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Title

Interrogating cortical function with transcranial magnetic stimulation: Insights from neurodegenerative disease and stroke

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Review

Authors

Smriti Agarwal[1], Giacomo Koch[2] Argye E Hillis[3], William Huynh[1], Nick S Ward[4], Steve Vucic[5], Matthew C Kiernan[1]

1. Brain and Mind Centre, University of Sydney, and Institute of Clinical Neurosciences, Royal Prince Alfred Hospital Sydney NSW 2050, Australia
2. Non-Invasive Brain Stimulation Unit, Neurologia Clinica e Comportamentale, Fondazione Santa Lucia IRCCS, Rome, Italy; Stroke Unit, Department of Neuroscience, Policlinico Tor Vergata, Viale Oxford 81, 00133, Rome, Italy.
3. Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, 21287, USA; Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD, 21224, USA; Cognitive Science, Johns Hopkins University, Baltimore, MD, 21218, USA.
4. Sobell Department of Motor Neuroscience, UCL Institute of Neurology, University College London, 33 Queen Square, London WC1N 3BG, UK; The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK; UCLPartners Centre for Neurorehabilitation, UCL Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK.
5. Westmead Clinical School, University of Sydney, Sydney 2006, Australia

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Corresponding author:

Smriti Agarwal
Visiting research fellow

ForeFront | Kiernan Group
The University of Sydney
Brain and Mind Centre, Room 416
Level 4, M02F, 94 Mallett Street Camperdown NSW 2050
T +61 (2) 9114 4258
F: +61 (2) 9114 4254
E: smriti.agarwal@cantab.net

Abstract

Transcranial magnetic stimulation (TMS) is an accessible, non-invasive technique to study cortical function in vivo. TMS studies have provided important pathophysiological insights across a range of neurodegenerative disorders and enhanced our understanding of brain reorganisation after stroke. In neurodegenerative disease, TMS has provided novel insights into the function of cortical output cells and the related intracortical interneuronal networks. Characterisation of cortical hyperexcitability in amyotrophic lateral sclerosis and altered motor cortical function in frontotemporal dementia, demonstration of cholinergic deficits in Alzheimer's disease and Parkinson's disease are key examples where TMS has led to advances in understanding of disease pathophysiology and potential mechanisms of propagation,, with the potential for diagnostic applications. In stroke, TMS methodology has facilitated the understanding of cortical reorganisation that underlie functional recovery. These insights are critical to the development of effective and targeted rehabilitation strategies in stroke. The present Review will provide an overview of cortical function measures obtained using TMS and how such measures may provide insight into brain function. Through an improved understanding of cortical function across a range of neurodegenerative disorders, and identification of changes in neural structure and function associated with stroke that underlie clinical recovery, more targeted therapeutic approaches may now be developed in an evolving era of precision medicine.

Introduction

The ability to modify human brain function is a long held scientific aspiration. Centuries ago, cognitive neuroscientists used torpedo fish and eels to electrically stimulate the brain, while more conventional electricity was first used for brain stimulation in the 18th century. It was only three decades ago that Pat Merton and colleagues [1] achieved electrical stimulation of the motor cortex through the intact scalp to generate a relatively synchronous muscle response. One of the issues with this methodology of transcranial electrical stimulation (TES), however, was the stimulation of pain fibres on the scalp. Subsequently, Barker and his team [2] became the first to use magnetic stimulation (TMS) in the human brain to achieve simultaneous muscle activity. Over 18000 scientific publications relating to TMS have appeared (http://www.webofknowledge.com, topic = “transcranial magnetic stimulation” search) since Barker’s first description, with over a third of these in the last 5 years alone, indicative of the pace at which the field is moving forward.

The aim of the present Review is to provide the clinician with an overview of physiological considerations involved with TMS, including cortical output measures that provide important information regarding pathophysiological alterations in neurodegenerative disorders and post stroke reorganisation of neural structure and function. This Review aims to provide an overview of TMS applications and their utility in providing a functional understanding of disease mechanisms and the potential for development of novel diagnostic and prognostic tools in neurological disease.

Measures of cortical function

TMS induces current flows in the brain by application of a pulsed magnetic field leading to depolarisation of the underlying cortical neurons (Figure 1). The resultant electrical activity in the brain can be modified by the shape and orientation of the coil used, combined with underlying neuronal anatomy and orientation relative to the coil, magnetic pulse wave form, intensity, frequency and pattern of stimulation [3-6].

The precise nature of the neuronal circuitry activated by TMS remains incompletely understood. Applying TMS over the motor cortex (Figure 2), generates a corticomotor neuronal volleys which may be a result of direct excitation of cortical

neurons (Direct or D-waves) or trans synaptic excitation (Indirect or I-waves). The I-waves are thought to originate through a complex interaction between cortical output cells (Betz cells, layer V) and interneuronal cells [3,7-9].

