

Cortical excitability and neurology: insights into the pathophysiology

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Summary

Transcranial magnetic stimulation (TMS) is a technique developed to non-invasively investigate the integrity of human motor corticospinal tracts. Over the last three decades, the use of stimulation paradigms including single-pulse TMS, paired-pulse TMS, repetitive TMS, and integration with EEG and functional imaging have been developed to facilitate measurement of cortical excitability. Through the use of these protocols, TMS has evolved into an excellent tool for measuring cortical excitability. TMS has high sensitivity in detecting subtle changes in cortical excitability, and therefore it is also a good measure of disturbances associated with brain disorders. In this review, we appraise the current literature on cortical excitability studies using TMS in neurological disorders. We begin with a brief overview of current TMS measures and then show how these have added to our understanding of the underlying mechanisms of brain disorders.

KEY WORDS: cortical excitability, neurological disorders, transcranial magnetic stimulation

Introduction

Cortical excitability

The nervous system is a complex cellular network composed of as many as 10 billion neurons and 60 trillion synapses that mediate interneuronal communication. Each neuron can be regarded as a component in a com-

plex system of highly specialised, distinct neural circuits. Every aspect of behaviour, from primitive reflexes to abstract thinking and emotion, relies on the precision of the computational processes performed by these circuits, which in turn is critically dependent on healthy excitatory and inhibitory systems (1). These systems are facilitated by the interaction of neurotransmitters and cellular receptors to determine the level of neuronal excitability (excited or inhibited) either directly by controlling flow of ions through ion channels or through a complex cascade of intracellular interactions via secondary messengers. Excitation is mainly facilitated by the action of glutamate on N-methyl-d-aspartate (NMDA), and non-NMDA receptors, while inhibition is mainly mediated by the action of gamma-aminobutyric acid (GABA) on GABA_A and GABA_B receptors. The patterns of interneuronal connections and communication are not irrevocably fixed; they show variability and can be reorganized. Normally this plays a critical role in growth and development, and in learning and memory (2), however abnormal reorganization of brain circuits can also result in disturbed function and manifest as various neurological disorders (3-5).

Neurological disorders are associated with a high degree of disability, marked psychosocial problems and in some cases death. Despite the rapid advances made in the field, leading to improved control of many neurological disorders previously considered untreatable, a significant fraction remain difficult to manage. One of the main challenges hindering the development of more optimized therapeutic options for these patients is that the pathophysiological basis of many neurological disorders remains obscure. This is because the hypotheses developed to explain these disease rely on animal experimental studies. There is thus a huge need for a safe and non-invasive measure of neuronal functions *in vivo*, in order to achieve a better understanding of how they are altered in neurological disorders.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive, painless tool which can be used in humans to measure parameters of cortical excitability *in vivo* (6-8). TMS stimuli, delivered through a coil to selected scalp locations overlying the primary motor cortex, mainly activate pyramidal neurons transsynaptically. This produces indirect waves descending along the corticospinal fibres. Applied over the motor cortex this discharge can produce a twitch in a corresponding muscle. This muscle activity, referred to as a motor evoked potential (MEP), can be recorded on electromyography (EMG) from many muscles, including the small muscles of the hand (9). Similarly, stimulation over the occipital cortex leads to the perception of 'phosphenes' (flashes of light) which are reported by the subject under stimulation. TMS evokes action potentials in a local population of

neurons (6). Highly excitable neurons need to be stimulated less than depressed neurons in order to elicit muscle activity, or to induce the perception of phosphenes. Measurements made using TMS are dependent on small networks of interneurons (excitatory and inhibitory) and their synaptic interactions with each other (6). Thus, in the motor cortex, the stimulus required to produce a typical MEP reflects the global excitability/conductivity of cortical interneurons, fast corticospinal pathways, as well as spinal motoneurons (10). Varying the intensity of stimulation and using different stimulation paradigms can help probe these circuits separately, providing a number of different measures of cortical excitability. Hence TMS is uniquely able to obtain information about the state of excitability of neuronal circuits *in vivo* in the human brain, and has the potential to link information obtained experimentally (cellular, synaptic, small local networks) with clinical observations. This makes it an excellent tool for studying the pathophysiology underlying many neurological disorders (7,8).

Measures of cortical excitability probed using TMS

TMS was initially used in evaluation of the integrity of the corticospinal tract in humans through conductivity studies (11). It was then progressively applied to the measurement of the excitatory and inhibitory properties of the primary motor cortex itself. There are several physiological protocols utilizing the two broad classes of TMS paradigms: single- or paired-pulse TMS and repetitive TMS (rTMS). The stimulation paradigms used in neurological disorders to date and their pathophysiological significance are summarized in table 1 and figure 1 (over). These parameters have disclosed various defects in cortical excitability associated with these disorders as discussed below.

