Motor Priming in Neurorehabilitation

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Priming is a type of implicit learning wherein a stimulus prompts a change in behavior. Priming has been long studied in the field of psychology. More recently, rehabilitation researchers have studied motor priming as a possible way to facilitate motor learning. For example, priming of the motor cortex is associated with changes in neuroplasticity that are associated with improvements in motor performance. Of the numerous motor priming paradigms under investigation, only a few are practical for the current clinical environment, and the optimal priming modalities for specific clinical presentations are not known. Accordingly, developing an understanding of the various types of motor priming paradigms and their underlying neural mechanisms is an important step for therapists in neurorehabilitation. Most importantly, an understanding of the methods and their underlying mechanisms is essential for optimizing rehabilitation outcomes. The future of neurorehabilitation is likely to include these priming methods, which are delivered prior to or in conjunction with primary neurorehabilitation therapies. In this Special Interest article, we discuss those priming paradigms that are supported by the greatest amount of evidence, including (i) stimulation-based priming, (ii) motor imagery and action observation, (iii) sensory priming, (iv) movement-based priming, and (v) pharmacological priming.

Video Abstract available. (see Supplemental Digital Content 1, http://links.lww.com/JNPT/A86) for more insights from the authors.

Key words: *Motor cortex, priming, brain stimulation, Bilateral movement, Sensory stimulation*

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INTRODUCTION

Priming is defined as a change in behavior based on previous stimuli. Priming, which may occur after a single learning episode, is a type of implicit learning. The role of implicit learning in physical therapy (PT) has been the subject of recent investigation.[1–4] Priming-induced learning is different from other types of implicit learning because skill-learning requires repetition.[5] Studies of priming originated in psychology, but have since been investigated in neuroscience, neurorehabilitation, and cognitive neuroscience using behavioral and brain mapping techniques. These studies, both translational and clinical, have been examining motor priming as a tool for inducing neuroplasticity and enhancing the effects of rehabilitation. Priming can be categorized as a restorative intervention that reduces impairment by targeting underlying neural mechanisms in neurological disorders.[6]

Priming stimuli can be from the same modality as the accompanying task (modal-specific) or from a different modality (cross-modal). An example of modal-specific priming is bilateral mirror symmetrical movement (a form of movement-based priming) that is performed prior to a motor task practice and has been found to increase the rate of motor learning in neurologically healthy subjects.[7] Cross-modal priming can also be used to enhance motor learning. For example, semantic priming, reading relevant words describing an action, can produce more efficient movements in young, neurologically healthy adults compared with a control condition.[8] Although there are examples of cross-modal priming producing positive results, results from studies in the psychology literature have reported that the effects of priming are smaller with cross-modal priming as compared with priming using the same modality.[9]

Initial interest in priming was fueled by popular psychology research completed several decades ago that included the isolation of memory subtypes and examination of individuals with amnesia.[10] Priming is an action that generates a type of implicit memory; therefore, researchers were surprised when individuals with amnesia had intact priming as this indicates that priming, unlike explicit memory, is not controlled by the medial temporal lobe. In contrast to explicit memory, priming is believed to arise from facilitated neural processing in a variety of cortical regions that are specific to the stimulus and the accompanying task. For example, the posterior cortex (extratriatal area) is implicated in perceptual priming, whereas the prefrontal cortex is implicated in conceptually based semantic priming.[9]

The general theory underlying priming is that the brain, that has been primed by prior activation is generally more responsive to the accompanying or subsequent training. Priming presupposes that enhanced neural activity before or during training can facilitate the activation of long-term potentiation- (LTP) or long-term depression- (LTD) like mechanisms.[11] Two proposed neural mechanisms for priming include *gating* and *homeostatic plasticity*.[12] Gating occurs by disinhibition of intracortical inhibitory circuits as a result of an increase in

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calcium in the targeted cortical neurons. Gating occurs instantaneously and is achieved *concurrently with* motor training.[11] Homeostatic plasticity is the ability of neurons to increase excitability after a period of low synaptic activity (and conversely, to decrease excitability after a period of high synaptic activity) and is related to changes in postsynaptic glutamate receptors.[11,12] The time scale of homeostatic metaplasticity, in comparison to gating, is protracted, and hence the resting state of neurons is modulated *prior to* motor training to induce synaptic plasticity.

Neural mechanisms mediating motor priming vary according to priming method. However, they may produce similar effects that may include increased excitability or normalization of inhibition, which coincide with improvements in motor behavior.[13] Methods of priming the motor cortex that are most relevant to rehabilitation include (1) stimulation-based priming[14–22]; (2) motor imagery and action observation[23–28]; (3) manipulation of sensory input[29–31]; (4) movement-based priming[7,32–36]; and (5) pharmacology-based priming.[37] Studies examining priming for the primary motor cortex (M1) are increasing in number. Hence, it is important for neurorehabilitation professionals to be aware of the basic principles of priming and how they influence motor training (Table 1).

A search of the literature through December 2013 was performed using the search engines: PubMed, Web of Science, and Ovid. Key words used were "priming" combined with one of the following terms: "brain plasticity," "motor recovery," "TMS," "rTMS," "tDCS," "PAS," "PNS," "motor imagery," "action observation," "movement based," "bilateral movements," unilateral movements, "aerobic exercise," "pharmacology based," "sensory priming," "peripheral nerve stimulation," "temporary functional deafferentation," and "vibration." Peer-reviewed articles were selected if they met the following criteria: (1) written in English, (2) involved more than 1 human participant, and (3) included at least 1 motor performance-based outcome measure, and (4) fit the definition of "priming" as described in the "Introduction" section. Papers that were cited in the selected articles, such as mechanistic or studies using animal models, were also included for background information. We also included studies that cited the selected articles. The 5 priming paradigms are described later.

Table 1. Paradigms of Motor Priming

Stimulation-based priming
Repetitive transcranial magnetic stimulation
Transcranial direct current stimulation
Paired associative stimulation
Peripheral electrical nerve stimulation[a]
Motor imagery/action observation
Mirror therapy
Video directed
Audio directed
Therapist directed
Movement-based priming
Repetitive movements: unilateral and/or bilateral symmetrical, active and/or passive
Aerobic exercise
Pharmacological based priming
Amphetamines
Dopaminergic agents
Norepinephrine
Sensory-based priming
Peripheral electrical nerve stimulation[a]
Muscle vibration
Temporary functional deafferentation

[a]Cross-referenced under 2 paradigms.

STIMULATION-BASED MOTOR PRIMING

Four categories of stimulation-based priming are discussed in this section: (1) repetitive transcranial magnetic stimulation (rTMS); (2) transcranial direct current stimulation (tDCS); (3) paired associative stimulation (PAS); and (4) peripheral nerve stimulation (PNS). Stimulation-based motor priming has been gaining popularity with the advent of painless noninvasive brain-stimulation techniques such as rTMS and tDCS. Depending on the pulse rate of TMS or polarity of tDCS, these protocols facilitate or inhibit cortical activity and produce changes in associated cognitive and motor behavior. Following a single session (5-15 minutes) of these stimulation protocols, neural changes have persisted poststimulation for up to 2 hours.[22,38] These stimulation protocols, in combination with motor task practice (2-4 weeks; 15 minutes/session; 3 sessions/week), have lasting functional effects up to 3 months.[39]

