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Treatment and Physiology in Parkinson's Disease and Dystonia: Using TMS to Uncover the Mechanisms of Action

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Abstract

Transcranial magnetic stimulation (TMS) has served as an important technological breakthrough in the field of movement disorders physiology over the last three decades. TMS has grown popular due to the ease of application as well as its painless and noninvasive character. The technique has shed important insights into understanding the pathophysiology of movement disorders particularly Parkinson's disease and dystonia. The basic applications have included the study of motor cortex excitability, functioning of excitatory and inhibitory circuits, study of interactions between sensory and motor systems, and the plasticity response of the brain. TMS has also made important contributions in understanding response to treatments such as the dopaminergic medications, botulinium toxin injections and deep brain stimulation surgery. This review summarizes the knowledge gained to date with TMS in Parkinson's disease and dystonia and highlights the current challenges in utilization of TMS technology.

Keywords

Transcranial magnetic stimulation; Parkinson's disease; dystonia

Introduction

Transcranial magnetic stimulation (TMS) is a safe and non-invasive method of stimulating the cortical neurons.[1] More than three decades ago, Merton and Morton [2] developed a technique known as transcranial electrical stimulation (TES) that stimulated the motor areas

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Conflict of Interest

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Human and Animal Rights and Informed Consent

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of the human brain through intact scalp. In this technique a brief, high-voltage electric shock was delivered to the primary motor cortex (M1) which in turn produced a brief, relatively synchronous muscle response, the motor-evoked potential (MEP)[2]. Since this technique was painful, a few years later, Barker et al [3] refined the stimulation method and showed it was possible to stimulate the brain with painless magnetic pulses. This refined technique was called transcranial magnetic stimulation (TMS) where a magnetic field generator sends a large short duration current through an induction coil placed on the scalp. This large current creates a magnetic field that is perpendicular to the coil (Faraday's Law) and this passes through the skull and stimulates the underlying brain parallel to the coil [3]. Since most of the intracortical horizontally oriented neural elements near the cortical surface are interneurons, TMS is more likely to activate pyramidal cells transynaptically[4]. The motor cortex when stimulated with sufficient intensity sends descending volleys along the corticospinal pathway, and the resulting activation of muscles can be recorded by surface electromyography [1].

Several TMS paradigms have since been developed to investigate the physiology of the motor system. These paradigms range from simple measurement of motor cortex excitability, assessment of central motor conduction time to complex examples of applying paired stimuli to study the inhibitory and excitatory circuits, measurement of interaction of peripheral stimulus with central motor cortex stimulation to measurement of motor cortex plasticity. These paradigms, discussed in subsequent sections, have been used widely to better understand the pathophysiology of movement disorders.[5] Furthermore TMS has shed substantial insight into the mechanisms underlying therapy for movement disorders such as dopaminergic medications for Parkinson's disease, botulinium toxin injections for treatment of dystonia and deep brain stimulation for PD and dystonia. The main focus of this review is to discuss the role of TMS in revealing potential mechanisms.

Standard TMS paradigms and basic concepts

Physiological activity in the motor cortex depends on the balance between excitatory and inhibitory influences. TMS can test different excitatory and inhibitory circuits in the brain based on the individual stimulus parameters [6,7]. Table 1 summarizes the major TMS paradigms and the effects on Parkinson's disease and dystonia. Single-pulse TMS when applied to the motor cortex determines the motor threshold that is believed to represent a measure of membrane excitability of pyramidal neurons [8]. While there is considerable information on these circuits, far less is understood about how these circuits are related to each other and how they interact.[6] Paired pulse TMS studies have established paradigms for at least two types of intracortical inhibition referred to as short-interval intracortical inhibition (SICI)[9] and long-interval intracortical inhibition (LICI)[10]. SICI is a complex cortical phenomenon that encompasses study of different inhibitory circuits at different interstimulus intervals (ISIs) [11,12]. SICI involves a subthreshold conditioning stimulus followed by a suprathreshold test stimulus applied to the primary motor cortex (M1) using a "figure-of-eight" TMS coil. The motor evoked potentials (MEPs) recorded from peripheral surface EMG muscles are found to be inhibited at ISIs of 1–6 ms. LICI is elicited by a suprathreshold conditioning pulse followed by a test pulse applied at ISIs of approximately 50-200 ms[13,14]. "Silent period" refers to a period of suppression of voluntary muscle

