

Assessing the mechanisms of brain plasticity by transcranial magnetic stimulation

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive technique for focal brain stimulation based on electromagnetic induction where a fluctuating magnetic field induces a small intracranial electric current in the brain. For more than 35 years, TMS has shown promise in the diagnosis and treatment of neurological and psychiatric disorders in adults. In this review, we provide a brief introduction to the TMS technique with a focus on repetitive TMS (rTMS) protocols, particularly theta-burst stimulation (TBS), and relevant rTMS-derived metrics of brain plasticity. We then discuss the TMS-EEG technique, the use of neuronavigation in TMS, the neural substrate of TBS measures of plasticity, the inter- and intraindividual variability of those measures, effects of age and genetic factors on TBS aftereffects, and then summarize alterations of TMS-TBS measures of plasticity in major neurological and psychiatric disorders including autism spectrum disorder, schizophrenia, depression, traumatic brain injury, Alzheimer's disease, and diabetes. Finally, we discuss the translational studies of TMS-TBS measures of plasticity and their therapeutic implications.

Keywords: transcranial magnetic stimulation; plasticity; neurology; psychiatry; diagnostics; therapeutics.

Introduction

In this review, we begin by providing an overview of the fundamentals of the transcranial magnetic stimulation (TMS) technique and its various forms, with a focus on TMS protocols that enable measures of brain *plasticity*, i.e., an intrinsic capacity for use-dependent change that is essential for normal learning and development [1]. We then focus on alterations of TMS-derived plasticity measures in common neuropsychiatric disorders including autism spectrum disorder, schizophrenia, depression, traumatic brain injury, Alzheimer's disease, and diabetes. Our goal in discussing these disorders and in the dedicated section on therapeutics is not to cover the entire array of therapeutic TMS studies in each disorder but to focus on the implications of TMS measures of plasticity and brain states for diagnostic, predictive, and therapeutic purposes. We anticipate that the reader will appreciate how brain plasticity can be measured by TMS and the potential neural substrates of TMS-derived indices of brain plasticity. We will also review factors that can influence TMS plasticity measures, how TMS can be combined with other techniques such as EEG, and how the corresponding TMS plasticity measures can be obtained in translational (preclinical) studies in rodents.

Foundations of the TMS technique

TMS is a noninvasive brain stimulation technique first proposed by Barker and colleagues in 1985 [2] based on the principles of electromagnetic induction discovered by Faraday in the 19th century [3]: a brief and rapidly changing, high-intensity electric current (the *TMS pulse*) is passed through loops of conducting wire within a protective case and held against a given area of the scalp. The change in the electrical current induces a powerful fluctuating magnetic field that readily penetrates the skull and can induce a second electric current (in the opposite direction of the original current) within the excitable tissues of the brain [4,5]. When delivered with sufficient intensity over the cortex, the induced current depolarizes cortical neuronal assemblies located directly underneath the coil as well as in nearby and remote brain regions, thereby generating neurophysiological and behavioral effects [6–9]. To evoke activity in the human brain, the initial current typically needs to be in the order of 4–8 kA with a peak-to-peak rate of change of 100–200 μs , which induces an electric current perpendicular to the coil surface and in the order of 7–15 mA/cm^2 [3,10]. The intensity of the induced current is proportional to that of the original current and attenuates with distance by bone, air, tissues, subdural and subarachnoid cerebrospinal fluid, and alterations in the cortical structure [11,12]. TMS is considered safe when applied

according to the recommended safety and application guidelines endorsed by the International Federation of Clinical Neurophysiology [13,14].

Single-pulse and repetitive TMS

Single-pulse TMS (spTMS) protocols consist of discharges of single pulses often separated by 4–8s intervals. Applying a TMS pulse over the primary motor cortex (M1) can activate the corticospinal tract and associated neural circuits and cause a twitch in the muscle(s) represented by the stimulated brain region [2,15,16]. The electrical activity associated with the muscle twitch can be recorded in the form of a *motor evoked potential* (MEP) via surface electromyography (EMG). Applying a TMS pulse to the primary visual cortex can induce a percept such as a brief flash of light, called *phosphenes*, in the location of the visual field retinotopically represented by the stimulated visual cortex [17–19] or posterior parietal cortex [20]. Higher cognitive functions such as attention, memory, language, etc. can also be probed by applying TMS pulses to higher cortices and associated networks, transiently disrupting physiological processes and/or behavioral activities subserved by the stimulated brain regions [8,21–26]. Importantly, beyond local effects, TMS can have remote neurophysiological or behavioral effects in regions that have structural (white-matter) connectivity [27,28] or functional connectivity [29–33] with the targeted brain region.

