

Journal of
**Neurology, Neurosurgery
& Psychiatry**

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

Journal:	<i>Journal of Neurology, Neurosurgery, and Psychiatry</i>
Manuscript ID	jnnp-2017-317371.R3
Article Type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Agarwal, Smriti; University of Sydney Brain and Mind Research Institute Koch, Giacomo; Fondazione Santa Lucia IRCCS Hillis, A; Johns Hopkins Hospital Huynh, William; Brain and Mind Centre, ; Prince of Wales Clinical School, Ward, Nick; UCL Institute of Neurology, Sobell Department of Motor Neuroscience Vucic, Steve; The Brain Dynamics Centre, Westmead Millennium Institute; Sydney Medical School, University of Sydney Kiernan, Matthew C.; Prince of Wales Hospital, Institute of Neurological Sciences
Keywords:	MAGNETIC STIMULATION, STROKE, MOTOR NEURON DISEASE, DEMENTIA, PARKINSON'S DISEASE
Specialty:	Other

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Manuscripts

Title**Interrogating cortical function with transcranial magnetic stimulation: Insights from neurodegenerative disease and stroke****Article Type**

Review

Authors

Smriti Agarwal¹, Giacomo Koch² Argye E Hillis³, William Huynh¹, Nick S Ward⁴, Steve Vucic⁵, Matthew C Kiernan¹

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

Word count Abstract 208, main text 4775 (excluding table, figure legends and references)

References 189

Figures 3 (colour figures 3); Tables 1

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.

87 Introduction

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

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

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110 Measures of cortical function

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

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

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3 119 neurons (Direct or D-waves) or trans synaptic excitation (Indirect or I-waves). The I-
4 120 waves are thought to originate through a complex interaction between cortical output
5 121 cells (Betz cells, layer V) and interneuronal cells [3,7-9].

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8 122 Following a brief overview of TMS output measures, their application as potential
9 123 diagnostic and prognostic markers will be further considered.

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12 124 A widely used experimental paradigm involves application of TMS to the motor
13 125 cortex with recording electrodes placed over an intrinsic hand muscle in the
14 126 contralateral limb (Figure 2). The resultant motor-evoked potential (MEP) on
15 127 electromyography (EMG) is typically recorded from the abductor pollicis brevis (APB),
16 128 abductor digiti minimi (ADM) or the first dorsal interosseous (FDI) muscle. This
17 129 paradigm can be applied to quantify excitability characteristics of the underlying
18 130 motor cortex.
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26 132 **Motor Threshold** (MT) indicates the ease with which motor cortex output cells and
27 133 corticomotor neurons can be excited. MT is thought to reflect the density of
28 134 corticomotor neuronal projections onto the anterior horn cells. It thus, follows, that
29 135 MTs tend to be lower in the dominant hand [10] and correlate with the performance
30 136 of fine motor tasks [11]. MTs have the potential of providing a biomarker of cortical
31 137 neuronal membrane excitability. Voltage gated sodium channels are critical to
32 138 cortical axon excitability [12] while excitatory synaptic neurotransmission in the
33 139 neocortex is mediated by the glutaminergic alpha-amino-3-hydroxy-5-methyl-4-
34 140 isoxazolepropionic acid (AMPA) receptors [13]. Thus voltage gated sodium channel
35 141 blocking drugs increase MT [14,15] while glutaminergic agonists decrease it [16].
36 142 Interestingly, neuromodulatory agents affecting GABA, dopaminergic, noradrenergic
37 143 and cholinergic systems, do not affect the motor threshold [17].

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40 144 MT was initially defined as the minimum stimulation intensity (% maximum stimulator
41 145 output) required to achieve an MEP response of (amplitude >50 μ V) in the target
42 146 muscle in 50% of stimulus trials [18]. Evolving studies in threshold tracking TMS
43 147 have led to redefinition of the MT as stimulus required to achieve and maintain a
44 148 target MEP response of 0.2mV (\pm 20 %) [19,20]. MT tends to be lower in a
45 149 voluntarily contracting muscle (active motor threshold, AMT) when compared to that
46 150 in a muscle at rest (resting motor threshold, RMT) [21].
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151 **Single Pulse TMS measures**

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

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

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

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

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

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3 183 gender, hand dominance and neck position
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5 184 **Cortical Silent Period** (CSP) refers to a transient cessation of voluntary activity on
6 185 electromyography (EMG) in a target muscle measured after magnetic stimulation of
7 186 the contralateral motor cortex. CSP is a reflection of GABA_B receptor mediated
8 187 cortical inhibition [31,32] and also appears to be influenced by the density of
9 188 corticomotor neuronal projections onto the spinal motor neuron [27]. It is, thus, the
10 189 longest in the upper limb muscles.

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15 190 CSP is calculated as the time interval between the onset of the MEP response and
16 191 resumption of voluntary EMG activity following TMS [31], and increases with stimulus
17 192 intensity.

18 19 20 193 **Paired Pulse TMS Paradigms**

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22 194 Paired pulse techniques provide insights into functioning of intracortical excitatory
23 195 and inhibitory circuits [27] by measuring the modulation of the cortical response to a
24 196 test stimulus preceded by a conditioning stimulus. The two commonly applied paired
25 197 pulse paradigms comprise are referred to as the constant stimulus [33] and threshold
26 198 tracking [19] techniques. Either can be used to measure the short interval
27 199 intracortical inhibition (SICI), long interval intracortical inhibition (LICI) and
28 200 intracortical facilitation (ICF), each of which is an index of cortical motor function.

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34 201 Paired pulse TMS paradigms (Figure 2) used to determine the SICI and ICF consist
35 202 of a subthreshold conditioning stimulus followed, at prespecified intervals (ISI), by a
36 203 suprathreshold test stimulus. The *constant stimulus* paired pulse paradigms [33]
37 204 measure the variation in MEP responses, while keeping the test and conditioning
38 205 stimuli constant. Inhibition is observed at ISI of 0-5 ms facilitation at longer intervals
39 206 between the stimuli. To overcome the issue of inherent MEP variability, which was
40 207 used as an output measure in the constant stimulus protocols, threshold tracking
41 208 protocols [19,34] were developed. These rely on using a fixed target amplitude MEP
42 209 response and track the test stimulus intensity required to achieve this response.
43 210 Higher stimulus intensity required to maintain this target response indicates inhibition
44 211 while a lower intensity suggests facilitation. The target MEP response is chosen from
45 212 the steepest part of the stimulus response curve (Figure 2c), thus reducing the
46 213 variation in the outcome variable.

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49 214 Studies using cervical epidural electrode recordings suggest that SICI is associated
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3 215 with a reduction in the amplitude of I waves in a temporal pattern consistent with
4 216 inhibitory post synaptic potentials mediated via GABA_A receptors [35,36]. Drugs
5 217 potentiating GABA_A receptor mediated neurotransmission, thus, increase the SICI.
6 218 Other neurotransmitter systems may have an indirect role via modulation of GABA_A
7 219 receptors, as indicated by SICI alterations using glutaminergic agents, dopamine
8 220 agonists and noradrenergic blockers [37,38]. The cortical signature of SICI is likely to
9 221 be a combination of synaptic processes, inhibitory interneuronal interactions and
10 222 axonal refractoriness [20,39-41].

11 223 The physiological processes driving ICF remain even less well understood.
12 224 Interestingly, ICF is decreased by ant glutaminergic agents [37] and is not associated
13 225 with changes in I waves [27] which coincide with SICI [15].

14 226 LICI occurs when a suprathreshold conditioning stimulus is followed by a test
15 227 stimulus at an ISI of 50-300 ms [3]. LICI seems to be mediated via GABA_B receptors
16 228 [42,43].

17 229 **Short latency afferent inhibition (SAI)** is the suppression of TMS induced MEP
18 230 response after peripheral nerve stimulation [44,45]. Thus, when a median sensory
19 231 stimulation is administered approximately 20 ms prior to the TMS pulse over the
20 232 contralateral motor cortex, the MEP response from the APB muscle is suppressed. It
21 233 reflects inhibitory modulation of large sensory fibres on the motor cortex and is likely
22 234 to involve central cholinergic transmission [46,47].

23 235 Repetitive TMS paradigms (rTMS)

24 236 **Repetitive TMS (rTMS)** with applications of trains of TMS pulses over several
25 237 minutes duration [48], produces cortical changes that last beyond the duration of
26 238 stimulation, in a frequency dependent manner [14,49]. *Simple* rTMS protocols
27 239 involve application of single stimuli at fixed interstimulus intervals (ISI) and their
28 240 effects depend of the frequency of stimuli used. A low frequency stimulation (≤ 1 Hz)
29 241 depresses cortical excitability, while high frequency (5-20Hz) stimulation increases
30 242 excitability (Figure 1). *Patterned* rTMS protocols utilise a combination of different ISIs,
31 243 a common example of this being theta burst TMS (TBS), that incorporates triplet
32 244 TMS pulses (bursts of 3 pulses at 50 Hz repeated at 200 ms intervals) to induce
33 245 longer lasting effects than conventional rTMS protocols for a relatively shorter
34 246 duration of application [50]. Continuous theta burst stimulation (cTBS), usually

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3 247 involving trains of uninterrupted stimulation for 20-40 s, has an inhibitory effect on
4 248 corticospinal excitability whereas intermittent theta burst stimulation (iTBS) has the
5 249 opposite effect.

8 250 At a larger scale, TMS may enhance the understanding of systems level changes in
9 251 brain circuitry. The application of rTMS over a specified cortical region has effects on
10 252 remote brain areas [51] that may modulate network activity in the brain leading to
11 253 behavioural alterations not directly related to the area being stimulated by the TMS
12 254 directly [52]. In terms of specificity, the same output can be elicited using a variety of
13 255 stimulation sites. For instance, motor activity changes are associated with stimulation
14 256 of the primary motor cortex M1 [50], supplementary motor area SMA [53] dorsal pre-
15 257 motor cortex PmD [54], as well as non-motor areas such as the cerebellum [55] and
16 258 dorsolateral pre frontal cortex (DLPFC) [56]. The potential for rTMS effects to last
17 259 beyond the duration of stimulation this has been observed in a number of therapeutic
18 260 applications in neurological disorders [57,58]. However, therapeutic applications of
19 261 rTMS are outside the scope of this article.

