor command and the reafferent sensory feedback (e.g. Leube et al., 2003). It has been highlighted recently that, even in circumstances in which the afference generated by EMG-triggered NMES is dominated by that which arises from direct activation of sensory axons (i.e. for intensities ≈ MT), conduction delays within the central and peripheral nervous systems dictate that stimulus-evoked activity is unlikely to be able alter the state of circuits in M1 sooner than 60 ms following the voluntary activity that generated the triggering EMG (Brown et al., 2016). In the event that the afference generated by NMES is dominated by reafference produced by the resulting contraction (i.e. such as with FES), and given electromechanical delays in the order of 40 ms (Cavanagh & Komi, 1979), the latency will be very much greater. If the FES is triggered by joint displacement (rather than by EMG), it will be longer still. We have emphasized in preceding sections that the induction of associative effects that can be observed at a systems level in humans does not require adherence to the defining characteristics of STDP (i.e. precisely circumscribed relative timing, with presynaptic firing occurring no more than 50 ms in advance of postsynaptic firing (Feldman, 2000)). Nonetheless, if the interval over which the contingent relationship is defined exceeds certain bounds, the effects of the association are likely to be diminished (Carson & Rankin, 2018). Indeed, even in STDP schemes, it is predicted that the magnitude of potentiation is inversely related to the delay between pre- and post-synaptic activity (Markram et al., 1997).

Such considerations raise the possibility that the failure of EMG triggered FES to bring about functional adaptations that are greater than those achieved by cyclic FES is attributable to the extended delay between initiation of the voluntary command (that generates the EMG), and the reafference produced by the resulting contraction. In the case of EMG triggered NMES delivered at intensities sufficient to activate only a relatively small proportion of motor axons (i.e. around motor threshold), in which the resulting afference is dominated by that which arises from direct activation of sensory axons, the delay following the voluntary command will be shorter. It is notable therefore that such protocols appear (at least based on evidence currently available) to more consistently yield positive changes in functional capacity that exceed those brought about by NMES alone.

General conclusions

It is widely held that the application of NMES in a rehabilitation setting can bring about effects that are both adaptive and restorative. Direct compensation for motor disability (i.e. the "adaptive" response) aside, assessment of the evidence gathered in contemporary systematic reviews and meta-analyses suggests that NMES delivered at levels sufficient to generate a fused contractions (Howlett et al., 2015; Monte-Silva et al., 2019; Nascimento et al., 2014; Yang et al., 2019) is capable of promoting restorative changes in a number of neurological disorders that are at least equivalent to those brought about by conventional therapy. It also appears to have a positive effect on the functional status of older adults who do not have neurological conditions (Langeard et al., 2017). There is preliminary evidence that it may elevate serum levels of brain-derived neurotrophic factor (BDNF) – a neurotrophin that plays a well documented role in the expression of neural plasticity (Kimura et al., 2019).

With respect to lower levels of stimulation (e.g. using intensities in the vicinity of motor threshold) the picture is less clear. This is partly due to the fact that the widely heterogeneous (in terms of stimulation parameters and target muscles) nature of the studies that have been conducted, generally precludes their combination in meta-analyses (Chipchase et al., 2011a; Wattchow et al., 2018). Given conflicting evidence concerning the efficacy of stimulation delivered at intensities that evokes paresthesia but generally no motor response (Grant et al., 2018), a restorative effect of low-level NMES cannot necessarily be assumed. Nonetheless, on the basis of a small scale meta-analysis of studies restricted to those that adopted a variant of the stimulation protocol described by Ridding et al. (2000) (i.e. ulnar, median or radial nerve stimulation (10 Hz, 1 ms pulse width, duty cycle 1 s, 500 ms on–500 ms off) for period of two hours), it can be inferred that NMES at an intensity close to MT may improve upper limb motor function in (chronic) stroke survivors (Conforto et al., 2018). Although not yet supported by sufficient evidence derived from RCTs, there are some indications that adjuvant techniques, such as voluntary contractions; and mental imagery may further promote restorative responses to NMES delivered at around motor threshold.

That which is common to all forms of NMES is the absence of a clear understanding of the mechanisms that mediate its influence on motor function. Evidence derived using a range of methodologies both in humans and non-human primates indicates clearly that NMES alters the state of circuits in many parts of the brain, often extending beyond the classical sensory and

motor networks. An increase in the excitability of corticospinal projections from primary motor cortex (generally assayed using TMS) is a pervasive feature of the immediate physiological response to NMES. Nonetheless, there is presently no indication of which we are aware that the increases in CSE brought about by NMES are instrumentally related to any improvements in function. We base this conclusion on the fact that there have been no reports of statistical associations between alterations in CSE and motor function following the administration of NMES. In addition, there are interventions that can be distinguished in terms of the changes in CSE to which they give rise, that do not differ with respect to the changes in movement function that they bring about. This analysis highlights the more general concern (e.g. Carson et al., 2016) that TMS is perhaps not the best tool for the purpose of discriminating neural mechanisms that mediate the restorative effects of NMES (Veldman et al., 2016).

The augmentation of the effects of NMES that occurs when it is combined with adjuvant techniques such as voluntary contractions and mental imagery bears the hallmarks of associative plasticity. As we have noted elsewhere (Carson & Kennedy, 2013) the induction of associative effects that can be observed at a systems level in humans does not necessarily require protocols that adhere to the defining characteristics of STDP. The appeal to constructs that have been elaborated in the context of reduced slice or animal preparations is however seductive. It can also be reinforced (perhaps inadvertently) by the identification at a systems level of features that bear a resemblance to those that have been studied and manipulated in vitro. It appears that in closed loop control – such as EMG-triggered FES, temporal congruency of the initiating (i.e. efferent) and consequential (i.e. afferent) endogenous neural activity is critical for the induction of restorative effects. This should not however be taken as reflecting adherence to STDP rules as they apply to individual presynaptic and postsynaptic neurons. In seeking to provide a deeper understanding of the mechanisms that mediate the effects of NMES, it might also be useful to consider the influence of the integrative properties of the brain (e.g. cortical “rhythms”) that only emerge as a consequence of its topological network properties, and the coupling of individual neural (and non-neural) elements to which this architecture gives rise (e.g. Guggenberger et al., 2018; Kraus et al., 2018). There is certainly also scope for greater consideration of the potential role of subcortical structures such as the thalamus in mediating the changes in functional capacity that can be induced by NMES (e.g. Kimura et al., 1999; see also Veldman et al., 2018).

References

Allison, T., McCarthy, G., Wood, C.C., Darcey, T.M., Spencer, D.D., Williamson, P.D. (1989a). Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. J Neurophysiol 62, 694–710.

Allison, T., McCarthy, G., Wood, C.C., Williamson, P.D., Spencer, D.D. (1989b). Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. J Neurophysiol 62, 711–722. Allison, T., McCarthy, G., Wood, C. C., & Jones, S. J. (1991). Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. A review of scalp and intracranial recordings. *Brain*, *114 (Pt 6)*, 2465–2503.

Allison, T., McCarthy, G., & Wood, C. C. (1992). The relationship between human long-latency somatosensory evoked potentials recorded from the cortical surface and from the scalp. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 84(4), 301-314.

Anderson, M. L. (2008). Circuit sharing and the implementation of intelligent systems. Connection Science, 20(4), 239-251.

Andrews, R. K., Schabrun, S. M., Ridding, M. C., Galea, M. P., Hodges, P. W., & Chipchase, L. S. (2013). The effect of electrical stimulation on corticospinal excitability is dependent on application duration: a same subject pre-post test design. *Journal of Neuroengineering and Rehabilitation*, *10*, 51. doi:10.1186/1743-0003-10-51

Andrews, R. K., Schabrun, S. M., Ridding, M. C., Galea, M. P., Hodges, P. W., & Chipchase, L. S. (2013). The effect of electrical stimulation on corticospinal excitability is dependent on application duration: a same subject pre-post test design. *Journal of Neuroengineering and Rehabilitation*, *10*, 51. doi:10.1186/1743-0003-10-51

Arienzo D, Babiloni C, Ferretti A, Caulo M, Del Gratta C, Tartaro A, Rossini PM, Romani GL (2006): Somatotopy of anterior cingulate cortex (ACC) and supplementary motor area (SMA) for electric stimulation of the median and tibial nerves: An fMRI study. *Neuroimage* 33, 700–705.

Avanzini, P., Abdollahi, R. O., Sartori, I., Caruana, F., Pelliccia, V., Casaceli, G., ... & Orban, G. A. (2016). Four-dimensional maps of the human somatosensory system. Proceedings of the National Academy of Sciences, 113(13), E1936-E1943.

Avanzini, P., Pelliccia, V., Russo, G. L., Orban, G. A., & Rizzolatti, G. (2018). Multiple time courses of somatosensory responses in human cortex. NeuroImage, 169, 212-226.

