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Transforming neurorehabilitation of walking following stroke: The promise of non-invasive brain stimulation – a review

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Abstract. *Purpose:* This narrative review discusses the neurophysiology of human motor cortex as it influences gait, and recent advances in the application of non-invasive brain stimulation to the lower limb motor cortex of stroke survivors. Although walking is a high priority following stroke, the efficacy of promising new therapies has yet to warrant their widespread clinical use. For the upper limb, numerous brain stimulation protocols have been described. These protocols, adapted for the leg, are now being used to examine the cortical control of gait. This research discounts the long-held notion that "we walk from our spinal cords".
Methods: Our review describes this research as it relates to the lower limb, especially the use of non-invasive brain stimulation to enhance neuroplasticity. The review also discusses the possible development of a prognostic algorithm for walking recovery after stroke.
Conclusion: This review concludes with the expectation that novel brain stimulation protocols combined with therapy will eventually demonstrate a level of effectiveness sufficient to promote their wide acceptance in neurorehabilitation settings.

Keywords: Non-invasive brain stimulation, stroke, gait

1. Introduction

Recovering functional independence after stroke is a treasured outcome for the patient and a very important public health issue (Hankey, 1999). Fewer than 50% of survivors at 6-months after stroke have achieved their independence (Wade and Hewer, 1987), which translates to around 650 stroke survivors per million population who fail to regain their independence being added *every year* to the number of individuals in developed countries such as the US, the UK, Europe, Australia and New Zealand (Hankey, 1999). Major barriers prevent many patients from regaining their independence after stroke including an inability to walk sufficiently well to again become active in the community. Because presently attained gains in walking quality and velocity of $\sim$ 0.13–0.19 m/s, many patients are prevented from becoming community walkers (Perry et al., 1995; Tilson et al., 2010).

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A breakthrough in gait therapy in the near future that yields a large margin of superior effectiveness over currently available therapies would increase stroke survivor independence and reduce the social and financial burden on caregivers and the community. Insufficient literature prevents a meaningful systematic review to be conducted; therefore this narrative review discusses non-invasive brain stimulation as it has been used to reveal the role of motor cortex during walking, and the development of non-invasive brain stimulation as a therapeutic adjuvant. We argue that the latter is likely to transform neurorehabilitation of walking following stroke.

Although our understanding of the neural mechanisms that drive recovery of the paretic upper limb has progressed substantially over the last two decades, our understanding of mechanisms involved in the recovery of the paretic lower limb is limited. Paradoxically, the discovery of "fictive locomotion" in the cat (Grillner and Rossignol, 1978) may have led many to think of the control of walking as being exclusively a spinal mechanism, despite the animal's need to voluntarily influence walking patterns by cortical inputs to avoid obstacles and change direction (Drew, 1993). This notion, along with the difficulty of examining human brains *in vivo*, may have slowed the progress of research that examines the role of the cortex in human walking. For the upper limb, some technical barriers were largely dismantled by the introduction of transcranial magnetic stimulation (TMS) (Barker et al., 1985). This non-invasive, safe and painless technique allows researchers to study corticospinal pathways (Amassian et al., 1987; Eyre et al., 2007), intracortical neural circuitry (Kujirai et al., 1993), and the interaction of motor systems between the two hemispheres (Ferbert et al., 1992). The latter is particularly important after stroke because disordered interhemispheric inhibition impairs the ability of the upper limbs to function independently of each other (Traversa et al., 1998; Trompetto et al., 2000). An asymmetry of interhemispheric inhibition (Stinear et al., 2008), paretic limb weakness and the persistence of primitive muscle synergies (Brunnstrom, 1966), contribute to poor paretic upper limb motor recovery.

A controversial issue in regard to the neural mechanisms that drive upper limb recovery after stroke is the role of the non-lesioned motor cortex. The idea that the non-lesioned hemisphere might exert control over the paretic limb via ipsilateral corticospinal pathways has been promoted by some (Nathan and Smith, 1973; Chollet et al., 1991) and questioned by others (Weiller et al., 1992; Schwerin et al., 2007). Although less well-recovered patients have greater evidence of active ipsilateral pathways from the non-lesioned hemisphere to paretic upper limb motoneurons than better-recovered patients, how this is related to recovery is an issue yet to be resolved. A neural mechanism that appears to promote functional recovery of the upper limb is the re-balancing of interhemispheric inhibition. Evidence in support of this idea comes from studies that revealed a therapy-induced enhanced symmetry in interhemispheric inhibition that was associated with paretic hand recovery (Traversa et al., 1998; Feydy et al., 2002; Johansen-Berg et al., 2002). It appears that the more excitable non-lesioned motor cortex imposes greater transcallosal inhibition on the lesioned motor cortex than vice versa, further impairing the ability of the lesioned cortex to control movement. In addition to between-hemisphere mechanisms of impairment and recovery, non-primary areas within the lesioned hemisphere also appear to be involved. Some functional imaging and TMS studies have linked activity in premotor cortical areas to the recovery of upper limb function following stroke (Johansen-Berg et al., 2002). A few infrared and MR studies have revealed greater activity in non-primary motor cortices either during gait, or during voluntary lower limb muscle contractions (Miyai et al., 2002; Kapreli et al., 2006). Studies attempting to characterize the pathology underlying lower limb function point to a diffuse network of cortical and subcortical structures, however, the specific role of each during gait is yet to be revealed (Alexander et al., 2009; Hiraga et al., 2009). However, these studies do not provide direct evidence of clinically important gait recovery being driven by ipsilateral corticospinal tract activity, a reduction of between-hemisphere asymmetry in motor excitability, or by plastic changes in premotor cortices. Notwithstanding the differences in neuroanatomy and neurophysiology between upper and lower limbs, it is useful to conduct lower limb neurorehabilitation research by adapting techniques successfully applied to upper limb research.