contraction which is elicited by application of suprathreshold TMS pulses. We have found evidence that LICI is likely related to the silent period [14]. LICI has been shown to be abnormal in Parkinson's disease (increased)[15], and dystonia(decreased)[16]. Amongst the excitatory circuits for the motor system, intracortical facilitation (ICF) is a commonly tested phenomenon using protocols similar to SICI [9]. ICF involves a subthreshold conditioning stimulus followed by suprathreshold test stimulus at ISIs of 8–30ms. Similar to SICI, ICF also occurs in the cortex [17] rather than subcortical structures, but ICF is mediated by neuronal populations separate from SICI [17,18].

In addition to motor system excitability, the interaction of sensory and motor systems can be examined with TMS paradigms of short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI). In these paradigms, the effects of peripheral sensory stimulation on motor cortex excitability is assessed with application of a sensory stimulus such as median nerve stimulation followed by a test stimulus over the contralateral motor cortex. Inhibition of the test MEP is most consistent at two distinct ISIs of approximately 20ms and 200ms [19]. At short latencies (less than 40ms) the contralateral S1 and secondary somatosensory cortex (S2) are primarily activated, while at longer latencies (more than 40ms) there is more widespread activation of sensory areas, including S1, bilateral S2, and the contralateral posterior parietal cortex [20,21]. Short latency afferent inhibition (SAI), also exhibits a somatotopic organization [22] such that cortical inhibition due to electrical stimulation of a digit near a target muscle (i.e., homotopic) is stronger than cortical inhibition due to stimulation of a digit distant from a target muscle (i.e., heterotopic)[23].

Furthermore, interactions between the cerebellum and motor cortex can be examined with magnetic stimulation of the cerebellum. Stimulation using a double cone coil followed by stimulation of the contralateral motor cortex at an ISI of 5–7ms has been found to inhibit the MEPs. This is referred to as cerebellar inhibition (CBI) [24,25]. In this inhibitory circuit, cerebellar stimulation with TMS probably activates Purkinje cells in the cerebellar cortex, leading to inhibition of deep cerebellar nuclei such as the dentate nucleus which then projects to the motor cortex via a disynaptic excitatory pathway passing through the ventral thalamus [26,27]. CBI has been found to be normal in essential tremor, [28] however is reduced in Parkinson's disease [29].

Finally the plasticity response of the neuronal synapse can be examined with TMS which refers to the ability of a neuron to modify its synaptic structure or function in response to stimuli that outlast the stimulation period [30], [31]. Long-term potentiation (LTP) generally defined as a long-lasting increase in synaptic strength and long-term depression (LTD) refers to decrease in synaptic strength are examples of synaptic plasticity that represent key mechanisms for adaptive motor control [32]. Protocols such as intermittent theta burst stimulation (iTBS), high-frequency rTMS, and PAS25 (25ms between peripheral nerve stimulation and motor cortex) are considered LTP-like protocols whereas continuous theta burst stimulation (cTBS), low-frequency rTMS, and PAS10 (10ms between peripheral nerve stimulation and motor cortex) are considered LTD-like protocols [33].

Although TMS paradigms are well-established, they have been criticized for exhibiting wide variability in effects. Several factors have been identified that contribute to this variation and

should be kept in consideration when interpreting the physiological effects. These factors are either extrinsic: cortical target, frequency, intensity, duration, number of sessions or patient based intrinsic factors: genetic polymorphisms of neurotransmitters and receptors, hormonal level, attention level, spontaneous variation in cortical excitability, fatigue of subjects, individual variability and symptoms, state of medication treatment [34]. Another important limitation of the current round or focal figure-of-eight coils are lack of ability to stimulate deep brain regions, however with technological advances in coil configuration, this may likely change[1]. For example, a H coil with complex windings that permit a slower fall-off of the intensity of the magnetic field with depth was recently introduced to allow stimulation of deep brain regions [35]. In another configuration, the windings of a coil were designed around an iron core rather than air; to focus the field and allow greater strength and depth of penetration [36].