Avendaño, C., Isla, A. J., & Rausell, E. (1992). Area 3a in the cat II. Projections to the motor cortex and their relations to other corticocortical connections. Journal of Comparative Neurology, 321(3), 373-386.

Backes, W. H., Mess, W. H., van Kranen-Mastenbroek, V., & Reulen, J. P. H. (2000). Somatosensory cortex responses to median nerve stimulation: fMRI effects of current amplitude and selective attention. Clinical neurophysiology, 111(10), 1738-1744.

Barker, R. N., Brauer, S. G., Barry, B. K., Gill, T. J., & Carson, R. G. (2012). Training-induced modifications of corticospinal reactivity in severely affected stroke survivors. *Experimental brain research*, *221*(2), 211-221.

Barker, R. N., Brauer, S. G., & Carson, R. G. (2008). Training of reaching in stroke survivors with severe and chronic upper limb paresis using a novel nonrobotic device: a randomized clinical trial. Stroke, 39(6), 1800-1807.

Barker, R. N., Hayward, K. S., Carson, R. G., Lloyd, D., & Brauer, S. G. (2017). SMART Arm Training With Outcome-Triggered Electrical Stimulation in Subacute Stroke Survivors With Severe Arm Disability: A Randomized Controlled Trial. *Neurorehabilitation and neural repair*, *31*(12), 1005-1016.

Barsi, G. I., Popovic, D. B., Tarkka, I. M., Sinkjær, T., & Grey, M. J. (2008). Cortical excitability changes following grasping exercise augmented with electrical stimulation. *Experimental brain research*, *191*(1), 57-66.

Berghuis, K. M., Semmler, J. G., Opie, G. M., Post, A. K., & Hortobágyi, T. (2017). Age-related changes in corticospinal excitability and intracortical inhibition after upper extremity motor learning: a systematic review and meta-analysis. *Neurobiology of aging*, *55*, 61-71.

Bergquist, A. J., Clair, J. M., Lagerquist, O., Mang, C. S., Okuma, Y., & Collins, D. F. (2011). Neuromuscular electrical stimulation: implications of the electrically evoked sensory volley. *European journal of applied physiology*, *111*(10), 2409.

Ben Taib, N.O., Nordeyn, O.B.T., Manto, M., Mario, M., Pandolfo, M., Massimo, P., Brotchi, J., Jacques, B. (2005). Hemicerebellectomy blocks the enhancement of cortical motor output associated with repetitive somatosensory stimulation in the rat. The Journal of Physiology 567, 293–300. doi:10.1113/jphysiol.2005.088229

Bi, G. Q., & Poo, M. M. (1998). Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. Journal of neuroscience, 18(24), 10464-10472.

Blickenstorfer, A., Kleiser, R., Keller, T., Keisker, B., Meyer, M., Riener, R., & Kollias, S. (2009). Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. *Human Brain Mapping*, *30*(3), 963–975. doi:10.1002/hbm.20559

Blickenstorfer, A., Kleiser, R., Keller, T., Keisker, B., Meyer, M., Riener, R., & Kollias, S. (2009). Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. *Human brain mapping*, *30*(3), 963-975.

Boakye, M., Huckins, S. C., Szeverenyi, N. M., Taskey, B. I., & Hodge, C. J. (2000). Functional magnetic resonance imaging of somatosensory cortex activity produced by electrical stimulation of the median nerve or tactile stimulation of the index finger. Journal of neurosurgery, 93(5), 774-783.

Boisgontier, M., Vuillerme, N., & Iversen, M. (2010). Superimposed electrical stimulation decreases maximal grip force. The Journal of sports medicine and physical fitness, 50(2), 152-8.

Brown, K. I., Williams, E. R., de Carvalho, F., & Baker, S. N. (2016). Plastic changes in human motor cortical output induced by random but not closed-loop peripheral stimulation: the curse of causality. Frontiers in human neuroscience, 10, 590.

Burton, H., Fabri, M. (1995). Ipsilateral intracortical connections of physiologically defined cutaneous representations in areas 3b and 1 of macaque monkeys: projections in the vicinity of the central sulcus. J Comp Neurol 355, 508–538. doi:10.1002/cne.903550404

Burton, H., & Kopf, E. M. (1984). Ipsilateral cortical connections from the second and fourth somatic sensory areas in the cat. Journal of Comparative Neurology, 225(4), 527-553.

Cabric, M., & Appell, H. J. (1987). Effect of electrical stimulation of high and low frequency on maximum isometric force and some morphological characteristics in men. *International journal of sports medicine*, *8*(04), 256-260.

Carson, R. G., & Kennedy, N. C. (2013). Modulation of human corticospinal excitability by paired associative stimulation. Frontiers in human neuroscience, 7, 823.

Carson, R. G., Nelson, B. D., Buick, A. R., Carroll, T. J., Kennedy, N. C., & Mac Cann, R. (2013). Characterizing changes in the excitability of corticospinal projections to proximal muscles of the upper limb. *Brain stimulation*, *6*(5), 760-768.

Carson, R. G., & Rankin, M. L. (2018). Shaping the effects of associative brain stimulation by contractions of the opposite limb. Frontiers in psychology, 9, 2249.

Carson, R. G., Ruddy, K. L., & McNickle, E. (2016). What Do TMS-Evoked Motor Potentials Tell Us About Motor Learning? In Progress in Motor Control (pp. 143-157). Springer, Cham.

Carvalho, S., French, M., Thibaut, A., Lima, W., Simis, M., Leite, J., & Fregni, F. (2018). Median nerve stimulation induced motor learning in healthy adults: A study of timing of stimulation and type of learning. *European Journal of Neuroscience*, *48*(1), 1667-1679.

Caspers, S., Zilles, K., Laird, A. R., & Eickhoff, S. B. (2010). ALE meta-analysis of action observation and imitation in the human brain. Neuroimage, 50(3), 1148-1167.

Cavanagh, P. R., & Komi, P. V. (1979). Electromechanical delay in human skeletal muscle under concentric and eccentric contractions. European journal of applied physiology and occupational physiology, 42(3), 159-163.

Charlton, C. S., Ridding, M. C., Thompson, P. D., & Miles, T. S. (2003). Prolonged peripheral nerve stimulation induces persistent changes in excitability of human motor cortex. Journal of the neurological sciences, 208(1-2), 79-85.

Chipchase, L. S., Schabrun, S. M., & Hodges, P. W. (2011a). Peripheral electrical stimulation to induce cortical plasticity: a systematic review of stimulus parameters. *Clin Neurophysiol*, *122*(3), 456–463. doi:10.1016/j.clinph.2010.07.025

Chipchase, L. S., Schabrun, S. M., & Hodges, P. W. (2011b). Corticospinal excitability is dependent on the parameters of peripheral electric stimulation: a preliminary study. *Archives of Physical Medicine and Rehabilitation*, *92*(9), 1423–1430. doi:10.1016/j.apmr.2011.01.011

Chipchase, L. S., Schabrun, S. M., & Hodges, P. W. (2011b). Corticospinal excitability is dependent on the parameters of peripheral electric stimulation: a preliminary study. *Archives of Physical Medicine and Rehabilitation*, *92*(9), 1423–1430. doi:10.1016/j.apmr.2011.01.011

Christensen, M. S., & Grey, M. J. (2013). Modulation of proprioceptive feedback during functional electrical stimulation: an fMRI study. *European Journal of Neuroscience*, *37*(11), 1766-1778.

Christova, M., Rafolt, D., Golaszewski, S., Nardone, R., & Gallasch, E. (2014). Electrical stimulation during skill training with a therapeutic glove enhances the induction of cortical plasticity and has a positive effect on motor memory. *Behavioural brain research*, *270*, 171-178.

Clarac, F., Massion, J., & Smith, A. M. (2009). Duchenne, Charcot and Babinski, three neurologists of La Salpetrière Hospital, and their contribution to concepts of the central organization of motor synergy. *Journal of Physiology, Paris*, 103, 361–376.

Collins, D. F. (2007). Central contributions to contractions evoked by tetanic neuromuscular electrical stimulation. *Exercise and sport sciences reviews*, *35*(3), 102-109.

Conforto, A. B., dos Anjos, S. M., Bernardo, W. M., Silva, A. A. D., Conti, J., Machado, A. G., & Cohen, L. G. (2018). Repetitive Peripheral Sensory Stimulation and Upper Limb Performance in Stroke: A Systematic Review and Meta-analysis. Neurorehabilitation and neural repair, 32(10), 863-871.

Cooke, S. F., & Bliss, T. V. P. (2006). Plasticity in the human central nervous system. Brain, 129(7), 1659-1673.

