Sensorimotor Integration During Motor Learning: Transcranial Magnetic Stimulation Studies

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ABSTRACT

The effect of sensory signals coming from skin and muscle afferents on the sensorimotor cortical networks is entitled as sensory-motor integration (SMI). SMI can be studied electrophysiologically by the motor cortex excitability changes in response to peripheral sensory stimulation. These changes include the periods of short afferent inhibition (SAI), afferent facilitation (AF), and late afferent inhibition (LAI). During the early period of motor skill acquisition, motor cortex excitability increases and changes occur in the area covered by the relevant zone of the motor cortex. In the late period, these give place to the morphological changes, such as synaptogenesis. SAI decreases during learning the motor skills, while LAI increases during motor activity. In this review, the role of SMI in the process of motor learning and transcranial magnetic stimulation techniques performed for studying SMI is summarized.

Keywords: Sensorimotor integration, transcranial magnetic stimulation, TMS, motor learning, motor skill learning

INTRODUCTION

How does becoming competent in the use of tools, playing an instrument, riding a bike, or becoming professional in a sports area, in other words, the “motor learning” process take place in the human brain? Are there factors negatively or positively affecting the motor learning process and if so, what are these? There are several studies that have been conducted or are being conducted on animals and humans with the purpose of seeking an answer to these questions. The findings from these studies show that the primary motor cortex (M1), basal ganglia, cerebellum, brainstem, and spinal cord are responsible for the learning of a motor skill in the human brain (1). The M1 is a superordinate control center that directly or indirectly (through interneurons) gives the necessary command to the anterior horn motor neurons for deliberate movement to occur.

Transcranial magnetic stimulation (TMS), which is a painless, non-invasive stimulation method, has been being widely used since 1985 when it was invented for investigating the functions of the central nervous system or for regulating or changing these functions with repetitive TMS (rTMS) protocols (2). Studies done with TMS have shown that different plastic changes occur in the M1 in both the early and the late periods during repetitive motor functions and the acquisition of a new motor skill (3,4,5,6,7,8,9).

Sensory and motor cortices are in communication and cooperation with each other in the regulation of movement; in other words, there is a sensory-motor integration (SMI). The M1 provides flexibility of movement by ensuring that the muscle groups that control the joints work in synergy and expertly uses the information coming from the sensory afferents while doing this (10). It has been known for a long time that signals coming from skin and muscle afferents affect the sensorimotor cortical networks in humans and other primates (11,12,13). Sensory afferents influence M1 either directly through the intracortical connections between the primary sensory cortex (S1) and M1 or through thalamocortical pathways that reach M1 (14,15).

Our knowledge on how SMI functions in the process of motor learning is based on the information obtained from animal experiments, the examination of patients with damage to the peripheral or central sensory pathways, and functional neuro-imaging studies. For example, the remarkable proper movement of the Caenorhabditis elegans, which is a nematode, with very few neurons in different and complex environments by using sensory signs, due to the very well-developed sensorimotor connections, has been demonstrated with studies (16).

Both motor learning processes and the effect of proprioceptive and cutaneous afferent signals on corticospinal excitability can be studied using electrophysiological methods. Currently, it is known that SMI defects have also an underlying role in some movement disorders, such as dystonia (17). There is an accumulating evidence that SMI and motor learning can be changed through rTMS. Effects similar to long-term potentiation (LTP) and long-term depression (LTD) can be produced on cortical synaptic plasticity with different rTMS protocols (18,19,20). Nowadays, through the conditional proprioceptive feedback provided by the orthotic device called brain-robot-interface placed on the hand and arm during the motor imagery task, the completion of the sensorimotor cycle is ensured and additional benefits for regaining the motor function.
functions are aimed in patients with permanent and severe motor deficits following stroke (21).