TMS in Parkinson's disease

Pathophysiology of PD

Bradykinesia that refers to slowness of voluntary movements is a cardinal feature of PD. Simple reaction time tasks that involve subjects making the same response to a given stimulus on every trial has been found to be prolonged in PD [37]. The accuracy of movements, particularly if they have to move as fast as possible, are affected [38]. In one study, Cunnington et al asked patients to make a rapid sequence of finger movements from left to right by pressing buttons along a tapping board [39]. When a TMS pulse was delivered to supplementary motor area (SMA) early in the interval between button presses this slowed the next button press, indicating that SMA function is compromised in PD [39]. Although cortico-motor-neuronal conduction time and motor thresholds are both normal in PD [40], the slope of the relationship between stimulus intensity and response size when tested at rest is steeper than normal [41]. This implies that the distribution of cortical excitability is skewed towards higher than normal values and it has been speculated to be an attempt on the part of motor cortex to compensate for a slow recruitment of commands to move. Furthermore TMS studies have shown abnormal excitability of cortical inhibitory circuits. The silent period is shorter and SICI is reduced in PD[15]. Again reduced SICI could be a compensatory mechanism that allows the motor commands to have an easier access to cortical output. Finally, sensory symptoms [42] and objective sensory deficits, especially diminished proprioception and kinesthesia [43,44], are well documented and considered to play an important role in the pathophysiology of PD. TMS studies have shown there is an abnormal sensorimotor integration in PD when measured with paired pulse paradigms of short latency afferent inhibition (SAI) and long latency afferent inhibition (LAI) [45].

Understanding the physiological effects of dopaminergic therapies

Levodopa (L-DOPA) therapy is the cornerstone treatment for motor symptoms in PD. Table 2 summarizes the TMS findings from treatment studies of medication and DBS for both Parkinson's disease and dystonia.

Levodopa therapy in PD has been found to affect motor cortex excitability, by improving the silent period and SICI[15]. Levodopa has also been shown to influence the connectivity between the premotor cortex (PMd) and primary cortex. In early stage PD patients, 1Hz repetitive transcranial magnetic stimulation (rTMS) delivered to PMd was found to restore a deficient intracortical inhibition of the primary motor cortex (M1) seen in the presence of levodopa [46]. The inhibitory circuit in this case was measured with a paired pulse protocol where a subthreshold conditioning stimulus was followed by a suprathreshold test stimulus delivered to M1 at an ISI of 5ms. The authors of the study concluded that 1Hz rTMS to PMd modulates M1 intracortical circuits. TMS studies have also shown that dopaminergic therapies modulate sensorimotor integration in PD. Sailer et al [45] found that SAI is unaffected by PD however it is reduced in the presence of dopaminergic medication whereas LAI is reduced regardless of the medication status suggesting thereby, SAI plays a role in the pathophysiology of dopaminergic complications and LAI probably reflects a non-dopaminergic manifestation of the disease.

Levodopa therapy when administered for prolonged periods of 5–10 years [47], is associated with motor fluctuations and dyskinesias [48]. Chronic ‘pulsatile’ nonphysiologic stimulation of dopamine receptors located on the striatal neurons has been shown to induce post-synaptic signaling abnormalities and an abnormal plasticity response [49]. A recent TMS study examined the plasticity response and the effects of acute challenge with non-physiological dopamine in three groups of PD patients: patients who were stable responders to levodopa, patients who had motor fluctuations but no dyskinesia and those who had motor fluctuations as well as dyskinesia. They found that the LTP- and LTD-like plasticity responses were normal in the first group, LTD was impaired in the second, and both types of plasticity response were absent in the third group. When an acute levodopa challenge was provided there was worsening of LTD in all three groups, and worsening of LTP in the second group suggesting an adverse effect of non-physiological dopamine on the plasticity response [• 50]. These findings were suggested to be related to a persistent dysfunction of the intracellular signaling cascade in the striatum that resulted from repeated exposure to non-physiological surges in synaptic dopamine involved in the maintenance of both forms of plasticity.

