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Motor Priming in Neurorehabilitation

Mary Ellen Stoykov, PhD, OTR/L¹ [Assistant Professor] and Sangeetha Madhavan, PhD, P.T.² [Assistant Professor]

Mary Ellen Stoykov: mary_stoykov@rush.edu

¹Department of Occupational Therapy, Rush University Medical Center, 600 S. Paulina Street, Chicago, IL 60612

²Department of Physical Therapy, University of Illinois in Chicago

Abstract

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.

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 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 to 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 to 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 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 (extrastriatal 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, which has been primed by a prior method of activation, is generally more responsive to the accompanying training. Priming presupposes that enhanced neural activity prior to or during training can facilitate the acquisition 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 increase in 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 in order 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.

A search of the literature through December 2013 was performed using the search engines: PubMed, Web of Science and Ovid. Keywords 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 one human participant, and 3) included at least one motor performance-based outcome measure and 4) fit the definition of “priming” as described in the Introduction. 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 five priming paradigms are described below.

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 non-invasive 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 min) of these stimulation protocols, neural changes have persisted post-stimulation 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

TMS 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 (TBS), involving bursts of 3-5 pulses at 50-100 Hz repeated at 5 Hz (theta rhythm), can elicit similar changes as rTMS using less stimulation time and lower intensities.⁴² TBS that 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 in downregulation. During stimulation, effects of tDCS arise from modulation of neuronal membrane potential, altering the conductance of sodium and calcium channels. The after-effects of tDCS, similar to rTMS,

may also be due to mechanisms similar to LTP and LTD, involving the modulation of *N*-Methyl-D-aspartate (NMDA) receptors and inhibitory GABA-ergic synapses.⁴⁶

Neural recovery mechanisms after stroke are only partially understood, however, evidence indicates that a balance of excitability between the lesioned and non-lesioned 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 post-stroke 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 hemisphere³³ and abnormally high inhibition from contralesional to ipsilesional.⁴⁷ A balance of hemispheric excitability is associated with improved post-stroke 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.¹³ Low frequency rTMS to the contralesional^{15, 50-54} or anodal tDCS to the ipsilesional M1⁵⁵ have been associated with significant changes in upper-limb and lower-limb functional tasks in participants with stroke.⁵⁶ Other areas of stimulation can include non-primary 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 are currently approved by the Food and Drug Administration as therapies for persons with stroke, therefore, in the U.S., their use is limited to research studies. There is also great variability among individuals in magnitude and duration of rTMS after-effects, 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, paired associative stimulation (PAS) represents a third category of stimulation-based priming. The PAS approach involves paired pulses, one from peripheral nerve stimulation 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 two 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 non-paretic vastus medialis of participants with chronic stroke and the right limb motor system of neurologically healthy participants at a frequency of 0.19 Hz. As hypothesized, downregulation occurred in the cortex controlling the non-paretic 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 will discuss PNS and underlying mechanisms in a subsequent section related to sensory-based priming.

Motor Imagery and Action Observation

Many psychological and neurophysiologic 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 pre-motor 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 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 colleagues⁶⁸ recommend continued research in mental practice techniques especially in the subacute phase of post-stroke 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-Amft⁸⁴ for ideas for introducing concepts and facilitating adherence during imagery training, and by Malouin and colleagues for a detailed review of the various modes of delivery of motor imagery in neurorehabilitation.⁶⁸

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 extension³⁵ 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 towards 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 prior to 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 two 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 post-stroke 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 min of upper limb occupational or physical therapy. The bilateral priming plus therapy group experienced an accelerated recovery course, compared to 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 flexibility⁹¹ 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 (BDNF), which supports the survival of existing neurons and encourages growth and differentiation of new neurons and synapses.⁹³ Aerobic exercise increases brain BDNF levels.⁹⁴ Exercise also enhances neuroplastic responses to non-invasive brain stimulation in healthy individuals.^{64, 92} The potential for exercise to serve as a motor priming intervention remains under-explored, 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, five groups of pharmacological agents have been proposed to enhance motor recovery after neurological injury: amphetamines, dopaminergic agents (DA), norepinephrines (NE), cholinergic agents (ACh), and selective serotonin re-uptake inhibitors (SSRI).

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 ten 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 - 10 mg/daily 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 (e.g., atomoxetine) in the stroke model, indicate the efficacy of these drugs in enhancing motor outcomes.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 LTP¹¹⁰⁻¹¹¹ while cholinergic lesions reduce reorganization and learning.¹¹² In humans, deficits in cholinergic transmission are related to memory loss, while acetyl cholinesterase-inhibitors (AChET inhibitor) 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 limb¹¹⁵⁻¹¹⁶ and improved speech¹¹⁷ 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. SSRIs 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 disease¹²³⁻¹²⁴ 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 SSRI's 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 one 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 two cortical areas.