Cui, F., Arnstein, D., Thomas, R. M., Maurits, N. M., Keysers, C., & Gazzola, V. (2014). Functional magnetic resonance imaging connectivity analyses reveal efference-copy to primary somatosensory area, BA2. *PLoS One*, *9*(1), e84367.

Dan, Y., & Poo, M. M. (2006). Spike timing-dependent plasticity: from synapse to perception. *Physiological reviews*, *86*(3), 1033-1048.

Darian‐Smith, C., & Darian‐Smith, I. (1993). Thalamic projections to areas 3a, 3b, and 4 in the sensorimotor cortex of the mature and infant macaque monkey. Journal of Comparative Neurology, 335(2), 173-199.

Darian-Smith, C., Darian-Smith, I., Burman, K., Ratcliffe, N. (1993). Ipsilateral cortical projections to areas 3a, 3b, and 4 in the macaque monkey. J Comp Neurol 335, 200–213. doi:10.1002/cne.903350205

Dawson, G. D. (1956). The relative excitability and conduction velocity of sensory and motor nerve fibres in man. *The Journal of Physiology*, *131*(2), 436–451.

Debru, A. (2006). The power of torpedo fish as a pathological model to the understanding of nervous transmission in Antiquity. *Comptes Rendus Biologies*, *329*(5-6), 298–302. doi:10.1016/j.crvi.2006.03.001

Deletis, V., Schild, J. H., Berić, A., & Dimitrijević, M. R. (1992). Facilitation of motor evoked potentials by somatosensory afferent stimulation. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 85(5), 302-310.

Del Gratta, C., Della Penna, S., Tartaro, A., Ferretti, A., Torquati, K., Bonomo, L., ... & Rossini, P. M. (2000). Topographic organization of the human primary and secondary somatosensory areas: an fMRI study. Neuroreport, 11(9), 2035-2043.

Del Vecchio, M., Caruana, F., Sartori, I., Pelliccia, V., Russo, G. L., Rizzolatti, G., & Avanzini, P. (2019). Ipsilateral somatosensory responses in humans: the tonic activity of SII and posterior insular cortex. *Brain Structure and Function*, *224*(1), 9-18.

Desmedt, J. E., & Ozaki, I. (1991). SEPs to finger joint input lack the N20-P20 response that is evoked by tactile inputs: contrast between cortical generators in areas 3b and 2 in humans. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 80(6), 513-521.

Devanne, H., Degardin, A., Tyvaert, L., Bocquillon, P., Houdayer, E., Manceaux, A., ... & Cassim, F. (2009). Afferent‐induced facilitation of primary motor cortex excitability in the region controlling hand muscles in humans. European journal of neuroscience, 30(3), 439-448.

Edwards, D. J., Dipietro, L., Demirtas-Tatlidede, A., Medeiros, A. H., Thickbroom, G. W., Mastaglia, F. L., ... & Pascual-Leone, A. (2014). Movement-generated afference paired with

transcranial magnetic stimulation: an associative stimulation paradigm. Journal of neuroengineering and rehabilitation, 11(1), 31.

Feldman, D. E. (2000). Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. Neuron, 27(1), 45-56.

Feldman, D. E. (2012). The spike-timing dependence of plasticity. Neuron, 75(4), 556-571.

Filimon, F., Rieth, C. A., Sereno, M. I., & Cottrell, G. W. (2014). Observed, executed, and imagined action representations can be decoded from ventral and dorsal areas. *Cerebral Cortex*, *25*(9), 3144-3158.

Finger, S., & Piccolino, M. (2011). The shocking history of electric fishes: from ancient epochs to the birth of modern neurophysiology. Oxford University Press.

Forss, N., Hari, R., Salmelin, R., Ahonen, A., Hämäläinen, M., Kajola, M., ... & Simola, J. (1994). Activation of the human posterior parietal cortex by median nerve stimulation. Experimental brain research, 99(2), 309-315.

Francis, S., Lin, X., Aboushoushah, S., White, T. P., Phillips, M., Bowtell, R., & Constantinescu, C. S. (2009). fMRI analysis of active, passive and electrically stimulated ankle dorsiflexion. Neuroimage, 44(2), 469-479.

Gandevia, S. C., & Burke, D. (1990). Projection of thenar muscle afferents to frontal and parietal cortex of human subjects. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 77(5), 353-361.

Gandolla, M., Ferrante, S., Molteni, F., Guanziroli, E., Frattini, T., Martegani, A., ... & Ward, N. S. (2014). Re-thinking the role of motor cortex: context-sensitive motor outputs?. *Neuroimage*, *91*, 366-374.

Gatica Tossi, M.A., Lillemeier, A.-S., Dinse, H.R. (2013). Influence of stimulation intensity on paired-pulse suppression of human median nerve somatosensory evoked potentials. 24, 451–456. doi:10.1097/WNR.0b013e3283616378

Ghosh, S., Brinkman, C., & Porter, R. (1987). A quantitative study of the distribution of neurons projecting to the precentral motor cortex in the monkey (M. fascicularis). Journal of Comparative Neurology, 259(3), 424-444.

Golaszewski, S. M., Bergmann, J., Christova, M., Kunz, A. B., Kronbichler, M., Rafolt, D., et al. (2012). Modulation of motor cortex excitability by different levels of whole-hand afferent electrical stimulation. *Clin Neurophysiol*, *123*(1), 193–199. doi:10.1016/j.clinph.2011.06.010

Golaszewski, S. M., Siedentopf, C. M., Koppelstaetter, F., Rhomberg, P., Guendisch, G. M., Schlager, A., et al. (2004). Modulatory effects on human sensorimotor cortex by whole-hand afferent electrical stimulation. *Neurology*, *62*(12), 2262–2269.

Grant, G., Landgren, S., & Silfvenius, H. (1975). Columnar distribution of U-fibres from the postcruciate cerebral projection area of the cat's group I muscle afferents. Experimental brain research, 24(1), 57-74.

Grant, V. M., Gibson, A., & Shields, N. (2018). Somatosensory stimulation to improve hand and upper limb function after stroke—a systematic review with meta-analyses. Topics in stroke rehabilitation, 25(2), 150-160.

Grezes, J., & Decety, J. (2001). Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta‐analysis. Human brain mapping, 12(1), 1-19.

Guggenberger, R., Kraus, D., Naros, G., Leão, M. T., Ziemann, U., & Gharabaghi, A. (2018). Extended enhancement of corticospinal connectivity with concurrent cortical and peripheral stimulation controlled by sensorimotor desynchronization. Brain stimulation, 11(6), 1331-1335.

Gunther, Robert William Theodore, and John Goodyer. *The Greek Herbal of Dioscorides, Illustrated by a Byzantine AD 512; Englished by John Goodyer AD 1655; Edited and First Printed AD 1933*. Hafner Publishing Company, 1959.

Halonen, J. P., Jones, S., & Shawkat, F. (1988). Contribution of cutaneous and muscle afferent fibres to cortical SEPs following median and radial nerve stimulation in man. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 71(5), 331-335.

Han, B. S., Jang, S. H., Chang, Y., Byun, W. M., Lim, S. K., & Kang, D. S. (2003). Functional magnetic resonance image finding of cortical activation by neuromuscular electrical stimulation on wrist extensor muscles. *American Journal of Physical Medicine & Rehabilitation /*

Association of Academic Physiatrists, *82*(1), 17–20. doi:10.1097/01.PHM.0000043516.69441.15

Hara, Y., Obayashi, S., Tsujiuchi, K., & Muraoka, Y. (2013). The effects of electromyography-controlled functional electrical stimulation on upper extremity function and cortical perfusion in stroke patients. *Clinical Neurophysiology*, *124*(10), 2008-2015.

Hardwick, R. M., Caspers, S., Eickhoff, S. B., & Swinnen, S. P. (2018). Neural correlates of action: Comparing meta-analyses of imagery, observation, and execution. Neuroscience & Biobehavioral Reviews.

Hari, R., Reinikainen, K., Kaukoranta, E., Hämäläinen, M., Ilmoniemi, R., Penttinen, A., ... & Teszner, D. (1984). Somatosensory evoked cerebral magnetic fields from SI and SII in man. Electroencephalography and clinical Neurophysiology, 57(3), 254-263.

Heath, C. J., Hore, J., & Phillips, C. G. (1976). Inputs from low threshold muscle and cutaneous afferents of hand and forearm to areas 3a and 3b of baboon's cerebral cortex. The Journal of physiology, 257(1), 199-227.

Hebb, D. O. (2005). The organization of behavior: A neuropsychological theory. Psychology Press.

Herman, D., Kang, R., MacGillis, M., Zarzecki, P. (1985). Responses of cat motor cortex neurons to cortico-cortical and somatosensory inputs. Exp Brain Res 57, 598–604.