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26 263 **Safety considerations**

28 264 With the rapid increase in TMS applications in research and rehabilitation trials,
29 265 safety in the clinical setting remains an important consideration. Although rare,
30 266 seizure risk is mainly pertinent to rTMS protocols with an estimated risk in the region
31 267 of 0.1% [59,60]. Most reported cases of seizures with TMS occurred before 1998
32 268 when higher frequency trains were routinely administered and typically occurred in
33 269 patients who had a previous history of seizures. Resting EEG abnormalities have
34 270 been noted during TMS, though mostly in patients with epilepsy and they do not
35 271 predict occurrence of seizures [61,62]. Isolated rare cases in patients have been
36 272 reported since with concomitant seizure threshold lowering drugs (e.g. SSRI) or after
37 273 sleep deprivation [59]. Risk of minor adverse events such as mild headache, tinnitus,
38 274 cutaneous discomfort, neck muscle contraction, nausea, light headedness or
39 275 syncope, unilateral eye pain and lacrimation remains less than 5%. To put this into
40 276 perspective, the risk of seizures with penicillins and carbapenem drugs is up to 5%
41 277 [63] and increases further with predisposing factors. To date, meta analyses of
42 278 published treatment trials of TMS [64-66] have been reassuring and support safe use

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3 279 of TMS in patients and healthy volunteers.

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7 281 TMS is considered safe in individuals with other stimulator devices such as VNS
8 282 systems, cardiac pacemakers, and spinal cord stimulators provided that the TMS coil
9 283 is not activated near the implanted wires [59]. Due to risk of induced currents, TMS
10 284 should be avoided in patients with DBS, cochlear implants and with epidural
11 285 electrodes. Additional safety studies are required to establish safe levels of currents
12 286 that could be used with these implanted devices. Ex vivo studies have, reassuringly,
13 287 demonstrated minimal, well below prescribed safety limits, heating of metal stents
14 288 and aneurysm clips with rTMS protocols that have current approval for clinical uses
15 289 [67,68]. However, caution is still warranted before more definitive evidence of safety
16 290 becomes available from in vivo animal models and subsequently, human studies.

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24 25 26 292 **Cortical dysfunction in neurodegenerative disease**

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28 293 Assessment of cortical function in neurodegenerative disease has provided valuable
29 294 pathophysiological insights and has the potential for diagnostic applications (Table 1).

30 31 295 ***(i) Emerging biomarkers in amyotrophic lateral sclerosis (ALS)***

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33 296 Determining the relationship between upper and lower motor neuron dysfunction
34 297 remains key to understanding the pathogenesis of amyotrophic lateral sclerosis
35 298 (ALS) [69,70]. Initial studies using single pulse TMS approaches demonstrated a
36 299 reduction in motor threshold and the cortical silent period as features of early
37 300 disease, providing preliminary evidence for cortical hyperexcitability in ALS
38 301 [71,72]. Paired pulse techniques have, subsequently, provided more detailed
39 302 evidence cortical excitability in terms of reduction or absence of SICI and
40 303 increase in ICF [19]. SICI reductions precede electrophysiological evidence of
41 304 peripheral neurodegeneration [73] as well as clinical evidence of lower motor
42 305 neuron dysfunction in ALS [74]. SICI and ICF reduction are also seen in atypical
43 306 variants of ALS with phenotypic predominance of lower motor neuron dysfunction
44 307 [75], while these changes are not seen in ALS mimic disorders [76,77] such as
45 308 spinobulbar muscular atrophy, despite a comparable disease burden. These
46 309 findings strongly support the notion of cortical primacy in ALS [78]. Other
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3 310 contributory evidence for this theory is the demonstration of reduced transcallosal
4 311 inhibition in ALS [79]. Partial normalisation of SICl following the administration of
5 312 riluzole [80], an ant glutaminergic drug used in ALS points to a pathogenic role for
6 313 cortical hyperexcitability in ALS. This also highlights the potential application of
7 314 TMS parameters in future clinical trials of ALS.

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11 315 SICl has been shown to be the greatest sensitivity and specificity for as a
12 316 diagnostic marker in ALS [81]. Combining TMS measures with peripheral
13 317 neurophysiological measures can, thus, potentially greatly increase the
14 318 diagnostic accuracy in ALS [82].

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21 320 **(ii) Motor cortical alterations in Alzheimer's disease (AD)**

22 321 The appearance of motor signs in AD is a late event in the natural history
23 322 of the illness [83] and is likely due to the spread of pathology into the motor
24 323 cortices and striatal structures with disease progression [84]. TMS studies
25 324 have demonstrated a bimodal pattern for changes in the motor threshold in
26 325 AD. RMT appears to be reduced in early AD and shows progressive
27 326 decline despite anticholinergic treatment [85,86]. The early changes may be
28 327 related to modulation of glutaminergic pathways by changes in activity of
29 328 muscarinic cholinergic receptors [87], suggesting a degree of functional
30 329 reorganisation [88,89]. In later stages of AD, the observed increase in MT is
31 330 a likely due to cortical neuronal degeneration, indicative of more
32 331 widespread cortical dysfunction [86]. Evidence regarding SICl changes in
33 332 AD is more variable [47,90]. A more recent study has found alterations in
34 333 LICl which correlate with cognitive scores [91].

35 334 Loss of short latency afferent inhibition (SAI) appears to be a more consistent
36 335 feature in AD [47,92,93], and seems to be normalised by administration of
37 336 cholinesterase inhibitors [47]. SAI appears to be mediated by cholinergic neurons
38 337 [94] and indirectly by GABAergic interneuronal inputs to cholinergic pyramidal
39 338 neurons [95,96]. Muscarinic ACh receptor blockade with scopolamine specifically
40 339 inhibits SAI, while not affecting the short interval intracortical inhibition, cortical
41 340 silent period and intracortical facilitation, which are believed to be mediated by
42 341 GABAergic interneurons [39]. Interestingly, SAI does not seem to be affected in

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3 342 frontotemporal dementia (FTD), a disorder which does not directly involve the
4 343 cholinergic system [97] unlike AD [98].

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6 344 SAI changes have also been demonstrated in patients with Down's syndrome
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8 345 who are at risk of developing early onset AD [99]. These findings have the
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10 346 potential for translation to the clinic for differentiating FTD from AD and are likely
11 347 to be more cost effective than imaging modalities such as PET.

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13 348 TMS has also been used to demonstrate the disruption of long term potentiation
14 349 (LTP) related cortical changes early on in the disease trajectory [100] in keeping
15 350 with animal models of AD [101]. As such, LTP-like cortical alterations could
16 351 provide a viable biomarker useful to assess synaptic impairment and predict
17 352 subsequent cognitive decline progression in AD patients [102].

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24 354 (iii) **Quantifying motor cortex dysfunction in Parkinson's disease (PD)**
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26 355 **and other movement disorders**

27 356 While the degeneration of dopaminergic neurons in the substantia nigra and
28 357 involvement of nigrostriatal pathways are the primary pathogenic changes in
29 358 PD, functional changes in the motor cortices have been well recognised [103-
30 359 105]. SICI reductions have been reported in PD [106,107] particularly at
31 360 higher stimulus intensities [108] suggesting a dysfunction in intracortical
32 361 facilitatory pathways. Longitudinal evaluation of cortical dysfunction in PD
33 362 revealed alterations in CSP between the less and more affected brain
34 363 hemispheres which correlate with motor progression [109]. SAI reductions
35 364 have also been documented in PD [110], particularly in the context of
36 365 cognitive symptoms [111,112], suggesting a possible role for cholinergic
37 366 pathways in the pathogenesis of cognitive dysfunction. TMS studies have also
38 367 found alterations in interhemispheric inhibition, supporting the view that mirror
39 368 movements in PD patients originate from crossed corticospinal projections
40 369 rather than unmasking of ipsilateral projections PD [113,114]. In genetic forms
41 370 of PD, distinct patterns have been found using TMS. Reduction in SICI
42 371 recruitment have been found in asymptomatic *Parkin* mutation carriers,
43 372 without significant changes in overall SICI, indicative of altered cortical
44 373 function in asymptomatic carriers [115]. SICI reduction has not been noted in

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3 374 *Parkin* patients. Given that SICl appears normal in *Parkin* patients and CMCT
4 375 is prolonged, the reduced SICl recruitment may be indicative of a
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6 376 compensatory change in the motor cortex to subclinical dopaminergic
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8 377 dysfunction in mutation carriers.

9 378 On the other hand, patients with leucine-rich repeat kinase2 (LRRK2), appear
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11 379 to have a markedly hyperexcitable motor cortex when compared to those with
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13 380 idiopathic PD, which is a likely contributor to functional changes in patients
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15 381 [116].

16 382 Motor cortical changes appear in the early stages of Huntington's disease (HD)
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18 383 as shown by imaging studies [117,118] and pathological confirmation of
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20 384 neuronal loss in the primary motor and anterior cingulate cortices [119].

21 385 Moreover, motor symptomatology correlates with primary motor cortex
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23 386 involvement [119,120] while cognitive and behavioural features seem to
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25 387 correspond with changes in other regions including prefrontal and anterior
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27 388 cingulate cortical areas [118-120]. TMS studies have captured early motor
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29 389 cortical dysfunction in HD including a higher MT and a reduced SAI, the latter
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31 390 being related to motor symptoms [121]. In addition, cortical hyperexcitability in
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33 391 terms of decreased SICl and increased ICF [122,123] have also been shown
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35 392 in HD, especially in the context of motor symptoms, indicating a potential role
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37 393 for both GABA [124] and glutaminergic pathways in HD pathogenesis.