Transcranial magnetic stimulation involves rapidly changing magnetic fields to induce electrical currents in the neural tissue, which excites or inhibits the activity of the cortical neurons according to the pulse rate applied.[40] Long trains of low-frequency rTMS (1 Hz) applied over the M1 decrease resting corticospinal excitability; high-frequency (5-20 Hz) rTMS trains usually increase corticospinal excitability.[41] A more recent rTMS protocol, known as theta burst stimulation, involving bursts of 3 to 5 pulses at 50 to 100 Hz repeated at 5 Hz (theta rhythm), can elicit similar changes as rTMS using less stimulation time and lower intensities.[42] Theta burst stimulation, which is intermittent or continuous, upregulates or downregulates corticospinal excitability, respectively. Repetitive TMS-mediated changes in neural plasticity could be mediated by LTP-like or LTD-like mechanisms. Other investigators suggest that rTMS is more likely to change the level of excitability of the corticospinal system, rather than the effectiveness of synaptic transmission within the cortex.[43]

Transcranial direct current stimulation involves delivering low-intensity direct electric currents (0.5-2 mA) through an active electrode on the scalp overlying the cortical region to be targeted.[44,45] Some of this electrical current is thought to polarize or depolarize cortical neurons depending on the polarity of currents applied. Anodal currents result in upregulation of cortical excitability, while cathodal currents result in downregulation. During stimulation, effects of tDCS arise from modulation of neuronal membrane potential, altering the conductance of sodium and calcium channels. The aftereffects of tDCS, similar to rTMS, may also be due to mechanisms similar to LTP and LTD, involving the modulation of *N*-methyl-D-aspartate receptors and inhibitory GABA (γ-aminobutyric acid)-ergic synapses.[46]

Neural recovery mechanisms after stroke are only partially understood; however, evidence indicates that a balance

of excitability between the lesioned and nonlesioned hemispheres is associated with better recovery. Often the ipsilesional hemisphere has decreased excitability, while the contralesional hemisphere has increased excitability. The theory of asymmetric hemispheric excitability poststroke is well known in the stroke rehabilitation community and can explain some of the mechanisms of stimulation-based priming. Briefly, there is an imbalance of transcallosal inhibition resulting in reduced inhibition from the ipsilesional to the contralesional hemisphere[33] and abnormally high inhibition from contralesional to ipsilesional.[47] A balance of hemispheric excitability is associated with improved poststroke motor recovery.[48,49] In stroke, a balance of excitability can be produced by upregulating neuronal excitability in the ipsilesional cortex or downregulating the contralesional cortex.[49] Low-frequency rTMS to the contralesional[15,50–54] or anodal tDCS to the ipsilesional M1[55] has been associated with significant changes in upper-limb and lower-limb functional tasks in participants with stroke.[56] Other areas of stimulation can include nonprimary motor regions such as dorsal and ventral premotor areas, supplementary motor area,[57,58] or cerebellum. These techniques have also been investigated in other neurologically affected populations such as Parkinson's disease,[59] multiple sclerosis,[60] and cerebellar ataxia.[61] Neither rTMS nor tDCS is currently approved by the Food and Drug Administration as therapies for persons with stroke; therefore, in the United States, their use is limited to research studies. There is also great variability among individuals in magnitude and duration of rTMS aftereffects, which are influenced by stimulation parameters. Further research is needed to determine the most efficacious protocols and the individuals who will benefit most from these approaches.

Apart from rTMS and tDCS, PAS represents a third category of stimulation-based priming. The PAS approach involves paired pulses, one from PNS and the other from cortical stimulation (using TMS).[62] Developed from animal models, PAS emphasizes the potent interaction of somatosensory input and cortical motor circuits. Because the cortical modulation after PAS is long-lasting, the underlying mechanism may be similar to LTP or LTD. However, cortical changes following PAS occur in the absence of active movement. Characteristics of PAS include that the ensuing cortical modulation is rapid, persistent, and can be reversed.[63] The interval between the 2 stimuli can be timed to facilitate upregulation or downregulation of corticomotor excitability. If the afferent volley is timed to arrive prior to the TMS stimulation, upregulation of excitability will occur. A common paradigm is median nerve stimulation at the wrist followed by TMS to hand area of motor cortex with the afferent volley timed to arrive prior to TMS stimulation.[64] This paradigm of PAS has been shown to increase cortical excitability in neurologically healthy participants who are physically active. The opposite occurs when the afferent volley arrives just after stimulation. Rogers et al[65] applied a PAS paradigm to the lower limb in participants with stroke and neurologically healthy participants. Peripheral nerve stimulation applied to the femoral nerve was paired with TMS of the lower limb primary motor cortex. The estimated arrival of the afferent volley occurred 8 ms after delivery of the cortical stimulus. Paired associative stimulation was delivered to the nonparetic vastus medialis of participants with chronic stroke and the right limb motor system of neurologically health participants at a frequency of 0.19 Hz. As hypothesized, downregulation occurred in the cortex controlling the nonparetic limb of the participants with stroke and the left leg of neurologically healthy participants. However, results from participants with stroke were extremely variable. Further research is needed to determine the characteristics of persons with stroke who will benefit from either upregulation or downregulation PAS protocols.

A fourth category of stimulation-based priming is PNS. Electrical stimulation has long been used clinically to stimulate the motor nerves and activate muscle responses as part of rehabilitation. More recently however, PNS has been found to influence cortical excitability, and therefore PNS represents a viable approach to priming the nervous system. We discuss PNS and underlying mechanisms in a subsequent section related to sensory-based priming.

MOTOR IMAGERY AND ACTION OBSERVATION

Many psychological and neurophysiological studies indicate that intending to perform an action, imagining an action, observing an action, and execution of the action share the same functional networks in the brain.[66] Motor imagery has been defined as "a dynamic state during which the representation of a given motor act is internally rehearsed within working memory without any overt motor output."[66] We consider action observation, observing performance of a goal-directed action, as one type of motor imagery.[67] Other types of motor imagery include mirror therapy, computer-directed imagery, imagery directed by audiotape, or imagery directed by a therapist. These techniques can be used as the actual therapy or as priming approaches prior to subsequent motor practice. The structured and repetitive use of motor imagery is termed mental practice.[68] Although most of the early studies using mental imagery have been in sports science, mental imagery is increasingly being tested for efficacy in neurorehabilitation populations, including spinal cord injury,[69] Parkinson's disease,[70] and stroke.[71]

Mirror neurons, a class of neurons in the ventral premotor cortex and inferior parietal lobule, respond during action observation.[72,73] Grasping studies using brain imaging and magneto-encephalography have revealed an increase in regional cerebral blood flow during motor imagery and action observation.[72,74–79] Studies using TMS have reported that motor imagery and action observation influence corticospinal excitability.[80] This result is specific to the muscle involved in the action and to the type of movement performed.[80,81] For example, motor imagery of elbow flexion but not motor imagery of elbow extension influences the amplitude of motor evoked potentials of the elbow flexor muscles.[80] Thus, successful use of mental practice requires task specificity of practice. Other studies have shown that mental practice consisting of imagined performance of repeated maximal isometric contractions of the abductor muscles in the hand can improve muscle force.[82]

Malouin and colleagues[68] recommend continued research in mental practice techniques especially in the subacute phase of poststroke rehabilitation. One benefit of mental practice with physical practice is the opportunity to increase the repetitions when the severity of motor deficits

interferes with an increase in actual physical repetitions. A recent Cochrane review on mental imagery provides evidence that mental practice in combination with physical practice more effectively improves upper-extremity function than physical practice alone.[83] However, studies using mental imagery have been limited and even ambiguous because of small sample size, heterogeneity of intervention designs, and lack of an objective measure of mental practice. The reader is encouraged to review articles by Wondrusch and Schuster-Amft[84] for ideas for introducing concepts and facilitating adherence during imagery training, and by Malouin and colleagues[68] for a detailed review of the various modes of delivery of motor imagery in neurorehabilitation.