Hétu, S., Grégoire, M., Saimpont, A., Coll, M. P., Eugène, F., Michon, P. E., & Jackson, P. L. (2013). The neural network of motor imagery: an ALE meta-analysis. *Neuroscience & Biobehavioral Reviews*, *37*(5), 930-949.

von Holst E., Mittelstaedt H. (1950). The reafference principle. Interaction between the central nervous system and the periphery. In Selected Papers of Erich von Holst: The Behavioural Physiology of Animals and Man, London: Methuen. (From German) 1 : 1 39-73.

Hong, I. K., Choi, J. B., & Lee, J. H. (2012). Cortical changes after mental imagery training combined with electromyography-triggered electrical stimulation in patients with chronic stroke. *Stroke*, *43*(9), 2506-2509.

Hore, J., Preston, J. B., & Cheney, P. D. (1976). Responses of cortical neurons (areas 3a and 4) to ramp stretch of hindlimb muscles in the baboon. Journal of Neurophysiology, 39(3), 484-500.

Hortobágyi, T., Scott, K., Lambert, J., Hamilton, G., & Tracy, J. (1999). Cross-education of muscle strength is greater with stimulated than voluntary contractions. *Motor control*, *3*(2), 205-219.

Hortobágyi, T., & Maffiuletti, N. A. (2011). Neural adaptations to electrical stimulation strength training. European journal of applied physiology, 111(10), 2439-2449.

Hoseini, N., Munoz-Rubke, F., Wan, H. Y., & Block, H. J. (2016). Combined motor point associative stimulation (MPAS) and transcranial direct current stimulation (tDCS) improves plateaued manual dexterity performance. *Neuroscience letters*, *633*, 134-140.

Howlett, O. A., Lannin, N. A., Ada, L., & McKinstry, C. (2015). Functional electrical stimulation improves activity after stroke: a systematic review with meta-analysis. *Archives of physical medicine and rehabilitation*, *96*(5), 934-943.

Huang, L. P., Zhou, S., Lu, Z., Tian, Q., Li, X., Cao, L. J., ... & Wang, H. (2007). Bilateral effect of unilateral electroacupuncture on muscle strength. *The Journal of Alternative and Complementary Medicine*, *13*(5), 539-546.

Huerta, M. F., & Pons, T. P. (1990). Primary motor cortex receives input from area 3a in macaques. Brain research, 537(1-2), 367-371.

Huffman, K. J., & Krubitzer, L. (2001a). Thalamo‐cortical connections of areas 3a and M1 in marmoset monkeys. Journal of Comparative Neurology, 435(3), 291-310.

Huffman, K.J., Krubitzer, L. (2001b). Area 3a: topographic organization and cortical connections in marmoset monkeys. Cereb Cortex 11, 849–867.

Iftime-Nielsen, S. D., Christensen, M. S., Vingborg, R. J., Sinkjaer, T., Roepstorff, A., & Grey, M. J. (2012). Interaction of electrical stimulation and voluntary hand movement in SII and the cerebellum during simulated therapeutic functional electrical stimulation in healthy adults. *Human Brain Mapping*, *33*(1), 40–49. doi:10.1002/hbm.21191

Ikuno, K., Matsuo, A., & Shomoto, K. (2012). Sensory electrical stimulation for recovery of hand and arm function in stroke patients: a review of the literature. *J Nov Physiother S*, *1*, 2.

Ikuno, K., Matsuo, A., & Shomoto, K. (2012). Sensory electrical stimulation for recovery of hand and arm function in stroke patients: a review of the literature. *J Nov Physiother S*, *1*, 2

Isaacson, Walter. *Benjamin Franklin: An American Life*. Simon and Schuster, 2003.

Jaberzadeh, S., Mezhov, D., & Zoghi, M. (2017). What is the Effect of Motor Level Peripheral Electrical Stimulation on Corticospinal Excitability and Functional Outcome Measures in Both Healthy Participants and those with Neurological Disorders? A Systematic Review and Meta-Analysis. *Journal of Clinical Physiotherapy Research*, *2*(1), 1-14.

Jackson, A., & Zimmermann, J. B. (2012). Neural interfaces for the brain and spinal cord—restoring motor function. Nature Reviews Neurology, 8(12), 690.

Joa, K.-L., Han, Y.-H., Mun, C.-W., Son, B.-K., Lee, C.-H., Shin, Y.-B., et al. (2012). Evaluation of the brain activation induced by functional electrical stimulation and voluntary contraction using functional magnetic resonance imaging. *Journal of Neuroengineering and Rehabilitation*, *9*, 48. doi:10.1186/1743-0003-9-48

Jochumsen, M., Cremoux, S., Robinault, L., Lauber, J., Arceo, J., Navid, M., ... & Niazi, I. (2018). Investigation of Optimal Afferent Feedback Modality for Inducing Neural Plasticity with A Self-Paced Brain-Computer Interface. *Sensors*, *18*(11), 3761.

Jochumsen, M., Niazi, I. K., Signal, N., Nedergaard, R. W., Holt, K., Haavik, H., & Taylor, D. (2016). Pairing voluntary movement and muscle-located electrical stimulation increases cortical excitability. *Frontiers in human neuroscience*, *10*, 482.

Jones, E. G., Coulter, J. D., & Hendry, S. H. C. (1978). Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *Journal of Comparative Neurology*, *181*(2), 291-347.

Jones, E. G., & Porter, R. (1980). What is area 3a?. *Brain Research Reviews*, *2*(1-3), 1-43.

Jones, E. G., Wise, S. P., & Coulter, J. D. (1979). Differential thalamic relationships of sensory‐motor and parietal cortical fields in monkeys. Journal of Comparative Neurology, 183(4), 833-881.

Kaas, J. H. (1983). What, if anything, is SI? Organization of first somatosensory area of cortex. Physiological Reviews, 63(1), 206-231.

Kaas, J.H., Pons, T.P. (1988). The somatosensory system of primates. In: Steklis, H.D., Erwin, J.M. (Eds.), Neurosciences: Comparative Primate Biology. New York, pp. 421–468.

Kadri, M. A., Noé, F., Nouar, M. B., & Paillard, T. (2017). Effects of training programs based on ipsilateral voluntary and stimulated contractions on muscle strength and monopedal postural control of the contralateral limb. *European journal of applied physiology*, *117*(9), 1799-1806.

Kaelin‐Lang, A., Luft, A. R., Sawaki, L., Burstein, A. H., Sohn, Y. H., & Cohen, L. G. (2002). Modulation of human corticomotor excitability by somatosensory input. The Journal of physiology, 540(2), 623-633.

Karhu, J., & Tesche, C. D. (1999). Simultaneous early processing of sensory input in human primary (SI) and secondary (SII) somatosensory cortices. Journal of Neurophysiology, 81(5), 2017-2025.

Kawamura, T., Nakasato, N., Seki, K., Kanno, A., Fujita, S., Fujiwara, S., & Yoshimoto, T. (1996). Neuromagnetic evidence of pre-and post-central cortical sources of somatosensory evoked responses. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 100(1), 44-50.

Kellaway, P. (1946). The part played by electric fish in the early history of bioelectricity and electrotherapy. *Bulletin of the History of Medicine*, *20*(2), 112–137.

Khademi, F., Royter, V., & Gharabaghi, A. (2019). State-dependent brain stimulation: Power or phase?. *Brain stimulation*, *12*(2), 296-299.

Khaslavskaia, S., and Sinkjaer, T. (2005). Motor cortex excitability following repetitive electrical stimulation of the common peroneal nerve depends on the voluntary drive. *Exp. Brain Res.* 162, 497–502. doi: 10.1007/s00221-004-2153-1

Kimura, A., Grigor'yan, R., & Asanuma, H. (1999). Long-term increases in neuronal activity in the motor cortex evoked by simultaneous stimulation of the thalamus and somatosensory cortex in cats. *Neuroscience and behavioral physiology*, *29*(4), 475-481.

Kimura, T., Kaneko, F., Iwamoto, E., Saitoh, S., & Yamada, T. (2019). Neuromuscular electrical stimulation increases serum brain-derived neurotrophic factor in humans. Experimental brain research, 237(1), 47-56.

Klingner, C. M., Huonker, R., Flemming, S., Hasler, C., Brodoehl, S., Preul, C., ... & Witte, O. W. (2011). Functional deactivations: multiple ipsilateral brain areas engaged in the processing of somatosensory information. *Human brain mapping*, *32*(1), 127-140.

Klostermann, F., Wahl, M., Schomann, J., Kupsch, A., Curio, G., & Marzinzik, F. (2009). Thalamo‐cortical processing of near‐threshold somatosensory stimuli in humans. European Journal of Neuroscience, 30(9), 1815-1822.

Knutson, J. S., Gunzler, D. D., Wilson, R. D., & Chae, J. (2016). Contralaterally controlled functional electrical stimulation improves hand dexterity in chronic hemiparesis: a randomized trial. *Stroke*, *47*(10), 2596-2602.

