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Consensus: Can transcranial direct current stimulation and transcranial magnetic stimulation enhance motor learning and memory formation?

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Noninvasive brain stimulation has developed as a promising tool for cognitive neuroscientists. Transcranial magnetic (TMS) and direct current (tDCS) stimulation allow researchers to purposefully enhance or decrease excitability in focal areas of the brain. The purpose of this article is to review

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information on the use of TMS and tDCS as research tools to facilitate motor memory formation, motor performance, and motor learning in healthy volunteers. Studies implemented so far have mostly focused on the ability of TMS and tDCS to elicit relatively short-lasting motor improvements and the mechanisms underlying these changes have been only partially investigated. Despite limitations, including the scarcity of data, work that has been already accomplished raises the exciting hypothesis that currently available noninvasive transcranial stimulation techniques could modulate motor learning and memory formation in healthy humans and potentially in patients with neurologic and psychiatric disorders.

Q1 **Keywords** ■

Within the past 2 decades noninvasive brain stimulation has been used as a probe to modulate attention, memory, motor, and language functions in humans.[1-9] TMS and tDCS can enhance or decrease excitability in target cortical regions depending on the parameters of stimulation used.[10-13] TMS, and to a lesser extent tDCS (specific differences are described by Nitsche et al in this issue of *Brain Stimulation*) have been used as an interference technique ("virtual lesion") for understanding brain-behavior interactions and to explore possible cause-effect links between altered activity in specific brain areas and particular behaviors.[14,15] Improved understanding of the involvement of a brain region in a type of behavior was followed by attempts to modify activity in this area to secondarily influence performance, learning, and memory functions.[2-9] In this chapter we summarize the results from studies that aimed at eliciting improvements in motor performance and motor learning in healthy humans.

Motor learning

Formation of motor memories is required for learning the motor skills in daily life.[16,17] It is helpful to distinguish studies focused on the process of acquisition, consolidation, and long-term stability (also referred to as retention) of a new motor skill[8,18,19] from those that evaluate the return to baseline levels of performance in response to external perturbations.[20-23] An example of adaptation to an external perturbation is the response to directional errors in visually guided reaching movement caused by prism glasses:[22,24] with practice, performance returns to the "baseline" level. Importantly, adaptation may not require the acquisition of new motor synergies or movement patterns, as it engages movements that were achieved throughout life.

In contrast to adaptation, acquisition of a new motor skill involves the acquisition of new movement qualities and/or muscle synergies that enhance performance beyond preexisting levels. Skills seem to take longer to acquire than adaptation and sometimes do not reach plateau levels after years (ie, learning to play piano or basketball).[20,25-27] In engineering terms, adaptation may be modeled as error-based learning, whereas, for example, motor skill learning is better modeled in terms of reward-based signals.[28,29] However, it should be kept in mind that an overlap of reward- and error-based learning is possible.

Consolidation refers either to stabilization (reduced susceptibility to retrograde interference) or offline improvements.[30-33] Consolidation processes can depend on the type of task, the time between the end of practice and the testing of recall, and the presence or absence of sleep. Offline improvements, for instance, in the ability to perform a finger opposition task, correlated with the amount of time spent in REM sleep.[34] Similarly, offline improvements in a motor sequence learning task are sleep dependent when individuals are aware of the underlying sequence.[35] However, when individuals have little awareness for the sequence, offline improvements are able to develop over waking or over a night sleep.[35] Potentially, the effect of individuals' awareness on offline learning is mediated by their declarative knowledge for the sequence: disrupting declarative knowledge for the sequence can induce improvements over wake.[36] In adaptation studies, the successful return to baseline performance after the perturbation occurs often within one session, and therefore the possibility of offline improvements across days has not been thoroughly tested, although savings, an increase in the rate of readaptation, could be considered a form of offline learning.[37] One exception to this general statement is the study of Huber et al[38] in which overnight improvements in performance of a motor adaptation paradigm in which subjects had to adapt to a visual perturbation of a reaching movement correlated with increased less than 4 Hz activity during slow wave sleep. This activity is thought to reflect oscillatory changes in neuronal membrane potentials.[38]