One such technique is non-invasive brain stimulation (NIBS). The rationale supporting the use of NIBS as an adjunct therapy, or adjuvant to therapy, is that increasing the excitability of the lesioned motor system or suppressing the excitability of the non-lesioned motor system tends to normalize within- and between-hemisphere cortical physiology thereby

promoting neuroplasticity and recovery (Fregni et al., 2005). As an adjunct therapy, NIBS itself is expected to improve limb function. As an adjuvant therapy, NIBS is applied either before or during therapy to render the brain more susceptible to task-oriented training. These approaches show some promise, however, there are many critical knowledge gaps yet to be filled before NIBS can be considered for routine prescription as an adjuvant to enhance gait recovery following neurological injury. The principal aim of this review is to discuss the neurophysiological effects of non-invasive brain stimulation on lower limb motor cortex. We will begin by describing experiments that have probed lower limb motor system excitability, move on to experiments designed to better understand the interaction of spinal and supraspinal neuronal circuitry, and conclude with some recent studies that examined the ability of NIBS to modulate lower limb motor system excitability.

2. Corticospinal control of the human lower limb

A well-developed body of research has investigated the influence of sensory feedback, and of spinal and supraspinal circuit activity on lower limb motoneurons. Since 1910 when Paul Hoffman first reported the H-reflex (Hoffmann, 1910), many studies have utilized this electrical analogue of the stretch reflex to develop an understanding of the neural control of the lower limb, and less often, of the upper limb. Many techniques based on the H-reflex phenomenon have provided important insights into reflex and supraspinal influences including important inhibitory mechanisms, e.g. presynaptic, reciprocal Ia, recurrent, and Ib (Knikou, 2008). These studies have revealed that spinal reflexes are highly mutable by peripheral and central inputs. A finding that is of particular importance to gait function following neurological disease and stroke is that spinal inhibitory circuits have been linked to the presumed underlying mechanisms of spasticity (Morita et al., 2001) which may contribute to paretic limb impairment following stroke (Sommerfeld et al., 2004). Since walking is a phasic task, it is probable that sensory afference modulates cortical excitability in a phasic manner. The dissociation between afferent and efferent phasic modulation is technically difficult to establish. Duysens and colleagues demonstrated that sensory evoked potential latencies increased by ~5 ms from mid-swing through early stance during walking (Duysens et al., 1995). Others have demonstrated the inhibitory effects of median nerve stimulation on responses to TMS (Tokimura et al., 2000). Further, stimulation of the plantar surface of the foot has been shown to modulate the size of responses to TMS (Kasai et al., 1992). Called short interval afferent inhibition, this protocol suppresses the size of TMS-evoked potentials at a conditioning-test interval of 40 ms and facilitates responses at 80 ms. Notwithstanding the importance of spinal circuit excitability and afferent modulation, the present review is focused on cortical influences to which we now return.

Pijnappels and colleagues suggested that corticospinal input had a controlling influence on lower limb cutaneous reflexes during walking (Pijnappels et al., 1998). They found that TMS facilitated this reflex during the swing phase of gait when cortical control of knee flexion and ankle dorsiflexion would be functionally appropriate. Schubert and colleagues examined the effect of TMS on EMG activity in lower limb muscles during walking to assess interactions of spinal and supraspinal mechanisms (Schubert et al., 1999). They applied TMS to the lower limb motor cortex of healthy subjects while they walked on a treadmill. EMG was collected from tibialis anterior (TA) and gastrocnemius while TMS was delivered at 16 phases of the step cycle. EMG amplitude calculated for a window when the TMS-induced motor evoked potential was evident, was compared to the amplitude in the same window when no TMS was delivered. Their main finding was that the TMS-induced responses recorded in EMG were modulated in a phase-advanced manner. This modulation was more prominent in the dorsiflexor than the plantarflexor. Their findings suggests that the spinal motoneuron pool is being up-regulated prior to EMG onset and that the corticospinal pathway has access to spinal motoneurons at a time when descending inputs could help maintain postural stability during walking. Following this line of inquiry, Capaday and colleagues conducted a study, the findings of which largely supported those of Schubert and colleagues (Capaday et al., 1999). However, the Capaday study added important information regarding the extent of the interaction between spinal and supraspinal mechanisms during walking. They analyzed the effects of delivering TMS at times that could be expected to alter the timing of phasic muscle bursts. No phasic changes were revealed suggesting that the timing of muscle activity during walking is largely driven by spinal mechanisms. They also used TMS-intensity – response-amplitude