The motor cortex has been the most common targeted region in TMS studies conventionally because of its objective and easily obtainable neurophysiological output. The TMS-induced MEP is often characterized by its amplitude and latency relative to the onset of spTMS, reflecting the functional integrity of the corticospinal tract. The magnitude of the MEP provides a measure of motor cortical excitability, or the balance between cortical excitation and inhibition (E:I), two opposing forces that control the activity in the cortex [34,35]. The latency of the MEP provides a measure of conduction time along central corticospinal motor pathways.

TMS also has been used in other forms, including paired-pulse (ppTMS) and repetitive TMS (rTMS) at specific intensities, frequencies, and patterns or bursts of stimulation (**Figure 1**) to probe, modulate, or restore activity in the brain [8,14]. rTMS protocols involve combinations of more than two pulses or bursts of stimulation delivered at a fixed frequency of 0.5–20 Hz, with or without interruption by stimulation-free intervals, for durations from several seconds up to 30–40 minutes. rTMS can modulate cortical excitability beyond the stimulation period and can be used in both motor and non-motor brain regions,

with local and remote effects on brain activity [6,8,22,36]. When applied to M1, high-frequency (≥ 5 Hz) rTMS protocols often increase cortical excitability, as measured by the increased size of induced MEPs within and following the rTMS train [37,38]. In contrast, low-frequency (≤ 1 Hz) rTMS often decreases cortical excitability as measured by the post-rTMS decrease in MEP size [38,39]. However, it is important to emphasize the substantial interindividual variability of such modulatory effects of rTMS [40–42]. It is also critical to recognize that the effects vary depending on the state of the cortex at the stimulation time. Such state-dependency effects [43] can in turn be used to increase the specificity of the rTMS modulatory effects [44].

Paired associative stimulation

Paired associative stimulation (PAS) consists of repeated pairing (e.g., 90–200 pairs) of stimuli, either *peripheral-cortical* (pcPAS) or *cortico-cortical* (ccPAS). In pcPAS, a peripheral electrical pulse delivered to a nerve of the hand (commonly the median nerve at the wrist), which activates the primary somatosensory cortex (S1), is followed by delivering a single TMS pulse over the corresponding hand representation in the contralateral M1 [45]. This S1-M1 coupling can modulate corticospinal excitability as reflected by a change in MEP amplitude [45,46]. The characteristics of pcPAS modulatory effects are similar to those of Hebbian synaptic plasticity [47], including the dependency of the direction of MEP modulation on the interstimulus interval (ISI) between the peripheral stimulation and the cortical TMS pulse. Following a temporally asymmetric Hebbian rule [48], shorter intervals (e.g., ISI = 10 ms or PAS10) typically induce MEP suppression, whereas longer intervals (e.g., ISI = 25 ms or PAS25) induce MEP facilitation [45,46,48,49]. The aftereffects of pcPAS develop rapidly (often within 30 mins), are relatively long-lasting (up to 60 mins post-PAS), reversible, and cortically generated [45,46,50]. The effects of PAS10 and PAS25 are believed to be mediated by LTD- and LTP-like mechanisms of plasticity, respectively [45,48,50]. A variant of PAS known as PAS_{N20+2} commonly involves 225 pairs (at a rate of 0.25 Hz) of median-nerve stimulation followed by delivering a single TMS pulse to the hand area of the contralateral M1 after an ISI equal to the N20 latency of the individual somatosensory-evoked cortical potential plus 2 ms [46,51]. Similar interactions between a peripheral and a cortical stimulus can be induced by timing the interval between the two

stimuli so that interaction takes place at the spinal level rather than the somatosensory cortex (*spinal associative stimulation* or SAS) [52].

In ccPAS, pairs of TMS pulses are delivered to two brain regions at an appropriate ISI (e.g., 200 paired pulses with an ISI of 10 ms), which can modulate inter-regional coupling according to spike-timing dependent plasticity mechanisms, including LTP-like plasticity [53,54]. ccPAS can also induce behavioral changes in motor and visual systems [55]. Given an appropriate ISI, the plasticity effects of ccPAS follow the principles of Hebbian plasticity [56]. The TMS pulse over the first targeted brain region, e.g., the left dorsolateral prefrontal cortex (DLPFC), causes spikal activity to reach a second, functionally connected brain region, e.g., the left inferior parietal lobule (IPL). If a second TMS pulse is delivered to the left IPL at an appropriate time, the DLPFC-IPL connection is strengthened via an LTP-like mechanism. The repeated pairing of such two TMS pulses reinforces the synaptic efficacy between the two targeted brain regions, giving rise to the ccPAS aftereffects. Beyond modulating inter-regional connectivity, ccPAS can also be used to modulate network-to-network connectivity [57].