MOVEMENT-BASED PRIMING

Movement-based priming includes any type of repetitive or continuous movement that is done to enhance the effect of accompanying therapy. Movement-based priming typically includes bilateral or unilateral movements, mirror symmetric active or passive movements, or any type of exercise such as aerobic, isometric, and balance exercises. Repetitive movements can be single-joint movements such as repetitive unilateral wrist or elbow flexion and extension[35] or they can be bilateral symmetrical movements of both limbs such as bilateral wrist flexion-extension. The latter is known in the literature as active-passive bilateral therapy.[33,34]

The symmetry constraint is well-documented in the motor control literature.[85] That is, when increasing the speed of bilateral movements, there is a natural propensity toward symmetrical movement of both limbs. Training protocols using bilateral symmetrical movement (termed bilateral isokinematic training) have been used to rehabilitate the upper limb with varying results.[86–89] Bilateral priming is an offshoot of bilateral training but differs in purpose and proposed mechanisms. Bilateral training uses mirror-symmetric movements as the actual motor training movements, and the proposed mechanism is exploitation of the symmetry constraint. Bilateral motor priming, however, utilizes the same type of mirror-symmetric movements before implementing other functional training movements targeting the upper limb. The purpose of the symmetrical movements in bilateral priming is to prime the brain for accompanying functional motor training.[7]

Some bilateral priming studies provide strong evidence that improvement in motor function coincides with normalization of transcallosal inhibition, resulting in greater balance in excitability between the hemispheres.[32–35] In neurologically healthy subjects, mirror-symmetric movements, but not alternating movements, were associated with improvements in motor performance and interhemispheric disinhibition.[7] Active-passive bilateral therapy (also known as bilateral priming) uses a low-tech device known as "the rocker," which was first described by Stinear and Byblow.[34] With the forearms in neutral, both hands are positioned between 2 plates attached to axles. The individuals' wrists are aligned with the axles allowing wrist flexion and extension within the rotating plates. An actuator connects each axle allowing the less-affected limb to drive the more-affected one in symmetrical wrist flexion and extension while providing an inertial advantage that facilitates hundreds of repetitions. Active movement in the affected wrist is not essential for this technique. Thus, individuals at all levels of poststroke recovery can use this priming method. Bilateral priming with the rocker is not possible if the individual has such severe wrist spasticity that passive range-of-motion is extremely difficult.

Studies using bilateral priming in the subacute phase of stroke have reported beneficial results.[32,36] In a randomized controlled trial of stroke survivors in the subacute phase, the bilateral priming dosage was 15 min/day followed by 30 minutes of upper limb occupational or PT. The bilateral priming plus therapy group experienced an accelerated recovery course, compared with controls, and was approximately 3 times more likely to reach the primary endpoint (75% of the total Action Research Arm Test score) by 12 weeks.[32] Bilateral priming studies have also found improvements in participants in the chronic phase of stroke.[33,35]

The potential for aerobic exercise to promote motor learning and improve functional recovery is being explored. Regular exercise not only improves aerobic fitness but also leads to improved learning,[90] enhanced cognitive flexibility[91] and increased motor cortex excitability.[92] The mechanisms by which exercise promotes brain function are unclear. One potential mechanism is increased expression of brain-derived neurotrophic factor, which supports the survival of existing neurons and encourages growth and differentiation of new neurons and synapses.[93] Aerobic exercise increases brain brain-derived neurotrophic factor levels.[94] Exercise also enhances neuroplastic responses to noninvasive brain stimulation in healthy individuals.[64,92] The potential for exercise to serve as a motor priming intervention remains underexplored, but preliminary work in Parkinson's disease is promising.[95]

Other types of movement-induced priming could include voluntary teeth-clenching,[96] rhythmic arm-swinging,[97] and pedaling.[98] The effects of these paradigms on motor recovery are unknown; they have been suggested because of their documented effect on corticomotor excitability. Compared to stimulation-based priming, research on movement-based strategies to prime the motor system is minimal. However, more research in this area would be of great value for informing clinical practice. There are few contraindications to movement-based priming, and costs are minimal, making it a valuable alternative to rTMS or tDCS.

PHARMACOLOGY-BASED PRIMING

Pharmacological agents are among the oldest and most common adjuvants for inducing priming effects. The principles behind pharmacotherapy as an approach to motor priming have been mainly developed from animal studies and conflicting results are seen in human studies. Based on successful animal studies, 5 groups of pharmacological agents have been proposed to enhance motor recovery after neurological injury: amphetamines, dopaminergic agents, norepinephrines, cholinergic agents (ACh), and selective serotonin reuptake inhibitors (SSRIs).

Amphetamine, which increases levels of norepinephrine in the brain and spinal cord, has been studied extensively as an approach to motor priming. Amphetamine promotes recovery of function in animal models of brain injury. A single low dose of D-amphetamine given 24 hours after injury accelerated

recovery in a rat-stroke model.[99] A 2007 Cochrane Review based on 10 clinical trials indicated improvements in motor function when using amphetamine in combination with motor therapy for stroke.[37] In these studies, the typical dosage of amphetamine varied from 2.5 to 10 mg/day and this was combined with some form of rehabilitation training. In contrast, other amphetamine studies have failed to demonstrate beneficial effects on recovery in participants with stroke.[100,101] The range of potentially undesirable side effects (increases in blood pressure and heart rate, and death) and the conflicting results have limited the use of amphetamine for motor recovery.

Dopaminergic agents such as levodopa are increasingly being evaluated for beneficial effects on motor outcomes adjuvants because of their low incidence of side effects. Dopamine plays a significant role in synaptic plasticity and in the formation of motor memories. The use of levodopa has long been investigated in Parkinson's disease with promising results, such as decreases in symptoms and improvements in motor function. A few studies have demonstrated improvements in motor performance in participants with stroke when levodopa (100 mg/day) was combined with motor training,[102–104] while others have demonstrated no significant change.[105] The beneficial role of levodopa in other neurological populations is unclear because of the absence of large randomized controlled trials.[106]

Norepinephrine is another crucial mediator of neural plasticity by assisting in mediating learning and memory.[107,108] Numerous studies, investigating the effects of norepinephrine inhibitors (eg, atomoxetine) in the stroke model, indicate the efficacy of these drugs in enhancing motor outcomes. Atomoxetine is favorable for post-stroke rehabilitation because it has less side effects and a longer half-life which is beneficial for motor training.[109]

Cholinergic agents have also received attention as possible adjuvants to motor rehabilitation. Results from animal studies have demonstrated that cholinergic transmission contributes to learning and memory formation and influences LTP[110,111] while cholinergic lesions reduce reorganization and learning.[112] In humans, deficits in cholinergic transmission are related to memory loss, while acetyl cholinesterase inhibitors (AchET inhibitors) appear to have a beneficial effect on cognitive performance.[113] AchET inhibitors have shown to improve verbal memory encoding in individuals with multiple sclerosis.[114] A few studies of participants with stroke have reported improvements in sensorimotor function of the hemiplegic limb[115,116] and improved speech[117] when motor training was combined with AchET inhibitors such as donepezil. Although cholinergic agents are generally safe, they have potentially troubling side effects such as nausea, diarrhea, and weight loss, which do not make them a popular choice.