Following a brief overview of TMS output measures, their application as potential diagnostic and prognostic markers will be further considered.

A widely used experimental paradigm involves application of TMS to the motor cortex with recording electrodes placed over an intrinsic hand muscle in the contralateral limb (Figure 2). The resultant motor-evoked potential (MEP) on electromyography (EMG) is typically recorded from the abductor pollicis brevis (APB), abductor digiti minimi (ADM) or the first dorsal interosseous (FDI) muscle. This paradigm can be applied to quantity excitability characteristics of the underlying motor cortex.

Motor Threshold (MT) indicates the ease with which motor cortex output cells and corticomotor neurons can be excited. MT is thought to reflect the density of corticomotor neuronal projections onto the anterior horn cells. It thus, follows, that MTs tend to be lower in the dominant hand [10] and correlate with the performance of fine motor tasks [11]. MTs have the potential of providing a biomarker of cortical neuronal membrane excitability. Voltage gated sodium channels are critical to cortical axon excitability [12] while excitatory synaptic neurotransmission in the neocortex is mediated by the glutaminergic alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors [13]. Thus voltage gated sodium channel blocking drugs increase MT [14,15] while glutaminergic agonists decrease it [16]. Interestingly, neuromodulatory agents affecting GABA, dopaminergic, noradrenergic and cholinergic systems, do not affect the motor threshold [17].

MT was initially defined as the minimum stimulation intensity (% maximum stimulator output) required to achieve an MEP response of (amplitude >50 μV) in the target muscle in 50% of stimulus trials [18]. Evolving studies in threshold tracking TMS have led to redefinition of the MT as stimulus required to achieve and maintain a target MEP response of 0.2mV (± 20 %) [19,20]. MT tends to be lower in a voluntarily contracting muscle (active motor threshold, AMT) when compared to that in a muscle at rest (resting motor threshold, RMT) [21].

Single Pulse TMS measures

Motor Evoked Potential (MEP) amplitude represents summation of descending corticospinal volleys onto motor neurons comprising of direct (D) and indirect (I) waves on to the spinal motor neurons [22,23]. Increasing MEP amplitude with increase in stimulus intensity generates a sigmoid stimulus response curve [21]. MEP may be represented as a percentage of peripheral stimulation derived compound muscle action potential (CMAP), to account for the lower motor neuron contribution.

Although, the MEP reflects the density of corticomotor neuronal projections onto motor neurons similar to the MT, [24], the neurotransmitter pathways involved in the generation of the MEP are different. GABAergic agents acting via the $GABA_A$ receptor suppress the MEP while glutaminergic and noradrenergic agents increase the MEP amplitude [25,26].

The main limitation in utilising the MEP response as a biomarker of cortical motor neuronal function is the significant intersubject and intertrial variability in MEP latency and amplitude [27].

Central Motor Conduction Time (CMCT) is a measure of the time taken by a neural impulse to travel from the motor cortex to stimulate the spinal or bulbar motor neuron, and thus, is also indicative of the integrity of corticospinal tracts [28]. CMCT is an overall reflection of time to activation of the pyramidal cells and conduction time of neural impulses in the corticospinal tract.

In TMS studies, CMCT is usually calculated using the F wave method or cervical nerve root stimulation method [29,30]. Both these methods measure the delay between the MEP latency and time to generate a response using peripheral stimulation. The key distinction between these two methods is the inclusion of the spinal motor neuron while measuring the peripheral stimulation time. In the F wave method, a peripheral nerve is supramaximally stimulated leading to antidromic stimulation which travels up the nerve root to the spinal motor neuron. This, in turn stimulates the efferent root orthodromically, generating an F wave. In the cervical nerve root stimulation, the peripheral conduction time is estimated as the time taken to generate a CMAP by directly stimulating the spinal nerve root. The CMCT can be variable with a range of physiological and subject dependent factors such as age,

gender, hand dominance and neck position

Cortical Silent Period (CSP) refers to a transient cessation of voluntary activity on electromyography (EMG) in a target muscle measured after magnetic stimulation of the contralateral motor cortex. CSP is a reflection of $GABA_B$ receptor mediated cortical inhibition [31,32] and also appears to be influenced by the density of corticomotor neuronal projections onto the spinal motor neuron [27]. It is, thus, the longest in the upper limb muscles.

CSP is calculated as the time interval between the onset of the MEP response and resumption of voluntary EMG activity following TMS [31], and increases with stimulus intensity.

Paired Pulse TMS Paradigms

Paired pulse techniques provide insights into functioning of intracortical excitatory and inhibitory circuits [27] by measuring the modulation of the cortical response to a test stimulus preceded by a conditioning stimulus. The two commonly applied paired pulse paradigms comprise are referred to as the constant stimulus [33] and threshold tracking [19] techniques. Either can be used to measure the short interval intracortical inhibition (SICI), long interval intracortical inhibition (LICI) and intracortical facilitation (ICF), each of which is an index of cortical motor function.