Integration of TMS with EEG to assess non-motor cortical regions

Human electroencephalography (EEG) [58,59] is another non-invasive technique that enables the assessment of neural activity with millisecond temporal resolution by recording electrical fields from the scalp [60]. EEG reflects the activities of cortical neurons aligned perpendicular and radial to the scalp. The spatial and temporal summation of excitatory and inhibitory postsynaptic potentials of those neurons give rise to the EEG signal. When one or more large neuronal populations operate in synchrony, either spontaneously or in response to an event or external stimulation, a relatively strong electric field is generated and can be recorded via scalp EEG [61].

The combination of TMS and EEG techniques (TMS-EEG) is a powerful technique that enables non-invasive, in vivo assessment and modulation of cortical excitability, connectivity, and plasticity across motor and non-motor brain regions and networks [62–68]. One can also use the EEG oscillations to temporally coordinate the TMS pulse with ongoing or evoked brain activity in an effort to optimize brain states [69–71]. Thus, TMS-EEG can provide insights into the functional dynamics of the brain and brain-behavior relationships across the lifespan in healthy and clinical populations [29,30,32,57,64,65,72–78]. TMS-EEG studies have shown great potential for diagnostic, predictive, prognostic, and therapeutic

purposes in neurology and psychiatry [68,77,79–81,78,82–85]. Before such uses of this technique can become widespread, however, there are important aspects of TMS-EEG that need to be clarified, including to what extent TMS-evoked EEG potentials (TEPs) are peripherally evoked rather than direct cortical responses to the TMS pulse [86,87].

Neuronavigated TMS for spatial precision

Neuronavigated TMS involves the use of magnetic resonance imaging- (MRI-)based frameless stereotaxy for consistent and reliable intra- and inter-session coil positioning that improves the spatial precision and reliability of TMS delivery [88,89]. The use of neuronavigation can also improve the robustness of behavioral and neurophysiologic effects of TMS in healthy and clinical populations [90–92].

Theta-burst stimulation

A special form of patterned rTMS referred to as theta-burst stimulation (TBS) mimics neural oscillations considered to be associated with a type of non-Hebbian plasticity and typically consists of 50 Hz bursts of triplet pulses repeated at 5 Hz for a total of 600-1800 pulses [93,94]. As with other forms of rTMS, TBS protocols can be used to induce cortical plasticity in health and disease and to modulate neural activity for research and clinical purposes [95,96].

The two commonly used variants of the TBS protocol include (1) 190 seconds of stimulation in a 2-sec on, 8-sec off pattern called intermittent theta-burst stimulation (iTBS); and (2) 40 seconds of continuous stimulation called continuous theta-burst stimulation (cTBS). Studies of iTBS and cTBS of the primary motor cortex have found they typically produce lasting increased and decreased cortical plasticity, respectively, that often exceed those obtained with standard rTMS protocols [97–99].

TMS-TBS measures of mechanisms of plasticity

Combining plasticity-inducing rTMS protocols such as TBS with pre- and post-rTMS application of single TMS pulses allows for investigating the mechanisms of brain *plasticity* [1]. Plasticity-inducing protocols can have behavioral effects [6] and may be utilized for

therapeutic purposes [100–103]. When applied to M1, iTBS can induce MEP facilitation by ~35% for up to 60 min, whereas cTBS can induce MEP suppression by ~25% for up to 50 min post-TBS [97].

The facilitation and suppression of MEPs by iTBS and cTBS protocols, respectively, are considered to involve mechanisms similar to long-term potentiation (LTP) and long-term depression (LTD), respectively (**Figure 2**) [93,104,105]. As such, the return of post-TBS MEP amplitudes to their baseline levels is considered a neurophysiologic index of the efficacy of the mechanisms of cortical plasticity [64,98,106–108]. However, as discussed below, it is important in this context to consider the substantial inter- and intra-individual variability of the modulatory effects of rTMS and TBS, and their state-dependent effects [99].

Neural substrates of TMS-TBS measures of plasticity in humans

Three main lines of evidence support the notion that aftereffects of rTMS protocols involve mechanisms of synaptic plasticity. First, pharmacological characteristics of rTMS-induced changes in MEP amplitude are similar to those established for LTD or LTP of glutamatergic synapses in animal studies and drugs that modulate the function of critical receptors/channels for plasticity, e.g., *N*-methyl-*D*-aspartate (NMDA) receptors and Ca²⁺ channels, modify the TMS-induced plasticity effects [109]. Several pharmacological studies have shown that TMS-TBS measures of plasticity involve mechanisms of gamma-aminobutyric acid- (GABA-)ergic and NMDA-type glutamatergic synaptic plasticity [104,110–118].