As stated previously, another form of consolidation is stabilization, that is, maintenance of practice-induced performance improvements or skill (in opposition to forgetting or to offline improvements). After the end of a practice period, procedural memories for a task A may display different degrees of strength to interference. A classical approach to evaluate this strength is to introduce a task B as a source of interference and subsequently test the subject's ability to perform task A.[37,39,40] Interference to recall a newly learned motor task A by practicing a different motor task B has been described as "retroactive interference." Retroactive interference has a well-described time course diminishing with the length of the time interval between the end of practice of task A and the application of the interfering task B, becoming virtually absent after 6 hours.[37,40,41] Stabilization over hours after learning dynamic adaptation tasks has been well-documented.[41,42] Of note, Goedert and Willingham[40] showed that for motor sequence learning offline stabilization does not occur. Whether 15 minutes or 24 hours passes in between task A and B, task B continues to exert retrograde interference.[40] However, this finding might be task specific.

It is important to keep in mind that during motor learning, both kinds of consolidation, offline learning and stabilization, are likely occurring.[43,44] As stated previously, it is unclear if offline enhancement occurs for adaptation tasks as consolidation studies of adaptation have focused on stabilization. Other factors that may influence our ability to assess the stability of a procedural memory include the end point measure used (speed, accuracy, or speed accuracy ratios related to a motor task) and the practice schedule:[45,46] for instance, when a skill is acquired through interleaved rather than blocked practice schedules, motor memories may become more resistant to interference.

One important theoretical point to highlight is the difference between measurements of motor performance and motor skill. Improvements in speed or in accuracy of performance of a motor action have been often reported in isolation in the literature, occasionally indicating that changes in one of these two measures occurred in the absence of changes in the other. Such changes have been reported as changes in skill. It would be important to keep in mind that motor skill cannot always be reliably surmized from changes in only one of these two measures. Skill may be better described as a change in the speed-accuracy trade-off, which is task dependent. Taking into consideration this issue, would help future investigators avoid concluding a change in skill (skill improvements) when in fact subjects have only moved along the same speed/accuracy trade-off curve.

Noninvasive brain stimulation

Noninvasive brain stimulation has been used to identify the functional relevance of particular brain regions in motor learning and facilitate activity in specific cortical areas involved in motor learning in an attempt to improve motor function.

Functional role of the primary motor cortex in motor learning as studied with noninvasive cortical stimulation

Motor learning is associated with functional changes in a distributed network that includes the primary motor, premotor and supplementary motor cortices, the cerebellum, thalamic nuclei, and the striatum.[18,47-50] Most TMS and tDCS studies performed so far to study the role of motor areas in motor learning have focused on M1.

Role of M1 in encoding of an elementary motor memory: Butefisch et al[51] showed that the synchronous application of single-pulse TMS to M1 contralateral to a hand practicing a thumb abduction task enhanced the ability of healthy subjects to encode an elementary and short-lasting motor memory in the primary motor cortex.[2] Importantly, this effect was evident when M1 was stimulated in synchrony with the training motions but not when applied in between training movements. A second important finding from this study was that synchronous stimulation of the “resting” M1 with the training motions in the ipsilateral hand, cancelled training effects on motor memory formation, consistent with the hypothesis that interhemispheric interactions between M1s contribute to motor memory formation.[2] It has been proposed that formation of motor memories within M1 could represent a first step in the more complex chain of events leading to improve a motor skill, but it should not be interpreted as motor learning per se as skill improvements above naïve levels are typically not seen with this particular paradigm of motor memory formation.

Role of M1 in motor adaptation: As discussed previously, the concept of motor adaptation refers to learning to adjust to external perturbations.[21-23,52] In these experiments, subjects adjust their motor behavior to compensate for a particular perturbation to maintain a stable performance.[21] TMS and tDCS have been used to evaluate the role of M1 in motor adaptation. In general, stimulation over M1, using parameters that decrease excitability in that region like 1-Hz TMS, have been applied before or during adaptation paradigms (to evaluate its functional relevance for encoding of the necessary adjustments to compensate for the perturbation).[23,53] In one study, single TMS pulses applied to M1 at 120% of resting motor threshold (RMT) of the first dorsal interosseus muscle immediately after the end of each trial while adapting to a perturbation in the form of a visuomotor rotation did not impact adaptation, but caused faster deadaptation (forgetting) within the same session relative to single pulses applied 700 miliseconds after the end of each trial or relative to PMd stimulation.[53] In another study, 1-Hz rTMS applied to M1 at 90% of biceps RMT before force field adaptation did not affect the participants’ adaptation per se, but impaired retention relative to control subjects (who did not receive any rTMS) as tested the following day when subjects were exposed to the same force field to which they had previously adapted.[54] On the other hand, Baraduc et al[23] did not find a deleterious effect of 1-Hz TMS applied over M1 on adaptation to a dynamic force field. Potential areas of interest that remain to be investigated in more detail include the role of motor areas other than M1 in motor adaptation.