Safety

The only absolute contraindication for TMS/rTMS is the presence of metallic hardware (such as cochlear implants, an internal pulse generator or medication pumps) in close contact with the discharging coil. In such instances there is a risk of inducing malfunction of such implanted devices (45). Single- and paired-pulse TMS are generally considered to be safe even in patients with epilepsy (46), where the crude risk of a TMS-associated seizure ranges from 0.0 to 2.8% for single-pulse TMS and from 0.0 to 3.6% for paired-pulse TMS. With respect to rTMS, the current safety guidelines stipulate that in high risk patients the risk/benefit ratio should be weighed for the patient before each study (45). These include patients with conditions like epilepsy or stroke and those receiving medications that lower seizure threshold.

Cortical excitability in neurological disorders

Epilepsy

The epilepsies are a complex group of syndromes characterized by episodic brain dysfunction manifesting as

the occurrence of recurrent seizures (47). Epilepsy syndromes can be broadly classified into two main types: generalized, which mainly include idiopathic generalized epilepsy (IGE), and focal. IGE, as a group, is believed to have a strong underlying genetic basis (48), while focal epilepsies are mostly considered to be due to an underlying focal pathology, such as hippocampal sclerosis or an area of cortical dysgenesis (48), although a genetic basis is thought to underlie some focal epilepsy syndromes (49). Regardless of the type or cause, the proposed underlying mechanism for the epileptic process (based on animal and experimental data) is that it is mediated by a disturbance in the neuronal excitatory/inhibitory balance leading to the formation of hyperexcitable seizure networks (50). How this disturbance comes about (increased excitation, decreased inhibition or both) remains elusive. From this perspective, TMS studies in epilepsy have been very helpful. Results of TMS studies in epilepsy are summarized in table 2 (over). While findings vary somewhat between studies, and likely reflect subject and methodology differences, predominantly in terms of medication and timing of studies, overall, cortical hyperexcitability resulting from defective inhibitory mechanisms seems to be a common feature in most types of epilepsy. It also seems that the alterations occurring within intracortical inhibitory circuits depend on the type of epilepsy, the underlying aetiology, and the site of the epileptic focus. Furthermore, these changes have been found to vary with menstrual cycle (51,52), time of day (53), sleep (54) and sleep deprivation (55,56), suggesting that neuromodulatory transmitters and hormones act at the level of local neuronal network interactions. Alterations in cortical excitability have also been observed for 24 (57) and even up to 48 hours (58) before and after (59) seizures, providing direct evidence of prolonged peri-ictal changes within intracortical circuits.

Cortical excitability changes associated with epilepsy are also influenced by treatment, with reports of reduction of the baseline hyperexcitability after starting antiepileptic medication (60-65). One study also noted that reduction in cortical excitability to normal or near normal values only occurs in patients who become seizure-free, but not those who continue to have seizures (66). Effects were similar irrespective of the specific antiepileptic drug used. This suggests that despite what is known about the mechanisms of action of each drug, i.e. whether it works on specific channels or receptors, a common effect of anticonvulsants possibly occurs at the level of interneuronal interactions, and these interactions are complex. Patients who continued to have seizures showed evidence of progressive changes in hyperexcitability onset (67). These changes possibly reflect altered receptor properties or disturbed receptor interactions within the inhibitory intracortical circuits, which could be the result of the seizures or may reflect the course of other undefined epiphenomena contributing to the development of pharmaco-resistance. This was reversed with successful epilepsy surgery (68-70), treatment with vagal nerve stimulation (71), continuous anterior thalamic deep brain stimulation (72), and after multiple subpial transection in a single patient with unilateral cortical dysgenesis (73).

Table 1 - Summary of TMS paradigms used to date in neurological disorders with their pathophysiological significance.