Knutson, J. S., Harley, M. Y., Hisel, T. Z., Hogan, S. D., Maloney, M. M., & Chae, J. (2012). Contralaterally controlled functional electrical stimulation for upper extremity hemiplegia: an early-phase randomized clinical trial in subacute stroke patients. *Neurorehabilitation and neural repair*, *26*(3), 239-246.

Korvenoja, A., Huttunen, J., Salli, E., Pohjonen, H., Martinkauppi, S., Palva, J. M., ... & Aronen, H. J. (1999). Activation of multiple cortical areas in response to somatosensory stimulation: combined magnetoencephalographic and functional magnetic resonance imaging. Human brain mapping, 8(1), 13-27.

Kosar, E., Waters, R.S., Tsukahara, N., Asanuma, H. (1985). Anatomical and physiological properties of the projection from the sensory cortex to the motor cortex in normal cats: the difference between corticocortical and thalamocortical projections. Brain Research, 345, 68–78.

Kraus, D., Naros, G., Guggenberger, R., Leão, M. T., Ziemann, U., & Gharabaghi, A. (2018). Recruitment of additional corticospinal pathways in the human brain with state-dependent paired associative stimulation. *Journal of Neuroscience*, *38*(6), 1396-1407.

Krause, T., Kurth, R., Ruben, J., Schwiemann, J., Villringer, K., Deuchert, M., ... & Villringer, A. (2001). Representational overlap of adjacent fingers in multiple areas of human primary somatosensory cortex depends on electrical stimulus intensity: an fMRI study. *Brain research*, *899*(1-2), 36-46.

de Kroon, J. R., IJzerman, M. J., Chae, J., Lankhorst, G. J., & Zilvold, G. (2005). Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke.

Kuehn, E., Dinse, J., Jakobsen, E., Long, X., Schäfer, A., Bazin, P. L., ... & Margulies, D. S. (2017). Body topography parcellates human sensory and motor cortex. *Cerebral Cortex*, *27*(7), 3790-3805.

Kunesch, E., Knecht, S., Schnitzler, A., Tyercha, C., Schmitz, F., & Freund, H. J. (1995). Somatosensory evoked potentials elicited by intraneural microstimulation of afferent nerve fibers. *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*, *12*(5), 476-487.

Lakhani, B., Vette, A. H., Mansfield, A., Miyasike-daSilva, V., & McIlroy, W. E. (2012). Electrophysiological correlates of changes in reaction time based on stimulus intensity. PloS one, 7(5), e36407.

Langeard, A., Bigot, L., Chastan, N., & Gauthier, A. (2017). Does neuromuscular electrical stimulation training of the lower limb have functional effects on the elderly?: A systematic review. Experimental gerontology, 91, 88-98.

Laufer, Y., & Elboim-Gabyzon, M. (2011). Does sensory transcutaneous electrical stimulation enhance motor recovery following a stroke? A systematic review. *Neurorehabilitation and neural repair*, *25*(9), 799-809.

Lebedev, M. A., Denton, J. M., & Nelson, R. J. (1994). Vibration-entrained and premovement activity in monkey primary somatosensory cortex. *Journal of Neurophysiology*, *72*(4), 1654-1673.

Leube, D. T., Knoblich, G., Erb, M., Grodd, W., Bartels, M., & Kircher, T. T. (2003). The neural correlates of perceiving one's own movements. *Neuroimage*, *20*(4), 2084-2090.

Levy, W. B., & Steward, O. (1983). Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. Neuroscience, 8(4), 791-797.

Lewis, G. N., Byblow, W. D., & Carson, R. G. (2001). Phasic modulation of corticomotor excitability during passive movement of the upper limb: effects of movement frequency

and muscle specificity. *Brain Research*, *900*(2), 282–294. doi:10.1016/S0006-8993(01)02369-1

Liberson, W. T. (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Arch Phys Med*, *42*, 101-105.

Lin, T. Y., Wu, J. S., Lin, L. L., Ho, T. C., Lin, P. Y., & Chen, J. J. J. (2016). Assessments of muscle oxygenation and cortical activity using functional near-infrared spectroscopy in healthy adults during hybrid activation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *24*(1), 1-9.

Lin, Y. Y., Shih, Y. H., Chen, J. T., Hsieh, J. C., Yeh, T. C., Liao, K. K., ... & Ho, L. T. (2003). Differential effects of stimulus intensity on peripheral and neuromagnetic cortical responses to median nerve stimulation. *Neuroimage*, *20*(2), 909-917.

Litvak, V., Zeller, D., Oostenveld, R., Maris, E., Cohen, A., Schramm, A., et al. (2007). LTP-like changes induced by paired associative stimulation of the primary somatosensory cortex in humans: source analysis and associated changes in behaviour. *Eur J Neurosci*, *25*(9), 2862–2874. doi:10.1111/j.1460-9568.2007.05531.x

Luft, A. R., Kaelin-Lang, A., Hauser, T.-K., Buitrago, M. M., Thakor, N. V., Hanley, D. F., & Cohen, L. G. (2002). Modulation of rodent cortical motor excitability by somatosensory input. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale*, *142*(4), 562–569. doi:10.1007/s00221-001-0952-1

Luft, A. R., Manto, M.-U., & Oulad ben Taib, N. (2005). Modulation of motor cortex excitability by sustained peripheral stimulation: the interaction between the motor cortex and the cerebellum. *Cerebellum (London, England)*, *4*(2), 90–96.

Macé, M. J.-M., Levin, O., Alaerts, K., Rothwell, J. C., & Swinnen, S. P. (2008). Corticospinal facilitation following prolonged proprioceptive stimulation by means of passive wrist movement. *Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society*, *25*(4), 202–209. doi:10.1097/WNP.0b013e31817da170

MacKinnon, C. D., Verrier, M. C., & Tatton, W. G. (2000). Motor cortical potentials precede long-latency EMG activity evoked by imposed displacements of the human wrist. Experimental brain research, 131(4), 477-490.

Maffiuletti, N. A., Minetto, M. A., Farina, D., & Bottinelli, R. (2011). Electrical stimulation for neuromuscular testing and training: state-of-the art and unresolved issues.

Maffiuletti, N. A., Roig, M., Karatzanos, E., & Nanas, S. (2013). Neuromuscular electrical stimulation for preventing skeletal-muscle weakness and wasting in critically ill patients: a systematic review. *BMC medicine*, *11*(1), 137.

Manca, A., Hortobágyi, T., Rothwell, J., & Deriu, F. (2018). Neurophysiological adaptations in the untrained side in conjunction with cross-education of muscle strength: a systematic review and meta-analysis. *Journal of Applied Physiology*, *124*(6), 1502-1518.

Mang, C. S., Bergquist, A. J., Roshko, S. M., & Collins, D. F. (2012). Loss of short-latency afferent inhibition and emergence of afferent facilitation following neuromuscular electrical stimulation. *Neuroscience Letters*, *529*(1), 80–85. doi:10.1016/j.neulet.2012.08.072

Manganotti, P., Storti, S. F., Formaggio, E., Acler, M., Zoccatelli, G., Pizzini, F. B., ... & Beltramello, A. (2012). Effect of median-nerve electrical stimulation on BOLD activity in acute ischemic stroke patients. Clinical neurophysiology, 123(1), 142-153.

Manto, M., Oulad Ben Taib, N., & Luft, A. R. (2006). Modulation of excitability as an early change leading to structural adaptation in the motor cortex. Journal of neuroscience research, 83(2), 177-180.

Markram, H., Gerstner, W., & Sjöström, P. J. (2011). A history of spike-timing-dependent plasticity. Frontiers in synaptic neuroscience, 3, 4.

Markram, H., Lübke, J., Frotscher, M., & Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science, 275(5297), 213-215.

Mauguiere, F., Merlet, I., Forss, N., Vanni, S., Jousmäki, V., Adeleine, P., & Hari, R. (1997). Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: Location and activation timing of SEF sources. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 104(4), 281-289.

McKay, D., Brooker, R., Giacomin, P., Ridding, M., & Miles, T. (2002). Time course of induction of increased human motor cortex excitability by nerve stimulation. *Neuroreport*, *13*(10), 1271-1273.

McGie, S. C., Zariffa, J., Popovic, M. R., & Nagai, M. K. (2015). Short-Term Neuroplastic Effects of Brain-Controlled and Muscle-Controlled Electrical Stimulation. *Neuromodulation: Technology at the Neural Interface*, *18*(3), 233-240.

McLaughlin, D. F., & Kelly, E. F. (1993). Evoked potentials as indices of adaptation in the somatosensory system in humans: a review and prospectus. Brain Research Reviews, 18(2), 151-206.