Paired pulse TMS paradigms (Figure 2) used to determine the SICI and ICF consist of a subthreshold conditioning stimulus followed, at prespecified intervals (ISI), by a suprathreshold test stimulus. The *constant stimulus* paired pulse paradigms [33] measure the variation in MEP responses, while keeping the test and conditioning stimuli constant. Inhibition is observed at ISI of 0-5 ms facilitation at longer intervals between the stimuli. To overcome the issue of inherent MEP variability, which was used as an output measure in the constant stimulus protocols, threshold tracking protocols [19,34] were developed. These rely on using a fixed target amplitude MEP response and track the test stimulus intensity required to achieve this response. Higher stimulus intensity required to maintain this target response indicates inhibition while a lower intensity suggests facilitation. The target MEP response is chosen from the steepest part of the stimulus response curve (Figure 2c), thus reducing the variation in the outcome variable.

Studies using cervical epidural electrode recordings suggest that SICI is associated

with a reduction in the amplitude of I waves in a temporal pattern consistent with inhibitory post synaptic potentials mediated via $GABA_A$ receptors [35,36]. Drugs potentiating $GABA_A$ receptor mediated neurotransmission, thus, increase the SICI. Other neurotransmitter systems may have an indirect role via modulation of $GABA_A$ receptors, as indicated by SICI alterations using glutaminergic agents, dopamine agonists and noradrenergic blockers [37,38]. The cortical signature of SICI is likely to be a combination of synaptic processes, inhibitory interneuronal interactions and axonal refractoriness [20,39-41].

The physiological processes driving ICF remain even less well understood. Interestingly, ICF is decreased by antiglutaminergic agents [37] and is not associated with changes in I waves [27] which coincide with SICI [15].

LICI occurs when a suprathreshold conditioning stimulus is followed by a test stimulus at an ISI of 50-300 ms [3]. LICI seems to be mediated via $GABA_B$ receptors [42,43].

Short latency afferent inhibition (SAI) is the suppression of TMS induced MEP response after peripheral nerve stimulation [44,45]. Thus, when a median sensory stimulation is administered approximately 20 ms prior to the TMS pulse over the contralateral motor cortex, the MEP response from the APB muscle is suppressed. It reflects inhibitory modulation of large sensory fibres on the motor cortex and is likely to involve central cholinergic transmission [46,47].

Repetitive TMS paradigms (rTMS)

Repetitive TMS (rTMS) with applications of trains of TMS pulses over several minutes duration [48], produces cortical changes that last beyond the duration of stimulation, in a frequency dependent manner [14,49]. *Simple* rTMS protocols involve application of single stimuli at fixed interstimulus intervals (ISI) and their effects depend of the frequency of stimuli used. A low frequency stimulation (≤1Hz) depresses cortical excitability, while high frequency (5-20Hz) stimulation increases excitability (Figure 1). *Patterned* rTMS protocols utilise a combination of different ISIs, a common example of this being theta burst TMS (TBS), that incorporates triplet TMS pulses (bursts of 3 pulses at 50 Hz repeated at 200 ms intervals) to induce longer lasting effects than conventional rTMS protocols for a relatively shorter duration of application [50]. Continuous theta burst stimulation (cTBS), usually

involving trains of uninterrupted stimulation for 20-40 s, has an inhibitory effect on corticospinal excitability whereas intermittent theta burst stimulation (iTBS) has the opposite effect.

At a larger scale, TMS may enhance the understanding of systems level changes in brain circuitry. The application of rTMS over a specified cortical region has effects on remote brain areas [51] that may modulate network activity in the brain leading to behavioural alterations not directly related to the area being stimulated by the TMS directly [52] . In terms of specificity, the same output can be elicited using a variety of stimulation sites. For instance, motor activity changes are associated with stimulation of the primary motor cortex M1 [50], supplementary motor area SMA [53] dorsal pre-motor cortex PmD [54], as well as non-motor areas such as the cerebellum [55] and dorsolateral pre frontal cortex (DLPFC) [56].The potential for rTMS effects to last beyond the duration of stimulation this has been observed in a number of therapeutic applications in neurological disorders [57,58]. However, therapeutic applications of rTMS are outside the scope of this article.