Measure	Parameter	Definition	Pathophysiology
A. Membrane excitability	Motor threshold	Minimum level of a given stimulus required to produce a defined response (12).	Membrane excitability of cortical interneurons and reflects conductivity of ion (predominantly sodium) channels (13-15).
B. Corticospinal projections	MEP recruitment curves	Stimulus/response curves obtained by recording the size of MEP produced with TMS at a single site using a range of intensities.	Reflects changes in the GABA-ergic and monoaminergic systems as well as sodium and calcium channel properties (16).
C. Intracortical circuits	I. Cortical silent period	Period of electromyographic silence that occurs after the MEP when TMS is delivered to the motor cortex during a forceful muscle contraction.	Later part most likely mediated by GABA _B inhibitory mechanisms (17-21).
	II. Paired-pulse paradigms are used to investigate the cellular mechanisms underlying different forms of intracortical inhibition and facilitation (22). They involve a conditioning stimulus which precedes a test stimulus by a number of interstimulus intervals.		
	1. Intracortical inhibition and facilitation	<ul style="list-style-type: none"> • Short-interval intracortical inhibition: at ISIs of 1-6 ms. • Intracortical facilitation: at ISIs of 8-30 ms. • Long-interval intracortical inhibition: at ISIs of about 100-400 ms. 	<ul style="list-style-type: none"> • Most likely GABA_A receptor-mediated inhibition (23-26). • Possibly via excitatory glutamate-mediated interneuronal circuits (24, 26-28), although a role for GABA_A has also been suggested (29). • Most likely mediated by slow inhibitory post-synaptic potentials activated via GABA_B circuits (15, 30-32).
	2. Transcallosal inhibition	The relationship between the two motor cortices can be studied by paired-pulse TMS at both motor cortices (33,34).	Inter-hemispheric inhibition thought to be mediated through excitatory axons that cross the corpus callosum to act on local inhibitory (mainly GABA _B -mediated) neurons in the contralateral motor cortex (35).
D. Neuroplasticity changes	3. Short-latency afferent inhibition	Afferent sensory input through stimulation of the median nerve at the wrist or cutaneous fibres at the index finger can modify the excitability of the motor cortex with a complex time course (36).	Thought to be regulated by muscarinic and cholinergic cerebral circuits (36,37).
	RepetitiveTMS	<p>Can be used to induce sustained changes in excitability (synaptic efficacy) that significantly outlast the stimulation period.</p> <p>Low-frequency stimulation results in depression of the target brain area, while high-frequency stimulation induces facilitation of the region (38). Theta burst stimulation is a high-frequency stimulation paradigm that can produce either inhibitory (if applied continuously) or facilitatory (if applied intermittently) effects (39).</p>	Effects are due to mechanisms similar to the long-term potentiation and long-term depression effects elicited in animal models by low- and high-frequency electrical stimulation, respectively (38). These effects are thought to be predominantly mediated by NMDA receptors (39,40) as well as by modulation of GABA receptor functions (41).
	E. Corticocortical connectivity	I. TMS and EEG	<p>TMS-evoked surface potentials from any cortical region can be recorded with scalp EEG electrodes and used to estimate regional excitability of the extra-motor cortex (42,43).</p> <p>This increases spatial benefits and also the very high temporal resolution of EEG makes it possible to detect differential effects of brain disturbance on TMS-induced responses.</p>
II. TMS and fMRI		<p>Combining TMS and fMRI makes it possible to exploit both the good spatial resolution (can identify changes that occur in both cortical and subcortical structures) and the good temporal resolution of TMS.</p> <p>Such data can provide information on connectivity patterns. These patterns reflect the propagation of activity in the stimulated area to distal areas via neural connections (44).</p>	

Abbreviations: EEG=electroencephalography; GABA=gamma (γ)-aminobutyric acid; ISI=interstimulus interval; MEP=motor evoked potential; NMDA=N-methyl-d-aspartate; TMS=transcranial magnetic stimulation.

