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The Role of Primary Motor Cortex: More than Movement Execution

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Abstract

The predominant role of the primary motor cortex (M1) in motor execution is well acknowledged. However, additional roles of M1 are getting evident in humans owing to advances in noninvasive brain stimulation (NIBS) techniques. This review collates such studies in humans and proposes that M1 also plays a key role in higher cognitive processes. The review commences with the studies that have investigated the nature of connectivity of M1 with other cortical regions in light of studies based on NIBS. The review then moves on to discuss the studies that have demonstrated the role of M1 in higher cognitive processes such as attention, motor learning, motor consolidation, movement inhibition, somatomotor response, and movement imagery. Overall, the purpose of the review is to highlight the additional role of M1 in motor cognition besides motor control, which remains unexplored.

Key Words: Primary motor cortex, cognitive functions, motor learning.

Abbreviations:

PMA (premotor area), supplementary motor area (SMA), cingulate motor area (CMA), Noninvasive brain stimulation (NIBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), functional magnetic resonance imaging (fMRI), repetitive TMS (rTMS), primary sensory cortex (S1), motor evoked potentials (MEPs), electromyographic (EMG), paired-pulse TMS (ppTMS), electroencephalogram (EEG), cortical silence period (CSP), theta-burst stimulation (TBS), negative-motor area (NMA), short-interval intra-cortical inhibition (SICI).

1. **Introduction**

Early investigation of the motor cortex in humans (Penfield and Boldrey, 1937; Woolsey, 1952) had functionally divided the motor cortex into two major areas: the primary motor cortex (M1) and premotor area (PMA; Fulton, 1935). M1 is located in the precentral gyrus of the frontal lobe that plays a crucial role in the execution of voluntary movements (Pearson, 2000). Histological examination of M1 has revealed the presence of giant pyramidal neurons called Betz cells. Betz cells are also known as upper motor neurons because they send axons to the lower motor neurons situated in the gray column of the spinal cord. The upper motor neuron contributes to the corticospinal pathway, whereas the lower motor neurons innervate the skeletal muscle fibers situated at the periphery (Porter & Lemon, 1993). With this structural construct, M1 is predominantly considered to only have a role in motor execution.

In contrast, the PMA and other regions of the frontal lobe such as the supplementary motor area (SMA) and the cingulate motor area (CMA) (Chouinard & Paus, 2006) form the secondary motor areas. Many previous reviews have shown that these secondary motor areas are involved in cognitive processes such as planning, coordination, and selecting voluntary movement (Nachev, Kennard, & Husain, 2008; Rizzolatti, Fogassi, & Gallese, 2002). For example, Rizzolatti, Fogassi, & Gallese (2002) consolidated the results of the studies performed on primates and humans to conclude that the ventral sectors of the PMA (including Brodmann area 44) are involved in action organization, motor imagery, and action understanding. Similarly, Goldberg (1985) and Roland, Larsen, Lassen, & Skinhoj (1980) reported the involvement of SMA in the organization of voluntary motor movement. Borich, Brodie, Gray, Ionta, & Boyd (2015) reviewed the role of primary SMA in motor control, motor learning, and functional recovery. Though these studies open up vast opportunities for the exploration of M1, the possibility that M1 can play a crucial role in motor cognition remains understudied.

Noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have provided evidence that M1 might be involved in higher cognition. NIBS can directly modulate M1 (in isolation) and establish a causal relationship between the activity of the regions and the behavior. In this regard, it will be interesting to lay out the NIBS-based studies that have indicated (directly or indirectly) the role of M1 in higher cognition. The present review will begin with a short description of the anatomical, functional, and neurochemical connections of M1 with other cortical and subcortical regions. This will be followed by the description of the studies that have provided evidence for the involvement of M1 during attention, learning, consolidation, movement inhibition, observation, imagery, and sensory processes. Here, we would like to remind our readers that though the present review will mostly focus on the studies on humans, owing to the limited research on M1 in humans, relevant findings from animal studies will also be occasionally presented.

2. Overview of the connectivity of M1 with other cortical regions

M1 sends projections to the lower motor neurons in the spinal cord and is interconnected with multiple brain regions through afferent and efferent pathways. Such interregional structural connections of M1 have been extensively demonstrated in primates (Barbas & Pandya, 1987; Dum & Strick, 2002; Geyer, Matelli, Luppino, & Zilles, 2000; Holsapple, Preston, & Strick, 1991; Luppino, Matelli, Camarda, & Rizzolatti, 1993; Matelli, Luppino, Fogassi, & Rizzolatti, 1989; Orioli & Strick, 1989; Penfield & Boldrey, 1937; Petrides & Pandya, 1984; P. L. Strick & Preston, 1983; Peter L. Strick, 1985) as well as in other mammals (Kaas, 1991; Sanes & Donoghue, 2000). Several studies on humans have also suggested interregional connections of M1 with other cortical and subcortical regions using positron emission tomography (PET; Fink, Frackowiak, Pietrzyk, & Passingham, 1997; Grafton, Woods, & Mazziotta, 1993; Honda, Wise, Weeks, Deiber, & Hallett, 1998) and

functional magnetic resonance imaging (fMRI; Rao et al., 1997; Xiong, Parsons, Gao, & Fox, 1999). These neuroimaging techniques have good spatial resolution but mainly measure the level of oxygen in the blood (Davis, Kwong, Weisskoff, & Rosen, 1998) and do not directly measure the neural activity. Though the neural activity in the cortex and the level of oxygen in the blood are related, such an indirect way of measurement restricts our understanding of the complete functionality of an area in the brain. Moreover, because the connectivity defined between two cortical regions is based on the correlation measures between the imaging signals and the behavior (Hipp & Siegel, 2015), the precise nature and the causality-based dynamics behind functional connectivity remain elusive.

In this aspect, TMS has been widely utilized to modulate cortical regions of cortex. Two types of TMS—the sub- and supra-threshold repetitive TMS (rTMS)—have been used to stimulate M1. The resultant changes in the cortical and subcortical motor areas could be observed using fMRI. In one such study by Bestmann, Baudewig, Siebner, Rothwell, & Frahm (2004), signal change in the cortical and subcortical motor regions was measured when the subjects received high-frequency rTMS over the left sensorimotor cortex (M1/S1). They concluded that the activity in M1 propagates to other cortical and subcortical regions such as PMA, posterior SMA, CMA, cerebellum, thalamus, and putamen (Bestmann et al., 2004). Such cortical and subcortical networks have been demonstrated to be involved in motor sequence performance (Bapi, Miyapuram, Graydon, & Doya, 2006). Thus, Bestmann et al.'s (2004) finding of the interregional connections of M1 with these regions suggests a possible contribution of M1 in performing a sequence of motor actions. This is possible, as evidenced by another study showing the involvement of M1 and the primary sensory cortex (S1) in complex voluntary finger movement (Shibasaki et al., 1993). In an interesting work, Fox et al. (1997) recorded PET scans following the stimulation of M1 by TMS. They found excitatory connectivity of M1 with ipsilateral S1 and S2, ipsilateral ventral and lateral PMA,

and contralateral SMA. They also reported inhibitory connectivity of M1 with contralateral M1. Overall, the activation in other cortical regions following the stimulation of M1 suggested M1 to be a "well-coordinated relay" involved in sending as well as receiving information.

Motor evoked potentials (MEPs) can also investigate such intercortical connections of M1 because they can be used to characterize the interaction of M1 with other brain regions. MEPs are induced following single-pulse TMS over M1 (or any other brain region) and are measured from the surface of the muscles controlled by M1, such as the abductor pollicis brevis/longus muscle of the thumb, using electromyographic (EMG) recording (Thickbroom et al., 1999). MEPs generated by paired-pulse TMS (ppTMS) are also used to study various cortico-cortical connections. ppTMS is a kind of TMS where a subthreshold stimulus (conditioning stimulus) is followed by a suprathreshold stimulus (test stimulus) separated by an inter-stimulus interval. The suprathreshold stimulus determines the corticospinal output that leads to an MEP, while a subthreshold stimulus only excites the local cortical interconnections (Di Lazzaro et al., 2002). Thus, by combining a subthreshold pulse with a suprathreshold pulse, one can assess the effects of other cortical connections on the cortical output of M1 (Ziemann, Tergau, Wischer, Hildebrandt, & Paulus, 1998). An advantage of using ppTMS for investigating the cortico-cortical connection is that it can reveal whether the nature of the connection is excitatory or inhibitory (based on an increase or decrease in MEP).

Using ppTMS over the dorsal PMA with a conditioning pulse of 90% of the active motor threshold, Civardi, Cantello, Asselman, & Rothwell (2001) showed that the excitability of M1 (demonstrated by MEP amplitude) was significantly reduced. Alternatively, they also found that the excitability of M1 could be increased when the conditioning pulse was applied at 120% of the active motor threshold following PMA stimulation. Support for such findings come from the studies that have found both the inhibitory (Cash et al., 2017; Ferbert et al., 1992; Fiori et al., 2017) and excitatory (Hanajima et al., 2001; Massé-Alarie, Cancino,

Schneider, & Hodges, 2016) interactions of M1 with ipsilateral and contralateral cortical regions such as the dorsal PMA, posterior parietal cortices, SMA, and cerebellum (Reis et al., 2008). Mochizuki, Huang, & Rothwell (2004) specifically found an inhibitory connection between the dorsal PMA and contralateral M1. They applied conditioning and test stimulus over the right dorsal PMA and the left M1, respectively, with an inter-stimulus interval of 4, 6, 8, 10, 12, 16, and 20 ms. They found the MEP generated following test stimulus at M1 to be significantly reduced, and the effect was maximum at the inter-stimulus interval of 8–10 ms. Recently, Lafleur, Tremblay, Whittingstall, & Lepage (2016) have reviewed the studies using ppTMS to demonstrate the connectivity of M1 with the contralateral M1, PMA, and cerebellum. They have also specified that the nature of this connectivity (excitatory/inhibitory) could vary depending on the intensity and inter-stimulus interval of the ppTMS paradigm. Overall, these studies demonstrated that M1 is not only connected to other cortical regions by excitatory influences but also connected with the inhibitory interneurons from other cortical regions. The presence of both excitatory and inhibitory interconnections with other cortical regions provides a structural basis for the possible role of M1 in higher-order cognitive functions.