Genetic variations have been shown to affect the motor learning process. For example, it was shown that the Val66Met (rs6265) “single nucleotide polymorphism” in the “brain-derived neurotrophic factor” gene can affect the motor learning process in a negative way (22). Dopamine is an important neurotransmitter in motor skill learning and motor cortex plasticity. Variations in the five genes affecting the dopaminergic system (catechol O-methyltransferase [COMT]), that controls synaptic dopamine levels and those that encode the dopamine transfer protein and the D1, D2, and D3 dopamine receptors] have been reported to change motor learning (23).

This review summarizes the results of studies that seek answers to the questions: What are the plastic changes seen in the primary motor cortex during motor learning process?

How can SMI be assessed using electrophysiological methods? How does SMI affect the motor learning process?

WHAT ARE THE PLASTIC CHANGES SEEN IN THE PRIMARY MOTOR CORTEX DURING THE MOTOR LEARNING PROCESS?

The brain tissue has the capacity to develop functional and structural changes in response to experiences to which the body is exposed, which is expressed as “brain plasticity.” Brain plasticity is a mechanism that is utilized in physiological processes, such as memory and the repair of damaged tissue regaining of impaired functions in pathological conditions. It has been demonstrated in rats and mice that during motor skill learning, reorganization and expansion occurs in the related motor cortex region where movement is represented in the primary motor cortex and an increased complexification and cortical synaptogenesis develop in the dendritic spines of the pyramidal neurons (24). Quick cortical plastic changes in relation to learning occur with the functional changes in the synapses. These include changes toward LTP and LTD in post-synaptic neurons or the surfacing of pre-existing connections; in other words, the awakening of silent synapses (18,19,20,25,26,27). However, time is needed for morphological changes, such as synaptogenesis, the reshaping of synapses and neurogenesis to emerge (28). Pharmacological studies have shown that motor cortical plastic changes due to use are related to the activation of N-methyl-D-aspartate receptors and gamma-aminobutyric acid (GABAergic) and that motor skill learning decreases the GABAergic inhibition in intracortical cycles (29). The GABAergic inhibitory system can be studied with paired-pulse TMS stimulation in humans (30).

Changes in the M1 in the motor learning process shown with TMS studies can be summarized as the motor threshold (MT), short interval intracortical inhibition (SICI), intracortical facilitation (ICF) changes, and display of changes in the site and size in the localization of the motor area related to the movement in question for motor mapping.

Motor threshold and motor-evoked potential (MEP) amplitude are parameters that show cortical excitability. Resting MT is the lowest stimulation intensity that creates an MEP response >0.05 mV in at least 5 out of 10 tries, and activity MT is the lowest stimulation intensity that creates an MEP response >0.1 mV in at least 5 out of 10 tries when the target muscle is in a state of slight contraction (31). The subject of M1 excitability changes in only the early period of motor learning is disputable. It has been shown in functional neuroimaging and TMS studies that during complex motor learning, the area where the movement is represented in the motor cortex expands and that the excitation threshold of this motor cortex area is decreased (3,32,33,34,35). Passive movements that do not require skill however did not lead to plastic changes or created very short-term minor changes (32,35,36). It has also been reported that repetitive movements that do not require skill led to a decrease lasting about 30 minutes in the modulation of synaptic transmission due to activity and M1 excitability (37,38,39,40). This decrease in excitability also occurs in the non-activated ipsilateral hemisphere with a slight delay (38). Thus, how are the cortical plastic changes that occur in people who continue motor exercises for a long time? It has been shown that in elite tennis players, the cortical map of the hand being used shifted and that the resting and active MTs decreased; no such change was found in normal people or social tennis players (9). This can be interpreted to mean that motor activities requiring skill lead to long-lasting motor plastic changes. Pascal Leone et al. (41) have shown that during the acquisition of a motor skill the related sensorimotor area expands and that this expansion begins to regress once the person has become professional. This is an indicator that a portion of quick motor cortical plastic changes give way to structural changes in the long term (28).