Role of M1 in motor skill learning: As discussed previously, motor learning may (and often does) continue after the end of practice periods, referred to previously as consolidation in the form of offline learning. The role of M1 has been investigated in the process of acquisition and consolidation of motor skills.[13,50,55] Muellbacher et al[13] reported in an influential study, that 1-Hz rTMS over M1 at 115% of flexor pollicis brevis RMT applied immediately before a single-session practice of a thumb-to-finger opposition task did not disrupt within session improvements in speed and muscle force generation but had deleterious effects on retention of these improvements as tested the following day relative to stimulation applied 6 hours after practice or when applied to other cortical areas such as the occipital cortex or the left DLPFC. These results were interpreted as supportive of the view that M1 plays a functionally relevant role in consolidation of explicit motor memories.[13] The role of M1 was also explored in motor sequence learning[56] by using a modified version of the serial reaction time task (SRTT).[57] 1-Hz rTMS was applied over M1 immediately after training when subjects practiced the task early in the morning or late in the evening (different groups). The end point measure was offline enhancement in performance of the task 12 hours later (the evening of the practice day with no sleep in between in the first group and the following morning after a normal night sleep in the second group). It was reported that offline enhancements of the learned task were disrupted in the first group (no sleep) but not in the second group. The authors interpreted the result as indicative of different consolidation processes depending on how close sleep is to the practice period.[56] For a more detailed review of the effects of virtual lesion studies on motor learning, please refer to[15]. On the other hand, rTMS and tDCS have been used in an attempt to facilitate motor learning, the focus of this review.

Attempts to facilitate motor learning by noninvasive cortical stimulation

On the basis of human neuroimaging studies, it was proposed that application of noninvasive stimulation with parameters that enhance motor cortical excitability could secondarily facilitate motor learning. One key structure in the distributed network engaged in motor sequence learning is the primary motor cortex (M1).[13,58] Within M1, the extent of cortical reorganization associated with motor training correlates with performance improvements.[59] The interaction between the two M1s appears to play an important role in motor control in general,[20,60-64] and in motor sequence learning in particular.[64,65] However, the specific way in which these interactions operate during motor learning remain to be determined. According to these interactions, it would be theoretically possible to facilitate motor learning processes in which M1 is involved by enhancing excitability in the "learning" M1[5] or by decreasing excitability in the "resting" M1.[66-68] The intrinsic intracortical mechanisms by which these oversimplified models may operate remain to be identified[64,69,70] (see for discussion chapters by Walsh et al., Di Lazzaro et al., Berardelli et al.).

Several investigators proposed that noninvasive cortical stimulation that enhances excitability in the M1 contralateral to a training hand[5,71] might result in varying degrees of improvement in motor function in healthy humans. Kim et al[72] reported that 10-Hz rTMS at an intensity of 80% of RMT applied over M1 during practice of contralateral sequential finger movements resulted in improved motor sequence learning (as measured by target accuracy and speed on a sequential key press task) relative to sham stimulation. Anodal tDCS applied over M1 during practice also led to improvements in: (1) the number of correct key presses in a sequential finger movement task in a polarity-specific manner since cathodal tDCS failed to induce this effect[73]; (2) performance of a visuomotor coordination task that were transient (∼5 minutes)[74]; (3) reaction times in the sequence blocks relative to the random blocks in the SRTT,[57] in which subjects learn a sequence of 12 key presses without explicit awareness[75]; and (4) performance of the Jebsen Taylor Hand function test (JTT), a task often used in stroke research that mimics activities of daily living such as lifting cans and picking up small objects.[76] Interestingly, this effect has been reported as present in the nondominant hand only in young healthy adults.[77] Of note, tDCS in these two articles was applied after subjects reached stable JTT performance, likely reflecting a tDCS-induced performance improvement beyond a plateau level. It is not known if application of noninvasive cortical stimulation during the learning period of the task (before it reaches an asymptote) could speed up or enhance learning of the task.