Similar to ppTMS described above, the interregional connections can also be demonstrated by applying rTMS over a non-primary motor area followed by a single-pulse TMS over M1. The overall effect on M1 can be "excitatory" or "inhibitory" depending on the various stimulation paradigms used for rTMS (e.g., frequency; Fitzgerald, Fountain, & Daskalakis, 2006). The MEP amplitudes are reduced when low-frequency rTMS is applied over the dorsal PMA (Gerschlager, Siebner, & Rothwell, 2001), whereas they are enhanced when high-frequency rTMS is applied over the PMA (Fitzgerald et al., 2006). Such changes in MEP indicate that the PMA might have both inhibitory and excitatory connections with M1. This is further supported by Kobayashi, Hutchinson, Theoret, Schlaug, & Pascual-Leone

(2004) in a study where they asked the participants to perform a sequential key-pressing task with the index finger. These authors applied rTMS (1 Hz for 10 min with an intensity below the motor threshold) over the ipsilateral M1, contralateral M1, ipsilateral PMA, or vertex. The motor performance was monitored for each participant before and after rTMS. They found that the rTMS of M1 resulted in shorter execution times of the motor task performed by the ipsilateral hand, whereas the performance with the contralateral hand was unaffected. They concluded that rTMS over M1 can improve the motor function of the ipsilateral hand by releasing the contralateral M1 via transcallosal inhibition (Kobayashi et al., 2004). These functional connections of M1 are not limited only to the central nervous system. Stimulating the peripheral nerves (measured by H-reflex) before M1 is stimulated by a TMS impulse can cause excitatory changes in the resultant MEP (Devanne et al., 2009; Roy & Gorassini, 2008). These studies indicate that M1 receives multiple inputs from regions of both central and peripheral nervous systems, which could be both excitatory and inhibitory. In sum, the traditional view that M1 is only an endpoint of motor processing in the brain can be inferred to not be entirely accurate because it is also involved in the integration of signals along with other motor regions.

The methodologies mentioned above provided an idea about the type of spatial connectivity (excitatory/inhibitory) of M1 with other brain regions. The measurement of the electrophysiological response using electroencephalogram (EEG) following TMS is also helpful in understanding the spatio-temporal dynamics of the brain. In this technique, one particular cortical region is stimulated by TMS and the change in the electrophysiological signals across other cortical regions is recorded. Ilmoniemi et al. (1997) demonstrated that EEG responses were potentiated in the homologous contralateral area in about 22 ms following TMS over M1. Similarly, Esser et al. (2006) measured the cortical responses (with EEGs) to single-pulse TMS over M1 before and after applying rTMS to the PMA. They demonstrated that EEG

responses at latencies of 15–55 ms were significantly enhanced at the electrodes located at the PMA of both hemispheres. Similarly, Litvak et al. (2007) localized sources at the midline frontal area peaking after 28 ms of TMS over M1. They localized the sources in a temporal sequence and found sources peaking at an ipsilateral temporoparietal junction (with a delay of ~35 ms) and the ipsilateral (with a delay of ~30 ms) and middle cerebellum (with a delay of ~50 ms). The sequential activation of various cortical regions discussed above suggested the propagation of activity following stimulation over M1 not only to the lower motor neurons but also to the other cortical and subcortical regions. With that said, we want to emphasize that these studies also indicate that M1 must be involved in the integration of multiregional influences. In this process, it also executes the commands received from higher-order motor regions.

Similarly, tDCS has also been used to investigate the connectivity of M1 with other brain regions. tDCS studies are limited because the appropriate montage that could stimulate the target region (like the motor cortex) is difficult to ascertain, and there are inconsistencies regarding this in the literature (Ferreira et al., 2019). Although computational analysis paradigms that could help in the montage decision process for other cognitive functions are available (Bai, Dokos, Ho, & Loo, 2014; Bhattacharjee et al., 2019), the mechanism of action of tDCS still remains an area requiring investigation (Caumo et al., 2012; Pelletier & Cicchetti, 2015). Nevertheless, Polanía, Paulus, & Nitsche (2012) investigated the resting-state fMRI before and after tDCS over M1. They found that the anodal stimulation of M1 significantly increases the functional coupling between the left thalamus and ipsilateral M1. In contrast, the cathodal stimulation of M1 decreases the functional coupling between the left M1 and contralateral putamen. This shows that M1 is involved in the corticostriatal and thalamocortical pathways, which are crucial circuitries for motor cognition.

2.1 M1 and neurochemical pathways

The mesocorticolimbic projection that involves dopamine as a signaling pathway plays an essential role in higher cognitive functions (Alcaro, Huber, & Panksepp, 2007). Nieoullon & Coquerel (2003) reviewed the role of dopamine in action, emotion motivation, and cognition. In the context of M1, although its role in regulating movement via basal ganglia is known, its involvement in the dopaminergic signaling pathway is still not known. The cerebral cortex sends glutamatergic projections to the striatum that also receives dopaminergic projections from the substantia nigra and ventral tegmental area (Sesack & Pickel, 1992). These corticostriatal neurons project back to the cerebral cortex via the thalamus by a series of recurrent parallel loops (Bamford et al., 2004). Evidence shows that M1 also sends dopaminergic projections to the striatum. Strafella, Ko, Grant, Fraraccio, & Monchi (2005) applied rTMS over M1 and measured the changes in the extracellular dopamine concentration using [^{11}C] raclopride and PET in healthy human subjects. They found that rTMS over the left M1 resulted in the reduced binding of [^{11}C] raclopride in the left putamen. Thus, they demonstrated that rTMS over the left M1 activated the corticostriatal fibers that project to the putamen and lead to focal dopamine release at the projected site. The same inference was potentiated when Lang et al. (2008) demonstrated that administration of the dopamine receptor agonist, pergolide, resulted in the suppression of cortical excitability following a low-frequency rTMS over M1 compared with a placebo. Similarly, in rats, the stimulation thresholds necessary to evoke a motor response (after stimulation of the caudal M1) were increased when D2-receptors located in the M1 forelimb were blocked by the intracortical injection of raclopride (Hosp, Molina-Luna, Hertler, Atiemo, & Luft, 2009). We highlight the role of dopamine terminals and receptors in M1 because they play an important part in skill teaching (Molina-Luna et al., 2009). A review by Hosp & Luft (2013) suggested that these dopaminergic fibers innervating M1 might also be involved in motor learning and motor cortex

plasticity. The study further indicated that the investigation of the dopaminergic networks in M1 might be useful for the rehabilitation of learning and cognitive deficits seen in Parkinson's disease or other traumatic brain injuries. Altogether, the above findings indicate an involvement of M1 in modulating the dopaminergic corticostriatal pathway. This suggests the possibility of M1 to participate in higher cognitive processes such as skill learning.

3. M1 and attention

M1 is found to be differentially activated when attention is directed toward an action compared with when it is not. This is commonly observed in fMRI studies when participants are asked to simultaneously perform a motor movement and a distractor task such as counting backward (Johansen-Berg & Matthews, 2002). A significant reduction in the fMRI signal for the dual task (both motor movement and distractor task) compared with that for the single task (only motor movement) in the pre-central gyrus (M1) (especially in the motor subarea 4p posterior) was reported (Johansen-Berg & Matthews, 2002). Similarly, in a study by Binkofski et al. (2002), participants performed a visual task while constantly moving their index finger. They found different subareas of M1 to be active when motor action was accompanied by a visual attention task. In particular, they discovered that the subarea 4p within M1 is activated when attention is paid. The authors further reported that the subarea 4a (anterior) within M1 is activated when attention is not required for action. Because attention toward action is an important but subtle aspect of M1 activation, we highlight a few TMS studies that have investigated the role of M1 in motor action accompanied by attention. For example, Conte et al. (2007) applied the 5-Hz rTMS conditioning stimulus to the PMA and delivered test stimuli over the hand motor area at the suprathreshold intensity in trains of 10 stimuli. They recorded MEP size and cortical silence period (CSP) duration during three attention-demanding conditions: "relaxed," "target hand," and "non-target hand." rTMS trains elicited a larger MEP size facilitation when the subjects looked at the target hand, whereas the CSP remained

unchanged during all the three conditions. Furthermore, they found that the MEP facilitation during the "target hand" condition could be decreased if conditioning stimulation to the premotor cortex is provided. Overall, attention toward action influences the excitability of M1 through the connections from the premotor cortex to M1.

4. M1 and learning

Learning is an important higher-order cognition task that has wide implications for daily activities. In this section, we will discuss the crucial role of M1 in learning, particularly in the acquisition of motor skills. The involvement of M1 in learning can be researched by evaluating its activation in people who either learn new movements or practice certain motor skills for a long time, such as musicians. The overall volume of the motor areas in musicians is found to be more than that of the motor areas in their counterparts (Gaser & Schlaug, 2003; Münte, Altenmüller, & Jäncke, 2002). Moreover, the age at which a person begins their musical training is inversely related to the size of M1 in both hemispheres (Amunts et al., 1997). In addition to the long-term structural changes of M1, long-term functional changes occur when fine motor skills are trained over an extended period. Transient changes in cortical networks within M1 begin with minimal practice (Classen, Liepert, Wise, Hallett, & Cohen, 1998); however, long-term modifications of M1 require more extensive practice (Karni et al., 1998; Sanes & Donoghue, 2000). Karni et al. (1998) argued that the acquisition of proficiency in motor performance occurs in two distinct functional learning stages. In the first stage, the repetition of a given sequence increases the activation in the motor cortex, thereby expanding the representation of the repeated sequence. For example, Hund-Georgiadis & Von Cramon (1999) found musicians to recruit larger ipsilateral and contralateral M1 areas at the early stages of training, known as the "fast learning phase." In the second stage, after about three weeks of training, the trained sequence results in extensive representation in M1, known as the consolidation of learned sequence. This extensive representation in M1 further grows with

repeated practice and is highly correlated with specific gains in performance, also known as the "slow learning phase." Though studies on humans are limited, the in vivo studies on rat brain revealed that the late slow phase of skill learning is accompanied by motor map reorganization and synapse formation (Kleim, 2004). Altogether, the studies suggest that M1 not only structurally grows but also functionally develops as the practice of the motor skill is prolonged. Penhune & Steele (2012) reviewed the neuroimaging studies that demonstrate the role of M1, basal ganglia, and cerebellum in motor learning. Their review concluded that M1 is the storage site of a newly learned movement and probably grows as a part of the distributed network for learning that includes the PMA and parietal cortex.

The NIBS technique is extensively used in neuroimaging studies to investigate the role of M1 during motor learning (Münte et al., 2002; Gaser & Schlaug, 2003). For example, a TMS study found that training aimed at learning a piano sequence results in an increase in the M1 excitability (Pascual-Leone et al., 1995). These findings were further confirmed when a TMS study found that the cortical network representation in M1 changes following the prolonged practice of movements (Classen et al., 1998). In the study, focal TMS was applied over M1 to evoke isolated and directionally consistent thumb movement. The participants were asked to practice thumb movement in different directions. Subthreshold TMS was applied to evoke the movement in a recently practiced direction before returning to the original movement. It was found that at least 15–30 min of continuous practice is needed to elicit a TMS-induced movement in the practiced direction. Such changes suggest that the observed increase in the M1 volume and plasticity as the practice of the skill is prolonged is not associated with the increased motor execution. Instead, it is related to an increase in motor skills. Recently, Tanaka, Sandrini, & Cohen (2011) reviewed the studies that showed the modulation of motor memory formation and motor skill learning in both healthy humans and stroke patients following NIBS over M1. This led them to conclude that M1 must have a role in the retention of new motor

memories as well as in the consolidation of motor memory, which will be the topic of discussion in the next section.