recruitment curves to show that during the stance phase, there was an enhancement of the dorsiflexor response size relative to its size during voluntary plantarflexion. These findings support the idea that descending inputs are highly accessible to spinal motor circuitry even when the muscle is not active during stance, but may not strongly influence the timing of muscle activity. Although this evidence of accessibility reinforces the notion that the cortex has a somewhat limited role to play during walking, evidence was not yet available that corticospinal neurons participated *directly* in the phasic control of muscle activity during walking. Petersen and colleagues sought to clarify this point by observing the effect of weak TMS delivered to motor cortex on the amplitude of H-reflexes recorded in plantarflexors during treadmill walking and during voluntary tonic contraction (Petersen et al., 1998). TMS was subthreshold for eliciting a response in soleus (SOL) but facilitated the H-reflex in both muscle activation conditions. This effect was not revealed during standing or when TMS was replaced with transcranial electrical stimulation that is able to bypass cortical interneurons and activate corticospinal tracts directly (Day et al., 1989). These findings indicate that the intracortical circuitry is modulated during walking. So far these studies have indicated that motor system excitability, including cortical interneuronal excitability, is phasically modulated during walking. Petersen and colleagues took the next step and provided evidence that this phasic modulation was not merely entrained to spinal level activity, but represents cortical cells firing to drive spinal motor neurons during walking (Petersen et al., 2001). They used subthreshold repetitive TMS that suppressed soleus SOL motoneuron activity during mid-stance, and TA motoneuron activity during the first half of the swing phase, however, the suppression was not evident when single pulse transcranial electrical stimulation was applied. They concluded that their suppressive protocol reduced cortical drive to spinal circuitry, thereby providing evidence of descending control. For some time H reflexes have been conditioned by stimulating the nerve of an antagonist muscle to assess reciprocal inhibition (Crone and Nielsen, 1994). Recently, Roche and colleagues used this technique to assess the effects of 20 mins of facilitatory transcranial direct current stimulation (tDCS) applied to the lower limb motor cortex of healthy individuals (Roche et al., 2011). Using appropriately timed paired electrical stimulation to peripheral nerves they demonstrated a decrease in reciprocal inhibition from TA to SOL, and an increase in recurrent inhibition. Although the study was conducted with the lower limb at rest, these findings reinforce the notion that cortical inputs have a role to play in the control of cyclic motoneuron activity. Importantly, their study highlights the difficulty in developing brain stimulation to enhance lower limb therapy for patients with brain or spinal cord injuries. Decreasing reciprocal inhibition may increase spasticity and increasing recurrent inhibition may decrease spasticity. Nevertheless, techniques using brain and peripheral nerve stimulation may lead to the development of enhanced therapies that reduce functional disability in the lower limb. Hansen and colleagues who examined motor unit synchronization patterns during walking provided further support for descending control of spinal circuits in the lower limb (Hansen et al., 2001). EMG recordings from TA via fine wire electrodes and from a number of other thigh and shank muscles via surface electrodes were analyzed with cross-correlograms to determine the probability of synchronized events occurring. These analyses provided evidence of a common synaptic drive to motor units within a muscle and between synergistic muscles acting on the same joint during human gait. Therefore, supraspinal neurons appear to generate drive that is common to walking synergists, and spinal circuits likely refine this common drive. For example, Iglesias and colleagues demonstrated that heteronymous spinal excitation by group I and group II ankle dorsiflexor afferents on knee extensor motoneurons was under the control of descending inhibitory inputs that were activated by TMS delivered over motor cortex (Iglesias et al., 2008). Approximately 10 years ago sufficient evidence was available to support the notion that cortex plays a central role in the temporal modulation of spinal motor circuitry during walking. Studies published since then have typically supported this conclusion.

3. Inducing neuroplasticity of the lower limb motor cortex with NIBS

Armed with this knowledge, and with a long-term goal of transforming neurorehabilitation of walking after stroke, we asked two related questions: 1. Can we modulate the excitability of the lower limb motor cortex? 2. If so, can this be achieved in a hemisphere-specific manner? A decade ago it would be reasonable to assume that the answer to the first question was

yes, based on upper limb research, and the answer to the second question was no, because of the poor spatial resolution of NIBS and the close proximity of the two lower limb motor cortices located either side of the central fissure at the medial end of the precentral gyrus. The reason the latter question is important, is that many stroke patients have an asymmetry of between-hemisphere excitability that is thought to hinder recovery of paretic limb function (Traversa et al., 2000). Based on upper limb studies, an hypothesis worth testing would be that reducing the asymmetry of between-hemisphere excitability using NIBS enhances gait recovery. Uy and colleagues made a start using one form of NIBS called paired associative stimulation (PAS) as a trial adjunct therapy to enhance paretic leg recovery after stroke (Uy et al., 2003). The study provided weak yet promising evidence. TMS was paired with short 10 Hz trains of peroneal nerve stimulation delivered to stroke patients when their paretic leg was at rest. Stimulation was given every weekday over 4 weeks. Enhanced motor system excitability was revealed for some patients, and group data revealed gait measures such as cadence and stride length improved. Although the authors were not concerned about hemisphere specificity, PAS involves pairs of peripheral nerve and motor cortex stimuli, precisely timed to arrive in the cortex in a specific order. It is reasonable to assume the peripheral nerve stimulation (applied to one limb) confers a measure of hemispheric specificity. The next study to examine NIBS to the lower limb system was our 2005 study (Stinear and Hornby, 2005) where we applied PAS *during walking* using protocols adapted from Stefan and colleagues (Stefan et al., 2000) who examined the effects of PAS on hand motor cortex excitability maintained at rest. We present this study in some detail because this study is the base upon which several other studies pertinent to this review will be described. Our 2005 study was conducted in healthy adults and involved single pulses of peroneal nerve stimulation paired with TMS delivered over vertex (Stinear and Hornby, 2005). We deliberately did not optimize TMS to one hemisphere, preferring instead to stimulate both lower limb motor cortices equally and assess the ability of the peripheral nerve stimulation to specify the hemisphere in which motor excitability would be modulated. We applied facilitatory PAS using 120 peroneal nerve stimuli (at 0.1 Hz) timed to arrive in cortex no more than 10 ms prior to TMS being delivered during late swing (around heel-strike). As predicted from Stefan and colleagues' upper limb research (Stefan et al., 2000) this inter-spike interval produced a 20% increase in the amplitude of responses compared with TMS alone, assessed in TA at the same cycle phase in which PAS was delivered. Also assessed in our 2005 study were the effects of inhibitory PAS with an inter-spike interval where TMS is delivered no more than 10 ms prior to the peripheral volley arriving in cortex (Stinear and Hornby, 2005). Motor system excitability was down-regulated by approximately 20%. A series of control conditions indicated that the modulation we observed was not due to walking alone, or either type of stimulation alone. This was the first time NIBS had been shown to modulate motor cortex with a spike-timing-dependent positive or a negative sign, when the stimuli were delivered and excitability probed during walking. Of particular importance was that modulation was not evident in responses recorded from the limb to which peroneal stimulation *was not* delivered. The 2005 study began to inform the development of NIBS as an adjuvant to gait therapy by demonstrating lower limb-specific motor pathway modulation induced during walking.