TMS insight into DBS effects in PD

Since the 1990’s, DBS has been touted as an efficacious treatment for motor fluctuations and medication refractory tremors in PD. STN and GPi, are two preferred targets for stimulation, and they both have shown equivalent benefits [51]. STN activity in PD are characterized by augmented synchrony of neuronal firing, loss of specificity of the receptive fields, and increased firing rates with bursting activity.[52,53] A pathological drive from STN is hypothesized to disrupt the activity of the substantia nigra pars reticulata (SNr), globus pallidus pars interna (GPi), globus pallidus pars externa (GPe), pedunculopontine nucleus, thalamus, and various cortical areas [54,55]. TMS studies have shown STN DBS to modulate the activity of the motor cortex. Several authors following low frequency STN stimulation have recorded evoked potentials from scalp electrodes at short (2--8 ms) and medium (18--25 ms) latencies [56,57]. These potentials are evoked at these latencies if the current induced by the TMS coil is delivered in the anterior – posterior (AP) directions [58].

These potentials likely relate to short-latency antidromic stimulation of corticosubthalamic projections and the medium-latency facilitatory basal ganglia--thalamo--cortical interactions following STN stimulation. On the other hand application of a TMS pulse to the motor cortex has been found to change the firing rate of STN neurons [59] and the oscillatory activity of the STN [60].

Motor cortex excitability after STN DBS has been found to be changed only at specific time intervals. This was well explained when TMS studies found STN DBS to increase the motor cortical inhibition yet there were no effects on the motor threshold or MEP amplitude [61,62]. Cunic et al found bilateral GPi DBS to normalize the “silent period” that was abnormally shortened in PD [63] whereas STN stimulation under similar experimental conditions had little effect on silent period [61]. The disparity between the effects of STN and GPi DBS on the silent period was suggested to be related to the anti-dyskinetic effects of GPi stimulation.

Prior studies in PD had found an abnormal SAI in the presence of dopaminergic medications only and an abnormal LAI regardless of medication status probably related to nondopaminergic features of PD [45]. In patients with chronic STN DBS, SAI and LAI were found to be reduced in the on medication- off stimulation state however when the stimulators were turned ON these abnormalities normalized. The inference of the study was STN DBS in PD restores a deficient sensorimotor integration.[64] In a subsequent longitudinal study these modulatory effects of STN DBS were demonstrated only at six months and not at one month, these findings suggested chronic stimulation is important in elicitation and potentially maintenance of physiological changes. [• 65]

TMS in dystonia

Pathophysiology of dystonia

The term dystonia is used to describe a syndrome characterized by prolonged muscle contractions, causing twisting movements and abnormal postures of the affected body part(s). Dystonia may be focal, segmental or generalized according to the different body parts affected [66,67]. During standard clinical MRI, a typical read from a neuroradiologist of T1, T2, and other imaging does not reveal any structural changes in primary dystonia. However, when using TMS these physiological studies have identified several important functional abnormalities [68].

The pathophysiological substrate of dystonia comprises three general abnormalities which relate to each other. There is strong evidence to show that there is a loss of inhibition at the level of the spinal cord, brainstem, and cortex which explains the excess of movement and the overflow phenomena seen in dystonia [68]. The failure of short-interval intracortical inhibition (SICI) in focal hand dystonia suggests that there might well be a cortical abnormality of intracortical inhibitory neurons in dystonia [40,69]. Similar cortical abnormality was suggested by a silent period study that was found to be abnormally shortened in patients with writer’s cramp [16]. These alterations in inhibitory circuits are nonspecific in that they have been observed in a wide variety of other neurological conditions including psychogenic dystonia.[70,71] Interestingly, in dystonia an abnormal

intracortical inhibition is found to be present in both hemispheres despite unilateral symptoms and asymptomatic body parts [68]. It is reasonable to assume that abnormalities in the asymptomatic body parts reflect compensatory changes to prevent a clinical manifestation of dystonia. Although some argue that this seems unlikely since the abnormalities are generally the same as those in the symptomatic body parts and are in the direction that leads to motor dysfunction.