38 394 Atypical parkinsonian syndromes include progressive supranuclear palsy
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40 395 (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA)
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42 396 and are clinically and pathologically heterogeneous disorders. Motor cortical
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44 397 and corticospinal involvement is seen in these disorders to varying degrees
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46 398 [125-127]. Reduced SICl and abnormalities in interhemispheric inhibition have
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48 399 been demonstrated in PSP [128,129], the latter being more evident in the
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50 400 Richardson syndrome compared with parkinsonism predominant PSP [130].
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52 401 RMT is elevated in CBD [128,131] and along with reduced SICl and may
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54 402 correlate with primary motor cortex atrophy [132], indicating more severe
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56 403 neuronal loss in the motor cortex in CBD. Increased motor thresholds,
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58 404 reduced SICl and interhemispheric inhibition changes have also been
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60 405 demonstrated in MSA [128,133,134]. However, the correlation between these
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62 406 changes and clinical features remains less clear [135,136], and findings
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64 407 regarding interhemispheric inhibition are inconsistent [137]. Motor cortex

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3 408 functional alterations have also been reported in PSP [129] and MSA [134].
4 409 Overall, findings from TMS studies suggest that primary motor cortex
5 410 disinhibition may be an early process in PSP. In contrast, in CBD, global
6 411 changes in inhibitory process may be secondary to neurodegeneration in the
7 412 motor cortex.
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14 415 **(iv) Novel insights in frontotemporal dementia (FTD)**

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16 416 FTD encompasses three heterogeneous disorders including behavioural variant
17 417 frontotemporal dementia (bvFTD), semantic dementia and progressive nonfluent
18 418 aphasia. Characteristic phenotypic features in FTD include deficits in social
19 419 cognition, executive function, language and behaviour. There is emerging
20 420 evidence to suggest that ALS and FTD lie on a disease continuum with motor
21 421 features prominent at one end and cognitive features at the other [138,139].
22 422 Concurrence of these two conditions in patients with C9orf72 mutation [140,141],
23 423 occurrence of TAR DNA binding protein-43 (TDP-43) pathology in both conditions
24 424 [142], clinical and electrophysiological evidence of upper motor neuron
25 425 dysfunction in FTD [143], alongside evidence of behavioural and cognitive
26 426 function in ALS are all supportive of this notion [144,145].
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34 427 Motor cortex involvement in FTD occurs with the spread of pathology from frontal
35 428 regions posteriorly [138], and anterior cingulate and M1 involvement on imaging
36 429 overlaps with the imaging patterns seen in ALS [146]. TMS studies have shown
37 430 central motor circuit abnormalities in FTD (reduced or absent MEP, increased
38 431 MEP latency, increased CMCT) even in the absence of clinical evidence of
39 432 pyramidal tract involvement, while MT and SAI have been found to be normal
40 433 [97,143]. Earlier studies had found no significant changes in SICl and ICF, but
41 434 more recent studies indicate SICl reductions in FTD [143,147]. SICl reductions in
42 435 FTD seem to occur to a lesser degree than those seen in ALS. The preservation
43 436 of cholinergic pathways evidenced by relatively normal SAI in conjunction with
44 437 abnormalities in SICl and ICF have been utilised to distinguish FTD from AD
45 438 [147].
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440 **Understanding and predicting recovery after stroke**

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

448 **The ability to elicit and MEP response after stroke is a predictor of proportional**
449 **recovery, regardless of the severity of initial impairment [152,153].**

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

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

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

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3 472 increase in chronic stroke patients [161]. Both these patterns seem to interfere with
4 473 functional recovery [162,163]. A meta-analysis of TMS studies of post stroke cortical
5 474 changes found no asymmetry in interhemispheric inhibition in stroke patients in the
6 475 small number of available studies. In terms of experimental rehabilitation
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8 476 programmes, facilitating affected M1 excitability directly may be more beneficial than
9 477 suppressing unaffected M1 excitability to promote post-stroke recovery [164].
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11 478 Contralesional activity may play some role in improving function [165,166]. An
12 479 important determinant of recovery that interacts with excitability changes is the
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14 480 extent of structural damage to key pathways [167,168]. Current understanding of
15 481 recovery is well described under the '*bimodal balance recovery model*' [169]. This
16 482 model suggests that changes in interhemispheric activity interact with the extent of
17 483 surviving neural pathways, referred to as the 'structural reserve'. Thus, in strokes
18 484 with a smaller deficit and a large structural reserve, interhemispheric imbalance
19 485 predicts poorer outcomes. In these patients, restoration of activity towards the
20 486 physiological equilibrium should be a primary therapeutic goal. On the other hand, in
21 487 strokes with more severe deficits and lower structural reserve, the interhemispheric
22 488 imbalance may allow some compensatory changes leading to varying amounts of
23 489 functional recovery.

32 490 TMS has been used to interrogate cortical reorganisation in patients with stroke and
33 491 can be useful for prognosis. The ability to elicit an MEP response after stimulation of
34 492 the lesioned motor cortex might help predict motor function recovery [170,171].
35 493 Conversely, inability to elicit an MEP after ipsilesional TMS and increased MEP after
36 494 contralesional stimulation seems to predict poorer recovery of motor function
37 495 [172,173]. Likewise, appearance of MEP responses after ipsilesional stimulation,
38 496 when MEP responses were not elicited previously, is associated with better
39 497 functional recovery [174]. Alterations in cortical excitability in the lesioned
40 498 hemisphere have been demonstrated using TMS in stroke patients [175] (Figure 3).
41 499 Prolongation of CSP in the lesioned hemisphere, indicating increased intracortical
42 500 inhibition, has been demonstrated after subcortical stroke [176]. On the other hand,
43 501 SICI and long interval intracortical inhibition (LICI) are suppressed in the affected
44 502 hemisphere [177-179], while ICF seems to be unaltered after stroke [178,180-182].
45 503 Contralesional changes in excitability are less marked. MEP responses and motor
46 504 thresholds appear to be largely intact [170,181,183-186] in the paretic limb, while

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3 505 some studies suggest alteration in SICl [177,178,181,187]. Indeed, recent work
4 506 evaluating longitudinal changes in cortical excitability after stroke using TMS from as
5 507 early as the first week after stroke up to a year afterwards, shows that contralesional
6 508 hyperexcitability evolves differently in patients with different stroke types and may
7 509 have an adaptive role when ipsilesional pathways are significantly disrupted
8 510 [179,187]. SICl is decreased in both the affected and unaffected hemisphere after
9 511 stroke, but tends to remain suppressed only in patients with larger strokes and more
10 512 severe clinical deficits [187].

11 513 Clearer understanding of neuroplastic changes underlying recovery is essential for
12 514 development of personalised rehabilitation strategies for patients and application in
13 515 clinical trials [168] accounting for the topography of damaged and surviving neural
14 516 pathways after a stroke. The predicting recovery potential (PREP) algorithm
15 517 illustrates how a sequential consideration of clinical, TMS and imaging factors can
16 518 provide prognostic information for motor function recovery in stroke [188,189]. The
17 519 key factors incorporated into this algorithm are the extent of clinical weakness, ability
18 520 to elicit an MEP response in the paretic hand and the degree of corticospinal tract
19 521 involvement on diffusion tensor imaging. Such a sequential approach has been
20 522 shown to increase therapy efficiency while achieving good clinical outcomes in post
21 523 stroke rehabilitation [153].

22 524 In summary, TMS has evolved as a readily accessible, non-invasive
23 525 neurostimulation tool with potentially wide ranging diagnostic and prognostic
24 526 applications. Separately, TMS provides a unique research tool to investigate
25 527 pathophysiological changes in the cortex in stroke and neurodegenerative disorders.
26 528 Applications of TMS based biomarkers in clinical trials are likely to emerge. In an
27 529 evolving era of precision medicine, TMS based approaches have the potential to
28 530 make personalised rehabilitative and restorative interventions in the future a reality,
29 531 with better understanding of mechanisms of loss of function in neurodegeneration
30 532 and the trajectory of recovery in stroke.

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Table 1 Cortical function alterations across neurodegenerative disorders

	RMT %	MEP %	SICI (%)	ICF (%)	CSP (ms)	CMCT (ms)	SAI (%)
ALS [19,70,72]	Reduced Increased Inexcitabl e	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

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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)

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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

Funding

This work was supported by funding to Forefront, a collaborative research group dedicated to the study of motor neuron disease, from the National Health and Medical Research Council of Australia program grant (#1037746), the Motor Neuron Research Institute of Australia Ice Bucket Challenge Grant and grant aid from Magnetic Health Science Foundation.

SA is funded by the Ellison-Cliffe travelling fellowship from the Royal Society of Medicine, UK

AH is funded by NIH P50 DC014664 and NIH ROI DC05375.

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($\pm 20\%$) 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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References

- 1 Merton PA, Hill DK, Morton HB, *et al.* Scope of a technique for electrical stimulation of human brain, spinal cord, and muscle. 1982;**2**:597–600.
- 2 Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. 1985;**1**:1106–7.
- 3 Rossini PM, Burke D, Chen R, *et al.* Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;**126**:1071–107. doi:10.1016/j.clinph.2015.02.001
- 4 Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000;**406**:147–50.
- 5 Tofts PS. The distribution of induced currents in magnetic stimulation of the nervous system. *Phys Med Biol* 1990;**35**:1119–28.
- 6 Abdeen MA, Stuchly MA. Modeling of magnetic field stimulation of bent neurons. *IEEE Trans Biomed Eng* 1994;**41**:1092–5. doi:10.1109/10.335848
- 7 Di Lazzaro V, Profice P, Ranieri F, *et al.* I-wave origin and modulation. *Brain Stimul* 2012;**5**:512–25. doi:10.1016/j.brs.2011.07.008
- 8 Di Lazzaro V, Ziemann U, Lemon RN. State of the art: Physiology of transcranial motor cortex stimulation. *Brain Stimul* 2008;**1**:345–62. doi:10.1016/j.brs.2008.07.004
- 9 Ziemann U, Rothwell JC. I-waves in motor cortex. *Journal of Clinical Neurophysiology* 2000;**17**:397–405.
- 10 Macdonell RA, Shapiro BE, Chiappa KH, *et al.* Hemispheric threshold differences for motor evoked potentials produced by magnetic coil stimulation. *Neurology* 1991;**41**:1441–4.
- 11 Triggs WJ, Calvanio R, Levine M. Transcranial magnetic stimulation reveals a hemispheric asymmetry correlate of intermanual differences in motor performance. *Neuropsychologia* 1997;**35**:1355–63.
- 12 HODGKIN AL, HUXLEY AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol (Lond)* 1952;**117**:500–44. doi:10.1111/(ISSN)1469-7793
- 13 McCormick D. Membrane properties and neurotransmitter actions. In Douglas RJ, Martin K. *The synaptic organization of the brain* New York, USA: Oxford University Press, 2004:39-78.