5. M1 and motor consolidation

Electrophysiological experiments (Kashyap, Ouyang, Sommer, & Zhou, 2016b, 2016a; Praeg, Esslen, Lutz, & Jancke, 2006) and neuroimaging-based meta-analysis studies (Hardwick, Rottschy, Miall, & Eickhoff, 2013; Lohse, Wadden, Boyd, & Hodges, 2014) demonstrate the involvement of motor areas in various stages of learning. Motor areas such as the SMA, M1, PMA, parietal cortex, dorsolateral prefrontal, basal ganglia, parahippocampal cortex, and cerebellum are found to be involved in motor learning (Hardwick, Rottschy, Miall, & Eickhoff, 2013; Lohse, Wadden, Boyd, & Hodges, 2014). Though other regions have received considerable interest for their role in motor consolidation, little has been discussed about M1. In an electrophysiological study by Bender, Oelkers-Ax, Resch, & Weisbrod (2004), the activity in M1 was found to last as long as 600 ms after movement execution. In an fMRI study by Steele & Penhune (2010), the activity in M1 during the early learning process (task learned on day 1) was found to be predictive of the degree of consolidation in the later phases on day 2. These studies suggest that M1's involvement in the post-execution stage cannot be denied, but its specific role during this stage should be further investigated.

After a newly learned movement is executed, it gets consolidated over time as a part of the complete learning phase. Neuroimaging studies have shown that during the consolidation phase of a new motor skill, a shift in brain activity can be seen from the prefrontal regions to the PMA, posterior parietal cortex, and cerebellum. However, the specific phase in which the process of transition from motor execution to motor consolidation occurs is still elusive. An attempt to clarify this was made by Muellbacher et al. (2002) in their study, wherein they tested whether M1 plays a role during early motor consolidation. To this end, they asked their subjects to perform fast finger movements that could rapidly improve movement acceleration and

muscle force generation. They found that low-frequency rTMS specifically over M1 disrupted the retention of behavioral improvement. However, rTMS (over M1) did not affect the basal motor behavior, task performance, motor learning by subsequent practice, or recall of the newly acquired motor skill. Disruption in the retention of behavioral improvement indicated that human M1 is specifically engaged in the early stage of motor consolidation.

Besides the early stage of the motor consolidation process, some studies have demonstrated the necessity of adequate M1 functioning for the offline improvement of newly acquired motor skills. For example, Overduin, Richardson, & Bizzi (2009) found that the application of rTMS over M1 before a motor learning task did not interfere with the initial motor adaptation. However, the performance declined when the task was retested on the next day. It was also observed that in some situations, inhibition of M1 resulted in disruptive effects on motor preparation but not on motor execution (Perez & Cohen, 2009; Reis et al., 2009). Censor & Cohen (2011) found that rTMS applied over M1 on day 1 negatively affected the performance of subjects tested on day 2. Even applying single-pulse TMS over the contralateral M1 during a voluntary movement effected the motor training, thereby reflecting the presence of long-lasting motor memories (Buetefisch, Hines, Shuster, Pergami, & Mathes, 2011). Altogether, these studies suggest that M1 plays a role in the offline process of motor memory consolidation. Similarly, the causal role of M1 in learning was further demonstrated by disrupting the M1 activity by 15 min of 1-Hz rTMS in between learning of two separate hand movement tasks. It was found that inhibition of the M1 activity in the group receiving rTMS resulted in the better performance of task 2 compared with the group that did not receive rTMS (Richardson et al., 2006). This enhancement indicates that the existence of previous motor learning skills might interfere with learning a new one. Moreover, such retention of skills and interference between skill learnings are linked at the level of M1.

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Theta-burst stimulation (TBS) is another TMS technique that has helped to evaluate the role of M1 in memory consolidation. TBS produces long-lasting excitatory or inhibitory effects on motor physiology and behavior (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). TBS studies are referred here because there is no direct evidence that indicates the involvement of M1 in consolidating (along with other downstream motor areas) the memory of an already performed task. To decipher this, Wilkinson, Teo, Obeso, Rothwell, & Jahanshahi (2010) investigated the association of several cortical regions with implicit learning sequences. Five age- and IQ-matched groups of healthy participants were administered TBS with inhibitory effect over (1) M1, (2) SMA, (3) dorsolateral prefrontal cortex. They also received (4) intermittent TBS with excitatory effect over the areas and sham TBS. Interestingly, it was found that compared with sham TBS, sequence learning was abolished by TBS with an inhibitory effect over M1. However, sequence learning was not significantly affected by TBS with inhibitory effect over the other areas or by TBS with excitatory effect over M1. This establishes the crucial role of M1 in implicit sequence learning. Similar to this study, other studies observed the effect of intermittent TBS on M1 in subcortical stroke patients. It was found that intermittent TBS improves the training effects in a precision grip task (for details, refer to the reviews by Censor & Cohen, 2011; Reis et al., 2008; Tanaka et al., 2011).

A few studies have found the motor consolidation process in M1 to be dependent on the awake versus sleep state of the brain. Robertson et al. (2005) found that the disruption of M1 with rTMS interferes with the improvements over the day but not overnight. Participants were asked to learn a finger sequence, and movement and serial reaction time were measured. After skill acquisition either in the morning (8.00 a.m.) or evening (8:00 p.m.), rTMS was applied over M1 and the skill was retested after 12 h. Results showed that the group that received rTMS over the daytime showed significantly lesser improvement on a subsequent day compared with sham. However, the increase in performance was not impaired by rTMS over

M1 in the individuals who slept between two sessions. This was an important finding as it showed that the neural circuit that includes M1 contributes to the motor learning process. In a similar experimental paradigm, Cohen, Pascual-Leone, Press, & Robertson (2005) showed that M1 is involved in movement-based learning over the day but has no role in goal-based learning overnight. Similarly, Iezzi et al. (2010) reported the degradation of practice-related improvement in movement amplitude, peak velocity, and peak acceleration after applying TBS with inhibitory effect over M1. Participants were asked to perform two types of tasks involving either motor practice (task 1) or motor consolidation (task 2). TBS was applied over M1 to both the groups under either real or sham conditions while performing the tasks. In task 1 and task 2 groups, the motor retention was tested 30 and 15–30 min after the motor practice session ended, respectively. The motor consolidation in task 2 group was tested 24 h after the practice session. The task performance during practice and retention was found to be degraded following TBS in both the groups, but the motor consolidation process remained unchanged when tested on the following day. This shows that M1 is involved in practice-related improvement during early motor retention but not in the overnight motor consolidation process of a voluntary finger movement.

Learning can be modulated by the application of tDCS over certain regions. tDCS is a type of NIBS that can modulate cortical excitability. Anodal stimulation excites the underlying cortical region, whereas cathodal stimulation is inhibitory. Nitsche et al. (2003) demonstrated an enhancement in implicit motor learning with anodal stimulation over M1 (Antal et al., 2004). Reis et al. (2009) also demonstrated the role of M1 in the motor consolidation process by applying tDCS over M1 while a novel motor skill task was learned for five days. The anodal tDCS over M1 resulted in improved task performance, which was measured both within and between days. The study concluded that the existence of a motor consolidation mechanism within M1 could be modulated by tDCS. Recent meta-analyses by Hashemirad, Zoghi,

Fitzgerald, & Jaberzadeh (2016) and Savic & Meier (2016) have demonstrated that tDCS over M1 can modulate motor sequence learning and consolidation. In this regard, a natural step that follows after we construe motor learning and consolidation is to figure out if M1 has a role in motor inhibition. This discussion is significant because motor inhibition is important for motor learning (Kolasinski, Johnstone, Bachtiar, & Stagg, 2017). This will be discussed in the next section.

6. M1 and the inhibition of movement

Ebbesen & Brecht (2017) have reviewed the studies performed on eutherian mammals and concluded that M1 might have an important contribution to motor inhibition in addition to motor generation. The review starts with a discussion of the motor map, which is important for motor execution. The motor map was first demonstrated on a dog by Fritsch (1870), which was later confirmed on monkeys by Ferrier (1875). A decade later, neurosurgeons Penfield & Rasmussen (1950) confirmed the presence of motor homunculus in awake human subjects by stimulating the motor cortex during surgeries. These subjects often reported a sense of paralysis and numbness focal to specific body parts after the stimulation of the motor homunculus. Thus, it seems that motor homunculus is not a pure "motor map" but a map of "movement suppression." Subsequently, many studies have reported the presence of so-called negative-motor areas (NMAs: motor areas that cause movement inhibition) in the motor cortex (Ikeda et al., 1995; Lüders, Dinner, Morris, Wyllie, & Comair, 1995; Mikuni et al., 2006; Nii, Uematsu, Lesser, & Gordon, 1996).

The corticospinal tract (CST) plays a critical role in controlling voluntary movement (Lemon, 2008, 2019; Welniarz et al., 2017). It is the longest tract in the central nervous system, originating in layer 5 pyramidal neurons in the sensorimotor cortex and terminating in the spinal cord. In the spinal cord, the CST fibers project to the dorsal and intermediate portions of the gray matter and innervate interneurons, which in turn control motor neurons (Lemon,

2008; 2019, Welniarz et al., 2017). Finally and most importantly, they report that a lesion in the motor cortex of a rodent typically interferes with motor movement but does not exterminate it. Instead, the interference is also associated with impaired movement suppression (Ebbesen & Brecht, 2017). This can be typically seen in humans, where the immediate symptom of an acute cortical lesion is weakness and loss of movement; however, the chronic lesion produces the symptom of spasticity, signifying the loss of motor inhibition (Barnes & Johnson, 2008; Laplane, Talairach, Meininger, Bancaud, & Bouchareine, 1977).