The second major theme in the pathophysiology of dystonia is a defect in sensory function or in "sensorimotor integration."[72] Sensory dysfunction may clinically show only minor findings such as ill-defined bodily feelings (discomfort, pain, or kinesthetic sensations) [73], however these are believed to drive the motor system in an abnormal direction. Patients with focal dystonia have difficulty in discriminating sensory stimuli in both spatial and temporal domains [74]. These alterations may be related to a deranged somatotopic representation in the sensory cortex as revealed by neurophysiological and neuroimaging studies [75-77]. The basal ganglia and cerebellum are thought to play an important role in the sensory and perceptual defects seen in dystonia. The basal ganglia are believed to participate in sensory gating and filtering out the nature of sensory information that is "passed" to the motor cortex [78]. TMS studies found that although SAI and LAI were comparable to healthy controls in focal dystonia patients,[79],[80] there was an increased homotopic digital short afferent inhibition (dSAI), during flexion of the second digit. This suggests that this process was a compensatory act to diminish overflow during movement [23]. Unlike the basal ganglia which receive sensory information indirectly, the cerebellum is a direct recipient of sensory input from the spinal cord [81]. Patients with writer's cramp performed much slower and less efficient than healthy control subjects in a reaching task known to involve the cerebellum where a visuomotor conflict was generated by a random deviation (-40° to 40°) on the direction of movement of the mouse/cursor [82].

Third, in primary dystonia there is a derangement of plasticity response shown as an exaggerated responsiveness of the motor and sensory cortex to TMS conditioning protocols [83,84]. Using paired associative stimulation protocols in patients with writer's cramp both LTP-like facilitatory and LTD-like inhibitory effects on TMS-evoked motor evoked potentials have been found to be enhanced [83,85]. An important feature of PAS-induced associative plasticity is the spatial specificity of the recorded MEPs from the target muscles. This has been seen to be lost in patients with writer's cramp, in that the PAS tends also to change the cortical excitability of nearby muscle representations [83,86]. Then Hubsch and coworkers applied rTMS pulses to either excite or inhibit the cerebellar cortex in writers' cramp patients, before the sensorimotor plasticity response of the motor cortex could be tested with the PAS protocol. They found, cerebellar cortex excitation and inhibition were both ineffective in modulating sensorimotor plasticity. Another paradigm for study of plasticity involving use of theta burst stimulation showed a loss of response even in non-manifesting DYT1 gene carriers suggesting this may have represented an important endophenotypic trait that predisposes to a subsequent development of dystonia [87].

TMS insight into botulinum toxin injection effects in dystonia

Botulinum toxin type A (BT-A) is widely used medication for treatment of primary dystonia. The clinical benefits primarily depend on the toxin's peripheral action of inhibiting acetylcholine release from the presynaptic neuromuscular terminals, thus weakening contraction of the muscle fibers responsible for excessive involuntary movements. Although clinical improvement mostly parallels the weakness caused by injections, the clinical benefits often seem out of the proportion to the weakness, suggesting an additional, possibly central effect of BT-A [88,89]. In theory, BT-A that is injected locally, could produce central effects directly, by being transported into central structures, or indirectly, by altering the central sensorimotor integration through a peripheral mechanism [90]. Many experimental studies have shown support for a central action of BT-A. First, BT-A when injected into skeletal muscles has the property to act at the intrafusal as well the extrafusal neuromuscular junction. The toxin blocks the gamma motor endings of jaw muscles in the rat, reducing the spindle afferent discharge without altering the muscle tension [91]. Then there is evidence that intramuscularly injected BT-A influences the spinal cord circuitry. Weigand and colleagues [92], in a retrograde- tracing study showed that approximately 48 hours after injecting radiolabeled BT-A into the cat gastrocnemius muscle, a distal–proximal gradient of radioactivity developed first in the sciatic nerve, then in the ipsilateral spinal ventral roots, and ultimately in the spinal cord segments innervating the injected muscle.