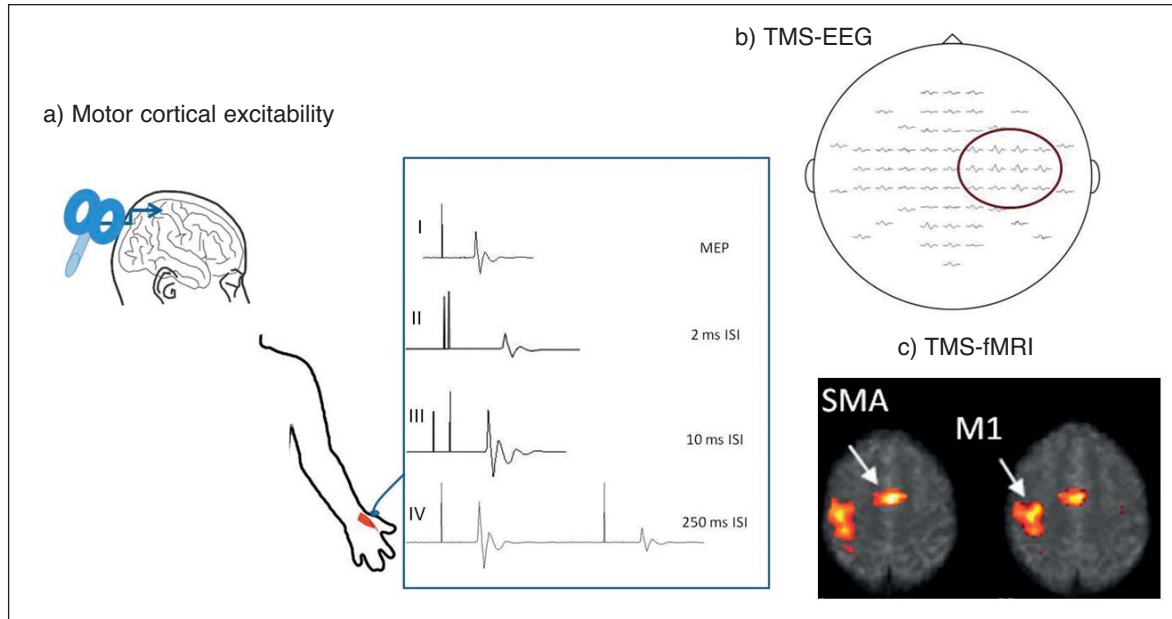


Figure 1 - Schematic representation of the different parameters measured using TMS.

a) Motor cortical excitability showing (I) motor evoked potential (MEP) recorded with a single pulse. Latency is measured from stimulus artefact to initial deflection in baseline; amplitude is measured peak to peak. Examples of (II) short-interval intracortical inhibition at the 2 ms interstimulus interval (ISI), (III) intracortical facilitation at the 10 ms ISI and (IV) long-interval intracortical inhibition at the 250 ms ISI.

b) Averaged EEG responses evoked by TMS. The signals are arranged according to the layout of the electrodes. The amplitudes of the responses are highest in the vicinity of the stimulated site (highlighted) and attenuate with increasing distance from stimulation.

c) Sample of a connectivity map obtained after rTMS of the right motor area on fMRI. SPMs are thresholded for corrected clusters ($p < 0.05$ corrected for multiple comparisons) and are superimposed on the mean EPI image. M1= motor area; SMA=supplementary motor area.

Stroke

Ipsilateral MEPs are rarely recorded in healthy subjects at rest. It is thus intriguing that one of the early findings in stroke patients was the presence of ipsilateral MEPs in the paretic limb (95-98). This finding also seemed to correlate with other measures of increased excitability in the unaffected hemisphere (99-101). Cortical silent period (CSP) duration was prolonged in the affected hemisphere after subcortical stroke (102,103), except in patients with post-stroke movement disorder or epilepsy (104). In contrast, short interval intracortical inhibition (SICI) was reduced in the affected hemisphere in the acute phase of a motor cortical stroke (103,105-107) and remained decreased thereafter, regardless of functional recovery. SICI was also reduced in parietal-motor circuits in the intact hemisphere in patients with neglect following stroke compared to patients without neglect and normal controls (108). Also in the unaffected hemisphere, SICI was usually initially reduced, but subsequently returned to normal values (109,110) or even became enhanced compared to the affected hemisphere in patients with good recovery (106,111). This suggests that in the early phases following a stroke, increased intracortical inhibition leads to reduced activity in the unaffected hemisphere, resulting in increased activity of the affected hemisphere, thereby promoting recovery. Further support for this comes from reports of loss of transcallosal inhibition from the affected to the unaffected

hemisphere in acute cortical stroke (107,109,112), which would increase the excitability of the unaffected hemisphere. There are also reports of increased transcallosal inhibition from the unaffected to the affected hemisphere just before movement onset in the paretic limb in patients with chronic stroke (113,114). A recent study used dynamic causal modelling to assess effective connectivity in the motor system before and after rTMS of the contralesional motor area in stroke patients (115). The authors reported reduced transcallosal connectivity between homologous parts of the motor area during motor task performance and enhanced intrinsic connectivity between the motor area in the affected hemisphere and the supplementary motor area. These changes in connectivity were accompanied by, and possibly responsible for, an improvement in motor performance, providing evidence of cerebral reorganization following stroke. Thus, the changes in cortical excitability following stroke appear to occur bilaterally, although the pattern seems to correlate with lesion location and stage of recovery.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of the motor neurons that results in progressive paresis of limb, bulbar and respiratory muscles (116). The mechanisms underlying motor neuron degeneration in ALS remain elusive, although

Table 2 - Summary of interictal TMS findings in patients with epilepsy.