Safety considerations

With the rapid increase in TMS applications in research and rehabilitation trials, safety in the clinical setting remains an important consideration. Although rare, seizure risk is mainly pertinent to rTMS protocols with an estimated risk in the region of 0.1% [59,60]. Most reported cases of seizures with TMS occurred before 1998 when higher frequency trains were routinely administered and typically occurred in patients who had a previous history of seizures. Resting EEG abnormalities have been noted during TMS, though mostly in patients with epilepsy and they do not predict occurrence of seizures [61,62]. Isolated rare cases in patients have been reported since with concomitant seizure threshold lowering drugs (e.g. SSRI) or after sleep deprivation [59]. Risk of minor adverse events such as mild headache, tinnitus, cutaneous discomfort, neck muscle contraction, nausea, light headedness or syncope, unilateral eye pain and lacrimation remains less than 5%. To put this into perspective, the risk of seizures with penicillins and carbapenem drugs is up to 5% [63] and increases further with predisposing factors. To date, meta analyses of published treatment trials of TMS [64-66] have been reassuring and support safe use

of TMS in patients and healthy volunteers.

TMS is considered safe in individuals with other stimulator devices such as VNS systems, cardiac pacemakers, and spinal cord stimulators provided that the TMS coil is not activated near the implanted wires [59]. Due to risk of induced currents, TMS should be avoided in patients with DBS, cochlear implants and with epidural electrodes. Additional safety studies are required to establish safe levels of currents that could be used with these implanted devices. Ex vivo studies have, reassuringly, demonstrated minimal, well below prescribed safety limits, heating of metal stents and aneurysm clips with rTMS protocols that have current approval for clinical uses [67,68]. However, caution is still warranted before more definitive evidence of safety becomes available from in vivo animal models and subsequently, human studies.

Cortical dysfunction in neurodegenerative disease

Assessment of cortical function in neurodegenerative disease has provided valuable pathophysiological insights and has the potential for diagnostic applications (Table 1).

(i) Emerging biomarkers in amyotrophic lateral sclerosis (ALS)

Determining the relationship between upper and lower motor neuron dysfunction remains key to understanding the pathogenesis of amyotrophic lateral sclerosis (ALS) [69,70]. Initial studies using single pulse TMS approaches demonstrated a reduction in motor threshold and the cortical silent period as features of early disease, providing preliminary evidence for cortical hyperexcitability in ALS [71,72]. Paired pulse techniques have, subsequently, provided more detailed evidence cortical excitability in terms of reduction or absence of SICI and increase in ICF [19]. SICI reductions precede electrophysiological evidence of peripheral neurodegeneration [73] as well as clinical evidence of lower motor neuron dysfunction in ALS [74]. SICI and ICF reduction are also seen in atypical variants of ALS with phenotypic predominance of lower motor neuron dysfunction [75], while these changes are not seen in ALS mimic disorders [76,77] such as spinobulbar muscular atrophy, despite a comparable disease burden. These findings strongly support the notion of cortical primacy in ALS [78]. Other

contributory evidence for this theory is the demonstration of reduced transcallosal inhibition in ALS [79]. Partial normalisation of SICI following the administration of riluzole [80], an antiglutaminergic drug used in ALS points to a pathogenic role for cortical hyperexcitability in ALS. This also highlights the potential application of TMS parameters in future clinical trials of ALS.

SICI has been shown to be the greatest sensitivity and specificity for as a diagnostic marker in ALS [81]. Combining TMS measures with peripheral neurophysiological measures can, thus, potentially greatly increase the diagnostic accuracy in ALS [82].

(ii) Motor cortical alterations in Alzheimer's disease (AD)

The appearance of motor signs in AD is a late event in the natural history of the illness [83] and is likely due to the spread of pathology into the motor cortices and striatal structures with disease progression [84]. TMS studies have demonstrated a bimodal pattern for changes in the motor threshold in AD. RMT appears to be reduced in early AD and shows progressive decline despite anticholinergic treatment [85,86]. The early changes may be related to modulation of glutaminergic pathways by changes in activity of muscarinic cholinergic receptors [87], suggesting a degree of functional reorganisation [88,89]. In later stages of AD, the observed increase in MT is a likely due to cortical neuronal degeneration, indicative of more widespread cortical dysfunction [86]. Evidence regarding SICI changes in AD is more variable [47,90]. A more recent study has found alterations in LICI which correlate with cognitive scores [91].

Loss of short latency afferent inhibition (SAI) appears to be a more consistent feature in AD [47,92,93], and seems to be normalised by administration of cholinesterase inhibitors [47]. SAI appears to be mediated by cholinergic neurons [94] and indirectly by GABAergic interneuronal inputs to cholinergic pyramidal neurons [95,96]. Muscarinic ACh receptor blockade with scopolamine specifically inhibits SAI, while not affecting the short interval intracortical inhibition, cortical silent period and intracortical facilitation, which are believed to be mediated by GABAergic interneurons [39]. Interestingly, SAI does not seem to be affected in

frontotemporal dementia (FTD), a disorder which does not directly involve the cholinergic system [97] unlike AD [98].