In humans with the help of TMS the central effects of BT-A became further elucidated. Pauri and coworkers investigated changes in motor evoked potentials in patients with lower limb spasticity requiring BT-A injections in the calf muscles [93]. They found that when TMS was applied to the leg area of the cortex, the MEP latency and central conduction time increased significantly in the injected muscles roughly two weeks after treatment in parallel to clinical benefits. They attributed these findings to a central change in spinal motor neuron responsiveness to descending impulses from the corticospinal tracts. TMS studies have also shown that after BT-A injections, there are changes in cortical organization. In a study of writers' cramp patients, Byrnes and coworkers [94] delivered TMS before and after BT-A injections and mapped the topography of the primary motor cortex projections to the upper limb muscles. They found concurrent to clinical improvement, the cortical maps had a distorted shape with extended lateral borders that became reversed with BT-A injections. As the clinical benefits with BT-A wore off, the cortical maps returned to their original topography suggesting BT-A may have transiently modulated the abnormal afferent inputs from the periphery to explain these central effects.

A similar study was conducted in patients with upper limb dystonia to investigate the before and after effects of BT-A on intracortical inhibitory circuits of the primary motor cortex [95]. Before treatment, patients showed intracortical inhibition to be reduced which returned to values seen in normal subjects one month after the injection. However, after three months of BT-A injections values of intracortical inhibition dropped again to pretreatment levels. This study suggests that BT-A can transiently modify the excitability of the motor cortical areas by reorganizing inhibitory and excitatory intracortical circuits [95]. In patients with blepharospasm, BT-A has also been shown to reduce the abnormally enhanced plasticity response of the trigeminal blink reflex [96]. These effects have again been explained by the

modulation of the afferent input from the muscle spindles by the injections [91]. Kojovic and colleagues applied the PAS protocol to 12 patients with cervical dystonia and studied the plasticity response of primary motor cortex before, one and three months after BT-A injections administered to the neck muscles. Before BT injections, PAS-protocol found MEPs in the hand muscles to be facilitated, and this was seen to be abolished one month after injections with a partial recovery seen after three months. These BT effects on plasticity were again attributed to the modulation of afferent input from the neck [• 97].

TMS insight into DBS effects in dystonia

Several medical therapies have been tried for treatment of primary dystonias with limited efficacy, leaving many patients with a profound disability and the related stigma. DBS of globus pallidus has been considered a well-established treatment for medication refractory primary generalized dystonia [98]. The first reports of DBS success in dystonia were published a decade ago [99] and recent long-term results demonstrate that benefits are maintained for more than 10 years after surgery [100,101]. Although mean postoperative results for clinical measures have generally been encouraging, there is a wide range (20-95% on dystonia scores) of clinical improvement. Many factors have been considered to explain this wide range of outcome including the use of precise target which is postero-ventral GPi stimulation for the greatest overall effect, presence of short disease duration [102,103] and increase in GPi stimulated volumes which all predict better outcome [104]. There is emerging evidence to show STN as an alternate target for dystonia with benefits in the similar range [105].

Finally, in contrast to almost immediate effects of DBS seen in most PD symptoms, it often takes several months before clinical benefits are observed in dystonia [98,99]. In a study of time course changes with GPi DBS, turning on GPi in parallel with clinical improvement was found to progressively reverse the spinal and brainstem disinhibition suggesting a gradual neural reorganization towards a more normal physiological pattern.[106,107] Similarly, the changes of LTP-like synaptic plasticity on PAS protocol were reduced below normal after surgery and required at least six months timeframe before showing any trend towards normalization though SICI got normalized at one month [• 108].