TMS measure	Generalized epilepsy	Focal epilepsy
Motor threshold	<ul style="list-style-type: none"> Decreased in subsets of untreated patients (63,74) Normal in drug-naive patients (56,66,75-78) and those on medication (79-81). Decreased in patients on the side contralateral to the side of version in treated IGE patients with versive seizures (all taking medication). 	<ul style="list-style-type: none"> Increased in the hemisphere with the epileptic focus compared to the non-affected hemisphere in untreated patients with focal epilepsy originating outside the primary motor area (66,75). Inter-hemispheric difference in a patient with motor focal epilepsy and cortical myoclonus originating from the motor cortex (82). No difference compared to controls in drug naïve patients (75,83) or those who discontinued medication at least 48 hours before the TMS study (84). Increased in patients with chronic epilepsy on multiple anticonvulsants (85-88).
Cortical silent period	<ul style="list-style-type: none"> Prolonged in some untreated patients with IGE (77,89). Normal in other groups of untreated patients with IGE (75,78) as well as in treated patients with juvenile and progressive myoclonic epilepsy (80,81). 	<ul style="list-style-type: none"> Shortened on the affected side in patients with focal motor epilepsy and cortical myoclonus originating from the motor cortex (82) and primary motor cortical dysgenesis (73). Prolonged on the affected side in patients with focal epilepsy associated with cortical dysgenesis outside the primary motor cortex (90) and another group with different focal epilepsy syndromes taking medication (88). Shortened in the hemisphere with the focus compared to the non-affected side in a study including patients with focal epilepsy outside the motor cortex (on medication) (85). Ipsilesionally shortened in patients with primary motor area lesions; prolonged in non-motor cortical lesions (91). Bilaterally prolonged in treated patients with focal epilepsy associated with unilateral clonic movements (87). No changes between the affected and non-affected in un-medicated patients with temporal and extra-temporal epilepsy (75,84) or compared to controls (75,78,84).
Intracortical inhibition and facilitation	<ul style="list-style-type: none"> Reduced SICI compared to controls both drug-naïve (75,80,92) and on treatment (80); most marked with progressive myoclonic epilepsy (79,92). Increased SICI in two treated patients (93). Marked reduction in LICl in different cohorts with untreated IGE (56,66,75,76) as well as treated progressive myoclonic epilepsy (79,81). No difference in LICl compared to controls in a cohort with juvenile myoclonic epilepsy (majority on medication) (80). No changes in ICF in any of the studies. 	<ul style="list-style-type: none"> Reduced SICI in the affected compared to non-affected hemisphere and controls in patients with untreated focal epilepsy not involving the primary motor area (56,66,75,83). No change in SICI in treated patients (84,85). Substantially defective SICI and excess ICF in patients with cryptogenic focal epilepsy on medication with a higher seizure frequency and a higher proportion of interictal generalized epileptic discharges on EEG (86). Decreased LICl only in the affected hemisphere in patients with untreated focal epilepsy (56,66,75). Reduced ICF in both hemispheres (84).
TMS-EEG		<ul style="list-style-type: none"> TMS-induced activation at various scalp sites elicited a late phase response in a majority of patients that was absent in healthy subjects (94). Abnormalities were detected in some epilepsy patients where interictal EEG records were normal.

Abbreviations: EEG=electroencephalography; IGE=idiopathic generalized epilepsy; ICF=intracortical facilitation; LICl=long-interval intracortical inhibition; SICI=short-interval intracortical inhibition; TMS=transcranial magnetic stimulation.

cortical hyperexcitability has been proposed as a possible mechanism (117). One of the hypotheses linked to this concept is a “dying forward” hypothesis whereby corticomotoneurons mediate anterograde degeneration of anterior horn cells via glutamate-mediated excitotoxicity (118). Many TMS studies reported an increased motor threshold (MT) in patients with ALS (119-128). Some found that MEPs could not even be elicited in some of their patients. Conversely, many other studies found a decreased MT (129-132). The reason for this discrepancy is not entirely clear. Because some investigators (133), but not others (134), have observed that MT correlates with disease duration and increases with disease progression (122,124,135,136), it has been suggested that a normal (or even reduced) MT early in the course of illness is consistent with an early phase of cortical hyperexcitability and glutamate-induced excitatory neurotoxicity (130,133). In support of this, several studies report reduction in the duration of the CSP (122,124,136-139), particularly early in the course of the illness (136,137). In addition, decreased SICI has also been demonstrated in ALS using conventional paired-pulse TMS (139-142) as well as using the threshold tracking paired-pulse paradigm. This paradigm in particular consistently showed reduced SICI across different levels of conditioning stimuli (143-146). The change was more prominent in patients with less severe symptoms studied early on but was also seen in advanced cases (143). It was also frequently accompanied by reduced MT, increased MEP recruitment, and shortened CSP (143,145). These findings all indicate increased cortical excitability. The authors postulated that SICI reduction in ALS represents degeneration of inhibitory intracortical circuits, combined with excessive excitation of high-threshold excitatory pathways (146). Interestingly, similar TMS paradigms were all found to be normal in spinobulbar muscular atrophy (Kennedy’s disease), a disorder that clinically may “mimic” ALS, suggesting a lack of significant cortical involvement in this disease (144).