In paired-pulse TMS stimulation studies, the test stimuli are given at supra-threshold intensities, and the effect of a subthreshold conditioning stimuli that are given before the test stimuli with predetermined interstimulus intervals (ISIs) on the motor responses evoked by the test stimuli are studied. Conditioning stimuli generally inhibit the motor responses if they are given with short ISIs (1-5 ms, short intracortical inhibition=SICI). This period is followed by an ICF with longer ISIs (8-25 ms) SICI and ICF are formed by different cortical interneuron groups (42). Short-term motor learning decreases SICI and may increase ICF or not affect it (43). It is different however in individuals who have a greatly developed control of the finger movements, for example musicians; while resting and active MTs are the same as controls, both SICI and ICF were found to be low (44). This may be indicative of extraordinary adaptation or maladaptation due to overuse.

HOW CAN SENSORY-MOTOR INTEGRATION BE ASSESSED USING ELECTROPHYSIOLOGICAL METHODS?

The recording of changes made on the motor response by sensory stimulation given a certain period before motor stimulation gives the electrophysiological information in the assessment of SMI. For this, TMS at suprathreshold intensity is applied to the motor cortex at certain ISIs by following peripheral nerve stimulation at suprathreshold submaximal intensity (Figure 1). Peripheral stimulation is performed through mixed or cutaneous nerves. The TMS intensity is usually at an intensity that forms a motor response at an amplitude of 1 mV in 5 out of 10 stimulations. A great majority of the studies have been performed on hand muscles. Different stimulation intensities, ISI, and the effect of register muscles were studied in detail. In studies conducted in the early period, TMS was performed with circular coils and then butterfly-shaped coils that can make more focal stimulation were used (45,46).

Motor-evoked potential amplitudes obtained with TMS change with peripheral stimulations given before it. This interaction consists of 3 stages depending on the period between peripheral nerve stimulation and TMS: short afferent inhibition (SAI), afferent facilitation (AF), and late afferent inhibition (LAI) (45,46,47,48,49,50,51) (Figure 2). While the differences shown by these interactions between people are significant, they are less in the examinations of the same person at different times. The degree of inhibition and facilitation are directly proportional to the intensity of nerve stimulation (52).
If the ISI between TMS and peripheral mixed-nerve stimulation is approximately close to the latency of the cortical N20 potential obtained in the somatosensory-evoked potential (SEP) examination (20-25 ms), it causes a reduction in the MEP amplitude. This condition is defined as EAI (47,49). EAI can develop by the afferent signals directly affecting the M1 neurons or indirectly through a sensory-motor short cycle. LAI is the second inhibition period and is shown for ISIs between 100 and 500 ms (48). Cortico-cortical or subcortical pathways probably play a role in their occurrence (50). Afferent signals also have a facilitating effect on the M1; this effect emerges with ISIs between 25 and 80 ms in the distal arm muscles (45,46) and with ISIs between 45 and 60 ms for leg muscles (45). AF has also been shown to continue while target muscles are in tonic contraction (51). Interestingly, AF occurs with the stimulation at the wrist level (mixed-nerve stimulation) of the median nerve but is not seen with the stimulation of skin branches (digital nerve) from the second finger. This may suggest that this facilitation occurs through thick afferent fibers stemming from muscle spindles (51,53). SMI shows topographic organization. This is because the greatest MEP changes are obtained by stimulation of the peripheral nerve innervating the register muscle (53,54).

Short afferent inhibition afferent inhibition is believed to occur through acetylcholine (Ach) at the cortex level (55). Sailer et al. (50) showed that SAI can be changed with dopamine, and Di Lazzaro et al. (56) showed that it can be changed with gamma amino butyric acid A (GABA-A) agonists. SAI interacts with neuronal cycles, such as SICI, driven by GABAergic interneurons (57,58) and long interval intracortical inhibition (59).

The magnitude of SAI can be changed. It increases with counting numbers (60) and decreases with finger movements or specific work (61,62). The rTMS also changes SAI. While low frequency rTMS applied to the S1 decreased SAI in patients with focal dystonia, it did not create any change in healthy controls (63). While 1 Hz rTMS applied to the M1 did not change SAI, it lowered MEP amplitudes in general (52). Intermittent theta burst stimulation (iTBS) on the M1 increased SAI in those with Parkinson's disease (64). While 30 Hz continuous TBS (cTBS) lowered MEP amplitudes when applied to the M1, it did not affect SAI; however, when it was applied to the S1 and S5 it increased MEP amplitudes and reduced SAI (65,66,67,68,69).