SAI changes have also been demonstrated in patients with Down's syndrome who are at risk of developing early onset AD [99]. These findings have the potential for translation to the clinic for differentiating FTD from AD and are likely to be more cost effective than imaging modalities such as PET.

TMS has also been used to demonstrate the disruption of long term potentiation (LTP) related cortical changes early on in the disease trajectory [100] in keeping with animal models of AD [101]. As such, LTP-like cortical alterations could provide a viable biomarker useful to assess synaptic impairment and predict subsequent cognitive decline progression in AD patients [102].

(iii) ***Quantifying motor cortex dysfunction in Parkinson's disease (PD) and other movement disorders***

While the degeneration of dopaminergic neurons in the substantia nigra and involvement of nigrostriatal pathways are the primary pathogenic changes in PD, functional changes in the motor cortices have been well recognised [103-105]. SICI reductions have been reported in PD [106,107] particularly at higher stimulus intensities [108] suggesting a dysfunction in intracortical facilitatory pathways. Longitudinal evaluation of cortical dysfunction in PD revealed alterations in CSP between the less and more affected brain hemispheres which correlate with motor progression [109]. SAI reductions have also been documented in PD [110], particularly in the context of cognitive symptoms [111,112], suggesting a possible role for cholinergic pathways in the pathogenesis of cognitive dysfunction. TMS studies have also found alterations in interhemispheric inhibition, supporting the view that mirror movements in PD patients originate from crossed corticospinal projections rather than unmasking of ipsilateral projections PD [113,114]. In genetic forms of PD, distinct patterns have been found using TMS. Reduction in SICI recruitment have been found in asymptomatic *Parkin* mutation carriers, without significant changes in overall SICI, indicative of altered cortical function in asymptomatic carriers [115]. SICI reduction has not been noted in

Parkin patients. Given that SICI appears normal in Parkin patients and CMCT is prolonged, the reduced SICI recruitment may be indicative of a compensatory change in the motor cortex to subclinical dopaminergic dysfunction in mutation carriers.

On the other hand, patients with leucine-rich repeat kinase2 (LRRK2), appear to have a markedly hyperexcitable motor cortex when compared to those with idiopathic PD, which is a likely contributor to functional changes in patients [116].

Motor cortical changes appear in the early stages if Huntington's disease (HD) as shown by imaging studies [117,118] and pathological confirmation of neuronal loss in the primary motor and anterior cingulate cortices [119]. Moreover, motor symptomatology correlates with primary motor cortex involvement [119,120] while cognitive and behavioural features seem to correspond with changes other regions including prefrontal and anterior cingulate cortical areas [118-120]. TMS studies have captured early motor cortical dysfunction in HD including a higher MT and a reduced SAI, the latter being related to motor symptoms [121]. In addition, cortical hyperexcitability in terms of decreased SICI and increased ICF [122,123] have also been shown in HD, especially in the context of motor symptoms, indicating a potential role for both GABA [124] and glutaminergic pathways in HD pathogenesis.

Atypical parkinsonian syndromes include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA) and are clinically and pathologically heterogeneous disorders. Motor cortical and corticospinal involvement is seen in these disorders to varying degrees [125-127]. Reduced SICI and abnormalities in interhemispheric inhibition have been demonstrated in PSP [128,129], the latter being more evident in the Richardson syndrome compared with parkinsonism predominant PSP [130]. RMT is elevated in CBD [128,131] and along with reduced SICI and may correlate with primary motor cortex atrophy [132], indicating more severe neuronal loss in the motor cortex in CBD. Increased motor thresholds, reduced SICI and interhemispheric inhibition changes have also been demonstrated in MSA [128,133,134]. However, the correlation between these changes and clinical features remains less clear [135,136], and findings regarding interhemispheric inhibition are inconsistent [137]. Motor cortex

functional alterations have also been reported in PSP [129] and MSA [134]. Overall, findings from TMS studies suggest that primary motor cortex disinhibition may be an early process in PSP. In contrast, in CBD, global changes in inhibitory process may be secondary to neurodegeneration in the motor cortex.

(iv) Novel insights in frontotemporal dementia (FTD)

FTD encompasses three heterogeneous disorders including behavioural variant frontotemporal dementia (bvFTD), semantic dementia and progressive nonfluent aphasia. Characteristic phenotypic features in FTD include deficits in social cognition, executive function, language and behaviour. There is emerging evidence to suggest that ALS and FTD lie on a disease continuum with motor features prominent at one end and cognitive features at the other [138,139]. Concurrence of these two conditions in patients with C9orf72 mutation [140,141], occurrence of TAR DNA binding protein-43 (TDP-43) pathology in both conditions [142], clinical and electrophysiological evidence of upper motor neuron dysfunction in FTD [143], alongside evidence of behavioural and cognitive function in ALS are all supportive of this notion [144,145].