The role of selective SSRIs has been well established in neurologically healthy and diseased animal brains. Selective serotonin reuptake inhibitors s are known to have a neurotrophic and neuroprotective effect and can indirectly affect the adrenergic system.[118,119] Beneficial effects of SSRIs have been noted in animal models of stroke, multiple sclerosis, and epilepsy. In humans, their main clinical use is for mood disorders. A few studies have demonstrated that the SSRI, fluoxetine, may have a favorable effect on motor recovery after stroke.[120,121] In a 2010 Cochrane review, meta-analysis of 52 SSRI trials involving participants with stroke concluded that SSRIs may positively affect motor recovery (disability and neurological deficits were some of the outcomes analyzed).[122] However, there was insufficient evidence to make recommendations for clinical practice. Conflicting results have been noted regarding the role of SSRIs in motor recovery for persons with Parkinson's disease[123,124] and traumatic brain injury.[125] Similar to other pharmacological agents, the role of SSRIs in motor recovery is still uncertain. Also as many persons with neurological disorders present with depression, the effect of SSRIs is unclear since results could be influenced either by improvements in the neural motor system or by improvement in the underlying depression.

In conclusion, the clinical studies using pharmacological agents as primers in humans are limited and do not provide evidence of the efficacy of one drug over another. Side effects and drug interactions limit participation by individuals with neurological disorders. Larger randomized controlled trials with more objective measures (such as pre- and post-fMRI and TMS measures) are needed to provide more conclusive evidence of the efficacy of pharmacotherapy for motor rehabilitation.

SENSORY PRIMING

Reduced somatosensory input to an extremity is severely disabling and may reduce safety and limit movement that is not reliant on visual feedback.[126] Neurorehabilitation therapists are responsible for teaching clients compensatory techniques to achieve safe performance of gait and activities of daily living by minimizing exposure of the impaired limb to potentially harmful situations. As part of their role, neurorehabilitation clinicians strive to reduce sensory impairment and, subsequently, improve sensory and movement function in their clients with neurological disorders.

Modulation of sensory input has been investigated as a motor priming technique especially when there is reduced sensation in 1 or more upper or lower extremities. Methods of priming that target the sensory system include both sensory stimulation and sensory deprivation. In both paradigms, changes in somatosensory cortex influence motor cortex due to strong connections between these 2 cortical areas.[127]

Prolonged peripheral nerve electrical stimulation can change spinal and supraspinal systems.[31,128] Repetitive sensory stimulation to the ulnar and median nerves prior to motor training (or administered without training) improved sensory and motor functions,[129–131] normalized somatosensory-evoked potentials,[130–131] and reduced short-interval cortical inhibition (SICI) in individuals who have survived a stroke.[129] Some authors recommend PNS as a treatment for individuals with little or no voluntary movement[30] or without the cognitive and/or physical endurance to participate in extensive practice.[131] In individuals with incomplete spinal cord injury, large improvements in motor function, sensory function, and cortical excitability were found when cutaneous sensory stimulation was delivered during motor task practice.[30]

Various paradigms using vibration of agonist[132] or antagonist muscles[133,134] have been described. Vibration of

forearm extensors (agonist muscles) resulted in improved scores on the Box and Block test, possibly because of stimulation of the cortical inhibitory circuits directed to the antagonist muscle (forearm flexors), thereby reducing spasticity and improving function.[132] Cordo and colleagues[133,134] found that vibration of the antagonist muscle during assisted movement with visual feedback reduced impairment and improved function in individuals with chronic upper extremity hemiparesis and chronic lower extremity hemiparesis due to stroke. For the upper extremity, vibration was applied to extensor digitorum communis and extensor pollicis longus while the participant was closing the hand, and then to flexor digitorum profundus and flexor pollicis longus while the participant attempted to open the hand.[133] It is possible that vibration of the antagonist muscle enhanced sensory feedback to the limb, thus enabling an increase in the magnitude of movement.

Changes occur in somatosensory cortex after deprivation of sensory input.[29,135–139] Alterations in the cortical map as a result of deafferentation are rapid and possibly the result of the unmasking of preexisting excitatory connections.[135] Researchers have investigated the use of temporary functional deafferentation (TFD), wherein temporary deafferentation of a body part is induced using mechanical (ie, tourniquet) or pharmacological as a priming mechanism prior to motor training of the hand in individuals with stroke.[126] Temporary functional deafferentation methods vary in both the anesthetized limb area and anesthetic modality. For example, TFD of the less-affected hand has been used for priming prior to distal motor training of the more-affected one.[140,141] Floel and colleagues[141] found improvement in hand function, after training, that was associated with a decrease in intercortical inhibition from the deafferented cortex, consistent with results from animal studies.[142] Other studies have investigated behavioral and neural effects of TFD by deafferenting the proximal aspect of the affected extremity. The anesthetic procedure was done in the affected forearm[137] or the affected shoulder[29] followed by motor training of the hand. Anesthetic modalities also vary. Although deafferentation to improve hand function was first examined through ischemic and pharmacological nerve blocks,[29] recent studies demonstrate that TFD using local anesthetic cream may provide similar outcomes, albeit with different neural mechanisms.[126,137] Petoe and colleagues[137] investigated the behavioral and neural effects of TFD applied via an anesthetic cream to the affected forearm in individuals with stroke. The treatment group showed greater improvement than controls in manual dexterity as measured by the grooved pegboard test. This change coincided with an increase in SICI in the ipsilesional hemisphere of the treatment group. The authors inferred that the increase in SICI may be due to a change in surround inhibition, active inhibition of adjacent muscles during performance of a task, which allows for more precise finger movements. While an increase in inhibition within the ipsilesional hemisphere was found after application of the anesthetic cream, the results of the anesthetic block of the less-affected upper extremity included a decrease in inhibition between the hemispheres. Note that sensory priming neural effects occur rapidly and anesthetic modalities have limited time frames. Thus, training should be immediate to take advantage of plasticity mechanisms.

Determinants of Priming

Priming modalities applied before or during motor training to enhance neurorehabilitation vary, and some priming modalities (eg, rTMS) and various protocols have been used. Effects of a given priming protocol depend on a multitude of factors, including the intensity, frequency, and duration of the priming intervention as well as other unknown variables. For example, Stagg and colleagues[46] demonstrated that response to tDCS may depend on GABA levels, and there is a large degree of interindividual variability in GABA and in other neurotransmitter levels. Also, the extent to which 2 priming protocols might interact when paired (eg, pharmacological and tDCS) is unclear. There is some evidence that if 2 facilitatory stimulation-based priming paradigms are applied sequentially, the result is downregulation. The same is true for 2 inhibitory stimulation-based priming paradigms. However, if one priming activity is facilitatory and the other inhibitory, the net output is upregulation of the targeted cortex.[12,143,144] This interaction has been shown true for some priming mechanisms and not for all.[145,146]

In addition, the order of priming and training is important in determining the direction of the interaction. Priming during motor training appears to enhance learning more than priming applied before training.[147,148] Further studies are needed to fully document this interaction. In a very recent randomized controlled trial where the order of rTMS and PT was manipulated, 4 groups of participants with chronic stroke receiving PT were compared.[149] The groups included (1) rTMS followed by PT; (2) PT followed by rTMS; (3) sham rTMS followed by PT; and (4) PT followed by sham rTMS. The 2 groups using real rTMS showed more robust changes in neurophysiological and behavioral measures at posttreatment. At follow-up, the rTMS followed by PT group persisted in their improvements in both neurophysiological and behavioral measures whereas PT followed by rTMS showed a decline in improvement relative to posttreatment values, although they did not return to baseline levels. The authors concluded that the order of rTMS followed by PT maximizes use-dependent neuroplasticity more than PT followed by rTMS.