- 1
2
3 672 14 Chen R, Classen J, Gerloff C, *et al.* Depression of motor cortex excitability by
4 673 low-frequency transcranial magnetic stimulation. *Neurology* 1997;**48**:1398–403.
- 5
6 674 15 Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical
7 675 inhibition and facilitation in human motor cortex. *J Physiol (Lond)*
8 676 1996;**496**:873–81.
- 9
10 677 16 Di Lazzaro V, Oliviero A, Pilato F, *et al.* Motor cortex hyperexcitability to
11 678 transcranial magnetic stimulation in Alzheimer's disease: evidence of impaired
12 679 glutamatergic neurotransmission? *Ann Neurol* 2003;**53**:824–authorreply824–5.
13 680 doi:10.1002/ana.10600
- 14
15 681 17 Ziemann U, Reis J, Schwenkreis P, *et al.* TMS and drugs revisited 2014. *Clin*
16 682 *Neurophysiol* 2015;**126**:1847–68. doi:10.1016/j.clinph.2014.08.028
- 17
18 683 18 Rossini PM, Berardelli A, Deuschl G, *et al.* Applications of magnetic cortical
19 684 stimulation. The International Federation of Clinical Neurophysiology.
20 685 *Electroencephalogr Clin Neurophysiol Suppl.* 1999;**52**:171–85.
- 21
22 686 19 Vucic S, Kiernan MC. Novel threshold tracking techniques suggest that cortical
23 687 hyperexcitability is an early feature of motor neuron disease. *Brain*
24 688 2006;**129**:2436–46. doi:10.1093/brain/awl172
- 25
26
27 689 20 Fisher RJ, Nakamura Y, Bestmann S, *et al.* Two phases of intracortical
28 690 inhibition revealed by transcranial magnetic threshold tracking. *Exp Brain Res*
29 691 2002;**143**:240–8. doi:10.1007/s00221-001-0988-2
- 30
31 692 21 Devanne H, Lavoie BA, Capaday C. Input-output properties and gain changes
32 693 in the human corticospinal pathway. *Exp Brain Res* 1997;**114**:329–38.
- 33
34 694 22 Amassian VE, Stewart M, Quirk GJ, *et al.* Physiological basis of motor effects
35 695 of a transient stimulus to cerebral cortex. *Neurosurgery* 1987;**20**:74–93.
- 36
37 696 23 Rusu CV, Murakami M, Ziemann U, *et al.* A model of TMS-induced I-waves in
38 697 motor cortex. *Brain Stimul* 2014;**7**:401–14. doi:10.1016/j.brs.2014.02.009
- 39
40 698 24 Ziemann U. Cortical threshold and excitability measurements. In: Eisen A.
41 699 *Clinical Neurophysiology of Motor Neuron Diseases: Handbook of Clinical*
42 700 *Neurophysiology.* Amsterdam: Elsevier, 2004: 317–35.
- 43
44 701 25 Paulus W, Classen J, Cohen LG, *et al.* State of the art: Pharmacologic effects
45 702 on cortical excitability measures tested by transcranial magnetic stimulation.
46 703 *Brain Stimul* 2008;**1**:151–63. doi:10.1016/j.brs.2008.06.002
- 47
48
49 704 26 Boroojerdi B, Battaglia F, Muellbacher W, *et al.* Mechanisms influencing
50 705 stimulus-response properties of the human corticospinal system. *Clinical*
51 706 *Neurophysiology* 2001;**112**:931–7.
- 52
53 707 27 Chen R, Cros D, Curra A, *et al.* The clinical diagnostic utility of transcranial
54 708 magnetic stimulation: report of an IFCN committee. *Clinical Neurophysiology*
55 709 2008;**119**:504–32. doi:10.1016/j.clinph.2007.10.014
- 56
57
58
59
60

- 1
2
3 710 28 Takeuchi N, Izumi S-I. Noninvasive brain stimulation for motor recovery after
4 711 stroke: mechanisms and future views. *Stroke Res Treat* 2012;**2012**:584727.
5 712 doi:10.1155/2012/584727
6
7 713 29 Claus D. Central motor conduction: method and normal results. *Muscle Nerve*
8 714 1990;**13**:1125–32. doi:10.1002/mus.880131207
9
10 715 30 Mills KR, Murray NM. Electrical stimulation over the human vertebral column:
11 716 which neural elements are excited? *Electroencephalogr Clin Neurophysiol*
12 717 1986;**63**:582–9.
13
14 718 31 Cantello R, Gianelli M, Civardi C, *et al.* Magnetic brain stimulation: the silent
15 719 period after the motor evoked potential. *Neurology* 1992;**42**:1951–9.
16
17 720 32 Siebner HR, Dressnandt J, Auer C, *et al.* Continuous intrathecal baclofen
18 721 infusions induced a marked increase of the transcranially evoked silent period
19 722 in a patient with generalized dystonia. *Muscle Nerve* 1998;**21**:1209–12.
20
21 723 33 Kujirai T, Caramia MD, Rothwell JC, *et al.* Corticocortical inhibition in human
22 724 motor cortex. *J Physiol (Lond)* 1993;**471**:501–19.
23
24 725 34 Vucic S, Howells J, Trevillion L, *et al.* Assessment of cortical excitability using
25 726 threshold tracking techniques. *Muscle Nerve* 2006;**33**:477–86.
26 727 doi:10.1002/mus.20481
27
28 728 35 Nakamura H, Kitagawa H, Kawaguchi Y, *et al.* Intracortical facilitation and
29 729 inhibition after transcranial magnetic stimulation in conscious humans. *J*
30 730 *Physiol (Lond)* 1997;**498**:817–23.
31
32 731 36 Hanajima R, Ugawa Y, Terao Y, *et al.* Paired-pulse magnetic stimulation of the
33 732 human motor cortex: differences among I waves. *J Physiol (Lond)*
34 733 1998;**509**:607–18. doi:10.1111/j.1469-7793.1998.607bn.x
35
36 734 37 Ziemann U, Chen R, Cohen LG, *et al.* Dextromethorphan decreases the
37 735 excitability of the human motor cortex. *Neurology* 1998;**51**:1320–4.
38 736 doi:10.1212/WNL.51.5.1320
39
40 737 38 Ziemann U. TMS and drugs. *Clinical Neurophysiology* 2004;**115**:1717–29.
41 738 doi:10.1016/j.clinph.2004.03.006
42
43 739 39 Di Lazzaro V, Oliviero A, Meglio M, *et al.* Direct demonstration of the effect of
44 740 lorazepam on the excitability of the human motor cortex. *Clin Neurophysiol*
45 741 2000;**111**:794–9.
46
47 742 40 Di Lazzaro V, Pilato F, Dileone M, *et al.* GABAA receptor subtype specific
48 743 enhancement of inhibition in human motor cortex. *J Physiol (Lond)*
49 744 2006;**575**:721–6. doi:10.1113/jphysiol.2006.114694
50
51 745 41 Ilić TV, Meintzschel F, Cleff U, *et al.* Short-interval paired-pulse inhibition and
52 746 facilitation of human motor cortex: the dimension of stimulus intensity. *J*
53 747 *Physiol (Lond)* 2002;**545**:153–67. doi:10.1113/jphysiol.2002.030122
54
55
56
57
58
59
60

- 1
2
3 748 42 Werhahn KJ, Kunesch E, Noachtar S, *et al.* Differential effects on motorcortical
4 749 inhibition induced by blockade of GABA uptake in humans. *J Physiol (Lond)*
5 750 1999;**517**:591–7. doi:10.1111/j.1469-7793.1999.0591t.x
6
7 751 43 Sanger TD, Garg RR, Chen R. Interactions between two different inhibitory
8 752 systems in the human motor cortex. *J Physiol (Lond)* 2001;**530**:307–17.
9 753 doi:10.1111/j.1469-7793.2001.0307l.x
10
11 754 44 Mariorenzi R, Zarola F, Caramia MD, *et al.* Non-invasive evaluation of central
12 755 motor tract excitability changes following peripheral nerve stimulation in
13 756 healthy humans. *Electroencephalogr Clin Neurophysiol* 1991;**81**:90–101.
14
15 757 45 Delwaide PJ, Olivier E. Conditioning transcranial cortical stimulation (TCCS)
16 758 by exteroceptive stimulation in parkinsonian patients. *Adv Neurol*
17 759 1990;**53**:175–81.
18
19 760 46 Tokimura H, Di Lazzaro V, Tokimura Y, *et al.* Short latency inhibition of human
20 761 hand motor cortex by somatosensory input from the hand. *J Physiol (Lond)*
21 762 2000;**523**:503–13.
22
23 763 47 Di Lazzaro V, Oliviero A, Pilato F, *et al.* Motor cortex hyperexcitability to
24 764 transcranial magnetic stimulation in Alzheimer's disease. *J Neurol Neurosurg*
25 765 *Psychiatr* 2004;**75**:555–9. doi:10.1136/jnnp.2003.018127
26
27 766 48 Pascual-Leone A, Tormos JM, Keenan J, *et al.* Study and modulation of
28 767 human cortical excitability with transcranial magnetic stimulation. *Journal of*
29 768 *Clinical Neurophysiology* 1998;**15**:333–43.
30
31 769 49 Pascual-Leone A, Valls-Solé J, Wassermann EM, *et al.* Responses to rapid-
32 770 rate transcranial magnetic stimulation of the human motor cortex. *Brain*
33 771 1994;**117**:847–58. doi:10.1093/brain/117.4.847
34
35 772 50 Huang Y-Z, Edwards MJ, Rounis E, *et al.* Theta Burst Stimulation of the
36 773 Human Motor Cortex. *Neuron* 2005;**45**:201–6.
37 774 doi:10.1016/j.neuron.2004.12.033
38
39 775 51 Siebner HR. Patients with focal arm dystonia have increased sensitivity to
40 776 slow-frequency repetitive TMS of the dorsal premotor cortex. *Brain*
41 777 2003;**126**:2710–25. doi:10.1093/brain/awg282
42
43 778 52 Huang Y-Z, Rothwell JC, Edwards MJ, *et al.* Effect of physiological activity on
44 779 an NMDA-dependent form of cortical plasticity in human. *Cereb Cortex*
45 780 2008;**18**:563–70. doi:10.1093/cercor/bhm087
46
47 781 53 Legon W, Dionne JK, Staines WR. Continuous theta burst stimulation of the
48 782 supplementary motor area: effect upon perception and somatosensory and
49 783 motor evoked potentials. *Brain Stimul* 2013;**6**:877–83.
50 784 doi:10.1016/j.brs.2013.04.007
51
52 785 54 Stinear CM, Barber PA, Coxon JP, *et al.* Repetitive stimulation of premotor
53 786 cortex affects primary motor cortex excitability and movement preparation.
54 787 *Brain Stimul* 2009;**2**:152–62. doi:10.1016/j.brs.2009.01.001
55
56
57
58
59
60