McNickle, E., & Carson, R. G. (2015). Paired associative transcranial alternating current stimulation increases the excitability of corticospinal projections in humans. *The Journal of physiology*, *593*(7), 1649-1666.

Miall, R. C., & Wolpert, D. M. (1996). Forward models for physiological motor control. Neural networks, 9(8), 1265-1279.

Mima, T., Terada, K., Maekawa, M., Nagamine, T., Ikeda, A., & Shibasaki, H. (1996). Somatosensory evoked potentials following proprioceptive stimulation of finger in man. Experimental brain research, 111(2), 233-245.

Molenberghs, P., Cunnington, R., & Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. Neuroscience & Biobehavioral Reviews, 36(1), 341-349.

Monte-Silva, K., Piscitelli, D., Norouzi-Gheidari, N., Batalla, M. A. P., Archambault, P., & Levin, M. F. (2019). Electromyogram-Related Neuromuscular Electrical Stimulation for Restoring Wrist and Hand Movement in Poststroke Hemiplegia: A Systematic Review and Meta-Analysis. *Neurorehabilitation and neural repair*, *33*(2), 96-111.

Mrachacz-Kersting N, Jiang N, Stevenson AJT et al. (2016). Efficient neuroplasticity induction in chronic stroke patients by an associative brain-computer interface. J Neurophysiology, 115:1410–1421. doi:10.1152/jn.00918.2015

Mrachacz-Kersting, N., Kristensen, S. R., Niazi, I. K., & Farina, D. (2012). Precise temporal association between cortical potentials evoked by motor imagination and afference induces cortical plasticity. *The Journal of physiology*, *590*(7), 1669-1682.

Mrachacz-Kersting, N., Stevenson, A. J., Jørgensen, H. R., Severinsen, K. E., Aliakbaryhosseinabadi, S., Jiang, N., & Farina, D. (2019). Brain state–dependent stimulation boosts functional recovery following stroke. *Annals of neurology*, *85*(1), 84-95.

Mrachacz-Kersting, N., Voigt, M., Stevenson, A. J. T., Aliakbaryhosseinabadi, S., Jiang, N., Dremstrup, K., & Farina, D. (2017). The effect of type of afferent feedback timed with motor imagery on the induction of cortical plasticity. Brain research, 1674, 91-100.

Müller-Dahlhaus, F., Ziemann, U., & Classen, J. (2010). Plasticity resembling spike-timing dependent synaptic plasticity: the evidence in human cortex. Frontiers in synaptic neuroscience, 2, 34.

Nascimento, L. R., Michaelsen, S. M., Ada, L., Polese, J. C., & Teixeira-Salmela, L. F. (2014). Cyclical electrical stimulation increases strength and improves activity after stroke: a systematic review. *Journal of physiotherapy*, *60*(1), 22-30.

Nelson, A. J., Staines, W. R., Graham, S. J., & McIlroy, W. E. (2004). Activation in SI and SII; the influence of vibrotactile amplitude during passive and task-relevant stimulation. Cognitive brain research, 19(2), 174-184.

Nelson, R. J. (1996). Interactions between motor commands and somatic perception in sensorimotor cortex. Current Opinion in Neurobiology, 6(6), 801-810.

Nelson, R. J., Smith, B. N., & Douglas, V. D. (1991). Relationships between sensory responsiveness and premovement activity of quickly adapting neurons in areas 3b and 1 of monkey primary somatosensory cortex. Experimental brain research, 84(1), 75-90.

Niazi, I. K., Mrachacz-Kersting, N., Jiang, N., Dremstrup, K., & Farina, D. (2012). Peripheral electrical stimulation triggered by self-paced detection of motor intention enhances motor evoked potentials. *IEEE transactions on neural systems and rehabilitation engineering*, *20*(4), 595-604.

Nihashi, T., Naganawa, S., Sato, C., Kawai, H., Nakamura, T., Fukatsu, H., ... & Aoki, I. (2005). Contralateral and ipsilateral responses in primary somatosensory cortex following electrical median nerve stimulation—an fMRI study. Clinical Neurophysiology, 116(4), 842-848.

Okuyama, K., Ogura, M., Kawakami, M., Tsujimoto, K., Okada, K., Miwa, K., ... & Liu, M. (2018). Effect of the combination of motor imagery and electrical stimulation on upper extremity motor function in patients with chronic stroke: preliminary results. *Therapeutic advances in neurological disorders*, *11*, 1-10.

Olsen, S., Signal, N., Niazi, I. K., Christensen, T., Jochumsen, M., & Taylor, D. (2018). Paired Associative Stimulation Delivered by Pairing Movement‐Related Cortical Potentials With Peripheral Electrical Stimulation: An Investigation of the Duration of Neuromodulatory Effects. *Neuromodulation: Technology at the Neural Interface*, *21*(4), 362-367.

Padel, Y., & Relova, J. L. (1991). Somatosensory responses in the cat motor cortex. I. Identification and course of an afferent pathway. Journal of neurophysiology, 66(6), 2041-2058.

Panizza, M., Nilsson, J., & Hallett, M. (1989). Optimal stimulus duration for the H reflex. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine, 12(7), 576-579.

Panizza, M., Nilsson, J., Roth, B. J., Basser, P. J., & Hallett, M. (1992). Relevance of stimulus duration for activation of motor and sensory fibers: implications for the study of H-reflexes and magnetic stimulation. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 85(1), 22-29.

Parain, D., & Delapierre, G. (1991). Effects of stimulus intensity increase on short-latency somatosensory evoked potentials: application of polynomial curvature coefficients. Brain topography, 4(1), 31-35.

Park, J. H. (2019). Effects of mental imagery training combined electromyogram-triggered neuromuscular electrical stimulation on upper limb function and activities of daily living in patients with chronic stroke: a randomized controlled trial. *Disability and Rehabilitation*, 4, 1-6.

Peckham, P. H., & Knutson, J. S. (2005). Functional electrical stimulation for neuromuscular applications. Annu. Rev. Biomed. Eng., 7, 327-360.

Pomeroy, V., Aglioti, S. M., Mark, V. W., McFarland, D., Stinear, C., Wolf, S. L., ... & Fitzpatrick, S. M. (2011). Neurological principles and rehabilitation of action disorders: rehabilitation interventions. *Neurorehabilitation and neural repair*, *25*(5_suppl), 33S-43S.

Pons, T. P., & Kaas, J. H. (1986). Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: a correlative anatomical and electrophysiological study. Journal of Comparative Neurology, 248(3), 313-335.

Porter, L. L., & Sakamoto, K. (1988). Organization and synaptic relationships of the projection from the primary sensory to the primary motor cortex in the cat. Journal of Comparative Neurology, 271(3), 387-396.

Porter, L.L., Sakamoto, T., Asanuma, H. (1990). Morphological and physiological identification of neurons in the cat motor cortex which receive direct input from the somatic sensory cortex. Exp Brain Res 80, 209–212.

Prochazka, A. (2018). Motor Neuroprostheses. *Comprehensive Physiology*, *9*, 127-148.

Ridding, M. C., Brouwer, B., Miles, T. S., Pitcher, J. B., & Thompson, P. D. (2000). Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. *Experimental Brain Research*, *131*(1), 135–143.

Ridding, M. C., McKay, D. R., Thompson, P. D., & Miles, T. S. (2001). Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. *Clinical Neurophysiology*, *112*(8), 1461–1469.

Ridding, M. C., & Taylor, J. L. (2001). Mechanisms of motor‐evoked potential facilitation following prolonged dual peripheral and central stimulation in humans. The Journal of physiology, 537(2), 623-631.

Rizzo, V., Terranova, C., Crupi, D., Sant'Angelo, A., Girlanda, P., & Quartarone, A. (2014). Increased transcranial direct current stimulation after effects during concurrent peripheral electrical nerve stimulation. *Brain Stimulation*, *7*(1), 113–121. doi:10.1016/j.brs.2013.10.002

Ruddy, K. L., Leemans, A., Woolley, D. G., Wenderoth, N., & Carson, R. G. (2017). Structural and functional cortical connectivity mediating cross education of motor function. Journal of Neuroscience, 37(10), 2555-2564.

Ruddy, K. L., Rudolf, A. K., Kalkman, B., King, M., Daffertshofer, A., Carroll, T. J., & Carson, R. G. (2016). Neural adaptations associated with interlimb transfer in a ballistic wrist flexion task. Frontiers in human neuroscience, 10, 204.

Rushton, D. N. (2003). Functional electrical stimulation and rehabilitation—an hypothesis. Medical engineering & physics, 25(1), 75-78.