Prolonged peripheral nerve electrical stimulation can change spinal and supraspinal systems.^{31,127} Repetitive sensory stimulation to the ulnar and median nerves prior to motor training (or administered without training) improved sensory and motor functions,¹²⁸⁻¹³⁰ normalized somatosensory evoked potentials,¹²⁹⁻¹³⁰ and reduced short-interval cortical inhibition (SICI) in individuals who have survived a stroke.¹²⁸ Some authors recommend peripheral nerve stimulation as a treatment for individuals with little or no voluntary movement³⁰ or without the cognitive and/or physical endurance to participate in extensive practice.¹³⁰ 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 agonist¹³¹ or antagonist muscles¹³²⁻¹³³ have been described. Vibration of forearm extensors (agonist muscles) resulted in improved scores on the Box and Block test, possibly due to stimulation of the cortical inhibitory circuits directed to the antagonist muscle (forearm flexors) thereby reducing spasticity and improving function.¹³¹ Cordo and colleagues¹³²⁻¹³³ 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 subject attempted to open the hand.¹³² 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.^{29,134-138} Alterations in the cortical map as a result of deafferentation are rapid, and possibly the result of the unmasking of pre-existing excitatory connections.¹³⁴ 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 TFD 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.¹³⁹⁻¹⁴⁰ Floel and colleagues¹⁴⁰ 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.¹⁴¹ 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 forearm¹³⁶ or the affected shoulder²⁹ 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.^{126,136} Petoe and colleagues¹³⁶ 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 prior to or during motor training to enhance neurorehabilitation vary, and some priming modalities (e.g., rTMS) 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 colleagues⁴⁶ demonstrated that response to tDCS may depend on GABA levels, and there is a large degree of inter-individual variability in GABA and in other neurotransmitter levels. Also, the extent to which two priming protocols might interact when paired (e.g., pharmacological and tDCS) is unclear. There is some evidence that, if

two facilitory stimulation-based priming paradigms are applied sequentially, the result is down regulation. The same is true for two inhibitory stimulation-based priming paradigms. However, if one priming activity is facilitory and the other inhibitory, the net output is upregulation of the targeted cortex.^{12,142-143} This interaction has been shown true for some priming mechanisms and not for all.¹⁴⁴⁻¹⁴⁵

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 prior to training.¹⁴⁶⁻¹⁴⁷ Further studies are needed to fully document this interaction. In a very recent randomized controlled trial where the order of rTMS and physical therapy (PT) was manipulated, 4 groups of participants with chronic stroke receiving PT were compared.¹⁴⁸ 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 two groups using real rTMS showed more robust changes in neurophysiologic and behavioral measures at post-treatment. At follow-up, the rTMS followed by PT group persisted in their improvements in both neurophysiologic and behavioral measures whereas PT followed by rTMS showed a decline in improvement relative to post-treatment 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 post-stroke, inpatient rehabilitation therapists should become familiar with those priming modalities that have limited safety concerns.

Implications for Neurologic 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 neurologic physical therapy 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 physical therapy 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. Additionally, 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, co-morbidities, psychosocial factors, genetic profile, environmental factors, and etc.

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, neurologic physical therapy 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 post-graduate education, residencies, and fellowships are an option for those who choose to specialize in neurologic physical therapy. 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 various rehabilitation diagnoses and how those with various levels of impairment and disability differentially respond to the various method available for priming.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Paradigms of Motor Priming

Stimulation based priming <ul style="list-style-type: none"> • Repetitive transcranial magnetic stimulation (rTMS) • Transcranial direct current stimulation (tDCS) • Paired associative stimulation (PAS) • Peripheral electrical nerve stimulation (PNS) *
Motor Imagery/Action observation <ul style="list-style-type: none"> • Mirror therapy • Video directed • Audio directed • Therapist directed
Movement based priming <ul style="list-style-type: none"> • Repetitive movements: unilateral and/or bilateral symmetrical, active and/or passive • Aerobic exercise
Pharmacological based priming <ul style="list-style-type: none"> • Amphetamines • Dopaminergic agents • Norepinephrine
Sensory based priming <ul style="list-style-type: none"> • Peripheral electrical nerve stimulation (PNS) * • Muscle vibration • Temporary functional deafferentation (TFD)

* Cross Referenced under two paradigms