Motor cortex involvement in FTD occurs with the spread of pathology from frontal regions posteriorly [138], and anterior cingulate and M1 involvement on imaging overlaps with the imaging patterns seen in ALS [146]. TMS studies have shown central motor circuit abnormalities in FTD (reduced or absent MEP, increased MEP latency, increased CMCT) even in the absence of clinical evidence of pyramidal tract involvement, while MT and SAI have been found to be normal [97,143]. Earlier studies had found no significant changes in SICI and ICF, but more recent studies indicate SICI reductions in FTD [143,147]. SICI reductions in FTD seem to occur to a lesser degree than those seen in ALS. The preservation of cholinergic pathways evidenced by relatively normal SAI in conjunction with abnormalities in SICI and ICF have been utilised to distinguish FTD from AD [147].

Understanding and predicting recovery after stroke

Recovery from stroke is modulated by the intrinsic capacity of the brain to reorganise surviving brain networks. This process takes place through a variety of complex cellular processes including inflammation, growth factors, changes in excitatory and inhibitory neurotransmitters, transcriptional changes, axonal sprouting, neurogenesis, gliogenesis and synaptogenesis [148]. While there is variation related to stroke subtype and individual patient factors [149], severity of the initial deficit after stroke is the predominant predictor of recovery, referred to as proportional recovery. [150,151]. The ability to elicit and MEP response after stroke is a predictor of proportional recovery, regardless of the severity of initial impairment [152,153].

Studies in the motor domain indicate that patients with mild to moderate upper limb deficit are able to recover 70% of lost function in the first three months after stroke. However, in patients with severe stroke, recovery is proportional to initial severity in about half of the patients with the other half making no recovery at all. Stroke lesion induced structural and functional changes in the brain occur in the early phase after stroke coinciding with a period of heightened reorganisation, which can support some restoration of function referred to as spontaneous biological recovery [150]. While the precise biological mechanisms underlying spontaneous biological recovery are incompletely understood, evidence from animal models [154] suggests that behavioural training administered in a critical time window [155,156] can facilitate this process. The overarching goal of neuromodulatory approaches is to augment the process of spontaneous recovery and to change the trajectory of poor recovery to proportional recovery.

Early after stroke, glutaminergic excitotoxicity leads to cell death and counteracts GABAergic inhibition [148,157,158] .The balance between glutaminergic excitotoxicity and GABAergic inhibition can influence regenerative processes and may reverse in later phases of recovery. TMS based approaches can be used to better understand these excitability changes and to guide therapeutic neuromodulation in an appropriate time window.

Increased transcallosal inhibition from the contralesional hemisphere [159,160], may suppress excitability of the lesioned hemisphere. More recent work has determined that transcallosal inhibition from ipsilesional to contralesional hemisphere may

increase in chronic stroke patients [161]. Both these patterns seem to interfere with functional recovery [162,163]. A meta-analysis of TMS studies of post stroke cortical changes found no asymmetry in interhemispheric inhibition in stroke patients in the small number of available studies. In terms of experimental rehabilitation programmes, facilitating affected M1 excitability directly may be more beneficial than suppressing unaffected M1 excitability to promote post-stroke recovery [164]. Contralesional activity may play some role in improving function [165,166]. An important determinant of recovery that interacts with excitability changes is the extent of structural damage to key pathways [167,168]. Current understanding of recovery is well described under the *'bimodal balance recovery model'* [169]. This model suggests that changes in interhemispheric activity interact with the extent of surviving neural pathways, referred to as the 'structural reserve'. Thus, in strokes with a smaller deficit and a large structural reserve, interhemispheric imbalance predicts poorer outcomes. In these patients, restoration of activity towards the physiological equilibrium should be a primary therapeutic goal. On the other hand, in strokes with more severe deficits and lower structural reserve, the interhemispheric imbalance may allow some compensatory changes leading to varying amounts of functional recovery.

TMS has been used to interrogate cortical reorganisation in patients with stroke and can be useful for prognosis. The ability to elicit an MEP response after stimulation of the lesioned motor cortex might help predict motor function recovery [170,171]. Conversely, inability to elicit an MEP after ipsilesional TMS and increased MEP after contralesional stimulation seems to predict poorer recovery of motor function [172,173]. Likewise, appearance of MEP responses after ipsilesional stimulation, when MEP responses were not elicited previously, is associated with better functional recovery [174]. Alterations in cortical excitability in the lesioned hemisphere have been demonstrated using TMS in stroke patients [175] (Figure 3). Prolongation of CSP in the lesioned hemisphere, indicating increased intracortical inhibition, has been demonstrated after subcortical stroke [176]. On the other hand, SICI and long interval intracortical inhibition (LICI) are suppressed in the affected hemisphere [177-179], while ICF seems to be unaltered after stroke [178,180-182]. Contralesional changes in excitability are less marked. MEP responses and motor thresholds appear to be largely intact [170,181,183-186] in the paretic limb, while

some studies suggest alteration in SICI [177,178,181,187]. Indeed, recent work evaluating longitudinal changes in cortical excitability after stroke using TMS from as early as the first week after stroke up to a year afterwards, shows that contralesional hyperexcitability evolves differently in patients with different stroke types and may have an adaptive role when ipsilesional pathways are significantly disrupted [179,187]. SICI is decreased in both the affected and unaffected hemisphere after stroke, but tends to remain suppressed only in patients with larger strokes and more severe clinical deficits [187].