- 1
2
3 788 55 Arasanz CP, Staines WR, Roy EA, *et al.* The cerebellum and its role in word
4 789 generation: a cTBS study. *Cortex* 2012;**48**:718–24.
5 790 doi:10.1016/j.cortex.2011.02.021
6
7 791 56 Bolton DAE, Staines WR. Age-related loss in attention-based modulation of
8 792 tactile stimuli at early stages of somatosensory processing. *Neuropsychologia*
9 793 2012;**50**:1502–13. doi:10.1016/j.neuropsychologia.2012.03.002
10
11 794 57 Cirillo G, Di Pino G, Capone F, *et al.* Neurobiological after-effects of non-
12 795 invasive brain stimulation. *Brain Stimul* 2017;**10**:1–18.
13 796 doi:10.1016/j.brs.2016.11.009
14
15 797 58 Hallett M. Transcranial Magnetic Stimulation: A Primer. *Neuron* 2007;**55**:187–
16 798 99. doi:10.1016/j.neuron.2007.06.026
17
18 799 59 Rossi S, Hallett M, Rossini PM, *et al.* Clinical Neurophysiology. *Clinical*
19 800 *Neurophysiology* 2009;**120**:2008–39. doi:10.1016/j.clinph.2009.08.016
20
21 801 60 Oberman LM, Pascual-Leone A. Report of seizure induced by continuous theta
22 802 burst stimulation. *Brain Stimul* 2009;**2**:246–7. doi:10.1016/j.brs.2009.03.003
23
24 803 61 Schulze-Bonhage A, Scheufler K, Zentner J, *et al.* Safety of single and
25 804 repetitive focal transcranial magnetic stimuli as assessed by intracranial EEG
26 805 recordings in patients with partial epilepsy. *J Neurol* 1999;**246**:914–9.
27
28
29 806 62 Boutros NN, Berman RM, Hoffman R, *et al.* Electroencephalogram and
30 807 repetitive transcranial magnetic stimulation. *Depress Anxiety* 2000;**12**:166–9.
31 808 doi:10.1002/1520-6394(2000)12:3<166::AID-DA8>3.0.CO;2-M
32
33 809 63 Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic
34 810 drugs. *Neurology* 2015;**85**:1332–41. doi:10.1212/WNL.0000000000002023
35
36 811 64 Machii K, Cohen D, Ramos-Estebanez C, *et al.* Safety of rTMS to non-motor
37 812 cortical areas in healthy participants and patients. *Clin Neurophysiol*
38 813 2006;**117**:455–71. doi:10.1016/j.clinph.2005.10.014
39
40 814 65 Loo CK, Mitchell PB. A review of the efficacy of transcranial magnetic
41 815 stimulation (TMS) treatment for depression, and current and future strategies
42 816 to optimize efficacy. *J Affect Disord* 2005;**88**:255–67.
43 817 doi:10.1016/j.jad.2005.08.001
44
45 818 66 Janicak PG, O'Reardon JP, Sampson SM, *et al.* Transcranial magnetic
46 819 stimulation in the treatment of major depressive disorder: a comprehensive
47 820 summary of safety experience from acute exposure, extended exposure, and
48 821 during reintroduction treatment. *J Clin Psychiatry* 2008;**69**:222–32.
49
50
51 822 67 BSE NV, Miranda D, PhD KAP-B, *et al.* Assessment of Vascular Stent Heating
52 823 with Repetitive Transcranial Magnetic Stimulation. *Journal of Stroke and*
53 824 *Cerebrovascular Diseases* 2017;**26**:1121–7.
54 825 doi:10.1016/j.jstrokecerebrovasdis.2016.12.030
55
56 826 68 Hsieh T-H, Dhamne SC, Chen J-JJ, *et al.* Minimal heating of aneurysm clips
57
58
59
60

- 1
2
3 827 during repetitive transcranial magnetic stimulation. *Clinical Neurophysiology*
4 828 2012;**123**:1471–3. doi:10.1016/j.clinph.2011.10.048
5
6 829 69 Kiernan MC, Vucic S, Cheah BC, *et al.* Amyotrophic lateral sclerosis.
7 830 2011;**377**:942–55. doi:10.1016/S0140-6736(10)61156-7
8
9 831 70 Vucic S, Ziemann U, Eisen A, *et al.* Transcranial magnetic stimulation and
10 832 amyotrophic lateral sclerosis: pathophysiological insights. *J Neurol Neurosurg*
11 833 *Psychiatr* 2013;**84**:1161–70. doi:10.1136/jnnp-2012-304019
12
13 834 71 Mills KR, Nithi KA. Corticomotor threshold is reduced in early sporadic
14 835 amyotrophic lateral sclerosis. *Muscle Nerve* 1997;**20**:1137–41.
15 836 doi:10.1002/(SICI)1097-4598(199709)20:9<1137::AID-MUS7>3.0.CO;2-9
16
17 837 72 Eisen A, Weber M. The motor cortex and amyotrophic lateral sclerosis. *Muscle*
18 838 *Nerve* 2001;**24**:564–73.
19
20 839 73 Menon P, Kiernan MC, Vucic S. Cortical hyperexcitability precedes lower
21 840 motor neuron dysfunction in ALS. *Clinical Neurophysiology* 2015;**126**:803–9.
22
23 841 74 Vucic S, Nicholson GA, Kiernan MC. Cortical hyperexcitability may precede
24 842 the onset of familial amyotrophic lateral sclerosis. *Brain* 2008;**131**:1540–50.
25 843 doi:10.1093/brain/awn071
26
27 844 75 Vucic S, Kiernan MC. Abnormalities in cortical and peripheral excitability in flail
28 845 arm variant amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatr*
29 846 2007;**78**:849–52. doi:10.1136/jnnp.2006.105056
30
31 847 76 Vucic S, Kiernan MC. Cortical excitability testing distinguishes Kennedy's
32 848 disease from amyotrophic lateral sclerosis. *Clinical Neurophysiology*
33 849 2008;**119**:1088–96. doi:10.1016/j.clinph.2008.01.011
34
35 850 77 Vucic S, Cheah BC, Yiannikas C, *et al.* Corticomotoneuronal function and
36 851 hyperexcitability in acquired neuromyotonia. *Brain* 2010;**133**:2727–33.
37 852 doi:10.1093/brain/awq188
38
39 853 78 Eisen A, Braak H, Del Tredici K, *et al.* Cortical influences drive amyotrophic
40 854 lateral sclerosis. *J Neurol Neurosurg Psychiatr* 2017;**88**:917–24.
41 855 doi:10.1136/jnnp-2017-315573
42
43 856 79 Zhang J, Ji B, Hu J, *et al.* Aberrant interhemispheric homotopic functional and
44 857 structural connectivity in amyotrophic lateral sclerosis. *J Neurol Neurosurg*
45 858 *Psychiatr* 2017;**88**:369.1–370. doi:10.1136/jnnp-2016-314567
46
47 859 80 Vucic S, Lin CS-Y, Cheah BC, *et al.* Riluzole exerts central and peripheral
48 860 modulating effects in amyotrophic lateral sclerosis. *Brain* 2013;**136**:1361–70.
49 861 doi:10.1093/brain/awt085
50
51 862 81 Menon P, Geevasinga N, Yiannikas C, *et al.* Sensitivity and specificity of
52 863 threshold tracking transcranial magnetic stimulation for diagnosis of
53 864 amyotrophic lateral sclerosis: a prospective study. *Lancet Neurol*
54 865 2015;**14**:478–84. doi:10.1016/S1474-4422(15)00014-9
55
56
57
58
59
60

- 1
2
3 866 82 Cheah BC, Lin CS-Y, Park SB, *et al.* Progressive axonal dysfunction and
4 867 clinical impairment in amyotrophic lateral sclerosis. *Clin Neurophysiol*
5 868 2012;**123**:2460–7. doi:10.1016/j.clinph.2012.06.020
6
7 869 83 Scarmeas N, Hadjigeorgiou GM, Papadimitriou A, *et al.* Motor signs during the
8 870 course of Alzheimer disease. *Neurology* 2004;**63**:975–82.
9
10 871 84 Grothe MJ, Barthel H, Sepulcre J, *et al.* In vivo staging of regional amyloid
11 872 deposition. *Neurology* 2017;**89**:2031–8. doi:10.1212/WNL.0000000000004643
12
13 873 85 Cantone M, Di Pino G, Capone F, *et al.* Clinical Neurophysiology. *Clinical*
14 874 *Neurophysiology* 2014;**125**:1509–32. doi:10.1016/j.clinph.2014.04.010
15
16 875 86 Ferreri F, Pauri F, Pasqualetti P, *et al.* Motor cortex excitability in Alzheimer's
17 876 disease: A transcranial magnetic stimulation study. *Ann Neurol* 2002;**53**:102–8.
18 877 doi:10.1002/ana.10416
19
20 878 87 Sevilla DF, Cabezas C, Prada ANO, *et al.* Selective muscarinic regulation of
21 879 functional glutamatergic Schaffer collateral synapses in rat CA1 pyramidal
22 880 neurons. *J Physiol (Lond)* 2002;**545**:51–63. doi:10.1113/jphysiol.2002.029165
23
24 881 88 Niskanen E, Könönen M, Määttä S, *et al.* New Insights into Alzheimer's
25 882 Disease Progression: A Combined TMS and Structural MRI Study. *PLoS ONE*
26 883 2011;**6**:e26113–8. doi:10.1371/journal.pone.0026113
27
28 884 89 Ferreri F, Vecchio F, Vollero L, *et al.* Sensorimotor cortex excitability and
29 885 connectivity in Alzheimer's disease: A TMS-EEG Co-registration study. *Hum*
30 886 *Brain Mapp* 2016;**37**:2083–96. doi:10.1002/hbm.23158
31
32 887 90 Liepert J, Bär KJ, Meske U, *et al.* Motor cortex disinhibition in Alzheimer's
33 888 disease. *Clinical Neurophysiology* 2001;**112**:1436–41.
34
35 889 91 Brem A-K, Atkinson NJ, Seligson EE, *et al.* Differential pharmacological effects
36 890 on brain reactivity and plasticity in Alzheimer's disease. *Front Psychiatry*
37 891 2013;**4**:124. doi:10.3389/fpsy.2013.00124
38
39 892 92 Di Lazzaro V, Oliviero A, Tonali PA, *et al.* Noninvasive in vivo assessment of
40 893 cholinergic cortical circuits in AD using transcranial magnetic stimulation.
41 894 *Neurology* 2002;**59**:392–7.
42
43 895 93 Nardone R, Bergmann J, Kronbichler M, *et al.* Abnormal short latency afferent
44 896 inhibition in early Alzheimer's disease: a transcranial magnetic demonstration.
45 897 *J Neural Transm* 2008;**115**:1557–62. doi:10.1007/s00702-008-0129-1
46
47 898 94 Di Lazzaro V, Oliviero A, Tonali PA, *et al.* Noninvasive in vivo assessment of
48 899 cholinergic cortical circuits in AD using transcranial magnetic stimulation.
49 900 *Neurology* 2002;**59**:392–7.
50
51 901 95 McCormick DA, Prince DA. Mechanisms of action of acetylcholine in the
52 902 guinea-pig cerebral cortex in vitro. *J Physiol (Lond)* 1986;**375**:169–94.
53
54 903 96 Müller CM, Singer W. Acetylcholine-induced inhibition in the cat visual cortex is
55
56
57
58
59
60