Priming techniques that are safe and do not require a skilled operator, expensive equipment, or a prescription include movement-based priming, imagery-based priming, action observation, and sensory stimulation. Priming techniques such as rTMS, tDCS, and TFD are safe when used according to safety guidelines. Since there is a window of opportunity for optimal effectiveness of restorative therapies poststroke, inpatient rehabilitation therapists should become familiar with those priming modalities that have limited safety concerns.

IMPLICATIONS FOR NEUROLOGICAL PHYSICAL THERAPY PRACTICE

Data from several studies suggest that motor priming techniques may be promising adjuvants to rehabilitation. These approaches provide opportunities for a paradigm shift in neurological PT practice. New information about neuroplasticity and techniques to enhance plasticity are accumulating as researchers are developing innovative ways to tap into the potential of the nervous system. The full clinical impact of these

findings is not yet realized. Given the constraints on access to PT services and emphasis on value-based payment, the use of cutting-edge adjunct therapies for motor priming may be a cost-efficient means for physical therapists to optimize treatment outcomes.

Translation of findings from priming research to clinical practice will require intermediary steps, such as larger clinical trials to provide strong evidence for safety and effectiveness. Mechanistic studies and smaller clinical trials can also identify optimal dosage and critical time windows within which the treatments can be safely delivered to produce the best outcomes. In addition, collaboration of neuroscientists and physical therapists will inform scientists about the challenges faced by clinicians in administering treatments within the context of current reimbursement guidelines. The ultimate test for clinicians and educators is to keep abreast of new findings and knowledge concerning neuroplasticity as a basis for identifying priming techniques that are optimal for specific individuals and their individual clinical presentations. It will be important to identify individual factors that may predict response to treatment, such as lesion size, age, comorbidities, psychosocial factors, genetic profile, and environmental factors.

The advancement of clinical practice begins with a strong emphasis on principles and determinants of neuroplasticity in the educational curriculum. Perhaps more than any other content area, neurological PT textbooks are in need of frequent updating to remain abreast of a rapidly changing body of knowledge. Subsequently, new physical therapist practitioners would benefit from early exposure to cutting-edge research so they have a better grasp of the potential of emerging technologies. Rigorous postgraduate education, residencies, and fellowships are an option for those who choose to specialize in neurological PT. Opportunities for frequent interactions between students, clinicians, and scientists will facilitate a more rapid translation of research principles into clinical application.

SUMMARY

There are an increasing number of available methods for priming the motor cortex to enhance neuroplasticity and motor learning; these approaches hold great promise as potential adjuncts to motor training. We have briefly reviewed priming techniques frequently used in rehabilitation research. We expect more guidelines to appear that will personalize treatments based on impairment and disability level as well as on the various stages of rehabilitation. The challenge will be to determine which methods are most effective for different clinical diagnoses and how those with disparate levels of impairment and disability differentially respond to the various methods available for priming.

REFERENCES

1. White L, Ford MP, Brown CJ, Peel C, Triebel KL. Facilitating the use of implicit memory and learning in the physical therapy management of individuals with Alzheimer disease: a case series. *J Geriatric Phys Ther.* 2014;37(1):35-44.
2. Vidoni ED, Boyd LA. Achieving enlightenment: what do we know about the implicit learning system and its interaction with explicit knowledge? *J Neurol Phys Ther.* 2007;31(3):145-154.
3. Ries JD, Drake JM, Marino C. A small-group functional balance intervention for individuals with Alzheimer disease: a pilot study. *J Neurol Phys Ther.* 2010;34(1):3-10.
4. Mount J, Pierce SR, Parker J, DiEgidio R, Woessner R, Spiegel L. Trial and error versus errorless learning of functional skills in patients with acute stroke. *NeuroRehabilitation.* 2007;22(2):123-132.
5. Hauptmann B, Karni A. (2002) From primed to learn: the saturation of repetition priming and the induction of long term memory. *Cog Brain Res.* 2002;13:313-322.
6. Pomeroy V, Aglioti SM, Mark VW, et al. Neurological principles and rehabilitation of action disorders: rehabilitation interventions. *Neurorehabil Neural Repair.* 2011;25(5):33S-43S.
7. Byblow WD, Stinear CM, Smith MC, Bjerre L, Flaskager BK, McCambrige AB. Mirror symmetric bimanual movement priming can increase corticomotor excitability and enhance motor learning. *PLoS ONE.* 2012;7(3):e33882.
8. Grossi JA, Maitra KK, Rice MS. Semantic priming of motor task performance in young adults: implications for occupational therapy. *Am J Occup Ther.* 2007;61(3):311-320.
9. Schacter DL, Buckner RL. Priming and the brain. *Neuron.* 1998;20:185-195.
10. Marsolek CJ. What is priming and why. In: Bowers JS, Marsolek CJ, eds. *Rethinking Implicit Memory.* Oxford: Oxford University Press; 2002.
11. Ziemann U, Siebner HR. Modifying motor learning through gating and homeostatic metaplasticity. *Brain Stimul.* 2008;1(1):60-66.
12. Siebner HR. A primer on priming the human motor cortex. *Clin Neurophysiol.* 2010;121(4):461-463.
13. Ward NS, Cohen LG. Mechanisms underlying recovery of motor function after stroke. *Arch Neurol.* 2004;61(12):1844-1848.
14. Dafotakis M, Grefkes C, Eickhoff SB, Karbe H, Fink GR, Nowak DA. Effects of rTMS on grip force control following subcortical stroke. *Exp Neurol.* 2008;211(2):407-412.
15. Nowak DA, Grefkes C, Dafotakis M, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Arch Neurol.* 2008;65(6):741-747.
16. Jayaram G, Stinear JW. Contralesional paired associative stimulation increases paretic lower limb motor excitability post-stroke. *Exp Brain Res.* 2008;185(4):563-570.
17. Bolognini N, Vallar G, Casati C, et al. Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabil Neural Repair.* 2011;25(9):819-829.
18. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 2012;5(3):175-195.
19. Nair DG, Renga V, Lindenberg R, Zhu L, Schlaug G. Optimizing recovery potential through simultaneous occupational therapy and non-invasive brain-stimulation using tDCS. *Restor Neurol Neurosci.* 2012;5(3):175-195.
20. Madhavan S, Stinear JW. Focal and bi-directional modulation of lower limb motor cortex using anodal transcranial direct current stimulation. *Brain Stimul.* 2010;3(1):42.
21. Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restor Neurol Neurosci.* 2007;25(2):123-129.
22. Hummel FC, Voller B, Celnik P, et al. Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neurosci.* 2006;7:73.
23. Simmons L, Sharma N, Baron JC, Pomeroy VM. Motor imagery to enhance recovery after subcortical stroke: who might benefit, daily dose, and potential effects. *Neurorehabil Neural Repair.* 2008;22(5):458-467.
24. Li S, Stevens JA, Rymer WZ. Interactions between imagined movement and the initiation of voluntary movement: a TMS study. *Clin Neurophysiol.* 2009;120(6):1154-1160.
25. Lotze M, Cohen LG. Volition and imagery in neurorehabilitation. *Cogn Behav Neurol.* 2006;19(3):135-140.
26. Levin O, Steyvers M, Wenderoth N, Li Y, Swinnen SP. Dynamical changes in corticospinal excitability during imagery of unimanual and bimanual wrist movements in humans: a transcranial magnetic stimulation study. *Neurosci Lett.* 2004;359(3):185-189.

27. Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J Neurophysiol.* 1995;74(3):1037-1045.
28. Facchini S, Muellbacher W, Battaglia F, Boroojerdi B, Hallett M. Focal enhancement of motor cortex excitability during motor imagery: a transcranial magnetic stimulation study. *Acta Neurol Scand.* 2002;105(3):146-151.
29. Muellbacher W, Richards C, Ziemann U, et al. Improving hand function in chronic stroke. *Arch Neurol.* 2002;59(8):1278-1282.
30. Beekhuizen KS, Field-Fote E. Sensory stimulation augments the effects of massed practice training in persons with tetraplegia. *Arch Phys Med Rehabil.* 2008;89:602-608.
31. Field-Fote E. Electrical stimulation modifies spinal and cortical neural circuitry. *Exercise Sport Sci Rev.* 2004;32(4):155-160.
32. Stinear CM, Petoe MA, Anwar S, Barber PA, Byblow WD. Bilateral priming accelerates recovery of upper limb function after stroke: a randomized controlled trial. *Stroke.* 2014;45(1):205-210.
33. Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. *Brain.* 2008;131(Pt 5):1381-1390.
34. Stinear JW, Byblow WD. Rhythmic bilateral movement training modulates corticomotor excitability and enhances upper limb motricity poststroke: a pilot study. *J Clin Neurophysiol.* 2004;21(2):124-131.
35. Stoykov ME, Corcos DM. Bilateral priming followed by task specific training can improve moderate to severe post-stroke upper extremity hemiparesis. *Stroke.* 2013;44. http://stroke.ahajournals.org/cgi/content/meeting_abstract/44/2_MeetingAbstracts/AWMP89.
36. Stoykov ME, Stinear JW. Active-passive bilateral therapy as a priming mechanism for individuals in the subacute phase of post-stroke recovery: a feasibility study. *Am J Phys Med Rehabil.* 2010;89(11):873-878.
37. Martinsson L, Hårdemark H, Eksborg S. Amphetamines for improving recovery after stroke. *Cochrane Database Syst Rev.* 2007(1). CD002090-CD002090.
38. Dafotakis M, Grefkes C, Wang L, Fink GR, Nowak DA. The effects of 1 Hz rTMS over the hand area of M1 on movement kinematics of the ipsilateral hand. *J Neural Transm.* 2008;115(9):1269-1274.
39. Madhavan S, Shah B. Enhancing motor skill learning with transcranial direct current stimulation—a concise review with applications to stroke. *Front Psychiatry.* 2012;3:66.
40. Ljubisavljevic M. Transcranial magnetic stimulation and the motor learning-associated cortical plasticity *Exp Brain Res.* 2006;173(2):215-222.
41. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology.* 1997;48(5):1398-1403.
42. Cárdenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schönfeldt-Lecuona C. Mechanisms and applications of theta-burst rTMS on the human motor cortex. *Brain Topogr.* 2010;22(4):294-306.
43. Touge T, Gerschlager W, Brown P, Rothwell JC. Are the after-effects of low-frequency rTMS on motor cortex excitability due to changes in the efficacy of cortical synapses? *Clin Neurophysiol.* 2001;112(11):2138-2145.
44. Nitsche MA, Doemkes S, Karaköse T, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol.* 2007;97(4):3109-3117.
45. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol.* 2000;527(3):633-639.
46. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist.* 2011;17(1):37-53.
47. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol.* 2004;55(3):400-409.
48. Rossini PM, Calautti C, Pauri F, Baron JC. Post-stroke plastic reorganisation in the adult brain. *Lancet Neurol.* 2003;2(8):493-502.
49. Kapur N. Paradoxical functional facilitation in brain-behaviour research: a critical review. *Brain.* 1996;119(5):1775-1790.
50. Seniow J, Bilik M, Lesniak M, Waldowski K, Iwanski S, Czlonkowska A. Transcranial magnetic stimulation combined with physiotherapy in rehabilitation of poststroke hemiparesis: a randomized, double-blind, placebo-controlled study. *Neurorehabil Neural Repair.* 2012;26(9):1072-1079.
51. Takeuchi N, Tada T, Toshima M, Chuma T, Matsuo Y, Ikoma K. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *J Rehabil Med.* 2008;40(4):298-303.
52. Takeuchi N, Toshima M, Chuma T, Matsuo Y, Ikoma K. Repetitive transcranial magnetic stimulation of the unaffected hemisphere in a patient who was forced to use the affected hand. *Am J Phys Med Rehabil.* 2008;87(1):74-77.
53. Liepert J, Zittel S, Weiller C. Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in acute stroke: a double-blind placebo-controlled crossover trial. *Restor Neurol Neurosci.* 2007;25(5/6):461-465.
54. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke.* 2005;36(12):2681-2686.
55. Bastani A, Jaberzadeh S. Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clin Neurophysiol.* 2012;123:644-657.
56. Wang RY, Tseng H, Liao KK, Wang CJ, Lai KL, Yang YR. rTMS combined with task-oriented training to improve symmetry of interhemispheric corticomotor excitability and gait performance after stroke: a randomized trial. *Neurorehabil Neural Repair.* 2012;26(3):222-230.
57. Johansen-Berg H, Rushworth MFS, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci U S A.* 2002;99(22):14518-14523.
58. Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG. Reorganization of the human ipsilesional premotor cortex after stroke. *Brain.* 2004;127(4):747-758.
59. Filipovic SR, Rothwell JC, Bhatia K. Slow (1 Hz) repetitive transcranial magnetic stimulation (rTMS) induces a sustained change in cortical excitability in patients with Parkinson's disease. *Clin Neurophysiol.* 2010;121(7):1129-1137.
60. Koch G, Rossi S, Prosperetti C, et al. Improvement of hand dexterity following motor cortex rTMS in multiple sclerosis patients with cerebellar impairment. *Mult Scler.* 2008;14(7):995-998.
61. Ihara Y, Takata H, Tanabe Y, Nobukuni K, Hayabara T. Influence of repetitive transcranial magnetic stimulation on disease severity and oxidative stress markers in the cerebrospinal fluid of patients with spinocerebellar degeneration. *Neurol Res.* 2005;27(3):310-313.
62. Carson RG, Kennedy NC. Modulation of human corticospinal excitability by paired associative stimulation. *Front Hum Neurosci.* 2013;7(823):eCollection.
63. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain.* 2000;123(Pt 3):572-584.
64. Cirillo J, Lavender AP, Ridding MC, Semmler JG. Motor cortex plasticity induced by paired associative stimulation is enhanced in physically active individuals. *J Physiol.* 2009;587(24):5831-5842.
65. Rogers LM, Brown DA, Stinear JW. The effects of paired associative stimulation on knee extensor motor excitability of individuals poststroke: a pilot study. *Clin Neurophysiol.* 2011;122(6):1211-1218.
66. Decety J, Grezes J. Neural mechanisms subserving the perception of human actions. *Trends Cogn Sci.* 1999;3(5):172-178.
67. Ertelt D, Small S, Solodkin A, et al. Action observation has a positive impact on rehabilitation of motor deficits after stroke. *Neuroimage.* 2007;36(suppl 2):T164-T173.
68. Malouin F, Jackson PL, Richards CL. Towards the integration of mental practice in rehabilitation programs. A critical review. *Front Hum Neurosci.* 2013;19(7):576.
69. Cramer SC, Orr EL, Cohen MJ, Lacourse MG. Effects of motor imagery training after chronic, complete spinal cord injury. *Exp Brain Res.* 2007;177(2):233-242.
70. Tamir R, Dickstein R, Huberman M. Integration of motor imagery and physical practice in group treatment applied to subjects with Parkinson's disease. *Neurorehabil Neural Repair.* 2007;21(1):68-75.