The next question we asked was: "Are the effects of PAS delivered during walking phasically modulated?" Using a similar protocol to the 2005 study we applied facilitatory PAS to healthy subjects' TA motor systems during the early swing, late swing and stance phases of the step cycle in three separate sessions (Prior and Stinear, 2006). PAS increased the amplitude of TA responses to 130% of baseline in the late swing phase, but intriguingly, this facilitation could be reversed to *suppression* if stimulus pairs with the same inter-spike interval were delivered in mid-swing. The results could not be explained by gating of movement-elicited afferent volleys (Duysens et al., 1995). Our findings supported the research of others that motor cortex plays a role in the phasic modulation of spinal circuitry during walking. Further progress in the understanding of NIBS applied to the lower limb motor cortex was provided in subsequent studies where PAS protocols were used to answer two more questions. Does PAS applied to the TA motor system at rest induce modulation that persists during subsequent walking? Does suppressive PAS delivered to the non-lesioned lower limb motor cortex of stroke patients increase paretic limb motor excitability during walking? Two separate studies provided affirmative evidence. We found that an equivalent extent of modulation was evident in healthy subjects' TA motor systems following PAS

applied either during rest or during walking, where excitability was probed during walking (Jayaram et al., 2007). In the study involving stroke patients, suppressing non-lesioned lower limb cortical excitability with the lower limbs at rest resulted in an up-regulation of paretic limb excitability assessed during subsequent walking (Jayaram and Stinear, 2008). Another study compared the effects of tDCS and repetitive transcranial magnetic stimulation (rTMS) with the facilitatory effects of PAS on the lesioned lower limb motor system of stroke patients (Jayaram and Stinear, 2009). Similar results were obtained illustrating that lower limb motor cortex is susceptible to all three types of NIBS. Interestingly lesioned cortex excitability was increased when inhibitory rTMS was applied to the non-lesioned motor cortex and when facilitatory tDCS was applied to the lesioned motor cortex. Although inhibitory PAS and rTMS were applied to non-lesioned motor systems, we applied facilitatory tDCS to the lesioned motor cortex because inhibitory tDCS does not appear to modulate lower limb motor cortex (Jeffery et al., 2007), unlike the inhibitory effects demonstrated for the upper limb (Nitsche et al., 2003). Together, the results of these experiments indicate that NIBS is effective at modulating lower limb motor system excitability, and given the demonstration of hemispheric specificity and persistence of effects during walking, is therefore a candidate adjuvant to gait therapy after stroke. In addition, NIBS has been shown to modulate spinal reflexes in the lower limb (as discussed above). Its use may therefore have particular relevance in aiding gait functional recovery in the spastic paretic limb where gait related reflex circuits are impaired following stroke (Crone et al., 1994). Importantly, the paretic TA motor system can be up-regulated regardless of whether excitatory NIBS is applied to the lesioned hemisphere or suppressive NIBS is applied to the non-lesioned hemisphere. However this may be specific to the TA as suppressive PAS to the non-lesioned hemisphere targeted to the quadriceps did not yield consistent facilitation of the lesioned hemisphere (Rogers et al., 2011). Taken together these findings may prove valuable if it can be shown that lesioned hemisphere stimulation is functionally effective for some patients and non-lesioned stimulation is functionally effective for others. At this stage, important caveats to keep in mind are that better gait recovery using NIBS, and the determinants of individual responsiveness, have yet to be demonstrated. Although it has been reported that lower limb skill acquisition improves hemiparetic gait velocity (Roy et al., 2011) it is not yet known whether NIBS improves gait measures in neurologically impaired individuals.