The findings from the neurosurgical stimulation study by Penfield & Rasmussen (1950) described above opened up a new field of investigation. Recently, Filevich et al. (2012) reviewed such studies and concluded that the inhibition of movement following the stimulation of NMAs might not reflect the only disruption of motor action. However, such observation might also indicate that NMAs contribute to inhibitory mechanisms depending on the ecological condition. They reported that such NMAs could be seen in the motor cortex, SMA, and inferior frontal gyrus in abundance. However, only a few studies have specifically investigated the NMAs in M1. Shibasaki & Hallett (2006) observed that the signals from cortical regions such as SMA, PMA, and M1 could recruit inhibitory interneurons in the spinal cord. This suggests that M1 might as well have a considerable role in inhibiting muscle activity. Likewise, Bonnard, Spieser, Meziane, De Graaf, & Pailhous (2009) found that a cognitive process of prior intention can resist the involuntary movement elicited by suprathreshold TMS applied over M1. They observed that the amplitude of the TMS-evoked N100 component was higher at the central electrodes (FCz, C1, Cz, CP1, and CP3) when participants tried to resist an involuntary motor movement (elicited by TMS) compared with the condition when they voluntarily did it. These studies point toward the possible role of M1 in the inhibition of voluntary action. Interhemispheric inhibitory control was also demonstrated in a TMS study by Schnitzler, Kessler, & Benecke (1996). These authors applied a conditioning TMS stimulus

to the M1 of one side of the brain. They then recorded the CSP following a test stimulus in the M1 on the other side of the brain with an inter-stimulus interval of 10–20 ms. They found a significant reduction in the CSP, which suggested that the inhibitory neurons within M1 received inhibitory connections from the opposite M1 as well (Schnitzler et al., 1996). With that said and considering that intensive research on the topic is required, we call for future studies to investigate the role of M1 in inhibiting a voluntary action.

7. M1 and sensory feedback

Some studies have reported that M1 is influenced by sensory feedback on the motor cortex triggered by sensory stimulation. For example, a TMS study (Ruge, Muggleton, Hoad, Caronni, & Rothwell, 2014) measured the MEP and short-interval intracortical inhibition (SICI) following TMS over M1. The participants received electrical stimulation at the dorsum of hand while performing a visual discrimination task. The authors found that attention to the skin overlying a muscle changed the corticospinal excitability but had no effect on the SICI of the muscle. However, attention to a distant area on the skin affected MEP but reduced the SICI. In both cases, H-reflex was unaffected, suggesting that sensory feedback from skin influences the excitability within circuits comprising M1. A review by Hatsopoulos & Suminski (2011) has listed the studies that point toward the heterogeneities in M1 responses to visual and somatosensory stimuli. We will, therefore, divide the topic of the role of M1 into two subsections related to the motor responses to visual and somatosensory stimuli and individually discuss them in detail.

7.1 Motor observation

The observation of another person's movement leads to the activation of the motor cortex of the observer (Ocampo & Kritikos, 2010). Such neuronal activity is referred to as "mirror" activity. Mirror neurons are visuomotor neurons that are activated when a monkey performs an action. They are also activated when the monkey observes another individual

(monkey or human) performing a similar action (Di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). The presence of mirror neurons was originally demonstrated in premotor and parietal cortices (Di Pellegrino et al., 1992; Gallese et al., 1996). Their presence in M1 has also been documented in macaques (Vigneswaran, Philipp, Lemon, & Kraskov, 2013) and humans, as summarized in a review (refer, Kilner & Lemon, 2013). However, the exact role of mirror neurons in M1 for humans needs further investigation.

Focusing on M1, Nishitani & Hari (2002) reported that M1 activates during the imitation of a movement. Here, they investigated the cortical dynamics using magnetoencephalography when subjects were under three conditions: (1) observing movement-related still pictures such as a performing athlete or a person lifting a glass, (2) imitating the action shown in the still pictures, and (3) executing the action. Under all the conditions, the activation bilaterally progressed from the occipital cortex to the temporal region, the inferior parietal lobule, the frontal lobe (Broca's area), and finally to M1. The signals of Broca's area and M1 were significantly stronger during the imitation of the movement than during observation and execution. These findings suggested that still pictures that imply motion activate the human motor neuron system in M1. This was supported by Caspers, Zilles, Laird, & Eickhoff (2010), who found that bilateral networks comprising the frontal premotor, parietal, and temporo-occipital cortices are activated during motor observation. Likewise, the electrophysiological techniques such as EEG and MEG have found alpha (~10 Hz) and beta (~20 Hz) band rhythms during movement execution as well as during motor observation (Babiloni et al., 2002; Cochin, Barthélémy, Roux, & Martineau, 1999; Hari et al., 1998). A recent study used MEG to compare the modulations of the M1 oscillatory activity between the execution, observation, and hearing of finger tapping movements (Caetano, Jousmaki, & Hari, 2007). The results showed highly similar activation patterns

before, during, and after the motor action under all three conditions. There is strong support from NIBS studies in this aspect. In particular, MEPs of hand muscles after TMS in the motor cortex were found to be increased in subjects who observed hand movements (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995). The MEP pattern was similar to the pattern of muscle activity recorded when the subjects executed the observed action. Roosink & Zijdewind (2010) compared the MEPs using TMS for rest, observation, imagery, and execution of simple and complex movements. They found an increase in corticospinal excitability during the observation of complex motor tasks. Similarly, using TMS, Naish, Houston-Price, Bremner, & Holmes (2014) reported the facilitation of corticospinal excitability during motor observation. In particular, they reported that early facilitation of the corticospinal excitability following action observation occurs around 90 ms from action onset. This is followed by the modulation of the activity specific to the muscles involved in the observed action at about 200 ms after action onset. Altogether, these studies indicate the possibility of the existence of mirror neurons in humans that become activated during motor observation.

The ability to understand the intention of a person by observing their actions has been explained from the framework of predictive coding by Kilner, Friston, & Frith (2007). These authors found that neurons from the ventral PMA (F5 area) and M1 are part of the mirror neuron system that analyzes the intent during motor observation. In addition, another study found that the onset times for the M1 activity for both "execution of the action" and "action observation" are similar (Babiloni et al., 2002). In a similar vein but from a different perspective, suppression of the M1 activity was seen approximately 2 s before the initiation of an action. This suppression occurred earlier for self-executed action compared with the observation of the action (Caetano et al., 2007). This demonstrates that M1 is involved in action prediction both in performance and observation of the action. The role of M1 in the language comprehension of action-related verbs has been demonstrated by Repetto, Colombo, Cipresso,

& Riva (2013). They found specific inhibition in processing verbs that refer to action compared with abstract verbs after applying rTMS over the bilateral hand-related region in M1. A possible explanation could be that the mechanisms that predict a motor action are also involved in analyzing the intent when a word with motor action is displayed.

7.2 Somatosensory responses in MI

Multiple studies have shown that M1 is activated following somatosensory stimulation such as tactile stimulation, perturbation, and passive movement (for details, refer to Nevalainen, Lauronen, & Pihko, 2014). However, most of these activations were thought to be the long-loop "reflex" activations. The function of this reflex was to use sensory muscle information to activate the same or synergistic muscle. It has been argued that these long-loop reflexes can also perform higher-order cognitive functions (Gielen, Ramaekers, & Van Zuylen, 1988). For example, when neurons in these loops receive information from multiple muscle inputs, they can integrate this sensory feedback to generate an appropriate response. Pruszynski et al. (2011) have demonstrated that shoulder muscle response occurs approximately 50 ms after pure elbow displacement, and this phenomenon can be potentiated by applying TMS over M1. This shows the potential link between M1 processing and multi-joint integration in humans. Because the research on this topic is limited, more research is needed to investigate the hypothesis that M1 permits feedback from the peripheral sensory information that can influence the voluntary control over motor execution.

8. Motor imagery

In the previous section on motor learning, we discussed that there are structural and functional changes following the motor skill practice that is continued over a long period. Interestingly, studies have suggested that mental rehearsal without actually performing the motor act can result in skill-enhancement effects (Carrasco & Cantalapiedra, 2016; Pascual-Leone et al., 1995). It has also been demonstrated that the combination of both physical and

mental training results in greater improvement in performance compared with any of the practice methods alone (Allami, Paulignan, Brovelli, & Boussaoud, 2008; Avanzino et al., 2009; Frank, Land, Popp, & Schack, 2014; Smith, Wright, Allsopp, & Westhead, 2007; Smith, Wright, & Cantwell, 2008). In this context, behavioral and neuroimaging studies have found that motor imagery shares mental representation and mechanism with motor execution (Decety & Ingvar, 1990; Di Rienzo et al., 2016; Eaves, Riach, Holmes, & Wright, 2016; O'Shea & Moran, 2017). These studies found that the activated cortical areas during motor imagery resemble those of motor planning and motor execution and are predominant in medial SMA, PMA, dorsolateral prefrontal cortex, and posterior parietal cortex (Decety, 1996; Hanakawa et al., 2003; Jeannerod, 2001; Miller et al., 2010). However, the exact role of M1 during motor imagery has been a topic of debate owing to inconsistent findings. For example, many fMRI studies supported the contribution of M1 to motor imagery (Lotze & Halsband, 2006; Lotze et al., 1999; Porro et al., 1996). However, some studies could not find any significant activation in M1 (Dechent, Merboldt, & Frahm, 2004; M. F. Lafleur et al., 2002; Stephan et al., 1995). In this scenario, NIBS studies proved to be important in elucidating the role of M1 in motor imagery. The role of M1 in motor imagery was supported when the amplitude of MEPs induced by TMS over M1 was found to be increased during a motor imagery task (Rossini, Rossi, Pasqualetti, & Tecchio, 1999). Such enhanced MEPs in the peripheral muscle could be attributable to the corticospinal facilitation effect of mental imaginations of the motor task. Ganis, Keenan, Kosslyn, & Pascual-Leone (2000) found that the role of M1 in motor imagery is time-specific. In their experiment, participants were asked to mentally rotate pictures of hands and feet while single-pulse TMS over M1 was applied at two different time points (400 and 650 ms after the onset of the visual stimulus). The aim was to investigate whether interference with M1 processing would affect the response times of the mental imagination of the rotation task. The response times were slower when TMS was applied at the later time point

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(650 ms), but they were not affected at the earlier time point (400 ms). This finding indicates that M1 might be involved in the processing of mental imagination of the rotation task, but its involvement occurs at relatively late time points. Similarly, interhemispheric inhibition by the contralateral M1 in motor imagery was found by Tomasino, Borroni, Isaja, & Rumiati (2005). They found that the ability to mentally rotate both right and left hands was reduced when TMS over the left M1 was applied. Following up on involvement of M1 during mental imagery tasks, Ruffino, Papaxanthis, & Lebon (2017) reviewed papers that applied single-pulse TMS over M1 and measured the MEPs. They concluded that motor excitability is increased during motor imagery. Along the same lines, Marconi, Pecchioli, Koch, & Caltagirone (2007) showed that this increase in motor excitability is specific to the muscle that is being included in the imagined movement. Some studies recorded the SICI following the application of ppTMS over M1. They found that SICI was significantly reduced during the imagination of finger movement (Abbruzzese, Assini, Buccolieri, Marchese, & Trompetto, 1999; Kumru, Soto, Casanova, & Valls-Sole, 2008; Liepert & Neveling, 2009). This showed that inhibition within M1 was reduced, which in turn facilitated the corticospinal signal (Ridding, Taylor, & Rothwell, 1995). Cortical mapping, another TMS technique, was used to estimate the cortical (re)organization within M1 during a specific task (Tyc & Boyadjian, 2006). This technique allows generating a TMS map by measuring and quantifying the intensity and amplitude of MEPs generated at the target scalp site (Thickbroom, Byrnes, & Mastaglia, 1999). Several studies have used this technique to assess cortical organization within M1 during motor imagery (Bassolino, Campanella, Bove, Pozzo, & Fadiga, 2013; Marconi et al., 2007; Vargas et al., 2004). These studies found that motor imagery and observation increased the map area and map volume only for the primary and synergist muscles. Interestingly, Vergeer & Roberts (2006) found that this cortical map in M1 was extended compared with rest when the posture was compatible with the imagined movement. The inverse pattern was also true when the posture was not

compatible. These findings suggested that there is interaction within M1 between the facilitatory activities of M1 and the proprioceptive inputs from the periphery. Considering the above facts, Ruffino, Papaxanthis, & Lebon (2017) suggested that M1 is involved in integrating the internal kinesthetic and external visual information to determine a neural representation of the imagined movements.