Clearer understanding of neuroplastic changes underlying recovery is essential for development of personalised rehabilitation strategies for patients and application in clinical trials [168] accounting for the topography of damaged and surviving neural pathways after a stroke. The predicting recovery potential (PREP) algorithm illustrates how a sequential consideration of clinical, TMS and imaging factors can provide prognostic information for motor function recovery in stroke [188,189]. The key factors incorporated into this algorithm are the extent of clinical weakness, ability to elicit an MEP response in the paretic hand and the degree of corticospinal tract involvement on diffusion tensor imaging. Such a sequential approach has been shown to increase therapy efficiency while achieving good clinical outcomes in post stroke rehabilitation [153].

In summary, TMS has evolved as a readily accessible, non-invasive neurostimulation tool with potentially wide ranging diagnostic and prognostic applications. Separately, TMS provides a unique research tool to investigate pathophysiological changes in the cortex in stroke and neurodegenerative disorders. Applications of TMS based biomarkers in clinical trials are likely to emerge. In an evolving era of precision medicine, TMS based approaches have the potential to make personalised rehabilitative and restorative interventions in the future a reality, with better understanding of mechanisms of loss of function in neurodegeneration and the trajectory of recovery in stroke.

Table 1 Cortical function alterations across neurodegenerative disorders

	RMT %	MEP %	SICI (%)	ICF (%)	CSP (ms)	CMCT (ms)	SAI (%)
ALS [19,70,72]	Reduced Increased Inexcitable	Increased Normal	Reduced	Increased Normal	Reduced	Increased Normal	N/A
AD [47,86,90,92,93]	Reduced Increased	Increased Normal	Reduced Normal	Normal	Normal Reduced	Normal	Reduced
PD [103,106,110-112]	Normal	Normal	Reduced Normal	Normal	Reduced Normal	Normal	Reduced Increased Normal
HD [121,122]	Increased	Reduced	Reduced	Increased	Increased Reduced	Normal	Reduced
FTD [97,147]	Normal	Absent Reduced	Reduced Normal	Normal	Normal	Increased Normal	Normal
MSA [128,133,134]	Increased Normal	Normal	Reduced	Normal	Increased	Normal	Reduced Normal
PSP [128-130]	Normal	Increased	Reduced	Normal	Reduced	Normal	Normal

ALS (amyotrophic lateral sclerosis), FTD (frontotemporal dementia), AD (Alzheimer's disease), PD (Parkinson's disease), PSP (progressive supranuclear palsy), MSA (multiple system atrophy), HD (Huntington's disease), RMT (resting motor threshold), MEP (motor evoked potential), CMCT (central motor conduction time), CSP (cortically silent period), SICI (short interval intracortical inhibition), ICF (intracortical facilitation), SAI (short latency afferent inhibition)

Contributors

MCK and SA conceived the idea for the article. SA drafted the manuscript. All authors revised the manuscript critically for important intellectual content, and gave final approval of the version to be published.

Competing interests

None declared

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Figure legends

Figure 1. TMS using a circular coil showing the lines of flux of the magnetic field and directions of stimulating and induced currents.

Figure 2. The paired-pulse threshold tracking TMS (TT-TMS) paradigm to measure cortical excitability. 2a) Short interval intracortical inhibition (SICI) occurs at an interstimulus interval (ISI) of 0-7 ms while intracortical facilitation (ICF) occurs at an ISI of 7-10 ms. 2b) TMS coil placed over the vertex stimulates the motor cortex and the response is recorded from the opposite abductor pollicis brevis muscle. 2c) Change in stimulus intensity required to achieve a target motor evoked potential (MEP) of 0.2 mV(±20%) is used to quantify the SICI and ICF.

Figure 3. TMS may be used to stimulate the perilesional cortex after stroke and/or suppress excitability of the opposite hemisphere.