In contrast to studies that focused on application of TMS or tDCS to the M1 contralateral to a practicing hand, the application of 1-Hz rTMS to the M1 ipsilateral to a training hand results in: (1) increases in motor cortical excitability of the opposite M1[66-68] relative to sham stimulation, and (2) improvements in motor sequence learning[65] relative to stimulation of the contralateral M1, ipsilateral premotor area, or vertex (Cz). One important consideration is that the effects of stimulating M1 with either TMS or tDCS are likely to be dependent on the complexity of the task. For example, performance of relatively simple repetitive finger abduction movements was not improved by high-frequency rTMS over the "learning" M1,[79] whereas more complex sequential motor tasks or encoding of a motor memory did improve (discussed previously). Similarly, another study showed no performance improvement in a task engaging single finger tracking motions when the ipsilateral M1 was stimulated with 1-Hz rTMS during practice.[80]

In contrast to studies focusing on motor sequence learning or motor performance, we are not aware of studies that used TMS or tDCS in an attempt to facilitate motor adaptation.

Caveats and future directions

Although the previous paragraphs depict a relatively consistent and homogenous picture on the effects of up- and down-regulation of excitability within M1 on motor learning and motor memory formation, several caveats should be kept in mind. First, induction of a "virtual lesion" or enhancement of activity in one cortical area may result in behavioral changes through specific effects on that area or secondarily through distant effects on other interconnected cortical areas. Second, the discussion of results in this article (as well as those of specific physiologic interactions across cortical regions[61]) assume, in general, that the surface of the brain is a smooth sphere, often neglecting that the folding of the cortex may result in hyperpolarization of neurons on one side of a gyrus but depolarization on the other. Third, the history of activity in the stimulated cortex may be of considerable importance. For example, the effects of stimulation may differ substantially if applied to a "fatigued" or to a "well-rested" cortex. In one example, 1-Hz rTMS may induce facilitatory effects if acting on a cortex that has been previously inhibited by cathodal tDCS.[81,82] This phenomenon, referred to as homeostatic plasticity or metaplasticity and discussed elsewhere,[83] may potentially impact motor learning.[84,85] Fourth, although most of the work in the field focused on studying the effects of stimulation over M1, some reports indicated that stimulation of the dorsal premotor or the lateral or medial prefrontal cortex failed to induce overt reaction time improvements in the SRTT task.[75] Similarly, anodal tDCS applied over the primary visual cortex (V1) did not improve performance of a visuomotor tracking task in healthy subjects.[74] However, findings indicating a lack of effect of stimulation in a particular site are not proof that the area is not involved. The most parsimonious interpretation of these findings is that more elaborated, hypothesis-driven behavioral paradigms or stimulation strategies may be necessary to study the functional role of these cortical regions in motor learning and memory formation. Alternatively, it is possible that the "threshold" for facilitating motor learning by M1 stimulation is lower than by stimulation of other cortical areas, an issue to be investigated in future experiments. Fifth, one caveat of many previous investigations has been the focus on short-term improvements in performance. More experiments are required to assess the effects of repeated applications of TMS or tDCS in association with multiple training sessions, their interaction with specific motor learning stages and tasks, and the extent to which these performance improvements are retained in the long term. Finally, it should be kept in mind that the effects of TMS and tDCS cannot be assumed to be the same. The mechanisms underlying the effects of each technique on motor cortical function are very likely to differ, as discussed by Nitsche et al in this issue of *Brain Stimulation*, and so will the effects on motor cortical networks and behavioral consequences of its application. Clearly, more work is needed in this area.

Summary

In summary, the scarce studies performed so far point to the encouraging conclusion that noninvasive brain stimulation can contribute to the understanding of mechanisms underlying motor learning and motor memory formation and raise the exciting hypothesis that this increased understanding could in the future result in the development of new strategies to enhance specific stages of learning and memory processing in healthy humans and in patients with brain lesions, as discussed by Gerloff et al in this issue of *Brain Stimulation*.

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