Summary and Conclusions

TMS is a noninvasive physiological tool for investigation of excitatory and inhibitory changes of relevance to the pathophysiology of PD and dystonia and can be used to uncover various underlying treatment mechanisms. TMS studies have shown levodopa and DBS therapy in PD has specific modulatory effects on the motor cortex excitability and the interaction of sensory and motor system. Furthermore, chronic administration of pulsatile levodopa results in a negative effect on the plasticity response of the motor cortex. Botulinium toxin, although injected to peripheral muscles in dystonia, has clear central effects on motor cortex excitability and plasticity. Finally, motor cortex plasticity demonstrates a time dependent response to DBS treatment in dystonia. Despite this growth in knowledge with TMS, one of the main challenges to date has been the extreme variability in response patterns and the lack of ability to probe deeper structures of the brain. In order to improve upon the sensitivity and specificity of the research findings, future studies should

apply TMS paradigms to large, well characterized and homogenous disease populations. With the advent of stimulation patterns coupled with novel stimulation coils, it will become probable to investigate deeper brain circuits that are of relevance to movement disorders. Researchers will likely continue to utilize TMS to understand disease processes, brain circuitries, and treatment interventions.

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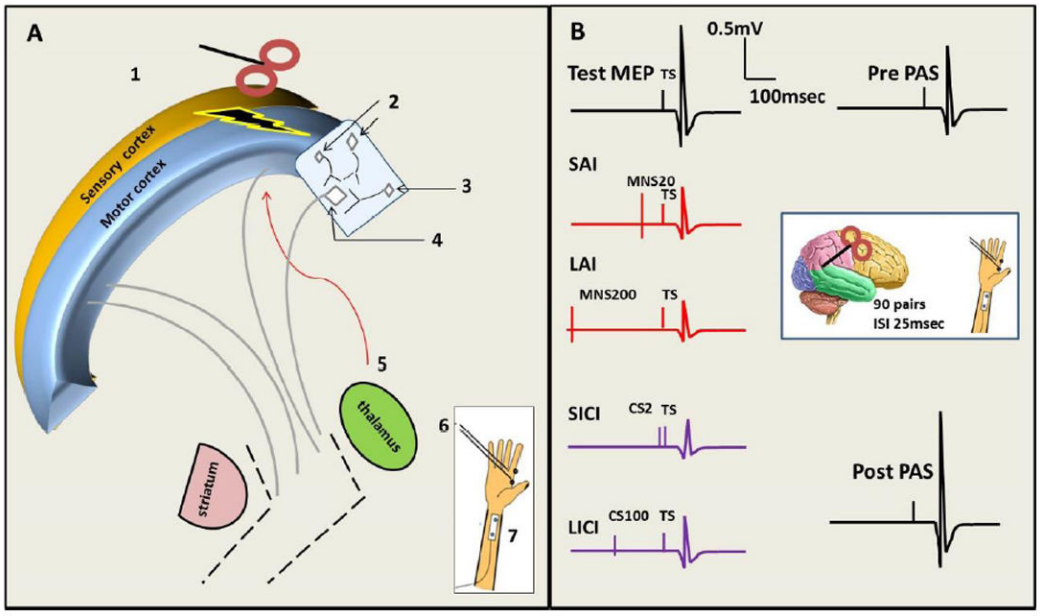

Figure 1.

A: Illustration of neurons and circuitries activated by TMS

1. TMS pulses applied to the motor cortex, 2. Motor cortex interneurons that mediate SICI and LICI, 3. Sensory cortex neurons that mediate sensorimotor integration such as SAI and LAI, 4. Corticospinal output neurons that generate motor evoked potentials are activated transsynaptically by the TMS pulse, 5. Sensory stimuli from the periphery are projected to sensory cortex by the thalamus, 6, Motor evoked potentials recording from the first dorsal interrosseus muscle, 7. Median nerve stimulation at the periphery that forms the conditioning stimulus.