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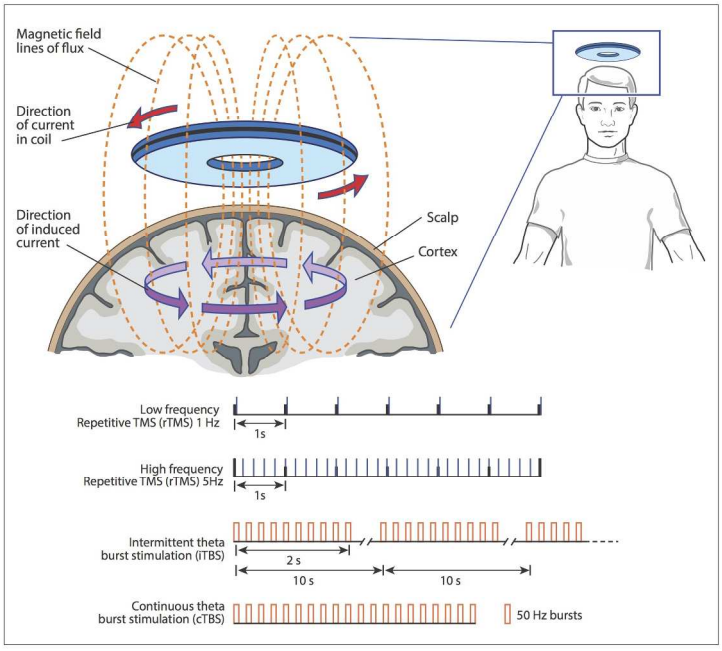

Figure 1. TMS using a circular coil showing the lines of flux of the magnetic field and directions of stimulating and induced currents.

209x296mm (300 x 300 DPI)

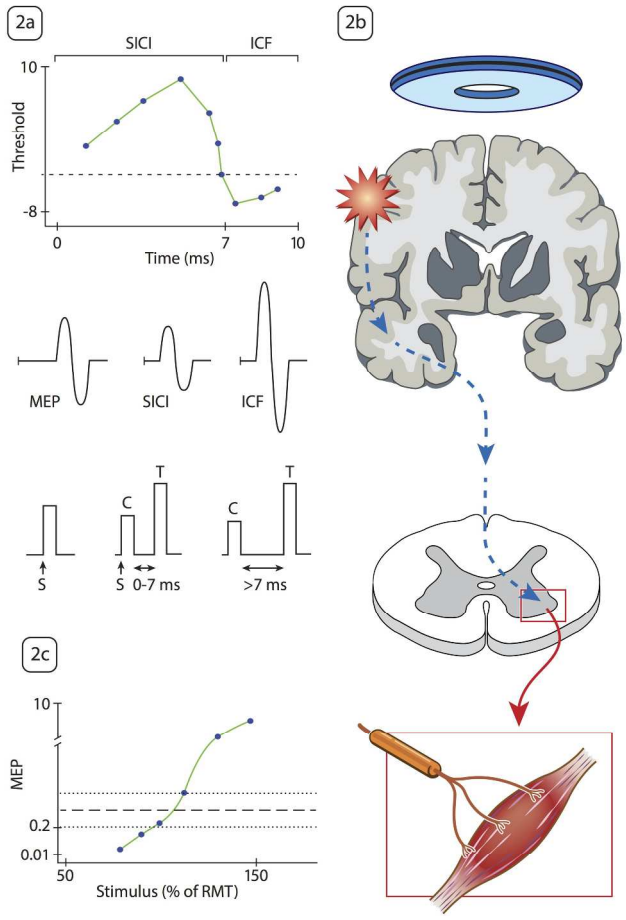

Figure 2. The paired-pulse threshold tracking TMS (TT-TMS) paradigm to measure cortical excitability. 2a) Short interval intracortical inhibition (SICI) occurs at an interstimulus interval (ISI) of 0-7 ms while intracortical facilitation (ICF) occurs at an ISI of 7-10 ms. 2b) TMS coil placed over the vertex stimulates the motor cortex and the response is recorded from the opposite abductor pollicis brevis muscle. 2c) Change in stimulus intensity required to achieve a target motor evoked potential (MEP) of 0.2 mV(±20%) is used to quantify the SICI and ICF.

296x420mm (300 x 300 DPI)

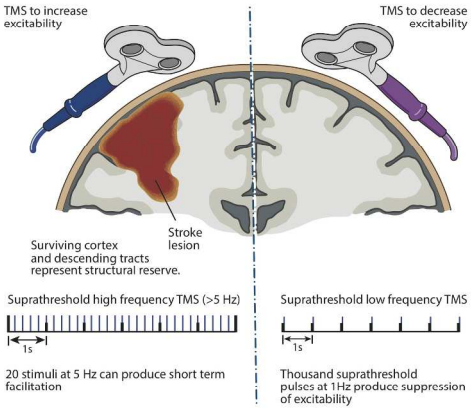

Figure 3. TMS may be used to stimulate the perilesional cortex after stroke and/or suppress excitability of the opposite hemisphere.

209x296mm (300 x 300 DPI)