- 1
2
3 904 mediated by a GABAergic mechanism. *Brain Res* 1989;**487**:335–42.
- 4
5 905 97 Di Lazzaro V, Pilato F, Dileone M, *et al.* In vivo cholinergic circuit evaluation in
6 906 frontotemporal and Alzheimer dementias. *Neurology* 2006;**66**:1111–3.
7 907 doi:10.1212/01.wnl.0000204183.26231.23
- 8
9 908 98 Davies P, Maloney AJ. Selective loss of central cholinergic neurons in
10 909 Alzheimer's disease. 1976;**2**:1403.
- 11
12 910 99 Nardone R, Marth R, Ausserer H, *et al.* Reduced short latency afferent
13 911 inhibition in patients with Down syndrome and Alzheimer-type dementia. *Clin*
14 912 *Neurophysiol* 2006;**117**:2204–10. doi:10.1016/j.clinph.2006.07.134
- 15
16 913 100 Koch G, Di Lorenzo F, Bonni S, *et al.* Impaired LTP- but not LTD-Like Cortical
17 914 Plasticity in Alzheimer's Disease Patients. *Journal of Alzheimer's Disease*
18 915 2012;**31**:593–9. doi:10.3233/JAD-2012-120532
- 19
20 916 101 Battaglia F, Wang H-Y, Ghilardi MF, *et al.* Cortical Plasticity in Alzheimer's
21 917 Disease in Humans and Rodents. *Biological Psychiatry* 2007;**62**:1405–12.
22 918 doi:10.1016/j.biopsych.2007.02.027
- 23
24 919 102 Di Lorenzo F, Ponzio V, Bonni S, *et al.* Long-term potentiation-like cortical
25 920 plasticity is disrupted in Alzheimer's disease patients independently from
26 921 age of onset. *Ann Neurol* 2016;**80**:202–10. doi:10.1002/ana.24695
- 27
28 922 103 Ridding MC, Inzelberg R, Rothwell JC. Changes in excitability of motor cortical
29 923 circuitry in patients with Parkinson's disease. *Ann Neurol* 1995;**37**:181–8.
30 924 doi:10.1002/ana.410370208
- 31
32 925 104 Goldberg JA, Boraud T, Maraton S, *et al.* Enhanced synchrony among primary
33 926 motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
34 927 primate model of Parkinson's disease. *J Neurosci* 2002;**22**:4639–53.
- 35
36 928 105 Lefaucheur J-P. Motor cortex dysfunction revealed by cortical excitability
37 929 studies in Parkinson's disease: influence of antiparkinsonian treatment and
38 930 cortical stimulation. *Clinical Neurophysiology* 2005;**116**:244–53.
39 931 doi:10.1016/j.clinph.2004.11.017
- 40
41 932 106 Barbin L, Leux C, Sauleau P, *et al.* Non-homogeneous effect of levodopa on
42 933 inhibitory circuits in Parkinson's disease and dyskinesia. *Parkinsonism Relat*
43 934 *Disord* 2013;**19**:165–70. doi:10.1016/j.parkreldis.2012.08.012
- 44
45 935 107 Ni Z, Bahl N, Gunraj CA, *et al.* Increased motor cortical facilitation and
46 936 decreased inhibition in Parkinson disease. *Neurology* 2013;**80**:1746–53.
47 937 doi:10.1212/WNL.0b013e3182919029
- 48
49 938 108 MacKinnon CD, Gilley EA, Weis-McNulty A, *et al.* Pathways mediating
50 939 abnormal intracortical inhibition in Parkinson's disease. *Ann Neurol*
51 940 2005;**58**:516–24. doi:10.1002/ana.20599
- 52
53 941 109 Kojovic M, Kassavetis P, Bologna M, *et al.* Transcranial magnetic stimulation
54 942 follow-up study in early Parkinson's disease: A decline in compensation with
- 55
56
57
58
59
60

- 1
2
3 943 disease progression? *Mov Disord* 2015;**30**:1098–106. doi:10.1002/mds.26167
- 4
5 944 110 Sailer A, Molnar GF, Paradiso G, *et al.* Short and long latency afferent
6 945 inhibition in Parkinson's disease. *Brain* 2003;**126**:1883–94.
7 946 doi:10.1093/brain/awg183
- 8
9 947 111 Manganelli F, Vitale C, Santangelo G, *et al.* Functional involvement of central
10 948 cholinergic circuits and visual hallucinations in Parkinson's disease. *Brain*
11 949 2009;**132**:2350–5. doi:10.1093/brain/awp166
- 12
13 950 112 Celebi O, Temuçin CM, Elibol B, *et al.* Short latency afferent inhibition in
14 951 Parkinson's disease patients with dementia. *Mov Disord* 2012;**27**:1052–5.
15 952 doi:10.1002/mds.25040
- 16
17 953 113 Cincotta M, Borgheresi A, Balestrieri F, *et al.* Mechanisms underlying mirror
18 954 movements in Parkinson's disease: A transcranial magnetic stimulation study.
19 955 *Mov Disord* 2006;**21**:1019–25. doi:10.1002/mds.20850
- 20
21 956 114 Spagnolo F, Coppi E, Chieffo R, *et al.* Interhemispheric balance in Parkinson's
22 957 disease: a transcranial magnetic stimulation study. *Brain Stimul* 2013;**6**:892–7.
23 958 doi:10.1016/j.brs.2013.05.004
- 24
25 959 115 Schneider SA, Talelli P, Cheeran BJ, *et al.* Motor cortical physiology in patients
26 960 and asymptomatic carriers of parkin gene mutations. *Mov Disord*
27 961 2008;**23**:1812–9. doi:10.1002/mds.22025
- 28
29
30 962 116 Ponzio V, Di Lorenzo F, Brusa L, *et al.* Impaired intracortical transmission in
31 963 G2019S leucine rich-repeat kinase Parkinson patients. *Mov Disord*
32 964 2017;**32**:750–6. doi:10.1002/mds.26931
- 33
34 965 117 Rosas HD, Salat DH, Lee SY, *et al.* Cerebral cortex and the clinical expression
35 966 of Huntington's disease: complexity and heterogeneity. *Brain* 2008;**131**:1057–
36 967 68. doi:10.1093/brain/awn025
- 37
38 968 118 Sax DS, Powsner R, Kim A, *et al.* Evidence of cortical metabolic dysfunction in
39 969 early Huntington's disease by single-photon-emission computed tomography.
40 970 *Mov Disord* 1996;**11**:671–7. doi:10.1002/mds.870110612
- 41
42 971 119 Thu DCV, Oorschot DE, Tippet LJ, *et al.* Cell loss in the motor and cingulate
43 972 cortex correlates with symptomatology in Huntington's disease. *Brain*
44 973 2010;**133**:1094–110. doi:10.1093/brain/awq047
- 45
46 974 120 Rosas HD, Salat DH, Lee SY, *et al.* Cerebral cortex and the clinical expression
47 975 of Huntington's disease: complexity and heterogeneity. *Brain* 2008;**131**:1057–
48 976 68. doi:10.1093/brain/awn025
- 49
50 977 121 Schippling S, Schneider SA, Bhatia KP, *et al.* Abnormal motor cortex
51 978 excitability in preclinical and very early Huntington's disease. *Biological*
52 979 *Psychiatry* 2009;**65**:959–65. doi:10.1016/j.biopsych.2008.12.026
- 53
54
55 980 122 Nardone R, Lochner P, Marth R, *et al.* Abnormal intracortical facilitation in
56 981 early-stage Huntington's disease. *Clinical Neurophysiology* 2007;**118**:1149–54.
- 57
58
59
60

- 1
2
3 982 doi:10.1016/j.clinph.2007.01.009
4
5 983 123 Abbruzzese G, Buccolieri A, Marchese R, *et al.* Intracortical inhibition and
6 984 facilitation are abnormal in Huntington's disease: a paired magnetic stimulation
7 985 study. *Neurosci Lett* 1997;**228**:87–90.
- 8
9 986 124 Tippett LJ, Waldvogel HJ, Thomas SJ, *et al.* Striosomes and mood dysfunction
10 987 in Huntington's disease. *Brain* 2007;**130**:206–21. doi:10.1093/brain/awl243
- 11
12 988 125 Wenning GK, Litvan I, Tolosa E. Milestones in atypical and secondary
13 989 Parkinsonisms. *Mov Disord* 2011;**26**:1083–95. doi:10.1002/mds.23713
- 14
15 990 126 Lee SE, Rabinovici GD, Mayo MC, *et al.* Clinicopathological correlations in
16 991 corticobasal degeneration. *Ann Neurol* 2011;**70**:327–40.
17 992 doi:10.1002/ana.22424
- 18
19 993 127 Nagao S, Yokota O, Nanba R, *et al.* Progressive supranuclear palsy
20 994 presenting as primary lateral sclerosis but lacking parkinsonism, gaze palsy,
21 995 aphasia, or dementia. *J Neurol Sci* 2012;**323**:147–53.
22 996 doi:10.1016/j.jns.2012.09.005
- 23
24 997 128 Kühn AA, Grosse P, Holtz K, *et al.* Patterns of abnormal motor cortex
25 998 excitability in atypical parkinsonian syndromes. *Clin Neurophysiol*
26 999 2004;**115**:1786–95. doi:10.1016/j.clinph.2004.03.020
- 27
28
29 1000 129 Conte A, Belvisi D, Bologna M, *et al.* Abnormal cortical synaptic plasticity in
30 1001 primary motor area in progressive supranuclear palsy. *Cereb Cortex*
31 1002 2012;**22**:693–700. doi:10.1093/cercor/bhr149
- 32
33 1003 130 Wittstock M, Pohley I, Walter U, *et al.* Interhemispheric inhibition in different
34 1004 phenotypes of progressive supranuclear palsy. *J Neural Transm*
35 1005 2013;**120**:453–61. doi:10.1007/s00702-012-0879-7
- 36
37 1006 131 Burrell JR, Hornberger M, Vucic S, *et al.* Apraxia and motor dysfunction in
38 1007 corticobasal syndrome. *PLoS ONE* 2014;**9**:e92944.
39 1008 doi:10.1371/journal.pone.0092944
- 40
41 1009 132 Burrell JR, Hornberger M, Vucic S, *et al.* Apraxia and Motor Dysfunction in
42 1010 Corticobasal Syndrome. *PLoS ONE* 2014;**9**:e92944.
43 1011 doi:10.1371/journal.pone.0092944
- 44
45 1012 133 Morita Y, Osaki Y, Doi Y. Transcranial magnetic stimulation for differential
46 1013 diagnostics in patients with parkinsonism. *Acta Neurol Scand* 2008;**118**:159–
47 1014 63. doi:10.1111/j.1600-0404.2007.00988.x
- 48
49
50 1015 134 Suppa A, Marsili L, Di Stasio F, *et al.* Primary motor cortex long-term plasticity
51 1016 in multiple system atrophy. *Mov Disord* 2014;**29**:97–104.
52 1017 doi:10.1002/mds.25668
- 53
54 1018 135 Marchese R, Trompetto C, Buccolieri A, *et al.* Abnormalities of motor cortical
55 1019 excitability are not correlated with clinical features in atypical parkinsonism.
56 1020 *Mov Disord* 2000;**15**:1210–4.