Two studies provided intriguing data revealing a potential role for NIBS-enhanced ankle movement practice as a therapy to improve gait. In the first study, anodal tDCS applied to lower limb motor cortex enhanced 1st and 2nd digit pinch force in healthy adults (Tanaka et al., 2009). In the second study, stroke patients' self-selected gait velocities and spatiotemporal gait symmetry improved following paretic ankle movement that was used to guide a cursor on a screen during eighteen one-hour sessions spread over six weeks (Forrester et al., 2011). These findings raised the question: can NIBS enhance motor control of the paretic ankle? In order to answer this question we examined the effect of NIBS applied during practice of a visuo-motor ankle-tracking task, where walking-related spinal circuitry was not active (Madhavan et al., 2011). A variable frequency and amplitude sine wave was generated on a large TV screen that patients attempted to match by dorsiflexing and plantarflexing their paretic ankle. The target sine wave was propagated at a rate patients could comfortably follow. The spatial error between the two traces was calculated as an index of tracking accuracy (Carey et al., 1998). Patients practiced tracking for 15 minutes during which one of three stimulation conditions was added. In three separate sessions, facilitatory anodal tDCS was applied to the lesioned hemisphere lower limb motor cortex, to the non-lesioned cortex, and sham stimulation was applied to the lesioned cortex. Tracking accuracy was calculated before and after the practice sessions. Group data revealed that anodal tDCS over the lesioned cortex approximately doubled ankle-tracking accuracy compared with sham, and anodal tDCS over non-lesioned cortex suppressed these practice-induced accuracy gains. The results indicate that patients can learn to control their ankle with practice, and that when the lesioned motor cortex is up-regulated practice effects are enhanced, but when the lesioned motor cortex is down-regulated (presumably via transcallosal circuitry), practice effects are blocked. The next step will be to determine if enhancing ankle, knee or hip joint control translates into better gait.

Important to consider in future research is the mechanism by which NIBS modulates lower limb motor cortical excitability. Very little is known, but the most direct work by Di Lazzaro and colleagues has identified neurons that are activated with single pulse TMS,

and modulated with different rTMS protocols (for a review of this work, see Di Lazzaro et al., 2010). Protocols such as theta-burst TMS, which have yet to be applied to the lower limb motor cortex, may influence different sets of interneurons (Di Lazzaro et al., 2005). The resting membrane potential of the neurons located under the electrode is changed with tDCS (Nitsche and Paulus, 2000; Furubayashi et al., 2008; Lang et al., 2005; Nitsche et al., 2005), which leads to changes in NMDA-receptor efficiency (Liebetanz et al., 2002) and neuronal membrane function (Ardolino et al., 2005). Although we have demonstrated that rTMS, PAS, and tDCS modulate to a similar extent the excitability of lower limb cortex during walking (Jayaram and Stinear, 2009), their mechanisms of action likely differ. An exciting prospect is that further research may reveal that these different mechanisms could be exploited to enhance gait therapy.

4. A prognostic algorithm for walking recovery?

Predicting functional recovery of the upper limb following stroke has been the topic of many studies. Making decisions on the appropriate therapy, when and how long it should be delivered, and the goals of rehabilitation are often based on the patient's potential for recovery of motor function. A sensitive and specific prognostic algorithm has yet to be adopted. However, excellent progress has recently been made in developing such an algorithm using residual joint control and the ability to induce muscle responses to TMS delivered over the non-lesioned motor cortex. The present status of these developments was recently summarized in a Review article (Stinear, 2010). The author of this review included a model algorithm that, if supported with empirical evidence will "enable selection of appropriate motor rehabilitation strategies for individual patients on the basis of the integrity of the motor system and its capacity for functional reorganization". For the lower limb it will be some time before our understanding of the lower limb motor cortex during the recovery process after stroke has developed to a point where a similar algorithm can be constructed and tested. An early insight to the difficulty of constructing such an algorithm for walking recovery was provided by one of our recent studies that revealed a possible maladaptive role for the non-lesioned cortex (Madhavan et al., 2010). Using the ankle-tracking task described above we found that patients with reasonably well-recovered gait had greater difficulty performing an antiphase tracking task when there was evidence of ipsilateral conductivity between the non-lesioned hemisphere and their paretic limb TA (assessed with a novel TMS protocol). The antiphase pattern of movement involved simultaneous rhythmical dorsiflexion of one ankle together with plantarflexion of the other ankle (and vice versa) analogous to walking. Successful gait recovery prediction for the individual patient is likely to depend on several factors, including lesion location and size; residual muscle activation and balance; and more than one laboratory-based measure. An individual with a lesion involving the putamen is more likely to have an asymmetrical gait pattern (Alexander et al., 2009), and there is evidence that individuals with sub-cortical stroke may be more responsive to NIBS than individuals with cortical stroke (Ameli et al., 2009). While many individual parameters may play a role in recovery, lesion location, the integrity of the lesioned motor pathway and the involvement of the ipsilateral pathway assessed with TMS and MRI together with the assessment of residual muscle strength and balance are likely to be the main ingredients in developing a prognostic algorithm for walking recovery in the acute to subacute stage of stroke.