Dementia

Dementia is defined as a serious loss of cognitive ability in a previously unimpaired person, beyond what might be expected from normal aging. Alzheimer’s disease (AD) is the most common form of dementia (147). One of the prevailing theories regarding the cause of AD-related brain degeneration is the amyloid hypothesis, which suggests that accumulation of beta amyloid peptides triggers neuron degeneration through disruption of calcium ion homeostasis (148). The MT was reported to decrease in patients with AD (149) and also a slight and variable reduction in SICI has been observed in some studies (149-151), suggesting hyperexcitability, which in turn suggests reduced inhibition. This seems to be contradicted by the reportedly normal SICI in another study (152), however, TMS-evoked P30 amplitude was reduced in AD subjects in a combined TMS-EEG study (153). This reduction was prominent in the temporo-parietal area, ipsilateral to the stimulation side as well as in the contralateral fronto-central cortex corresponding to the sensorimotor area. P30 is also thought to reflect GABA_A mediated activity (154), and thus reduction in its amplitude would support defective inhibition. TMS studies also suggest a cholinergic deficit in AD given that the

abnormality most commonly reported in these patients is found in short latency afferent inhibition (SAI) (149,150,155). This is supported by the report of abnormal SAI in dementia with Lewy bodies (a form of dementia that responds to cholinergic medications) (156) and normal SAI in frontotemporal dementia (157), a non-cholinergic form of dementia.

Migraine

Migraine is a common medical disorder that has multiple phenotypes with complex and poorly understood underlying mechanisms (158,159). Many hypotheses exist. Among these, disturbances in neurotransmitters, especially calcitonin gene-related peptide and serotonin (160), channelopathies (familial hemiplegic migraine) (161), and cortical spreading depression with subsequent release of inflammatory mediators (162) are the most widely accepted, however, the nature of the underlying pathogenesis remains to be clarified. An increased MT was reported in some migraine studies (163-167) but not in others (168,169), a discrepancy that could be due to differences within the cohorts studied. In patients with migraine with or without aura, shortened CSP was found in the hand muscles (170) as well as facial muscles (171) suggesting defective inhibition. But other studies found a normal CSP (163,167,168,172) and one study even found a prolonged CSP in patients with chronic migraine (172). In patients with migraine with or without aura, SICI tested between attacks was normal in one study (163) and ICF was increased in another (165), whereas in another group of migraineurs with aura SICI was decreased with normal intracortical facilitation (ICF) (173). Long-interval intracortical inhibition (LICI) was investigated in only one study that compared patients with and without aura to controls and patients with new-onset epilepsy (174). The authors found that the pattern of reduced LICI in migraine was very similar to that seen in epilepsy, although of much smaller magnitude. This provides more evidence supporting an overlap between the two paroxysmal disorders. Nevertheless, there is a marked variability in the overall results, which seems to suggest that motor cortical excitability measures are highly dependent on the type of migraine studied and on the stage of illness. In view of this and because of the high prevalence of visual symptoms associated with migraine, many authors chose to study occipital cortical excitability instead. Some of these studies found evidence of occipital cortical hyperexcitability, in particular in migraine with aura, as suggested by reduced threshold for occipital TMS to induce phosphenes in migraineurs (168,175-178) using single or paired pulses. However, other authors found that this threshold was increased in the interictal period (169) or showed increased variability over time (179). Therefore, while there is some evidence to support motor and visual hyperexcitability probably due to decreased inhibition, this remains to be confirmed.

Movement disorders

DYSTONIA

Dystonia is a disorder characterized by sustained muscle contractions causing twisting and repetitive movements or abnormal postures. The disorder may be ge-

netically determined (primary dystonia) or caused by other factors such as birth-related or other physical trauma, infection, or reaction to pharmaceutical drugs, particularly neuroleptics. It can be localized to a certain group of muscles or can be generalized (180). The precise mechanism is not known, although primary dystonia is suspected to be caused by decreased activity within GABA-ergic circuits including those in the basal ganglia and Purkinje neurons (181). An interplay with environmental conditions is also thought to play a role especially in focal dystonia brought on after trauma, or induced by certain movements or drugs.

A shortened CSP was observed in patients with dystonia involving hand (182) and facial muscles (183). This did not normalize with botulinum toxin injection (184). The CSP was even shorter when the dystonia affected upper and lower facial muscles concurrently than when it affected either alone (183). These findings are consistent with cortical hyperexcitability due to decreased GABA-ergic inhibition. Further evidence of decreased inhibition comes from the reports of reduction in both task-specific (185) and rest (186,187) SICI in patients with upper limb dystonia. SICI was also decreased in DOPA-responsive dystonia (188) and in asymptomatic carriers of the DYT1 gene mutation (one of the genetic abnormalities associated with dystonia) (189). There was also a report of decreased active LICI in patients with writer's cramp (190), although in another study increased LICI was found using a slightly different paradigm in patients with different types of dystonia (191). Intracortical facilitation on the other hand was found to be normal or slightly increased in patients with dystonia (192). Moreover, decreased SICI was not site-specific and was observed on both the affected and unaffected sides in patients with focal arm dystonia (186), as well as in hand muscles in patients with cervical dystonia (193) and blepharospasm (192). This suggests that the disturbance of inhibitory circuits and the resultant hyperexcitability is not restricted to the circuits clinically affected by the disorder. Support for this comes from evidence of enhanced TMS-induced plasticity changes in focal dystonia even in patients who show no dystonic symptoms in the hand on paired associative studies (194,195) and in patients compared to controls in a continuous theta burst stimulation study (196). There is evidence that this abnormality in SICI is transiently restored with botulinum toxin injection in the dystonic muscles (187), but this was not found in another study in patients with pure writer's cramp (197).