- 1
2
3 1021 136 Papp MI, Lantos PL. The distribution of oligodendroglial inclusions in multiple
4 1022 system atrophy and its relevance to clinical symptomatology. *Brain* 1994;**117**
5 1023 (Pt 2):235–43.
- 6
7 1024 137 Wolters A, Classen J, Kunesch E, *et al.* Measurements of transcallosally
8 1025 mediated cortical inhibition for differentiating parkinsonian syndromes. *Mov*
9 1026 *Disord* 2004;**19**:518–28. doi:10.1002/mds.20064
- 10
11 1027 138 Burrell JR, Halliday GM, Kril JJ, *et al.* The frontotemporal dementia-motor
12 1028 neuron disease continuum. 2016;**388**:919–31. doi:10.1016/S0140-
13 1029 6736(16)00737-6
- 14
15 1030 139 Ahmed RM, Irish M, Piguet O, *et al.* Amyotrophic lateral sclerosis and
16 1031 frontotemporal dementia: distinct and overlapping changes in eating behaviour
17 1032 and metabolism. *Lancet Neurol* 2016;**15**:332–42. doi:10.1016/S1474-
18 1033 4422(15)00380-4
- 19
20
21 1034 140 Renton AE, Majounie E, Waite A, *et al.* A hexanucleotide repeat expansion in
22 1035 C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*
23 1036 2011;**72**:257–68. doi:10.1016/j.neuron.2011.09.010
- 24
25 1037 141 DeJesus-Hernandez M, Mackenzie IR, Boeve BF, *et al.* Expanded GGGGCC
26 1038 hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome
27 1039 9p-linked FTD and ALS. *Neuron* 2011;**72**:245–56.
28 1040 doi:10.1016/j.neuron.2011.09.011
- 29
30 1041 142 Neumann M, Sampathu DM, Kwong LK, *et al.* Ubiquitinated TDP-43 in
31 1042 frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*
32 1043 2006;**314**:130–3. doi:10.1126/science.1134108
- 33
34 1044 143 Burrell JR, Kiernan MC, Vucic S, *et al.* Motor Neuron dysfunction in
35 1045 frontotemporal dementia. *Brain* 2011;**134**:2582–94. doi:10.1093/brain/awr195
- 36
37 1046 144 Elamin M, Bede P, Byrne S, *et al.* Cognitive changes predict functional decline
38 1047 in ALS: A population-based longitudinal study. *Neurology* 2013;**80**:1590–7.
39 1048 doi:10.1212/WNL.0b013e31828f18ac
- 40
41 1049 145 Lillo P, Mioshi E, Zoing MC, *et al.* How common are behavioural changes in
42 1050 amyotrophic lateral sclerosis? *Amyotrophic Lateral Sclerosis* 2010;**12**:45–51.
43 1051 doi:10.3109/17482968.2010.520718
- 44
45
46 1052 146 Lillo P, Mioshi E, Burrell JR, *et al.* Grey and white matter changes across the
47 1053 amyotrophic lateral sclerosis-frontotemporal dementia continuum. *PLoS ONE*
48 1054 2012;**7**:e43993. doi:10.1371/journal.pone.0043993
- 49
50 1055 147 Benussi A, Di Lorenzo F, Dell'Era V, *et al.* Transcranial magnetic stimulation
51 1056 distinguishes Alzheimer disease from frontotemporal dementia. *Neurology*
52 1057 2017;**89**:665–72. doi:10.1212/WNL.0000000000004232
- 53
54 1058 148 Cramer SC. Repairing the human brain after stroke: I. Mechanisms of
55 1059 spontaneous recovery. *Ann Neurol* 2008;**63**:272–87. doi:10.1002/ana.21393
- 56
57
58
59
60

- 1
2
3 1060 149 Grefkes C, Ward NS. Cortical reorganization after stroke: how much and how
4 1061 functional? *Neuroscientist* 2014;**20**:56–70. doi:10.1177/1073858413491147
5
6 1062 150 Ward NS. Restoring brain function after stroke — bridging the gap between
7 1063 animals and humans. *Nat Rev Neurol* 2017;**13**:244–55.
8 1064 doi:10.1038/nrneurol.2017.34
9
10 1065 151 Prabhakaran S, Zarahn E, Riley C, *et al*. Inter-individual variability in the
11 1066 capacity for motor recovery after ischemic stroke. *Neurorehabil Neural Repair*
12 1067 2008;**22**:64–71. doi:10.1177/1545968307305302
13
14 1068 152 Byblow WD, Stinear CM, Barber PA, *et al*. Proportional recovery after stroke
15 1069 depends on corticomotor integrity. *Ann Neurol* 2015;**78**:848–59.
16 1070 doi:10.1002/ana.24472
17
18 1071 153 Stinear CM, Byblow WD, Ackerley SJ, *et al*. Predicting Recovery Potential for
19 1072 Individual Stroke Patients Increases Rehabilitation Efficiency. *Stroke*
20 1073 2017;**48**:1011–9. doi:10.1161/STROKEAHA.116.015790
21
22 1074 154 Krakauer JW, Carmichael ST, Corbett D, *et al*. Getting neurorehabilitation right:
23 1075 what can be learned from animal models? 2012;**26**:923–31.
24 1076 doi:10.1177/1545968312440745
25
26 1077 155 Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience
27 1078 declines with time after focal ischemic brain injury. *J Neurosci* 2004;**24**:1245–
28 1079 54. doi:10.1523/JNEUROSCI.3834-03.2004
29
30
31 1080 156 Zeiler SR, Hubbard R, Gibson EM, *et al*. Paradoxical Motor Recovery From a
32 1081 First Stroke After Induction of a Second Stroke: Reopening a Postischemic
33 1082 Sensitive Period. *Neurorehabil Neural Repair* 2016;**30**:794–800.
34 1083 doi:10.1177/1545968315624783
35
36 1084 157 Carmichael ST. Brain excitability in stroke: the yin and yang of stroke
37 1085 progression. *Arch Neurol* 2012;**69**:161–7. doi:10.1001/archneurol.2011.1175
38
39 1086 158 Clarkson AN, Huang BS, Macisaac SE, *et al*. Reducing excessive GABA-
40 1087 mediated tonic inhibition promotes functional recovery after stroke. *Nature*
41 1088 2010;**468**:305–9. doi:10.1038/nature09511
42
43 1089 159 Murase N, Duque J, Mazzocchio R, *et al*. Influence of interhemispheric
44 1090 interactions on motor function in chronic stroke. *Ann Neurol* 2004;**55**:400–9.
45 1091 doi:10.1002/ana.10848
46
47 1092 160 Duque J, Hummel F, Celnik P, *et al*. Transcallosal inhibition in chronic
48 1093 subcortical stroke. *NeuroImage* 2005;**28**:940–6.
49 1094 doi:10.1016/j.neuroimage.2005.06.033
50
51 1095 161 Borich MR, Neva JL, Boyd LA. Evaluation of differences in brain
52 1096 neurophysiology and morphometry associated with hand function in individuals
53 1097 with chronic stroke. *Restor Neurol Neurosci* 2015;**33**:31–42. doi:10.3233/RNN-
54 1098 140425
55
56
57
58
59
60