5. Conclusion

Together the studies discussed in this brief review provide strong evidence that a) instead of spinal circuits controlling walking with the assistance of motor cortex, motor cortex controls walking assisted by spinal circuits, and b) NIBS can be used to reduce the between-hemisphere asymmetry in motor system excitability after stroke despite the poor spatial resolution of NIBS and the close proximity of the two lower limb motor cortices. Early indications are that NIBS can be used to enhance fine motor control of ankle movement. However, this finding should not be construed to mean that enhanced motor control of a lower limb joint will translate into better walking recovery following neural insult such as stroke. Even if NIBS-enhanced motor control does yield promising functional outcomes, we should not assume that NIBS would be effective for all patients. These findings are intriguing but there are many questions still to be answered. For example, which part of the brain should we stimulate? Does stimulating a non-

motor area result in similar changes to motor cortical excitability? Are the effects of brain stimulation at least partly due to general arousal? Which therapies and stimulation types result in the best functional recovery? How soon after stroke should NIBS be applied? What is the best approach for an individual patient based on their surviving neural anatomy and physiology? Closely allied to this last question is: can we reliably predict lower limb recovery of a patient soon after stroke onset? Addressing these questions in future studies would strengthen our understanding of the neural mechanisms of recovery, likely promote some therapeutic approaches, and possibly retire others. Research is urgently needed to predict which patients have adequate surviving anatomical and physiological resources to enable walking recovery; which patients would benefit from NIBS; and to identify the optimal stimulation and therapeutic regimen for individual patients. The research conducted over the last decade or two has provided us with a sound platform upon which future research has a very good chance of transforming neurorehabilitation of walking recovery following stroke.

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References

Alexander, L.D., Black, S.E., Patterson, K.K., Gao, F., Danells, C.J. & McIlroy, W.E. (2009). Association between gait asymmetry and brain lesion location in stroke patients. *Stroke, 40*, 537-544.

Amassian, V.E., Stewart, M., Quirk, G.J. & Rosenthal, J.L. (1987). Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery, 20*, 74-93.

Ameli, M., Grefkes, C., Kemper, F., Riegg, F.P., Rehme, A.K., Karbe, H., Fink, G.R. & Nowak, D.A. (2009). Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Ann Neurol, 66*, 298-309.

Ardolino, G., Bossi, B., Barbieri, S. & Priori, A. (2005). Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *J Physiol, 568*, 653-663.

Barker, A.T., Jalinous, R. & Freeston, I.L. (1985). Non-invasive stimulation of human motor cortex. *Lancet, 1(8437)*, 1106-1107.

Brunnstrom, S. (1966). Motor testing procedures in hemiplegia: Based on sequential recovery stages. *Phy Ther, 46*, 357-375.

Capaday, C., Lavoie, B.A., Barbeau, H., Schneider, C. & Bonnard, M. (1999). Studies on the corticospinal control of human walking I. Responses to focal transcranial magnetic stimulation of the motor cortex. *J Neurophysiol*, *81*, 129-139.

Carey, J.R., Baxter, T.L. & Di Fabio, R.P. (1998). Tracking control in the nonparetic hand of subjects with stroke. *Arch Phys Med Rehabil, 79*, 435-441.

Chollet, F., DiPiero, V., Wise, R.J., Brooks, D.J., Dolan, R.J. & Frackowiak, R.S.J. (1991). The functional anatomy of motor recovery after stroke in humans: A study with positron emission tomography. *Ann Neurol, 29*, 63-71.

Crone, C. & Nielsen, J. (1994). Central control of disynaptic reciprocal inhibition in humans. *Acta Physiol Scand, 152*, 351-363.

Crone, C., Nielsen, J., Petersen, N., Ballegaard, M. & Hultborn, H. (1994). Disynaptic reciprocal inhibition of ankle extensors in spastic patients. *Brain, 117*, 1161-1168.

Day, B.L., Dressler, D., Maertens de Noordhout, A., Marsden, C.D., Nakashima, K., Rothwell, J.C. & Thompson, P.D. (1989). Electric and magnetic stimulation of human motor cortex: Surface EMG and single motor unit responses. *J Physiol, 412*, 449-473.

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone, P., Insola, A., Tonali, P.A., Ranieri, F., Huang, Y.Z. & Rothwell, J.C. (2005). Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *J Physiol, 565*, 945-950.

Di Lazzaro, V., Profice, P., Pilato, F., Dileone, M., Oliviero, A. & Ziemann, U. (2010). The effects of motor cortex rTMS on corticospinal descending activity. *Clin Neurophysiol, 121*, 464-473.

Drew, T. (1993). Motor cortical activity during voluntary gait modifications in the cat. I. Cells related to the forelimbs. *J Neurophysiol*, *70*, 179-199.

Duysens, J., Tax, A.A., Nawijn, S., Berger, W., Prokop, T. & Altenmuller, E. (1995). Gating of sensation and evoked potentials following foot stimulation during human gait. *Exp Brain Res, 105*, 423-431.

Eyre, J.A., Smith, M., Dabydeen, L., Clowry, G.J., Petacchi, E., Battini, R., Guzzetta, A. & Cioni, G. (2007). Is hemiplegic cerebral palsy equivalent to amblyopia of the corticospinal system? *Ann Neurol*, *62*, 493-503.

Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G. & Marsden, C.D. (1992). Interhemispheric inhibition of the human motor cortex. *J Physiol, 453*, 525-546.

Feydy, A., Carlier, R., Roby-Brami, A., Bussel, B., Cazalis, F., Pierot, L., Burnod, Y. & Maier, M.A. (2002). Longitudinal study of motor recovery after stroke: Recruitment and focusing of brain activation. *Stroke, 33*, 1610-1617.

Forrester, L.W., Roy, A., Krebs, H.I. & Macko, R.F. (2011). Ankle training with a robotic device improves hemiparetic gait after a stroke. *Neurorehabil Neural Repair, 25*, 369-377.

Fregni, F., Boggio, P.S., Mansur, C.G., Wagner, T., Ferreira, M.J.L., Lima, M.C., Rigonatti, S.P., Marcolin, M.A., Freedman, S.D., Nitsche, M.A. & Pascual-Leone, A. (2005). Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport, 16,* 1551-1555.