Miller et al. (2010) provided convincing evidence in support of the involvement of M1 in motor imagery. They recorded the M1 activity during the motor imagery process using an intracranial cortical electrophysiological recording in epilepsy patients. Their study confirmed that the spatiotemporal distribution of cortical activity during actual movements overlaps with the distribution of the activity during the imagery of the same movement. However, it is important to point out that the electrocorticographic activity during imagery was approximately 25% of the motor activity during actual motor action. Nevertheless, the magnitude was still sufficiently strong to control a computer cursor in the brain–computer interface task. Altogether, these findings explain why mental imagery practice can improve motor performance even in the absence of physical motor training (Pascual-Leone et al., 2001). To summarize, we conclude that in addition to a pivotal role in motor performance, M1 has a subtle but important role in motor cognition.

9. Conclusion

The present review focuses on various studies that investigated the involvement of M1 in cognitive processes related to motor action. In particular, the review finds M1 to be (1) involved in motor action, which is either accompanied or not accompanied by attention toward the task, (2) involved in the learning of sequential motor skills with structural and functional changes in M1 following long-term skill practice, (3) playing a crucial role in the early stages of motor consolidation, (4) involved in somatosensory functions such as the observation of motor tasks and integration of multiple sensory inputs, (5) involved in the inhibition of

involuntary movement, and (6) involved in imagining a motor sequence. The purpose of this review was to highlight the additional roles of M1 in the cognitive processes that are often undervalued. With the findings presented in our review, we want to draw attention to the need for the further investigation of M1 as a facilitator of cognition and motor rehabilitation.

 Reference

Abbruzzese, G., Assini, A., Buccolieri, A., Marchese, R., & Trompetto, C. (1999). Changes of intracortical inhibition during motor imagery in human subjects. *Neuroscience Letters*, *263*(2–3), 113–116.

Alcaro, A., Huber, R., & Panksepp, J. (2007). Behavioral Functions of the Mesolimbic Dopaminergic System: An Affective Neuroethological Perspective. *Brain Research Reviews*, *56*(2), 283–321. https://doi.org/10.1016/j.brainresrev.2007.07.014

Allami, N., Paulignan, Y., Brovelli, A., & Boussaoud, D. (2008). Visuo-motor learning with combination of different rates of motor imagery and physical practice. *Experimental Brain Research*, *184*(1), 105–113.

Amunts, K., Schlaug, G., Jäncke, L., Steinmetz, H., Schleicher, A., Dabringhaus, A., & Zilles, K. (1997). Motor cortex and hand motor skills: Structural compliance in the human brain. *Human Brain Mapping*, *5*(3), 206–215.

Antal, A., Nitsche, M. A., Kincses, T. Z., Kruse, W., Hoffmann, K.-P., & Paulus, W. (2004). Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. *European Journal of Neuroscience*, *19*(10), 2888–2892. https://doi.org/10.1111/j.1460-9568.2004.03367.x

Avanzino, L., Giannini, A., Tacchino, A., Pelosin, E., Ruggeri, P., & Bove, M. (2009). Motor imagery influences the execution of repetitive finger opposition movements. *Neuroscience Letters*, *466*(1), 11–15.

Babiloni, C., Babiloni, F., Carducci, F., Cincotti, F., Cocozza, G., Del Percio, C., … Rossini, P. M. (2002). Human Cortical Electroencephalography (EEG) Rhythms during the Observation of Simple Aimless Movements: A High-Resolution EEG Study. *NeuroImage*, *17*(2), 559–572. https://doi.org/10.1006/nimg.2002.1192

Bai, S., Dokos, S., Ho, K.-A., & Loo, C. (2014). A computational modelling study of transcranial direct current stimulation montages used in depression. *Neuroimage*, *87*, 332–344.

Bamford, N. S., Robinson, S., Palmiter, R. D., Joyce, J. A., Moore, C., & Meshul, C. K. (2004). Dopamine Modulates Release from Corticostriatal Terminals. *The Journal of Neuroscience*, *24*(43), 9541–9552.

Bapi, R. S., Miyapuram, K. P., Graydon, F. X., & Doya, K. (2006). FMRI investigation of cortical and subcortical networks in the learning of abstract and effector-specific representations of motor sequences. *Neuroimage*, *32*(2), 714–727.

Barbas, H., & Pandya, D. N. (1987). Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *Journal of Comparative Neurology*, *256*(2), 211–228.

Barnes, M. P., & Johnson, G. R. (2008). *Upper motor neurone syndrome and spasticity: Clinical management and neurophysiology*. Cambridge University Press.

Bassolino, M., Campanella, M., Bove, M., Pozzo, T., & Fadiga, L. (2013). Training the motor cortex by observing the actions of others during immobilization. *Cerebral Cortex*, *24*(12), 3268–3276.

Bender, S., Oelkers-Ax, R., Resch, F., & Weisbrod, M. (2004). Motor processing after movement execution as revealed by evoked and induced activity. *Cognitive Brain Research*, *21*(1), 49–58.

Bestmann, S., Baudewig, J., Siebner, H. R., Rothwell, J. C., & Frahm, J. (2004). Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *European Journal of Neuroscience*, *19*(7), 1950–1962.

Bhattacharjee, S., Kashyap, R., Rapp, B., Oishi, K., Desmond, J., & Chen, S. (2019). *Simulation Analyses of tDCS Montages for the Investigation of Dorsal and Ventral Pathways*.

Binkofski, F., Fink, G. R., Geyer, S., Buccino, G., Gruber, O., Shah, N. J., … Freund, H.-J. (2002). Neural activity in human primary motor cortex areas 4a and 4p is modulated differentially by attention to action. *Journal of Neurophysiology*, *88*(1), 514–519.

Bonnard, M., Spieser, L., Meziane, H. B., De Graaf, J. B., & Pailhous, J. (2009). Prior intention can locally tune inhibitory processes in the primary motor cortex: Direct evidence from combined TMS-EEG. *European Journal of Neuroscience*, *30*(5), 913–923. https://doi.org/10.1111/j.1460-9568.2009.06864.x

Borich, M. R., Brodie, S. M., Gray, W. A., Ionta, S., & Boyd, L. A. (2015). Understanding the role of the primary somatosensory cortex: Opportunities for rehabilitation. *Neuropsychologia*, *79*, 246–255.

Buetefisch, C. M., Hines, B., Shuster, L., Pergami, P., & Mathes, A. (2011). Motor demand-dependent improvement in accuracy following low-frequency transcranial magnetic stimulation of left motor cortex. *Journal of Neurophysiology*, *106*(4), 1614–1621. https://doi.org/10.1152/jn.00048.2011

Caetano, G., Jousmaki, V., & Hari, R. (2007). Actor's and observer's primary motor cortices stabilize similarly after seen or heard motor actions. *Proceedings of the National Academy of Sciences*, *104*(21), 9058–9062. https://doi.org/10.1073/pnas.0702453104

Carrasco, D. G., & Cantalapiedra, J. A. (2016). Effectiveness of motor imagery or mental practice in functional recovery after stroke: A systematic review. *Neurología (English Edition)*, *31*(1), 43–52.

Cash, R. F., Noda, Y., Zomorrodi, R., Radhu, N., Farzan, F., Rajji, T. K., … Blumberger, D. M. (2017). Characterization of Glutamatergic and GABA A-Mediated Neurotransmission in Motor and Dorsolateral Prefrontal Cortex Using Paired-Pulse TMS–EEG. *Neuropsychopharmacology*, *42*(2), 502.

Caspers, S., Zilles, K., Laird, A. R., & Eickhoff, S. B. (2010). ALE meta-analysis of action observation and imitation in the human brain. *Neuroimage*, *50*(3), 1148–1167.

CAUMO, W., Souza, I. C., Torres, I. L., Medeiros, L., Souza, A., Deitos, A., … Volz, M. S. (2012). Neurobiological effects of transcranial direct current stimulation: A review. *Frontiers in Psychiatry*, *3*, 110.

Censor, N., & Cohen, L. G. (2011). Using repetitive transcranial magnetic stimulation to study the underlying neural mechanisms of human motor learning and memory. *The Journal of Physiology*, *589*(Pt 1), 21–28. https://doi.org/10.1113/jphysiol.2010.198077

Chouinard, P. A., & Paus, T. (2006). The primary motor and premotor areas of the human cerebral cortex. *The Neuroscientist*, *12*(2), 143–152.

Civardi, C., Cantello, R., Asselman, P., & Rothwell, J. C. (2001). Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. *Neuroimage*, *14*(6), 1444–1453.

Classen, J., Liepert, J., Wise, S. P., Hallett, M., & Cohen, L. G. (1998). Rapid Plasticity of Human Cortical Movement Representation Induced by Practice. *Journal of Neurophysiology*, *79*(2), 1117–1123. https://doi.org/10.1152/jn.1998.79.2.1117

Cochin, S., Barthélémy, C., Roux, S., & Martineau, J. (1999). Observation and execution of movement: Similarities demonstrated by quantified

electroencephalography. *The European Journal of Neuroscience*, *11*(5), 1839–1842. https://doi.org/10.1046/j.1460-9568.1999.00598.x

Cohen, D. A., Pascual-Leone, A., Press, D. Z., & Robertson, E. M. (2005). Off-line learning of motor skill memory: A double dissociation of goal and movement. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(50), 18237–18241. https://doi.org/10.1073/pnas.0506072102

Conte, A., Gilio, F., Iezzi, E., Frasca, V., Inghilleri, M., & Berardelli, A. (2007). Attention influences the excitability of cortical motor areas in healthy humans. *Experimental Brain Research*, *182*(1), 109–117. https://doi.org/10.1007/s00221-007-0975-3

Davis, T. L., Kwong, K. K., Weisskoff, R. M., & Rosen, B. R. (1998). Calibrated functional MRI: Mapping the dynamics of oxidative metabolism. *Proceedings of the National Academy of Sciences*, *95*(4), 1834–1839.