PARKINSONIAN DISORDERS

Parkinsonism refers to a group of neurological disorders characterized by tremor, hypokinesia, rigidity, and postural instability (198). While the neurodegenerative condition Parkinson's disease (PD) is the most common cause of parkinsonism, a wide range of other aetiologies can lead to a similar set of symptoms (199). PD is a degenerative disorder that results from the death of dopaminergic cells in the substantia nigra (midbrain) for an unknown reason. One of the theories proposed to explain the symptoms associated with PD relates to the brainstem-basal ganglia-motor systems (200). Dopaminergic circuits are important for the action of the basal ganglia, which normally exert a constant in-

hibitory influence on the motor systems. This prevents the motor systems from becoming active at inappropriate times. When a decision is made to perform a particular action, inhibition of the required motor system is reduced, thereby releasing it for activation. Dopamine acts to facilitate this release of inhibition, and thus the net effect of dopamine depletion is to produce hypokinesia. Progressive supra-nuclear palsy is also a degenerative disorder which in its early stages can be mistaken for PD, however later on patients develop difficulty swallowing, ophthalmoparesis especially with vertical gaze, and dementia (201). Multiple system atrophy is another degenerative disorder associated with parkinsonian symptoms together with disturbances in balance and autonomic functions (202). Decreased MT and increased MEP recruitment were found in early- and late-stage patients with PD (203). When these patients were re-studied after proper therapy, the MT was found to have increased in early-stage patients but still remained lower than in normal controls. The CSP was also found to be shorter in patients with PD (203,204) especially at high stimulation intensities (205,206); while this finding supports disturbances within inhibitory circuits, it could also reflect defective dopaminergic circuits, as the CSP was shown to become prolonged following dopaminergic medications (207) as well as surgical lesions of the internal globus pallidus (208,209). In addition, the CSP became longer in early-stage patients after therapy (203) and was found to be more prolonged in patients with PD studied while on dopaminergic medications, compared to controls (210,211). Trains of subthreshold 5-Hz rTMS over the primary motor hand area resulted in prolongation of the CSP (206). This effect could be influenced by dopaminergic circuits as rTMS of the motor area has been shown to induce dopamine release in the striate nucleus (212). Furthermore, the fact that the absence of this effect was not seen in controls suggests that PD patients may be particularly susceptible to modulatory effects of rTMS on intracortical inhibition. Paired-pulse TMS also provides evidence of defective intracortical inhibition. SICI decreased when measured during rest, showing a subsequent improvement with dopaminergic medications (210), deep brain stimulation of the subthalamic nucleus (213) or low-frequency rTMS over the motor cortex (214). Of note, active SICI remained unchanged (211,215), which is interesting considering the static nature of tremor associated with PD. LICI was reported to increase, with subsequent normalization following dopaminergic medications in one study (215). Conversely, decreased LICI, which also normalized in response to dopaminergic medications, was reported in another (216). Some studies observed decreased ICF in advanced PD patients denoting hypo-activity within excitatory circuits (214,217,218). These data suggest impairment of intracortical inhibitory and perhaps even facilitatory circuits. The pattern of this, however, seems to be strongly modulated by the dopaminergic system. There is also a suggestion of changes in cholinergic circuits, whose pattern varies between the different parkinsonian disorders. In PD, SAI was found to be normal in patients off medications but administration of dopaminergic medication led to reduced SAI (219). In a study that included PD patients with dementia, SAI was found to be increased whereas patients with progressive supra-nuclear palsy showed normal SAI (220). In con-

trast, patients with multiple system atrophy with parkinsonian features showed reduced SAI (221).