- 1
2
3 1099 162 Taub E, Uswatte G, King DK, *et al.* A placebo-controlled trial of constraint-
4 1100 induced movement therapy for upper extremity after stroke. *Stroke*
5 1101 2006;**37**:1045–9. doi:10.1161/01.STR.0000206463.66461.97
6
7 1102 163 Mang CS, Borich MR, Brodie SM, *et al.* Diffusion imaging and transcranial
8 1103 magnetic stimulation assessment of transcallosal pathways in chronic stroke.
9 1104 *Clin Neurophysiol* 2015;**126**:1959–71. doi:10.1016/j.clinph.2014.12.018
10
11 1105 164 McDonnell MN, Stinear CM. TMS measures of motor cortex function after
12 1106 stroke: A meta-analysis. *Brain Stimul* 2017;**10**:721–34.
13 1107 doi:10.1016/j.brs.2017.03.008
14
15 1108 165 Gerloff C, Bushara K, Sailer A, *et al.* Multimodal imaging of brain
16 1109 reorganization in motor areas of the contralesional hemisphere of well
17 1110 recovered patients after capsular stroke. *Brain* 2006;**129**:791–808.
18 1111 doi:10.1093/brain/awh713
19
20 1112 166 Lotze M, Markert J, Sauseng P, *et al.* The Role of Multiple Contralesional
21 1113 Motor Areas for Complex Hand Movements after Internal Capsular Lesion. *J*
22 1114 *Neurosci* 2006;**26**:6096–102. doi:10.1523/JNEUROSCI.4564-05.2006
23
24 1115 167 Seghier ML, Patel E, Prejawa S, *et al.* The PLORAS Database: A data
25 1116 repository for Predicting Language Outcome and Recovery After Stroke.
26 1117 *NeuroImage* 2016;**124**:1208–12. doi:10.1016/j.neuroimage.2015.03.083
27
28 1118 168 Boyd LA, Hayward KS, Ward NS, *et al.* Biomarkers of stroke recovery:
29 1119 Consensus-based core recommendations from the Stroke Recovery and
30 1120 Rehabilitation Roundtable. *International Journal of Stroke* 2017;**12**:480–93.
31 1121 doi:10.1177/1747493017714176
32
33 1122 169 Di Pino G, Pellegrino G, Assenza G, *et al.* Modulation of brain plasticity in
34 1123 stroke: a novel model for neurorehabilitation. *Nat Rev Neurol* 2014;**10**:597–608.
35 1124 doi:10.1080/08990220220133261
36
37 1125 170 Delvaux V, Alagona G, Gérard P, *et al.* Post-stroke reorganization of hand
38 1126 motor area: a 1-year prospective follow-up with focal transcranial magnetic
39 1127 stimulation. *Clin Neurophysiol* 2003;**114**:1217–25.
40
41 1128 171 Heald A, Bates D, Cartlidge NE, *et al.* Longitudinal study of central motor
42 1129 conduction time following stroke. 2. Central motor conduction measured within
43 1130 72 h after stroke as a predictor of functional outcome at 12 months. *Brain*
44 1131 1993;**116**:1371–85.
45
46 1132 172 Stinear CM, Barber PA, Smale PR, *et al.* Functional potential in chronic stroke
47 1133 patients depends on corticospinal tract integrity. *Brain* 2007;**130**:170–80.
48 1134 doi:10.1093/brain/awl333
49
50 1135 173 Trompetto C, Assini A, Buccolieri A, *et al.* Motor recovery following stroke: a
51 1136 transcranial magnetic stimulation study. *Clin Neurophysiol* 2000;**111**:1860–7.
52
53 1137 174 Traversa R, Cicinelli P, Bassi A, *et al.* Mapping of motor cortical reorganization
54 1138 after stroke. A brain stimulation study with focal magnetic pulses. *Stroke*
55
56
57
58
59
60

- 1
2
3 1139 1997;**28**:110–7.
4
5 1140 175 Boniface SJ. Plasticity after acute ischaemic stroke studied by transcranial
6 1141 magnetic stimulation. *J Neurol Neurosurg Psychiatr* 2001;**71**:713–5.
7
8 1142 176 Liepert J, Restemeyer C, Kucinski T, *et al.* Motor strokes: the lesion location
9 1143 determines motor excitability changes. *Stroke* 2005;**36**:2648–53.
10 1144 doi:10.1161/01.STR.0000189629.10603.02
11
12 1145 177 Manganotti P, Patuzzo S, Cortese F, *et al.* Motor disinhibition in affected and
13 1146 unaffected hemisphere in the early period of recovery after stroke. *Clin*
14 1147 *Neurophysiol* 2002;**113**:936–43.
15
16 1148 178 Liepert J, Storch P, Fritsch A, *et al.* Motor cortex disinhibition in acute stroke.
17 1149 *Clin Neurophysiol* 2000;**111**:671–6.
18
19 1150 179 Huynh W, Vucic S, Krishnan AV, *et al.* Longitudinal Plasticity Across the
20 1151 Neural Axis in Acute Stroke. 2012;**27**:219–29. doi:10.1177/1545968312462071
21
22 1152 180 Di Lazzaro V, Oliviero A, Pilato F, *et al.* Direct recording of the output of the
23 1153 motor cortex produced by transcranial magnetic stimulation in a patient with
24 1154 cerebral cortex atrophy. *Clin Neurophysiol* 2004;**115**:112–5.
25
26 1155 181 Bütetfisch CM, Netz J, Wessling M, *et al.* Remote changes in cortical
27 1156 excitability after stroke. *Brain* 2003;**126**:470–81.
28
29 1157 182 Swayne OBC, Rothwell JC, Ward NS, *et al.* Stages of motor output
30 1158 reorganization after hemispheric stroke suggested by longitudinal studies of
31 1159 cortical physiology. *Cereb Cortex* 2008;**18**:1909–22.
32 1160 doi:10.1093/cercor/bhm218
33
34 1161 183 Pennisi G, Rapisarda G, Bella R, *et al.* Absence of response to early
35 1162 transcranial magnetic stimulation in ischemic stroke patients: prognostic value
36 1163 for hand motor recovery. *Stroke* 1999;**30**:2666–70.
37
38 1164 184 Shimizu T, Hosaki A, Hino T, *et al.* Motor cortical disinhibition in the unaffected
39 1165 hemisphere after unilateral cortical stroke. *Brain* 2002;**125**:1896–907.
40
41 1166 185 Fridman EA. Reorganization of the human ipsilesional premotor cortex after
42 1167 stroke. *Brain* 2004;**127**:747–58. doi:10.1093/brain/awh082
43
44 1168 186 Catano A, Houa M, Caroyer JM, *et al.* Magnetic transcranial stimulation in non-
45 1169 haemorrhagic sylvian strokes: interest of facilitation for early functional
46 1170 prognosis. *Electroencephalogr Clin Neurophysiol* 1995;**97**:349–54.
47
48 1171 187 Huynh W, Vucic S, Krishnan AV, *et al.* Exploring the Evolution of Cortical
49 1172 Excitability Following Acute Stroke. 2016;**30**:244–57. doi:10.1155/2011/614329
50
51 1173 188 Stinear CM, Barber PA, Petoe M, *et al.* The PREP algorithm predicts potential
52 1174 for upper limb recovery after stroke. *Brain* 2012;**135**:2527–35.
53 1175 doi:10.1093/brain/aws146
54
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57
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59
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1176 189 Stinear CM, Byblow WD, Ackerley SJ, *et al.* PREP2: A biomarker-based
1177 algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol*
1178 2017;**4**:811–20. doi:10.1002/acn3.488

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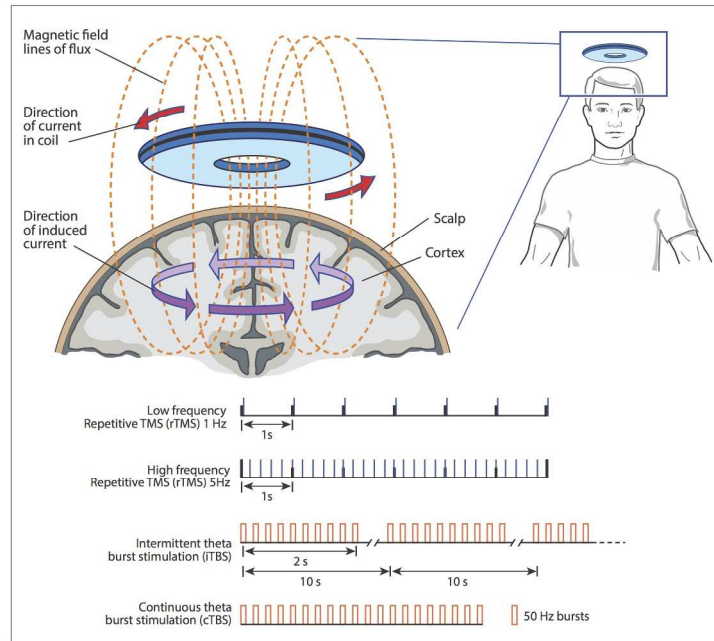


Figure 1. TMS using a circular coil showing the lines of flux of the magnetic field and directions of stimulating and induced currents.

209x296mm (300 x 300 DPI)

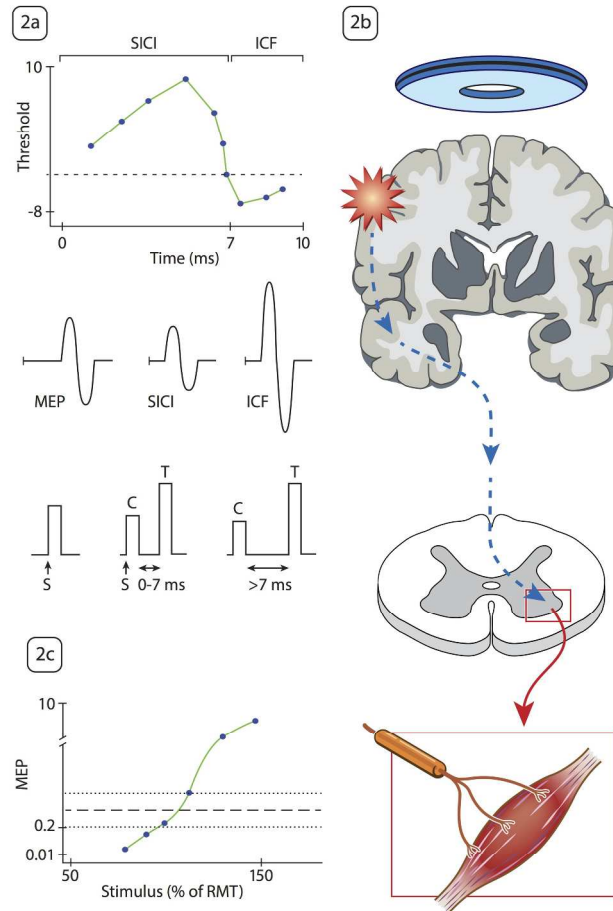


Figure 2. The paired-pulse threshold tracking TMS (TT-TMS) paradigm to measure cortical excitability. 2a) Short interval intracortical inhibition (SICI) occurs at an interstimulus interval (ISI) of 0-7 ms while intracortical facilitation (ICF) occurs at an ISI of 7-10 ms. 2b) TMS coil placed over the 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 ($\pm 20\%$) is used to quantify the SICI and ICF.

296x420mm (300 x 300 DPI)

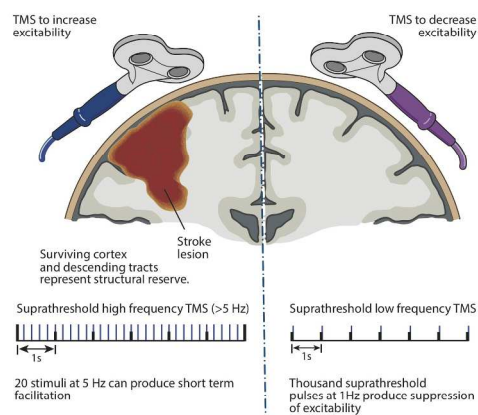


Figure 3. TMS may be used to stimulate the perilesional cortex after stroke and/or suppress excitability of the opposite hemisphere.

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