Saito, K., Sugawara, K., Miyaguchi, S., Matsumoto, T., Kirimoto, H., Tamaki, H., & Onishi, H. (2014). The modulatory effect of electrical stimulation on the excitability of the corticospinal tract varies according to the type of muscle contraction being performed. *Frontiers in Human Neuroscience*, *8*, 835. doi:10.3389/fnhum.2014.00835

Sakamoto, T., Porter, L. L., & Asanuma, H. (1987). Long-lasting potentiation of synaptic potentials in the motor cortex produced by stimulation of the sensory cortex in the cat: a basis of motor learning. Brain research, 413(2), 360-364.

Sasaki, R., Kotan, S., Nakagawa, M., Miyaguchi, S., Kojima, S., Saito, K., ... & Onishi, H. (2017). Presence and absence of muscle contraction elicited by peripheral nerve electrical stimulation differentially modulate primary motor cortex excitability. *Frontiers in human neuroscience*, *11*, 146.

Savaki, H. E., & Raos, V. (2019). Action perception and motor imagery: Mental practice of action. *Progress in neurobiology*, 175:107-125. doi: 10.1016/j.pneurobio.2019.01.007.

Savaki, H. E., & Raos, V. (2019). Action perception and motor imagery: Mental practice of action. *Progress in neurobiology*, 175:107-125.

Schabrun, S. M., & Ridding, M. C. (2007). The influence of correlated afferent input on motor cortical representations in humans. Experimental Brain Research, 183(1), 41-49.

Schabrun, S. M., Ridding, M. C., Galea, M. P., Hodges, P. W., & Chipchase, L. S. (2012). Primary sensory and motor cortex excitability are co-modulated in response to peripheral electrical nerve stimulation. *PloS One*, *7*(12), e51298. doi:10.1371/journal.pone.0051298

Schwark, H.D., Esteky, H., Jones, E.G. (1992). Corticocortical connections of cat primary somatosensory cortex. *Experimental Brain Research*, 91, 425–434.

Scribonius Largus. Compositiones Medicae, XL, CLXII. Trans. In P. Kellaway 1946.

Seeman, S. C., Mogen, B. J., Fetz, E. E., & Perlmutter, S. I. (2017). Paired stimulation for spike-timing-dependent plasticity in primate sensorimotor cortex. Journal of Neuroscience, 37(7), 1935-1949.

Sheffler, L. R., & Chae, J. (2007). Neuromuscular electrical stimulation in neurorehabilitation. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine, 35(5), 562-590.

Shen, Y., Yin, Z., Fan, Y., Chen, C. F., Dai, W., Yi, W., ... & Huang, Y. (2015). Comparison of the effects of contralaterally controlled functional electrical stimulation and neuromuscular electrical stimulation on upper extremity functions in patients with stroke. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *14*(10), 1260-1266.

Sherrington, C. S. (1894). On the Anatomical Constitution of Nerves of Skeletal Muscles; with Remarks on Recurrent Fibres in the Ventral Spinal Nerve-root. *The Journal of Physiology*, *17*(3-4), 210.2–258.

Shulga, A., Zubareva, A., Lioumis, P., & Mäkelä, J. P. (2016). Paired associative stimulation with high-frequency peripheral component leads to enhancement of corticospinal transmission at wide range of interstimulus intervals. Frontiers in human neuroscience, 10, 470.

Simos, P. G., Kavroulakis, E., Maris, T., Papadaki, E., Boursianis, T., Kalaitzakis, G., & Savaki, H. E. (2017). Neural foundations of overt and covert actions. Neuroimage, 152, 482-496.

Smith, G. V., Alon, G., Roys, S. R., & Gullapalli, R. P. (2003). Functional MRI determination of a dose-response relationship to lower extremity neuromuscular electrical stimulation in healthy subjects. Experimental Brain Research, 150(1), 33-39.

Song, S., Miller, K. D., & Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nature neuroscience, 3(9), 919.

Spiegel, J., Tintera, J., Gawehn, J., Stoeter, P., & Treede, R. D. (1999). Functional MRI of human primary somatosensory and motor cortex during median nerve stimulation. *Clinical Neurophysiology*, *110*(1), 47-52.

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. Brain, 123(3), 572-584.

Stefan, K., Wycislo, M., & Classen, J. (2004). Modulation of associative human motor cortical plasticity by attention. Journal of neurophysiology, 92(1), 66-72.

Stein, R. B., Everaert, D. G., Roy, F. D., Chong, S., & Soleimani, M. (2013). Facilitation of corticospinal connections in able-bodied people and people with central nervous system disorders using eight interventions. *Journal of Clinical Neurophysiology*, *30*(1), 66-78.

Summers, S. J., Schabrun, S. M., Marinovic, W., & Chipchase, L. S. (2017). Peripheral electrical stimulation increases corticomotor excitability and enhances the rate of visuomotor adaptation. *Behavioural brain research*, *322*, 42-50.

Suppa, A., Quartarone, A., Siebner, H., Chen, R., Di Lazzaro, V., Del Giudice, P., ... & Classen, J. (2017). The associative brain at work: evidence from paired associative stimulation studies in humans. Clinical Neurophysiology, 128(11), 2140-2164.

Takahashi, Y., Kawakami, M., Yamaguchi, T., Idogawa, Y., Tanabe, S., Kondo, K., & Liu, M. (2019). Effects of Leg Motor Imagery Combined With Electrical Stimulation on Plasticity of Corticospinal Excitability and Spinal Reciprocal Inhibition. *Frontiers in neuroscience*, *13*.

Taylor, L., Lewis, G. N., & Taylor, D. (2012). Short-term effects of electrical stimulation and voluntary activity on corticomotor excitability in healthy individuals and people with stroke. *Journal of Clinical Neurophysiology*, *29*(3), 237-243.

Tolmacheva, A., Mäkelä, J. P., & Shulga, A. (2019). Increasing the frequency of peripheral component in paired associative stimulation strengthens its efficacy. *Scientific reports*, *9*(1), 3849.

Traversa, R., Cicinelli, P., Bassi, A., Rossini, P. M., & Bernardi, G. (1997). Mapping of motor cortical reorganization after stroke: a brain stimulation study with focal magnetic pulses. Stroke, 28(1), 110-117.

Turco, C. V., El-Sayes, J., Savoie, M. J., Fassett, H. J., Locke, M. B., & Nelson, A. J. (2018). Short-and long-latency afferent inhibition; uses, mechanisms and influencing factors. Brain stimulation, 11(1), 59-74.

Urasaki, E., Wada, S. I., Yasukouchi, H., & Yokota, A. (1998). Effect of transcutaneous electrical nerve stimulation (TENS) on central nervous system amplification of somatosensory input. Journal of neurology, 245(3), 143-148.

Uy, J., & Ridding, M. C. (2003). Increased cortical excitability induced by transcranial DC and peripheral nerve stimulation. Journal of neuroscience methods, 127(2), 193-197.

Vang, C., Dunbabin, D., & Kilpatrick, D. (1999). Correlation between functional and electrophysiological recovery in acute ischemic stroke. *Stroke*, *30*(10), 2126-2130.

Veale, J. L., Mark, R. F., & Rees, S. (1973). Differential sensitivity of motor and sensory fibres in human ulnar nerve. *Journal of Neurology, Neurosurgery & Psychiatry*, *36*(1), 75-86.

Veldman, M. P., Maffiuletti, N. A., Hallett, M., Zijdewind, I., & Hortobágyi, T. (2014). Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans. *Neuroscience & Biobehavioral Reviews*, *47*, 22-35.

Veldman, M. P., Maurits, N. M., Zijdewind, I., Maffiuletti, N. A., van Middelkoop, S., Mizelle, J. C., & Hortobágyi, T. (2018). Somatosensory electrical stimulation improves skill acquisition, consolidation, and transfer by increasing sensorimotor activity and connectivity. Journal of neurophysiology, 120(1), 281-290.

Veldman, M. P., Zijdewind, I., Solnik, S., Maffiuletti, N. A., Berghuis, K. M. M., Javet, M., ... & Hortobágyi, T. (2015). Direct and crossed effects of somatosensory electrical stimulation on motor learning and neuronal plasticity in humans. European journal of applied physiology, 115(12), 2505-2519.

Veldman, M. P., Zijdewind, I., Maffiuletti, N. A., & Hortobágyi, T. (2016). Motor skill acquisition and retention after somatosensory electrical stimulation in healthy humans. *Frontiers in human neuroscience*, *10*, 115.

Waters, R. S., Favorov, O., Mori, A., & Asanuma, H. (1982). Pattern of projection and physiological properties of cortico-cortical connections from the posterior bank of the ansate sulcus to the motor cortex, area 4γ, in the cat. Experimental brain research, 48(3), 335-344.

Wattchow, K. A., McDonnell, M. N., & Hillier, S. L. (2018). Rehabilitation interventions for upper limb function in the first four weeks following stroke: a systematic review and meta-analysis of the evidence. Archives of physical medicine and rehabilitation, 99(2), 367-382.