71. Kim JS, Oh DW, Kim SY, Choi JD. Visual and kinesthetic locomotor imagery training integrated with auditory step rhythm for walking performance of patients with chronic stroke. *Clin Rehabil.* 2011;25(2): 134-145.
72. Gallese V, Fadiga L, Fogassi L, Rizzolatti G. Action recognition in the premotor cortex. *Brain.* 1996;119(2):593-609.
73. Rizzolatti G, Fadiga L, Gallese V, Fogassi L. Premotor cortex and the recognition of motor actions. *Cogn Brain Res.* 1996;3(2):131-141.
74. Ryding E, Decety J, Sjöholm H, Stenberg G, Ingvar DH. Motor imagery activates the cerebellum regionally. A SPECT rCBF study with 99mTc-HMPAO. *Cogn Brain Res.* 1993;1(2):94-99.
75. Grafton ST, Arbib MA, Fadiga L, Rizzolatti G. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. *Exp Brain Res.* 1996;112(1):103-111.
76. Porro CA, Francescato MP, Cettolo V, et al. Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. *J Neurosci.* 1996;16(23):7688-7698.
77. Roth M, Decety J, Raybaudi M, et al. Possible involvement of primary motor cortex in mentally simulated movement: a functional magnetic resonance imaging study. *Neuroreport.* 1996;7(7):1280-1284.
78. Stephan KM, Fink GR, Passingham RE, et al. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *J Neurophysiol.* 1995;73(1):373-386.
79. Grèzes J, Decety J. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. *Hum Brain Mapp.* 2001;12(1):1-19.
80. Fadiga L, Buccino G, Craighero L, Fogassi L, Gallese V, Pavesi G. Corticospinal excitability is specifically modulated by motor imagery: a magnetic stimulation study. *Neuropsychologia.* 1999;37(2):147-158.
81. Fadiga L, Fogassi L, Pavesi G, Rizzolatti G. Motor facilitation during action observation: a magnetic stimulation study. *J Neurophysiol.* 1995;73(6):2608-2611.
82. Yue G, Cole KJ. Strength increases from the motor program: comparison of training with maximal voluntary and imagined muscle contractions. *J Neurophysiol.* 1992;67:1114–1123.
83. Barclay-Goddard RE, Stevenson TJ, Poluha W, Thalman L. Mental practice for treating upper extremity deficits in individuals with hemiparesis after stroke. *Cochrane Database Syst Rev.* 2011(5):CD005950.
84. Wondrusch C, Schuster-Amft C. A standardized motor imagery introduction program (MIIP) for neuro-rehabilitation: development and evaluation. *Front Hum Neurosci.* 2013;7:477.
85. Li Y, Levin O, Carson RG, Swinnen SP. Bimanual coordination: constraints imposed by the relative timing of homologous muscle activation. *Exp Brain Res.* 2004;156(1):27-38.
86. Whitall J, Waller SM, Sorkin JD, et al. Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: a single-blinded randomized controlled trial. *Neurorehabil Neural Repair.* 2011;25(2):118-129.
87. McCombe Waller S, Liu W, Whitall J. Temporal and spatial control following bilateral versus unilateral training. *Hum Mov Sci.* 2008;27(5):749-758.
88. Stoykov ME, Lewis GN, Corcos DM. Comparison of bilateral and unilateral training for upper extremity hemiparesis in stroke. *Neurorehabil Neural Repair.* 2009;23(9):945-953.
89. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscular stimulation and bilateral movements. *Stroke.* 2002;33(6):1589-1594.
90. Winter B, Breitenstein C, Mooren FC, et al. High impact running improves learning. *Neurobiol Learn Mem.* 2007;87(4):597-609.
91. Masley S, Roetzheim R, Gualtieri T. Aerobic exercise enhances cognitive flexibility. *J Clin Psychol Med Settings.* 2009;16(2):186-193.
92. McDonnell MN, Buckley JD, Opie GM, Ridding MC, Semmler JG. A single bout of aerobic exercise promotes motor cortical neuroplasticity. *J Appl Physiol.* 2013;114(9):1174-1182.
93. Binder DK, Scharfman HE. Brain-derived neurotrophic factor. *Growth Factors.* 2004;22(3):123-131.
94. Cotman CW, Engesser-Cesar C. Exercise enhances and protects brain function. *Exercise Sport Sci Rev.* 2002;30(2):75-79.
95. Hirsch MA, Farley BG. Exercise and neuroplasticity in persons living with Parkinson's disease. *Eur J Phys Rehabil Med.* 2009;45(2): 215-229.
96. Boroojerdi B, Battaglia F, Muellbacher W, Cohen LG. Voluntary teeth clenching facilitates human motor system excitability. *Clin Neurophysiol.* 2000;111(6):988-993.
97. Hiraoka K, Akizaki K, Ashida A, et al. Rhythmic arm swing enhances long latency facilitatory effect of transcranial magnetic stimulation on soleus motoneuron pool excitability. *Somatosens Mot Res.* 2011;28(3/4):94-101.
98. Yamaguchi T, Fujiwara T, Liu W, Liu M. Effects of pedaling exercise on the intracortical inhibition of cortical leg area. *Exp Brain Res.* 2012;218(3):401-406.
99. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science.* 1982;217(4562):855-857.
100. Martinsson L, Eksborg S, Wahlgren N. Intensive early physiotherapy combined with dexamphetamine treatment in severe stroke: a randomized, controlled pilot study. *Cerebrovas Dis.* 2003;16(4):338-345.
101. Platz T, Kim IH, Engel U, Pinkowski C, Eickhof C, Kutzner M. Amphetamine fails to facilitate motor performance and to enhance motor recovery among stroke patients with mild arm paresis: interim analysis and termination of a double blind, randomised, placebo-controlled trial. *Restorative Neurol Neurosci.* 2005;23(5/6):271-280.
102. Scheidtmann K. Advances in adjuvant pharmacotherapy for motor rehabilitation: effects of levodopa. *Restor Neurol Neurosci.* 2004;22 (3-5):393-398.
103. Acler M, Fiaschi A, Manganotti P. Long-term levodopa administration in chronic stroke patients. A clinical and neurophysiologic single-blind placebo-controlled cross-over pilot study. *Restor Neurol Neurosci.* 2009;27(4):277-283.
104. Rosser N, Floel A. Pharmacological enhancement of motor recovery in subacute and chronic stroke. *NeuroRehabilitation.* 2008;23(1): 95-103.
105. Sonde L, Lokk J. Effects of amphetamine and/or L-dopa and physiotherapy after stroke—a blinded randomized study. *Acta Neurolog Scand.* 2007;115(1):55-59.
106. Acler M, Manganotti P. Role, indications and controversies of levodopa administration in chronic stroke patients. *Eur J Phys Med Rehabil.* 2013;49(2):243-249.
107. Stanton PK, Sarvey JM, Moskal JR. Inhibition of the production and maintenance of long-term potentiation in rat hippocampal slices by a monoclonal antibody. *Proc Natl Acad Sci U S A.* 1987;84(6):1684-1688.
108. Murchinson C, Zhang XY, Zang WP, Ouyang M, Lee A, Thomas SA. A distinct role for norepinephrine in memory retrieval. *Cell.* 2004;117(1):131-143.
109. Foster D, Good D, Fowlkes A, Sawaki L. Atomoxetine enhances a short-term model of plasticity in humans. *Arch Phys Med Rehabil.* 2006;87(2):216-221.
110. Maalouf M, Miasnikov AA, Dykes RW. Blockade of cholinergic receptors in rat barrel cortex prevents long-term changes in the evoked potential during sensory preconditioning. *J Neurophysiol.* 1998;80(2):529-545.
111. Sarter M, Bruno JP. Trans-synaptic stimulation of cortical acetylcholine and enhancement of attentional functions: a rational approach for the development of cognition enhancers. *Brain Behav Res.* 1997;83(1/2): 7-14.
112. Conner JM, Culberson A, Packowski C, Chiba AA, Tuszynski MH. Lesions of the basal forebrain cholinergic system impair task acquisition and abolish cortical plasticity associated with motor skill learning. *Neuron.* 2003;38(5):819-829.
113. Blennow K, de Leon MJZ H. Alzheimer's disease. *Lancet [Review].* 2006;368(9533):387-403.
114. Krupp LB, Christodoulou C, Melville P, Scherl WF, MacAllister WS, Elkins LE. Donepezil improved memory in multiple sclerosis in a randomized clinical trial. *Neurology.* 2004;9(63):1579-1585.
115. Zorowitz RD. Road to recovery: drugs used in stroke rehabilitation. *Expert Rev Neurother.* 2004;4(2):219-231.
116. Nadeau SE, Behrman AL, Davis SE, et al. Donepezil as an adjuvant to constraint-induced therapy for upper-limb dysfunction after stroke: an exploratory randomized clinical trial. *J Rehabil Res Dev.* 2004;41(4):525-534.
117. Berthier ML, Green C, Higueras C, Fernández I, Hinojosa J, Martín MC. A randomized, placebo-controlled study of donepezil in poststroke aphasia. *Neurology.* 2006;67(9):1687-1689.