Decety, J. (1996). The neurophysiological basis of motor imagery. *Behavioural Brain Research*, *77*(1), 45–52. https://doi.org/10.1016/0166-4328(95)00225-1

Decety, J., & Ingvar, D. H. (1990). Brain structures participating in mental simulation of motor behavior: A neuropsychological interpretation. *Acta Psychologica*, *73*(1), 13–34. https://doi.org/10.1016/0001-6918(90)90056-L

Dechent, P., Merboldt, K.-D., & Frahm, J. (2004). Is the human primary motor cortex involved in motor imagery? *Cognitive Brain Research*, *19*(2), 138–144. https://doi.org/10.1016/j.cogbrainres.2003.11.012

Deschênes, M., Takatoh, J., Kurnikova, A., Moore, J. D., Demers, M., Elbaz, M., … Kleinfeld, D. (2016). Inhibition, not excitation, drives rhythmic whisking. *Neuron*, *90*(2), 374–387.

Devanne, H., Degardin, A., Tyvaert, L., Bocquillon, P., Houdayer, E., Manceaux, A., … Cassim, F. (2009). Afferent-induced facilitation of primary motor cortex excitability in the region controlling hand muscles in humans. *European Journal of Neuroscience*, *30*(3), 439–448.

Di Lazzaro, V., Oliviero, A., Mazzone, P., Pilato, F., Saturno, E., Dileone, M., … Rothwell, J. (2002). Short-term reduction of intracortical inhibition in the human motor cortex induced by repetitive transcranial magnetic stimulation. *Experimental Brain Research*, *147*(1), 108–113.

Di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: A neurophysiological study. *Experimental Brain Research*, *91*(1), 176–180.

Di Rienzo, F., Debarnot, U., Daligault, S., Saruco, E., Delpuech, C., Doyon, J., … Guillot, A. (2016). Online and Offline Performance Gains Following Motor Imagery Practice: A Comprehensive Review of Behavioral and Neuroimaging Studies. *Frontiers in Human Neuroscience*, *10*. https://doi.org/10.3389/fnhum.2016.00315

Dum, R. P., & Strick, P. L. (2002). Motor areas in the frontal lobe of the primate. *Physiology & Behavior*, *77*(4–5), 677–682.

Eaves, D. L., Riach, M., Holmes, P. S., & Wright, D. J. (2016). Motor Imagery during Action Observation: A Brief Review of Evidence, Theory and Future Research Opportunities. *Frontiers in Neuroscience*, *10*. https://doi.org/10.3389/fnins.2016.00514

Ebbesen, C. L., & Brecht, M. (2017). Motor cortex—To act or not to act? *Nature Reviews Neuroscience*, *18*(11), 694–705. https://doi.org/10.1038/nrn.2017.119

Esser, S. K., Huber, R., Massimini, M., Peterson, M. J., Ferrarelli, F., & Tononi, G. (2006). A direct demonstration of cortical LTP in humans: A combined TMS/EEG study. *Brain Research Bulletin*, *69*(1), 86–94.

Fadiga, L., Fogassi, L., Pavesi, G., & Rizzolatti, G. (1995). Motor facilitation during action observation: A magnetic stimulation study. *Journal of Neurophysiology*, *73*(6), 2608–2611. https://doi.org/10.1152/jn.1995.73.6.2608

Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., & Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *The Journal of Physiology*, *453*(1), 525–546.

Ferreira, I. S., Costa, B. T., Ramos, C. L., Lucena, P., Thibaut, A., & Fregni, F. (2019). Searching for the optimal tDCS target for motor rehabilitation. *Journal of Neuroengineering and Rehabilitation*, *16*(1), 90.

Ferrier, D. (1875). Experiments on the brain of monkeys.—No. I. *Proceedings of the Royal Society of London*, *23*(156–163), 409–430.

Filevich, E., Kühn, S., & Haggard, P. (2012). Negative motor phenomena in cortical stimulation: Implications for inhibitory control of human action. *Cortex*, *48*(10), 1251–1261. https://doi.org/10.1016/j.cortex.2012.04.014

Fink, G. R., Frackowiak, R. S., Pietrzyk, U., & Passingham, R. E. (1997). Multiple nonprimary motor areas in the human cortex. *Journal of Neurophysiology*, *77*(4), 2164–2174.

Fiori, F., Chiappini, E., Candidi, M., Romei, V., Borgomaneri, S., & Avenanti, A. (2017). Long-latency interhemispheric interactions between motor-related areas and the primary motor cortex: A dual site TMS study. *Scientific Reports*, *7*(1), 14936.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology*, *117*(12), 2584–2596. https://doi.org/10.1016/j.clinph.2006.06.712

Fox, P., Ingham, R., George, M. S., Mayberg, H., Ingham, J., Roby, J., … Jerabek, P. (1997). Imaging human intra-cerebral connectivity by PET during TMS. *Neuroreport*, *8*(12), 2787–2791.

Frank, C., Land, W. M., Popp, C., & Schack, T. (2014). Mental representation and mental practice: Experimental investigation on the functional links between motor memory and motor imagery. *PloS One*, *9*(4), e95175.

Fritsch, G. (1870). Uber die elektrische Erregbarkeit des Grosshirns. *Arch, Anat. Physiol. Wiss. Med.*, *37*, 300–332.

Fulton, J. F. (1935). A note on the definition of the "motor" and "premotor" areas. *Brain*, *58*(2), 311–316.

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119*(2), 593–609.

Ganis, G., Keenan, J. P., Kosslyn, S. M., & Pascual-Leone, A. (2000). Transcranial Magnetic Stimulation of Primary Motor Cortex Affects Mental Rotation. *Cerebral Cortex*, *10*(2), 175–180. https://doi.org/10.1093/cercor/10.2.175

Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *Journal of Neuroscience*, *23*(27), 9240–9245.

Gerschlager, W., Siebner, H. R., & Rothwell, J. C. (2001). Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. *Neurology*, *57*(3), 449–455.

Geyer, S., Matelli, M., Luppino, G., & Zilles, K. (2000). Functional neuroanatomy of the primate isocortical motor system. *Anatomy and Embryology*, *202*(6), 443–474.

Gielen, C. C., Ramaekers, L., & Van Zuylen, E. J. (1988). Long-latency stretch reflexes as co-ordinated functional responses in man. *The Journal of Physiology*, *407*(1), 275–292.

Goldberg, G. (1985). Supplementary motor area structure and function: Review and hypotheses. *Behavioral and Brain Sciences*, *8*(4), 567–588.

Grafton, S. T., Woods, R. P., & Mazziotta, J. C. (1993). Within-arm somatotopy in human motor areas determined by positron emission tomography imaging of cerebral blood flow. *Experimental Brain Research*, *95*(1), 172–176.

Hanajima, R., Ugawa, Y., Machii, K., Mochizuki, H., Terao, Y., Enomoto, H., … Kanazawa, I. (2001). Interhemispheric facilitation of the hand motor area in humans. *The Journal of Physiology*, *531*(3), 849–859.

Hanakawa, T., Immisch, I., Toma, K., Dimyan, M. A., Gelderen, P. van, & Hallett, M. (2003). Functional properties of brain areas associated with motor execution and imagery. *Journal of Neurophysiology*, *89*(2), 989–1002. https://doi.org/10.1152/jn.00132.2002

Hardwick, R. M., Rottschy, C., Miall, R. C., & Eickhoff, S. B. (2013). A quantitative meta-analysis and review of motor learning in the human brain. *Neuroimage*, *67*, 283–297.

Hari, R., Forss, N., Avikainen, S., Kirveskari, E., Salenius, S., & Rizzolatti, G. (1998). Activation of human primary motor cortex during action observation: A neuromagnetic study. *Proceedings of the National Academy of Sciences*, *95*(25), 15061–15065.

Hashemirad, F., Zoghi, M., Fitzgerald, P. B., & Jaberzadeh, S. (2016). The effect of anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: A systematic review and meta-analysis. *Brain and Cognition*, *102*, 1–12.

Hatsopoulos, N. G., & Suminski, A. J. (2011). Sensing with the Motor Cortex. *Neuron*, *72*(3), 477–487. https://doi.org/10.1016/j.neuron.2011.10.020

Hipp, J. F., & Siegel, M. (2015). BOLD fMRI correlation reflects frequency-specific neuronal correlation. *Current Biology*, *25*(10), 1368–1374.

Holsapple, J. W., Preston, J. B., & Strick, P. L. (1991). The origin of thalamic inputs to the" hand" representation in the primary motor cortex. *Journal of Neuroscience*, *11*(9), 2644–2654.

Honda, M., Wise, S. P., Weeks, R. A., Deiber, M.-P., & Hallett, M. (1998). Cortical areas with enhanced activation during object-centred spatial information processing. A PET study. *Brain: A Journal of Neurology*, *121*(11), 2145–2158.

Hosp, J. A., Molina-Luna, K., Hertler, B., Atiemo, C. O., & Luft, A. R. (2009). Dopaminergic modulation of motor maps in rat motor cortex: An in vivo study. *Neuroscience*, *159*(2), 692–700.

Hosp, Jonas A., & Luft, A. R. (2013). Dopaminergic Meso-Cortical Projections to M1: Role in Motor Learning and Motor Cortex Plasticity. *Frontiers in Neurology*, *4*. https://doi.org/10.3389/fneur.2013.00145

Huang, Y.-Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta Burst Stimulation of the Human Motor Cortex. *Neuron*, *45*(2), 201–206. https://doi.org/10.1016/j.neuron.2004.12.033

Hund-Georgiadis, M., & Von Cramon, D. Y. (1999). Motor-learning-related changes in piano players and non-musicians revealed by functional magnetic-resonance signals. *Experimental Brain Research*, *125*(4), 417–425.

Iezzi, E., Suppa, A., Conte, A., Agostino, R., Nardella, A., & Berardelli, A. A. (2010). Theta-burst stimulation over primary motor cortex degrades early motor learning. *European Journal of Neuroscience*, *31*(3), 585–592. https://doi.org/10.1111/j.1460-9568.2010.07090.x

Ikeda, A., Lüders, H. O., Shibasaki, H., Collura, T. F., Burgess, R. C., Morris III, H. H., & Hamano, T. (1995). Movement-related potentials associated with bilateral simultaneous and unilateral movements recorded from human supplementary motor area. *Electroencephalography and Clinical Neurophysiology*, *95*(5), 323–334.