B: Examples of TMS paradigms

The first column shows motor cortex inhibition (SICI and LICI) and sensorimotor integration (SAI and LAI) and the second column shows sensorimotor plasticity obtained with paired associative stimulation protocol (PAS). Traces show average motor evoked potential recordings with test pulse alone (TS) or preceded by median nerve stimulation delivered at interstimulus interval (ISI) of 20ms (MNS 20) and 200ms (MNS 200) or when preceded by a conditioned stimulus (CS) delivered to the motor cortex at an interstimulus interval of 2ms (CS2) and 100ms (CS100) For the PAS protocol, 90 pairs of median stimulation preceding the TMS pulse by 25 ms are delivered.

Table 1

Summary of basic TMS paradigms

	Short interval intracortical inhibition: SICI	**Long interval intracortical inhibition: LICI**	**Silent period**	**Short latency afferent inhibition SAI:**	**Long latency afferent inhibition: LAI**	**Paired associative stimulation: PAS protocol**
Conditioning stimulus	Subthresold TMS	Subthresold TMS		Median nerve stim	Median nerve stim	Median nerve stim
Test stimulus	Suprathresold TMS	Suprathresold TMS	Suprathresold TMS	Suprathresold TMS	Suprathresold TMS	Suprathresold TMS
Interstimulus interval	1-6ms	50-200ms	Not applicable	20ms	200ms	25ms
TMS protocol	Pairing of a conditioning pulse with test pulse at short interval suppresses test motor evoked potential; represents a cortical inhibitory phenomenon of the motor cortex	Pairing of a conditioning pulse with test pulse at long interval suppresses test motor evoked potential; represents a cortical inhibitory phenomenon of the motor cortex	A period of electromyography suppression caused by application of paired pulse TMS in a voluntary tonically contracting muscle; represents cortical inhibitory phenomenon	Application of peripheral sensory stimulus paired with motor cortex TMS pulse suppresses test motor evoked potential; represents integration of sensory input with motor output	Application of peripheral sensory stimulus paired with motor cortex TMS pulse at long interval suppresses test motor evoked potential; represents integration of sensory input with motor output	Application of 90 pairs of peripheral sensory stimuli followed by TMS motor pulses increase the size of motor evoked potential when compared to that recorded at baseline; these effects are maintained for atleast 30 minutes; effects reflect plasticity changes induced in output neurons by applying repeated sensory pulses through long-term potentiation mechanism
Parkinson’s disease	decreased	increased	shortened	No change OFF meds	decreased	
Dystonia	decreased	decreased	shortened	No change	decreased	increased

Table 2

TMS parameters and treatment effects in Parkinson's disease and dystonia

	Inhibitory circuits in motor cortex: SICI, LICI & Silent period	**Sensorimotor integration: SAI and LAI**	**Sensorimotor plasticity: PAS protocol**
Parkinson's Disease			
Levodopa medications	SICI is reduced in OFF medication state, is corrected with levodopa[42] Silent period is prolonged by levodopa[15]	SAI is reduced with levodopa and LAI remains unaffected[45]	Levodopa challenge worsens LTD-like plasticity in PD and worsens LTP-like plasticity in non-dyskinetic motor fluctuators[50]
DBS surgery	STN DBS increases SICI and LICI[61]; whereas GPi DBS normalizes silent period[62] suggesting differential effects	SAI and LAI are corrected with both meds and STN DBS ON[64] SAI and LAI are corrected at six months and not one month[65]	
Dystonia			
Botulinium toxin injection	SICI is seen as corrected at the time of peak botulinium injection effect[97]	SAI and LAI stay unchanged with administration of botulinium toxin[97]	PAS effect is reduced at the time of peak toxin effects (one month)[97]
DBS surgery	SICI is found to be normalized as early as one month after DBS surgery[108]		PAS effects that are found as increased in dystonia are reduced when DBS is turned ON. Effects on PAS require about six months for showing correction[108]

SICI: Short interval intracortical inhibition; LICI: Long interval intracortical inhibition; SAI: Short latency afferent inhibition; LAI: Long latency afferent inhibition; PAS: paired associative stimulation; LTP: Long term potentiation; LTD: Long term depression