118. Lim C, Kim SW, Park JY, Kim C, Yoon SH, Lee JK. Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-inflammatory effect. *J Neurosci Res*. 2009;87(4):1027-1045.
119. Pälvimäki EP, Laakso A, Kuoppamäki M, Syvälahti E, Hietala J. Up-regulation of beta 1-adrenergic receptors in rat brain after chronic citalopram and fluoxetine treatments. *Psychopharmacology (Berlin)*. 1994;115(4):543-546.
120. Dam M, Tonin P, De Boni A, et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. *Stroke*. 1996;27(7):1211-1214.
121. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol*. 2011;10(2):123-130.
122. Mead GE, Hsieh CF, Lee R, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev*. 2012;14(11):CD009286.
123. Rampello L, Chiechio S, Raffaele R, Vecchio I, Nicoletti F. The SSRI, citalopram, improves bradykinesia in patients with Parkinson's disease treated with L-dopa. *Clin Neuropharmacol*. 2002;25(1):21-24.
124. Chung KA, Carlson NE, Nutt JG. Short-term paroxetine treatment does not alter the motor response to levodopa in PD. *Neurology*. 2005;64(10):1797-1798.
125. Fann JR, Uomoto JM, Katon WJ. Cognitive improvement with treatment of depression following mild traumatic brain injury. *Psychosomatics*. 2001;42(1):48-54.
126. Weiss T, Sens E, Teschner U, et al. Deafferentation of the affected arm: a method to improve rehabilitation? *Stroke*. 2011;42(5):1363-1370.
127. Pavlides C, Miyashita E, Asanuma H. Projection from the sensory to the motor cortex is important in learning motor skills in the monkey. *J Neurophysiol*. 1993;70(2):733-741.
128. Ridding MC, McKay DR, Thompson PD, Miles TS. Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. *Clin Neurophys*. 2001;112(8):1461-1469.
129. Celnik P, Hummel F, Harris-Love M, Wolk R, Cohen LG. Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. *Arch Phys Med Rehabil*. 2007;88(11):1369-1376.
130. Peurala SH, Pitkänen K, Sivenius J, Tarkka M. Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clin Rehabil*. 2002;6:709-716.
131. Kattenstroth JC, Kalisch T, Peters S, Tegenthoff M, Dinse HR. Long-term sensory stimulation therapy improves hand function and restores cortical responsiveness in patients with chronic cerebral lesions. Three single case studies. *Front Hum Neurosci*. 2012;6(244):1-13.
132. Liepert J, Binder C. Vibration-induced effects in stroke patients with spastic hemiparesis—a pilot study. *Restor Neurol Neurosci*. 2010;28(6):729-735.
133. Cordo P, Wolf S, Lou JS, et al. Treatment of severe hand impairment following stroke by combining assisted movement, muscle vibration, and biofeedback. *J Neurol Phys Ther*. 2013;37(4):194-203.
134. Cordo P, Lutsep H, Cordo L, Wright WG, Cacciatore T, Skoss R. Assisted movement with enhanced sensation (AMES): coupling motor and sensory to remediate motor deficits in chronic stroke patients. *Neurorehabil Neural Repair*. 2009;23(1):67-77.
135. Ziemann U, Hallett M, Cohen LG. Mechanisms of deafferentation-induced plasticity in human motor cortex. *J Neurosci*. 1998;18:7000-7008.
136. Weiss T, Miltner WH, Liepert J, Meissner W, Taub E. Rapid functional plasticity in the primary somatomotor cortex and perceptual changes after nerve block. *Eur J Neurosci*. 2004;20(12):3413-3423.
137. Petoe M, Jaque FA, Byblow WD, Stinear CM. Cutaneous anesthesia of the forearm enhances sensorimotor function of the hand. *J Neurophys*. 2013;109(4):1091-1096.
138. Moore CEG, Schady W. Investigation of the functional correlates of reorganization within the human somatosensory cortex. *Brain*. 2000;123:1883-1895.
139. Schady W, Braune S, Watson S, Torebjork HE, Schmidt R. Responsiveness of the somatosensory system after nerve injury and amputation in the human hand. *J Neurosci*. 1994;36(1):68-75.
140. Voller B, Flöel A, Werhahn KJ, Ravindran S, Wu CW, Cohen LG. Contralateral hand anesthesia transiently improves poststroke sensory deficits. *Ann Neurol*. 2006;59(2):385-388.
141. Floel A, Hummel F, Duque J, Knecht S, Cohen LG. Influence of somatosensory input on interhemispheric interactions in patients with chronic stroke. *Neurorehabil Neural Repair*. 2008;22(5):477-485.
142. Calford MB, Tweedale R. Interhemispheric transfer of plasticity in the cerebral cortex. *Science*. 1990;249:805-807.
143. Cassidy JM, Gillick BT, Carey JR. Priming the brain to capitalize on metaplasticity in stroke rehabilitation. *Phys Ther*. 2014;94(1):139-150.
144. Lang N, Siebner HR, Ernst D, et al. Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. *Biol Psychiatry*. 2004;56(9):634-639.
145. Kuo MF, Unger M, Liebetanz D, Lang N, Tergau F, Paulus W, Nitsche MA. Limited impact of homeostatic plasticity on motor learning in humans. *Neuropsychologia*. 2008;46(8):2122-2128.
146. Jung P, Ziemann U. Homeostatic and nonhomeostatic modulation of learning in human motor cortex. *J Neurosci*. 2009;29(17):5597-5604.
147. Stagg CJ, Jayaram G, Pastor D, Kincses ZT, Matthews PM, Johansen-Berg H, Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. *Neuropsychologia*. 2011;49:800-804.
148. Sriraman A, Oishi T, Madhavan S. Timing-dependent priming effects of tDCS on ankle motor skill learning. *Brain Res*. 2014;1581:23-29.
149. Avenanti A, Coccia M, Ladavas E, Provinciali L, Ceravolo MG. Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke: a randomized trial. *Neurol*. 2012;78(4):256-264.