Late afferent inhibition increases during selective finger movements (62). Sensory impairments that are not in the least lacking in Parkinson's patients are known to contribute to motor deficits. Sailer et al. (50) showed that SAI decreases in the hemisphere that is more affected under dopaminergic treatment in Parkinson's patients and it is similar to normal controls when dopaminergic treatment was ended, but showed that LAI decreased independently of treatment. They have stated that the difference between the SAI and LAI results stemmed from the difference between the underlying mechanisms of these two inhibition periods. While

![Figure 1. Sensory-motor integration study protocol](image1)

![Figure 2. a, b. Effect of conditioning peripheral nerve stimulation on the size of motor evoked potentials evoked by transcranial magnetic stimulation of the motor cortex (TMS; test stimulation), which was applied after the conditioning stimuli with predetermined interstimulus intervals (a). The periods of sensory-motor integration: Short afferent inhibition (SAI), afferent facilitation (AF), and late afferent inhibition (LAI) (b)](image2)
SAI reflects the direct effect of the sensory stimulus on the motor cortex. LAI probably concerns the basal ganglia or cortical association areas.

**HOW DOES SENSORY-MOTOR INTEGRATION EFFECT THE MOTOR LEARNING PROCESS?**

Sensory feedback plays an important role in the learning of new motor skills. The effect of sensory input on motor learning is based on the information obtained from major animal experiments, the effects of sensory defects temporarily created in healthy people, and studies conducted with patients with peripheral sensory loss (70).

Peripheral sensory stimuli increase motor cortex excitability (71). While there is no reduction in strength in sensory neuropathies involving the thick myelinated fibers, motor skills are impaired (72). The somatosensory cortex is an important component in the acquisition of new motor skills. S1 probably increases M1 excitability with an LTP-like mechanism. When the S1 was cut off in macaque monkeys, it was found that the response characteristics of the cortical and spinal motor neurons had changed (73). When S1 ablation was performed in monkeys, it was seen that the acquisition of new motor skills was impaired in the opposite extremity but the previously learned skills continued without deterioration (74). One hertz rTMS applied to the S1 in healthy people impairs motor skill learning by causing the somatosensory feedback added to the internal model of movement organization or motor plan to be disrupted (70). A cTBS applied to the S1 decreases SEP amplitudes (75), while increases cortico-spinal excitability in the M1 (67,69). In the presence of post-central gyrus and intraparietal sulcus damage in patients who have had a stroke, the process of motor skill acquisition.

Carpal tunnel syndrome (CTS), which is a common entrapment neuropathy, can easily be studied as an appropriate disease model in investigating how a localized peripheral sensory impairment affects cortical SMI. Dropping objects and the impairment of manual skills requiring precision are seen very often in CTS. In a study we conducted, we found that in CTS patients who had and did not have a complaint of dropping objects, SMI started by the median and ulnar nerves topographically showed different shapes (77). We interpreted this to mean that brains with CTS responded by developing different strategies to the abnormal sensory information coming from the periphery. In another study, we investigated the change of SMI occurring during motor skill acquisition according to time and experience (78). We saw that basketball shots in sedentary subjects led to a decrease in SAI and an increase in AF and that this is more prominent in the early period; however, we found no such change in SMI in licensed basketball players. We interpreted the fact that there are no SMI changes in players who are still actively playing basketball to mean that these subjects are past the functional change stage seen in the early period during the process of motor skill acquisition.

**CONCLUSION**

The acquisition of motor skills leads to plastic changes in the motor cortex. Functional changes during the early period of learning mostly give way to permanent morphological changes in the late phase after motor memory has been formed. Peripheral sensory stimulation changes motor cortex excitability. Defects in sensory input impair motor skills. SMI can be studied electrophysiologically. While there is a decrease in SAI during the acquisition of a motor skill, LAI increases during motor activity.

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