HUNTINGTON DISEASE

Huntington disease (HD) is a neurodegenerative genetic disorder that affects muscle coordination and leads to cognitive decline and dementia. It is the most common genetic cause of chorea. Damage mainly occurs in the striatum, but as the disease progresses, other areas of the brain are also significantly affected (222). One of the proposed mechanisms underlying this is increased excitatory output. The CSP was slightly shortened in one study on patients with HD (223) and found to be prolonged and variable in two others (224,225). This difference may be partly explained by the clinical form of HD (224) and the technique used to collect CSP traces (225). The results of the small number of studies that used paired-pulse TMS in HD were also inconsistent: whereas some studies found reduced SICl and LICl (224,226), others did not find any abnormalities (227,228). ICF was found to be normal or slightly increased in patients with HD (226). Thus the limited data available point to disturbances within excitatory circuits leading to minimal hyperexcitability; however this needs to be confirmed in further studies and larger cohorts.

TOURETTE SYNDROME

Tourette syndrome is a childhood-onset neuropsychiatric disorder characterized by involuntary movements or vocalizations known as tics. Tics are typically reduced during task performance and concentration. Genetic and environmental factors play a role in the aetiology but the exact causes and pathophysiology are unknown. Cortical disinhibition has been proposed as a possible mechanism specifically within basal ganglia-thalamocortical circuits (229). The MT was reportedly similar in patients and in controls while in the resting state, whereas MEP recruitment was found to be more gradual in patients compared to controls (230). With pre-activation, similar recruitment of MEPs and CSP were found in patients and controls. This suggests that the distribution of excitability in the corticospinal system in patients at rest is different to that in healthy individuals (230). In addition, SICl was reduced with no difference in MEP amplitude and ICF at rest, while there was a subsequent increase in MEP amplitude in the pre-movement phase (231). SICl was reduced in these patients in the early phase of movement preparation (similar to rest) followed by a transition towards more inhibition. Subsequently modulation of SICl was comparable to controls, while MEP recruitment was reduced in later phases of movement preparation. These data suggest defective inhibition in Tourette syndrome. It also appears that early during movement preparation, patients start from an abnormally decreased level of SICl and show a subsequent modulation of inhibitory activity to become similar to healthy controls. This suggests that reduced cortical inhibition is one of the factors contributing to the difficulty that patients have in suppressing involuntary tics. Then, during motor performance, motor cortical excitability most likely underlies top-down control from higher motor areas and the prefrontal cortex, which overrides these abnormal subcortical inputs to guarantee adequate be-

havioural performance (231). SAI was also reduced in patients suggesting impaired activity within cholinergic circuits. This is supported by the report of a single dose of nicotine abolishing the difference between patients and controls in SICl and SAI, with no effect on MT (232).

TREMOR

Essential tremor (ET) is a slowly progressive neurological disorder whose most recognizable feature is a tremor of the arms that is apparent during voluntary movements (233). The underlying mechanism is not clear but there is some suggestion that it may be related to defective inhibition particularly in cerebellar cells (234). SICl was reduced in patients with ET and this correlated with motor hyperactivity (235). On the other hand, patients with primary writing tremor were found to have normal SICl and LICl (236). The CSP was normal in all types of tremor, but shortened in cortical myoclonus (82,237). Thus while further studies are needed, there seems to be some evidence supporting defective inhibition in ET but not other forms of tremor.

CEREBELLAR DISEASES

While the cerebellum does not serve to initiate most movement, it does interact with areas of the brain that do (238). In doing so, the cerebellum promotes the synchronicity and accuracy of movement required for purposeful motor activity. The main clinical features of cerebellar disorders include incoordination and imbalance. The MT was increased in the contralateral motor cortex in patients with cerebellar damage (239-241). SICl was found to be either normal (242) or increased together with reduced ICF (243-246) in cerebellar ataxia. Interestingly, reduced ICF was also found in patients with inherited spinocerebellar ataxia, specifically types 2 and 3 (244), suggesting a role for genetic properties in influencing the pattern of change in cortical excitability. Increased SICl and reduced ICF were also observed in patients with cerebellar stroke of the superior or the inferior cerebellar artery territories (247). In addition, the CSP was found to be prolonged in patients with cerebellar disease (248-250). Taken together, these results suggest that cerebellar diseases are associated with excessive inhibition and possibly also defective excitation within intracortical motor circuits resulting in *reduction* in motor cortical excitability.

Concluding remarks

A variety of TMS methods are now available to study cortical excitability changes associated with various neurological disorders. While the yield of these methods is much greater in disorders such as epilepsy, ALS, dystonia and stroke, than in others, TMS has provided some important and insightful *in vivo* inferences on the mechanisms underlying many neurological disorders. It is likely that studies including more homogenous cohorts and implementing more rigorous study designs and standardized stimulation paradigms will overcome the controversial findings in some of the reports and thus provide more conclusive inferences into even more neurological disorders. Neurophysiological interactions

within complex interconnected neuronal networks will also be amenable to further testing with the integration of TMS with EEG and neuroimaging techniques. This holds great promise for addressing more research questions and eventually for the translation of this knowledge into clinical practice.

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