Furubayashi, T., Terao, Y., Arai, N., Okabe, S., Mochizuki, H., Hanajima, R., Hamada, M., Yugeta, A., Inomata-Terada, S., Ugawa, Y., Furubayashi, T., Terao, Y., Arai, N., Okabe, S., Mochizuki, H., Hanajima, R., Hamada, M., Yugeta, A., Inomata-Terada, S. & Ugawa, Y. (2008). Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. *Exper Brain Res* 185, 279-286.

Grillner, S. & Rossignol, S. (1978). On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Res, 146,* 269-277.

Hankey, G.J. (1999). Stroke: How large a public health problem, and how can the neurologist help? *Arch Neurol*, *56*, 748-754.

Hansen, N.L., Hansen, S., Christensen, L.O.D., Petersen, N.T. & Nielsen, J.B. (2001). Synchronization of lower limb motor unit activity during walking in human subjects. *J Neurophysiol, 86(3)*, 1266-1276.

Hiraga, A., Uzawa, A., Tanaka, S., Ogawara, K. & Kamitsukasa, I. (2009). Pure monoparesis of the leg due to cerebral infarctions: A diffusion-weighted imaging study. *J Clin Neurosci, 16*, 1414-1416.

Hoffmann, P. (1910). Contributions to the knowledge of human reflexes with particular into account the electrical phenomena. *Arch Anat Physiol, 1*, 223-246.

Iglesias, C., Nielsen, J.B. & Marchand-Pauvert, V. (2008). Corticospinal inhibition of transmission in propriospinal-like neurones during human walking. *Eur J Neurosci, 28,* 1351-1361.

Jayaram, G., Santos, L. & Stinear, J.W. (2007). Spike-timing-dependent plasticity induced in resting lower limb cortex persists during subsequent walking. *Brain Res, 1153*, 92-97.

Jayaram, G. & Stinear, J.W. (2008). Contralesional paired associative stimulation increases paretic lower limb motor excitability post-stroke. *Exp Brain Res, 185*, 563-570.

Jayaram, G. & Stinear, J.W. (2009). The effects of transcranial stimulation on paretic lower limb motor excitability during walking. *J Clin Neurophysiol, 26*, 272-279.

Jeffery, D.T., Norton, J.A., Roy, F.D., Gorassini, M.A., Jeffery, D.T., Norton, J.A., Roy, F.D. & Gorassini, M.A. (2007). Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. *Exp Brain Res, 182*, 281-287.

Johansen-Berg, H., Dawes, H., Guy, C., Smith, S.M., Wade, D.T. & Matthews, P.M. (2002). Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain, 125*, 2731-2742.

Kasai, T., Hayes, K.C., Wolfe, D.L. & Allatt, R.D. (1992). Afferent conditioning of motor evoked potentials following transcranial magnetic stimulation of motor cortex subjects. *Electroencephalogr Clin Neurophysiol, 85*, 95-101.

Kapreli, E., Athanasopoulos, S., Papathanasiou, M., Van Hecke, P., Strimpakos, N., Gouliamos, A., Peeters, R. & Sunaert, S. (2006). Lateralization of brain activity during lower limb joints movement: An fMRI study. *Neuroimage, 32*, 1709-1721.

Knikou, M. (2008). The H-reflex as a probe: Pathways and pitfalls. *J Neurosci Methods, 171*, 1-12.

Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P. & Marsden, C.D. (1993). Corticocortical inhibition in human motor cortex. *J Physiol, 471*, 501-519.

Lang, N., Siebner, H.R., Ward, N.S., Lee, L., Nitsche, M.A., Paulus, W., Rothwell, J.C., Lemon, R.N., Frackowiak, R.S., Lang, N., Siebner, H.R., Ward, N.S., Lee, L., Nitsche, M.A., Paulus, W., Rothwell, J.C., Lemon, R.N. & Frackowiak, R.S. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur J Neurosci*, *22*, 495-504.

Liebetanz, D., Nitsche, M.A., Tergau, F. & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain, 125*, 2238-2247.

Madhavan, S., Rogers, L.M. & Stinear, J.W. (2010). A paradox: After stroke, the non-lesioned lower limb motor cortex may be maladaptive. *Euro J Neurosci, 32*, 1032-1039.

Madhavan, S., Weber, K.A. & Stinear, J.W. (2011). Non-invasive brain stimulation enhances fine motor control of the hemiparetic ankle: Implications for rehabilitation. *Exp Brain Res, 209*, 9-17.

Miyai, I., Yagura, H., Oda, I., Konishi, I., Eda, H., Suzuki, T. & Kubota, K. (2002). Premotor cortex is involved in restoration of gait in stroke. *Ann Neurol, 52*, 188-194.

Morita, H., Crone, C., Christenhuis, D., Petersen, N.T. & Nielsen, J.B. (2001). Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity. *Brain, 124*, 826-837.

Nathan, P.W. & Smith, M.C. (1973). Effects of two unilateral cordotomies on the motility of the lower limbs. *Brain, 96*, 471-494.

Nitsche, M.A., Nitsche, M.S., Klein, C.C., Tergau, F., Rothwell, J.C. & Paulus, W. (2003). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clin Neurophysiol, 114*, 600-604.

Nitsche, M.A. & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol, 527*, 633-639.

Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W. & Tergau, F. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol, 568*, 290-303.