Wegrzyk, J., Ranjeva, J. P., Fouré, A., Kavounoudias, A., Vilmen, C., Mattei, J. P., ... & Gondin, J. (2017). Specific brain activation patterns associated with two neuromuscular electrical stimulation protocols. Scientific reports, 7(1), 2742.

Wiesendanger, M. A. R. I. O., & Miles, T. S. (1982). Ascending pathway of low-threshold muscle afferents to the cerebral cortex and its possible role in motor control. Physiological Reviews, 62(4), 1234-1270.

Wilson, R. D., Page, S. J., Delahanty, M., Knutson, J. S., Gunzler, D. D., Sheffler, L. R., & Chae, J. (2016). Upper-limb recovery after stroke: a randomized controlled trial comparing EMG-triggered, cyclic, and sensory electrical stimulation. *Neurorehabilitation and neural repair*, *30*(10), 978-987.

Wu, C. W.-H., Van Gelderen, P., Hanakawa, T., Yaseen, Z., & Cohen, L. G. (2005). Enduring representational plasticity after somatosensory stimulation. *Neuroimage*, *27*(4), 872–884. doi:10.1016/j.neuroimage.2005.05.055

Wundt, W.M., 1863 Vorlesungen ueber Menschen-und Thierseele, vol 2. Leipzig Voss.

Xu, R., Wang, Y., Wang, K., Zhang, S., He, C., & Ming, D. (2018). Increased Corticomuscular Coherence and Brain Activation Immediately After Short-Term Neuromuscular Electrical Stimulation. *Frontiers in neurology*, *9*, 886.

Yamashiro, K., Inui, K., Otsuru, N., Kida, T., Akatsuka, K., & Kakigi, R. (2008). Somatosensory off-response in humans: an ERP study. Experimental brain research, 190(2), 207-213.

Yamashiro, K., Inui, K., Otsuru, N., Kida, T., & Kakigi, R. (2009). Somatosensory off-response in humans: an MEG study. Neuroimage, 44(4), 1363-1368.

Yang, J. D., Liao, C. D., Huang, S. W., Tam, K. W., Liou, T. H., Lee, Y. H., ... & Chen, H. C. (2019). Effectiveness of electrical stimulation therapy in improving arm function after stroke: a systematic review and a meta-analysis of randomised controlled trials. *Clinical rehabilitation*, 0269215519839165.

Yasui, T., Yamaguchi, T., Tanabe, S., Tatemoto, T., Takahashi, Y., Kondo, K., & Kawakami, M. (2019). Time course of changes in corticospinal excitability induced by motor imagery during action observation combined with peripheral nerve electrical stimulation. *Experimental brain research*, *237*(3), 637-645.

You, S. J., & Lee, J. H. (2013). Effects of Mental Activity Training Linked With Electromyogram-triggered Electrical Stimulation on Paretic Upper Extremity Motor Function in Chronic

Stroke Patients: A Pilot Trial. *Turkish Journal of Physical Medicine & Rehabilitation/Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi*, *59*(2), 133-139.

Yumiya, H., & Ghez, C. (1984). Specialized subregions in the cat motor cortex: anatomical demonstration of differential projections to rostral and caudal sectors. *Experimental brain research*, *53*(2), 259-276.

Zarzecki, P., Shinoda, Y., & Asanuma, H. (1978). Projection from area 3a to the motor cortex by neurons activated from group I muscle afferents. Experimental Brain Research, 33(2), 269-282.

Zheng, Y., Mao, M., Cao, Y., & Lu, X. (2019). Contralaterally Controlled Functional Electrical Stimulation Improves Wrist Dorsiflexion and Upper Limb Function in Patients with Early-Phase Stroke: A Randomized Controlled Trial. *Journal of rehabilitation medicine*, *51*(2), 103-108.

Zhou, S., Oakman, A., & Davie, A. J. (2002). Effects of unilateral voluntary and electromyostimulation training on muscular strength on the contralateral limb. *Hong Kong Journal of sports medicine and sports science*, *14*, 1.

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There are no competing interests of which the authors are aware.

Author contributions

Both authors contributed to the conception and writing of this review, and they approved the final version of the manuscript. They both agree to be accountable for all aspects of the work, and will ensure that any questions relating to the accuracy or integrity of any part of the work can, if necessary, be investigated appropriately. Both authors qualify for authorship

Abstract Figure Legend

The delivery of electrical current via a peripheral nerve (or across a muscle belly) activates contractile muscle fibres indirectly by depolarizing motor axons (1b). As the sensory axons in the same mixed nerve bundle have lower activation thresholds, ascending afferent volleys are also generated at intensities of electrical stimulation that exceed the motor threshold (1b). These volleys are followed by (secondary) reafference arising from the invoked muscle contraction (2). The goal of this review is to address the means through which the sensory-mediated consequences of the stimulation alter the state of "sensory" networks, and induce sustained "neuroplastic" modifications within central "motor" networks. Figure redrawn and adapted from the author's original artwork, which is available at: https://commons.wikimedia.org/wiki/File:Neuromuscular_electrical_stimulation_promoted_brain_plasticity.jpg (Original figure published under a Creative Commons Attribution-Share Alike 4.0 International license).

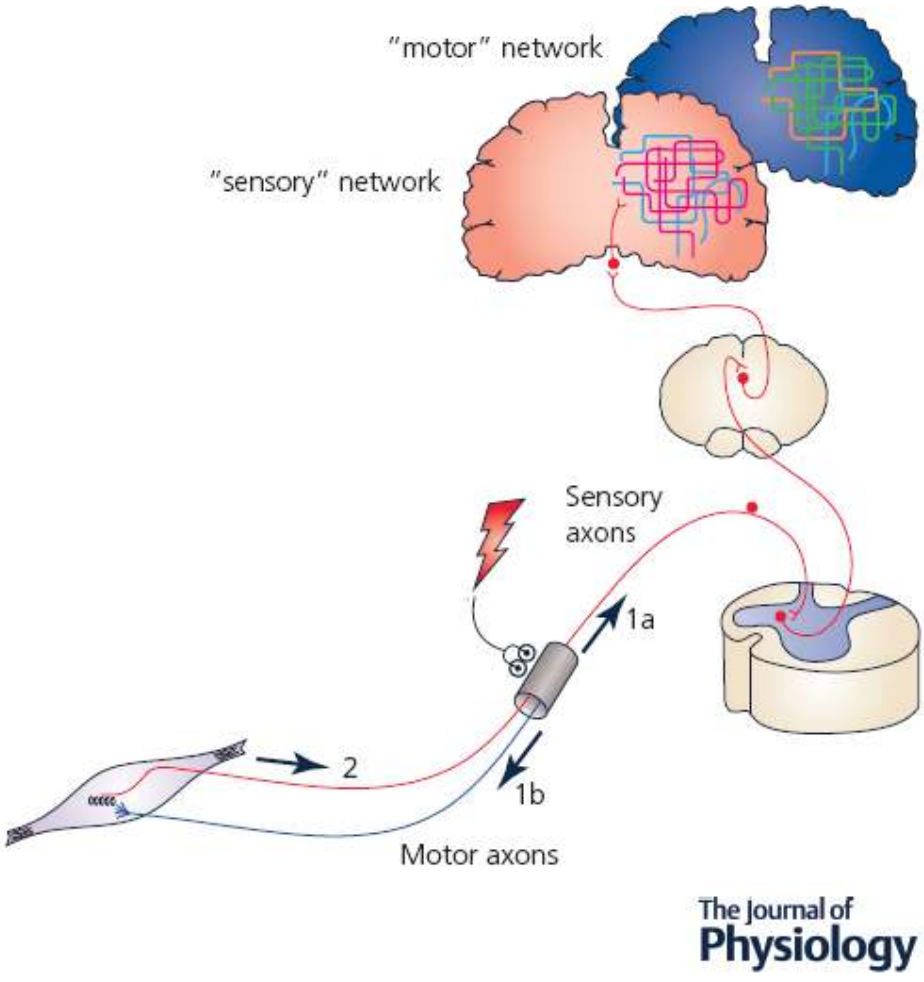

Table 1 is: Common variants of peripheral electrical stimulation

Type of Stimulation	Typical Intent	Typical Frequency Range	Typical Intensity
NMES	Activation of sensory and motor axons for diverse purposes	1-100 Hz	at or above motor threshold
FES	Activation of both sensory and motor axons with the specific goal of assisting motor function	20-60 Hz	above motor threshold
EST	Activation of both sensory and motor axons with the specific goal of preventing muscle weakness	35-100 Hz	above motor threshold
TENS	Activation of sensory axons for the goal of pain relief.	>50 Hz	below motor threshold

NMES - neuromuscular electrical stimulation; FES - functional electrical stimulation; EST - electrostimulation strength training; TENS - transcutaneous electrical nerve

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