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., & Katila, T. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport*, *8*(16), 3537–3540.

Jeannerod, M. (2001). Neural Simulation of Action: A Unifying Mechanism for Motor Cognition. *NeuroImage*, *14*(1), S103–S109. https://doi.org/10.1006/nimg.2001.0832

Johansen-Berg, H., & Matthews, P. (2002). Attention to movement modulates activity in sensori-motor areas, including primary motor cortex. *Experimental Brain Research*, *142*(1), 13–24. https://doi.org/10.1007/s00221-001-0905-8

Kaas, J. H. (1991). Plasticity of sensory and motor maps in adult mammals. *Annual Review of Neuroscience*, *14*(1), 137–167.

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1998). The acquisition of skilled motor performance: Fast and

slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences*, *95*(3), 861–868.

Kashyap, R., Ouyang, G., Sommer, W., & Zhou, C. (2016a). Improved Source Localization of Priming Effect of Face Recognition Based on RIDE. In *Advances in Cognitive Neurodynamics (V)* (pp. 533–539). Springer.

Kashyap, R., Ouyang, G., Sommer, W., & Zhou, C. (2016b). Neuroanatomic localization of priming effects for famous faces with latency-corrected event-related potentials. *Brain Research*, *1632*, 58–72.

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding. *Cognitive Processing*, *8*(3), 159–166. https://doi.org/10.1007/s10339-007-0170-2

Kilner, J. M., & Lemon, R. N. (2013). What we know currently about mirror neurons. *Current Biology*, *23*(23), R1057–R1062.

Kleim, J. A. (2004). Cortical Synaptogenesis and Motor Map Reorganization Occur during Late, But Not Early, Phase of Motor Skill Learning. *Journal of Neuroscience*, *24*(3), 628–633. https://doi.org/10.1523/JNEUROSCI.3440-03.2004

Kobayashi, M., Hutchinson, S., Theoret, H., Schlaug, G., & Pascual-Leone, A. (2004). Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. *Neurology*, *62*(1), 91–98.

Kolasinski, J., Johnstone, A., Bachtiar, V., & Stagg, C. J. (2017). The role of inhibition in motor performance and learning. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *10*(2), 417. https://doi.org/10.1016/j.brs.2017.01.238

K.r., L., K., W., L.a., B., & N.j., H. (2014). Motor skill acquisition across short and long time scales: A meta-analysis of neuroimaging data. *Neuropsychologia*, *59*, 130–141. https://doi.org/10.1016/j.neuropsychologia.2014.05.001

Kumru, H., Soto, O., Casanova, J., & Valls-Sole, J. (2008). Motor cortex excitability changes during imagery of simple reaction time. *Experimental Brain Research*, *189*(3), 373–378.

Lafleur, L.-P., Tremblay, S., Whittingstall, K., & Lepage, J.-F. (2016). Assessment of Effective Connectivity and Plasticity With Dual-Coil Transcranial Magnetic Stimulation. *Brain Stimulation*, *9*(3), 347–355. https://doi.org/10.1016/j.brs.2016.02.010

Lafleur, M. F., Jackson, P. L., Malouin, F., Richards, C. L., Evans, A. C., & Doyon, J. (2002). Motor Learning Produces Parallel Dynamic Functional Changes during the Execution and Imagination of Sequential Foot Movements. *NeuroImage*, *16*(1), 142–157. https://doi.org/10.1006/nimg.2001.1048

Lang, N., Speck, S., Harms, J., Rothkegel, H., Paulus, W., & Sommer, M. (2008). Dopaminergic potentiation of rTMS-induced motor cortex inhibition. *Biological Psychiatry*, *63*(2), 231–233.

Laplane, D., Talairach, J., Meininger, V., Bancaud, J., & Bouchareine, A. (1977). Motor consequences of motor area ablations in man. *Journal of the Neurological Sciences*, *31*(1), 29–49.

Lemon, R. N. (2008). Descending pathways in motor control. *Annu. Rev. Neurosci.*, *31*, 195–218.

Lemon R. (2019). Recent advances in our understanding of the primate corticospinal system. *F1000Res*. 2019;8:F1000 Faculty Rev-274. doi:10.12688/f1000research.17445.1

Liepert, J., & Neveling, N. (2009). Motor excitability during imagination and observation of foot dorsiflexions. *Journal of Neural Transmission*, *116*(12), 1613.

Litvak, V., Komssi, S., Scherg, M., Hoechstetter, K., Classen, J., Zaaroor, M., … Kahkonen, S. (2007). Artifact correction and source analysis of early electroencephalographic responses evoked by transcranial magnetic stimulation over primary motor cortex. *Neuroimage*, *37*(1), 56–70.

Lotze, M., & Halsband, U. (2006). Motor imagery. *Journal of Physiology-Paris*, *99*(4), 386–395. https://doi.org/10.1016/j.jphysparis.2006.03.012

Lotze, M., Montoya, P., Erb, M., Hülsmann, E., Flor, H., Klose, U., … Grodd, W. (1999). Activation of Cortical and Cerebellar Motor Areas during Executed and Imagined Hand Movements: An fMRI Study. *Journal of Cognitive Neuroscience*, *11*(5), 491–501. https://doi.org/10.1162/089892999563553

Lüders, H. O., Dinner, D. S., Morris, H. H., Wyllie, E., & Comair, Y. G. (1995). Cortical electrical stimulation in humans. The negative motor areas. *Advances in Neurology*, *67*, 115–129.

Luppino, G., Matelli, M., Camarda, R., & Rizzolatti, G. (1993). Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *Journal of Comparative Neurology*, *338*(1), 114–140.

Marconi, B., Pecchioli, C., Koch, G., & Caltagirone, C. (2007). Functional overlap between hand and forearm motor cortical representations during motor cognitive tasks. *Clinical Neurophysiology*, *118*(8), 1767–1775.

Massé-Alarie, H., Cancino, E. E., Schneider, C., & Hodges, P. (2016). Paired-pulse TMS and fine-wire recordings reveal short-interval intracortical inhibition and facilitation of deep multifidus muscle fascicles. *PloS One*, *11*(8), e0159391.

Matelli, M., Luppino, G., Fogassi, L., & Rizzolatti, G. (1989). Thalamic input to inferior area 6 and area 4 in the macaque monkey. *Journal of Comparative Neurology*, *280*(3), 468–488.

Mikuni, N., Ohara, S., Ikeda, A., Hayashi, N., Nishida, N., Taki, J., … Hashimoto, N. (2006). Evidence for a wide distribution of negative motor areas in the perirolandic cortex. *Clinical Neurophysiology*, *117*(1), 33–40.

Miller, K. J., Schalk, G., Fetz, E. E., den Nijs, M., Ojemann, J. G., & Rao, R. P. N. (2010). Cortical activity during motor execution, motor imagery, and imagery-based online feedback. *Proceedings of the National Academy of Sciences*, *107*(9), 4430–4435. https://doi.org/10.1073/pnas.0913697107

Mochizuki, H., Huang, Y.-Z., & Rothwell, J. C. (2004). Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. *The Journal of Physiology*, *561*(1), 331–338.

Molina-Luna, K., Pekanovic, A., Röhrich, S., Hertler, B., Schubring-Giese, M., Rioult-Pedotti, M.-S., & Luft, A. R. (2009). Dopamine in Motor Cortex Is Necessary for Skill Learning and Synaptic Plasticity. *PLoS One; San Francisco*, *4*(9), e7082. http://dx.doi.org.ezlibproxy1.ntu.edu.sg/10.1371/journal.pone.0007082

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., … Hallett, M. (2002). Early consolidation in human primary motor cortex. *Nature*, *415*(6872), 640–644. https://doi.org/10.1038/nature712

Münte, T. F., Altenmüller, E., & Jäncke, L. (2002). The musician's brain as a model of neuroplasticity. *Nature Reviews Neuroscience*, *3*(6), 473.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, *9*(11), 856.

Naish, K. R., Houston-Price, C., Bremner, A. J., & Holmes, N. P. (2014). Effects of action observation on corticospinal excitability: Muscle specificity, direction,

and timing of the mirror response. *Neuropsychologia*, *64*, 331–348. https://doi.org/10.1016/j.neuropsychologia.2014.09.034

Nevalainen, P., Lauronen, L., & Pihko, E. (2014). Development of Human Somatosensory Cortical Functions – What have We Learned from Magnetoencephalography: A Review. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00158

Nieoullon, A., & Coquerel, A. (2003). Dopamine: A key regulator to adapt action, emotion, motivation and cognition. *Current Opinion in Neurology*, *16*, S3–S9.

Nii, Y., Uematsu, S., Lesser, R. P., & Gordon, B. (1996). Does the central sulcus divide motor and sensory functions: Cortical mapping of human hand areas as revealed by electrical stimulation through subdural grid electrodes. *Neurology*, *46*(2), 360–367.

Nishitani, N., & Hari, R. (2002). Viewing Lip Forms: Cortical Dynamics. *Neuron*, *36*(6), 1211–1220. https://doi.org/10.1016/S0896-6273(02)01089-9

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2003). Facilitation of Implicit Motor Learning by Weak Transcranial Direct Current Stimulation of the Primary Motor Cortex in the Human. *Journal of Cognitive Neuroscience*, *15*(4), 619–626. https://doi.org/10.1162/089892903321662994

Ocampo, B., & Kritikos, A. (2010). Placing actions in context: Motor facilitation following observation of identical and non-identical manual acts. *Experimental Brain Research*, *201*(4), 743–751. https://doi.org/10.1007/s00221-009-2089-6

Orioli, P. J., & Strick, P. L. (1989). Cerebellar connections with the motor cortex and the arcuate premotor area: An analysis employing retrograde transneuronal transport of WGA-HRP. *Journal of Comparative Neurology*, *288*(4), 612–626.

O'Shea, H., & Moran, A. (2017). Does Motor Simulation Theory Explain the Cognitive Mechanisms Underlying Motor Imagery? A Critical Review. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00072

Overduin, S. A., Richardson, A. G., & Bizzi, E. (2009). Cortical Processing during Dynamic Motor Adaptation. In D. Sternad (Ed.), *Progress in Motor Control: A Multidisciplinary Perspective* (pp. 423–438). https://doi.org/10.1007/978-0-387-77064-2_22

Pascual-Leone, A., Nguyet, D., Cohen, L. G., Brasil-Neto, J. P., Cammarota, A., & Hallett, M. (1995). Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *Journal of Neurophysiology*, *74*(3), 1037–1045. https://doi.org/10.1152/jn.1995.74.3.1037

Pearson, K. (2000). Motor systems. *Current Opinion in Neurobiology*, *10*(5), 649–654.