Perry, J., Garrett, M., Gronley, J.K. & Mulroy, S.J. (1995). Classification of walking handicap in the stroke population. *Stroke, 26*, 982-989.

Petersen, N., Christensen, L.O. & Nielsen, J. (1998). The effect of transcranial magnetic stimulation on the soleus H reflex during human walking. *J Physiol 513*, 599-610.

Petersen, N.T., Butler, J.E., Marchand-Pauvert, V., Fisher, R.J., Ledebt, A., Pyndt, H.S., Hansen, N.L. & Nielsen, J.B. (2001). Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *J Physiol, 537.2*, 651-656.

Pijnappels, M., Van Wezel, B.M., Colombo, G., Dietz, V. & Duysens, J. (1998). Cortical facilitation of cutaneous reflexes in leg muscles during human gait. *Brain Res, 787*, 149-153.

Prior, M.M. & Stinear, J.W. (2006). Phasic spike-timing-dependent plasticity of human motor cortex during walking. *Brain Res, 1110*, 150-158.

Roche, N., Lackmy, A., Achache, V., Bussel, B. & Katz, R. (2011). Effects of anodal transcranial direct current stimulation over the leg motor area on lumbar spinal network excitability in healthy subjects. *J Physiol, 589*, 2813-2826.

Rogers, L.M., Brown, D.A. & Stinear, J.W. (2011). The effects of paired associative stimulation on knee extensor motor excitability of individuals post-stroke: A pilot study. *Clin Neurophysiol, 122*, 1211-1218.

Roy, A., Forrester, L.W. & Macko, R.F. (2011). Short-term ankle motor performance with ankle robotics training in chronic hemiparetic stroke. *J Rehabil Res Dev, 48*, 417-429.

Schubert, M., Curt, A., Colombo, G., Berger, W. & Dietz, V. (1999). Voluntary control of human gait: Conditioning of magnetically evoked motor responses in a precision stepping task. *Exp Brain Res, 126*, 583-588.

Schwerin, S., Dewald, J.P.A., Haztl, M., Jovanovich, S., Nickeas, M. & MacKinnon, C. (2007). Ipsilateral versus contralateral cortical motor projections to a shoulder adductor in chronic hemiparetic stroke: Implications for the expression of arm synergies. *Exp Brain Res, 185(3)*, 509-519, 10.1007/s00221-007-1169-8.

Sommerfeld, D.K., Eek, E.U.-B., Svensson, A.-K., Holmqvist, L.W. & von Arbin, M.H. (2004). Spasticity after stroke. *Stroke 35*, 134-140.

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*, 572-584.

Stinear, C.M. (2010). Prediction of recovery of motor function after stroke. *Lancet Neurology, 9*, 1228-1232.

Stinear, C.M., Barber, P.A., Coxon, J.P., Fleming, M.K. & Byblow, W.D. (2008). Priming the motor system enhances the effects of upper limb therapy in chronic stroke. *Brain, 131*, 1381-1390.

Stinear, J.W. & Hornby, T.G. (2005). Stimulation-induced changes in lower limb corticomotor excitability during treadmill walking in humans. *J Physiol, 567*, 701-711.

Tanaka, S., Hanakawa, T., Honda, M. & Watanabe, K. (2009). Enhancement of pinch force in the lower leg by anodal transcranial direct current stimulation. *Exp Brain Res, 196*, 459-465.

Tilson, J.K., Sullivan, K.J., Cen, S.Y., Rose, D.K., Koradia, C.H., Azen, S.P., Duncan, P.W. & Locomotor Experience Applied Post Stroke Investigative, T. (2010). Meaningful gait speed improvement during the first 60 days poststroke: Minimal clinically important difference. *Phys Ther, 90*, 196-208.

Tokimura, H., Di Lazzaro, V., Tokimura, Y., Oliviero, A., Profice, P., Insola, A., Mazzone, P., Tonali, P. & Rothwell, J.C. (2000). Short latency inhibition of human hand motor cortex by somatosensory input from the hand. *J Physiol, 523*, 503-513.

Traversa, R., Cicinelli, P., Oliveri, M., Giuseppina Palmieri, M., Filippi, M.M., Pasqualetti, P. & Rossini, P.M. (2000). Neurophysiological follow-up of motor cortical output in stroke patients. *Clin Neurophysiol, 111*, 1695-1703.

Traversa, R., Cicinelli, P., Pasqualetti, P., Filippi, M. & Rossini, P.M. (1998). Follow-up on interhemispheric differences of motor evoked potentials from the "affected" and "unaffected" hemispheres in human stroke. *Brain Res, 803*, 1-8.

Trompetto, C., Assini, A., Buccolieri, A., Marchese, R. & Abbruzzese, G. (2000). Motor recovery following stroke: A transcranial magnetic stimulation study. *Clin Neurophysiol, 111*, 1860-1867.

Uy, J., Ridding, M.C., Hillier, S., Thompson, P.D. & Miles, T.S. (2003). Does induction of plastic change in motor cortex improve leg function after stroke? *Neurology*, *61*, 982-984.

Wade, D.T. & Hewer, R.L. (1987). Functional abilities after stroke: Measurement, natural history and prognosis. *J Neurol Neurosurg Psychiatry, 50*, 177-182.

Weiller, C., Chollet, F., Friston, K., Wise, R. & Frackowiak, R. (1992). Functional reorganization of the brain in recovery from striatocapsular infarction in man. *Ann Neurol, 31*, 463-472.