Pelletier, S. J., & Cicchetti, F. (2015). Cellular and molecular mechanisms of action of transcranial direct current stimulation: Evidence from in vitro and in vivo models. *International Journal of Neuropsychopharmacology*, *18*(2), pyu047.

Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, *60*(4), 389–443.

Penfield, W., & Rasmussen, T. (1950). *The cerebral cortex of man; a clinical study of localization of function.*

Penhune, V. B., & Steele, C. J. (2012). Parallel contributions of cerebellar, striatal and M1 mechanisms to motor sequence learning. *Behavioural Brain Research*, *226*(2), 579–591. https://doi.org/10.1016/j.bbr.2011.09.044

Perez, M. A., & Cohen, L. G. (2009). Interhemispheric inhibition between primary motor cortices: What have we learned? *The Journal of Physiology*, *587*(4), 725–726. https://doi.org/10.1113/jphysiol.2008.166926

Petrides, M., & Pandya, D. N. (1984). Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *Journal of Comparative Neurology*, *228*(1), 105–116.

Polanía, R., Paulus, W., & Nitsche, M. A. (2012). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Human Brain Mapping*, *33*(10), 2499–2508. https://doi.org/10.1002/hbm.21380

Porro, C. A., Francescato, M. P., Cettolo, V., Diamond, M. E., Baraldi, P., Zuiani, C., … Prampero, P. E. di. (1996). Primary Motor and Sensory Cortex Activation during Motor Performance and Motor Imagery: A Functional Magnetic Resonance Imaging Study. *Journal of Neuroscience*, *16*(23), 7688–7698. https://doi.org/10.1523/JNEUROSCI.16-23-07688.1996

Porter, R., & Lemon, R. (1993). *Corticospinal function and voluntary movement*. Oxford University Press, USA.

Pascual-leone, a. (2001). The brain that plays music and is changed by it. *Annals of the New York Academy of Sciences* 930(1)**,** 315-329.

Praeg, E., Esslen, M., Lutz, K., & Jancke, L. (2006). Neuronal modifications during visuomotor association learning assessed by electric brain tomography. *Brain Topography*, *19*(1–2), 61–75.

Pruszynski, J. A., Kurtzer, I., Nashed, J. Y., Omrani, M., Brouwer, B., & Scott, S. H. (2011). Primary motor cortex underlies multi-joint integration for fast feedback control. *Nature*, *478*(7369), 387.

Rao, S. M., Harrington, D. L., Haaland, K. Y., Bobholz, J. A., Cox, R. W., & Binder, J. R. (1997). Distributed neural systems underlying the timing of movements. *Journal of Neuroscience*, *17*(14), 5528–5535.

Reis, J., Robertson, E., Krakauer, J. W., Rothwell, J., Marshall, L., Gerloff, C., … Cohen, L. G. (2008). Consensus: "Can tDCS and TMS enhance motor learning and memory formation?" *Brain Stimulation*, *1*(4), 363–369. https://doi.org/10.1016/j.brs.2008.08.001

Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., … Krakauer, J. W. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences*, *106*(5), 1590–1595. https://doi.org/10.1073/pnas.0805413106

Repetto, C., Colombo, B., Cipresso, P., & Riva, G. (2013). The effects of rTMS over the primary motor cortex: The link between action and language. *Neuropsychologia*, *51*(1), 8–13. https://doi.org/10.1016/j.neuropsychologia.2012.11.001

Richardson, A. G., Overduin, S. A., Valero-Cabré, A., Padoa-Schioppa, C., Pascual-Leone, A., Bizzi, E., & Press, D. Z. (2006). Disruption of primary motor cortex before learning impairs memory of movement dynamics. *Journal of Neuroscience*, *26*(48), 12466–12470.

Ridding, M. C., Taylor, J. L., & Rothwell, J. C. (1995). The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. *The Journal of Physiology*, *487*(2), 541–548.

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cognitive Brain Research*, *3*(2), 131–141.

Rizzolatti, G., Fogassi, L., & Gallese, V. (2002). Motor and cognitive functions of the ventral premotor cortex. *Current Opinion in Neurobiology*, *12*(2), 149–154. https://doi.org/10.1016/S0959-4388(02)00308-2

Roland, P. E., Larsen, B., Lassen, N. A., & Skinhoj, E. (1980). Supplementary motor area and other cortical areas in organization of voluntary movements in man. *Journal of Neurophysiology*, *43*(1), 118–136.

Roosink, M., & Zijdewind, I. (2010). Corticospinal excitability during observation and imagery of simple and complex hand tasks: Implications for motor rehabilitation. *Behavioural Brain Research*, *213*(1), 35–41. https://doi.org/10.1016/j.bbr.2010.04.027

Rossini, P. M., Rossi, S., Pasqualetti, P., & Tecchio, F. (1999). Corticospinal Excitability Modulation to Hand Muscles During Movement Imagery. *Cerebral Cortex*, *9*(2), 161–167. https://doi.org/10.1093/cercor/9.2.161

Roy, F. D., & Gorassini, M. A. (2008). Peripheral sensory activation of cortical circuits in the leg motor cortex of man. *The Journal of Physiology*, *586*(17), 4091–4105.

Ruffino, C., Papaxanthis, C., & Lebon, F. (2017). Neural plasticity during motor learning with motor imagery practice: Review and perspectives. *Neuroscience*, *341*, 61–78. https://doi.org/10.1016/j.neuroscience.2016.11.023

Ruge, D., Muggleton, N., Hoad, D., Caronni, A., & Rothwell, J. C. (2014). An unavoidable modulation? Sensory attention and human primary motor cortex

excitability. *European Journal of Neuroscience*, *40*(5), 2850–2858. https://doi.org/10.1111/ejn.12651

Sanes, J. N., & Donoghue, J. P. (2000). Plasticity and primary motor cortex. *Annual Review of Neuroscience*, *23*(1), 393–415.

Savic, B., & Meier, B. (2016). How transcranial direct current stimulation can modulate implicit motor sequence learning and consolidation: A brief review. *Frontiers in Human Neuroscience*, *10*, 26.

Schnitzler, A., Kessler, K. R., & Benecke, R. (1996). Transcallosally mediated inhibition of interneurons within human primary motor cortex. *Experimental Brain Research*, *112*(3), 381–391.

Sesack, S. R., & Pickel, V. M. (1992). Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. *Journal of Comparative Neurology*, *320*(2), 145–160.

Shibasaki, H., & Hallett, M. (2006). What is the Bereitschaftspotential? *Clinical Neurophysiology*, *117*(11), 2341–2356.

Shibasaki, H., Sadato, N., Lyshkow, H., Yonekura, Y., Honda, M., Nagamine, T., … Miyazaki, M. (1993). Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain*, *116*(6), 1387–1398.

Smith, D., Wright, C., Allsopp, A., & Westhead, H. (2007). It's all in the mind: PETTLEP-based imagery and sports performance. *Journal of Applied Sport Psychology*, *19*(1), 80–92.

Smith, D., Wright, C. J., & Cantwell, C. (2008). Beating the bunker: The effect of PETTLEP imagery on golf bunker shot performance. *Research Quarterly for Exercise and Sport*, *79*(3), 385–391.

Steele, C. J., & Penhune, V. B. (2010). Specific increases within global decreases: A functional magnetic resonance imaging investigation of five days of motor sequence learning. *Journal of Neuroscience*, *30*(24), 8332–8341.

Stephan, K. M., Fink, G. R., Passingham, R. E., Silbersweig, D., Ceballos-Baumann, A. O., Frith, C. D., & Frackowiak, R. S. (1995). Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *Journal of Neurophysiology*, *73*(1), 373–386. https://doi.org/10.1152/jn.1995.73.1.373

Strafella, A. P., Ko, J. H., Grant, J., Fraraccio, M., & Monchi, O. (2005). Corticostriatal functional interactions in Parkinson's disease: A rTMS/[11C] raclopride PET study. *European Journal of Neuroscience*, *22*(11), 2946–2952.

Strick, P. L., & Preston, J. B. (1983). Input-output organization of the primate motor cortex. *Advances in Neurology*, *39*, 321–327.

Strick, Peter L. (1985). How do the basal ganglia and cerebellum gain access to the cortical motor areas? *Behavioural Brain Research*, *18*(2), 107–123.

Tanaka, S., Sandrini, M., & Cohen, L. G. (2011). Modulation of motor learning and memory formation by non-invasive cortical stimulation of the primary motor cortex. *Neuropsychological Rehabilitation*, *21*(5), 650–675.

Thickbroom, G. W., Byrnes, M. L., & Mastaglia, F. L. (1999). A model of the effect of MEP amplitude variation on the accuracy of TMS mapping. *Clinical Neurophysiology*, *110*(5), 941–943.

Tomasino, B., Borroni, P., Isaja, A., & Rumiati, R. I. (2005). The role of the primary motor cortex in mental rotation: A TMS study. *Cognitive Neuropsychology*, *22*(3–4), 348–363. https://doi.org/10.1080/02643290442000185

Tyc, F., & Boyadjian, A. (2006). Cortical plasticity and motor activity studied with transcranial magnetic stimulation. *Reviews in the Neurosciences*, *17*(5), 469–496.

Vargas, C. D., Olivier, E., Craighero, L., Fadiga, L., Duhamel, J. R., & Sirigu, A. (2004). The influence of hand posture on corticospinal excitability during motor imagery: A transcranial magnetic stimulation study. *Cerebral Cortex*, *14*(11), 1200–1206.

Vergeer, I., & Roberts, J. (2006). Movement and stretching imagery during flexibility training. *Journal of Sports Sciences*, *24*(2), 197–208.

Vigneswaran, G., Philipp, R., Lemon, R. N., & Kraskov, A. (2013). M1 corticospinal mirror neurons and their role in movement suppression during action observation. *Current Biology*, *23*(3), 236–243.

Welniarz Q., Dusart I., Roze E. (2017a). The corticospinal tract: evolution, development, and human disorders. *Dev. Neurobiol.* 77 810–829. 10.1002/dneu.22455

Wilkinson, L., Teo, J. T., Obeso, I., Rothwell, J. C., & Jahanshahi, M. (2010). The Contribution of Primary Motor Cortex is Essential for Probabilistic Implicit Sequence Learning: Evidence from Theta Burst Magnetic Stimulation. *Journal of Cognitive Neuroscience*, *22*(3), 427–436. https://doi.org/10.1162/jocn.2009.21208

Xiong, J., Parsons, L. M., Gao, J.-H., & Fox, P. T. (1999). Interregional connectivity to primary motor cortex revealed using MRI resting state images. *Human Brain Mapping*, *8*(2–3), 151–156.

Ziemann, U., Tergau, F., Wischer, S., Hildebrandt, J., & Paulus, W. (1998). Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, *109*(4), 321–330.