The second line of evidence comes from invasive epidural recordings of efferent corticospinal neurons in patients with implanted electrodes [119–123] (**Figure 3**). A TMS-evoked corticospinal volley is often composed of a *D*-wave produced by direct activation of cortical layer-V pyramidal tract neurons (PTNs) and/or one or more *I*-waves, which reflect indirect (likely via presynaptic interneurons) and synchronous activation of PTNs [16,17,124,125]. These data have given rise to different theoretical cortical models of TMS–brain interactions [123,126,127]. cTBS has been shown to suppress the I1 wave while leaving the late I waves mostly unaffected [121], suggesting that cTBS exerts its effects mainly on the synapse between the inputs responsible for the I1 wave and the PTNs [123]. In contrast, iTBS induces a selective enhancement of late I waves while leaving the I1 wave unaffected [128], suggesting that iTBS selectively modulates the bursting cells of layers 2 and 3 that project upon PTNs and generate the later I waves [123]. The findings that TBS

mainly alters I-waves rather than the D-wave indicate that TBS effects occur trans-synaptically.

The third line of evidence in support of the role of synaptic plasticity in rTMS aftereffects comes from the observed interaction between the effect of TMS protocols and learning that is compatible with the common rules of synaptic plasticity, including (a) *metaplasticity*, i.e., modulation of synaptic plasticity by prior synaptic activity [129] and (b) reversal of previously induced synaptic plasticity [130]. Studies using priming stimulation by TMS have found evidence for Bienenstock-Cooper-Munro (BCM) homeostatic metaplasticity [131], i.e., reductions of corticospinal excitability by one TMS protocol causing stronger facilitatory effects by a subsequent protocol, in TBS [132,133] and between different non-invasive brain stimulation protocols [134,135]. The findings that rTMS aftereffects interact between protocols and motor- and cognitive learning indicate that rTMS effects are involved in motor and cognitive processes related to plasticity [109].

However, it is worth remembering that LTP and LTD refer to very specific neurophysiologic phenomena at the level of individual synaptic connections, and the changes induced by TMS or TBS are certainly not limited to specific individual synaptic terminals. Rather, the modulatory effects of rTMS or TBS likely involve neurons and glia, along with intra-cortical and cortico-(sub)cortical loops [123,136–139].

Variability of TMS-TBS measures of plasticity

In recent years, there has been an increased focus on the degree of inter- and intraindividual variability in TMS-TBS measures of plasticity and the factors contributing to such variability [94,99,140–156].

Some of the factors identified as potential contributors to the interindividual variability in TBS measures of plasticity include differentially activated intracortical networks [144], functional connectivity in the motor system [94,148], state-dependent factors and genetic polymorphisms [98], stimulation intensity [153], the target muscle, and baseline MEP amplitude [99].

Several factors can potentially influence the intraindividual variability of TBS measures of plasticity including age [156], genetic polymorphisms [151,153], phase of the menstrual cycle across visits [157,158], changes in the blood glucose levels and caffeine intake across visits [159–161], amount and quality of sleep the night before each visit

[162,163], intensity and duration of exercise before each visit [164,165], the intervisit interval [151], the time of day [166], the use of neuronavigation [88,89], changes in baseline MEP amplitude across visits [99,151], the use of robotic arms such as the TMS-Robot (Axilum Robotics, Schiltigheim, France), which can reduce trial-to-trial variability of MEP amplitude [167], and the use of closed-loop systems that time the delivery of TMS pulses based on EEG-derived indices of brain states [69–71].

Recent studies indicate that the modulatory effects of TBS may be overestimated [140,154,168]. One possible reason for this lack of reliable effects may be applying TBS at intensities that are insufficient to induce consistent plasticity across individuals. TBS is commonly applied at a subthreshold intensity, i.e., 80% of individual active motor threshold (aMT). There is some evidence suggesting that determining the TBS intensity based on the individual resting motor threshold (rMT), e.g., 70% of rMT, may enhance the consistency of TBS aftereffects [169]. However, in that context, it is important to remember that the modulatory effects of TBS depend on whether or not there is a contraction of the target muscle before the onset of the stimulation [170]. Moreover, recent clinical studies have found robust therapeutic TBS effects at substantially higher stimulation intensities, i.e., at 90–120% of individual RMT to the left DLPFC for treatment of major depressive disorder [171,172]. Determining the precise role of stimulation intensity and other potential factors influencing the robustness of TBS aftereffects within and across individuals requires further systematic investigations.

Effects of age in TMS-TBS measures

A cross-sectional study of individuals aged 19–81 found that cTBS-induced motor cortical plasticity linearly declined across the lifespan, suggesting that the efficiency of cTBS-induced LTD-like plasticity in the motor cortex is progressively reduced with aging [173]. In contrast, iTBS-induced LTP-like plasticity was generally found to be less impacted by aging [128,174]. Enhanced priming of iTBS aftereffects with preceding cTBS was observed in younger adults but not older adults, indicating reduced homeostatic metaplasticity with aging [175].

A longitudinal study of the effects of aging on iTBS-induced plasticity as measured by changes in resting-state functional connectivity (rsFC) of the default-mode network (DMN) found younger adults (age \leq 30 yrs) showed iTBS increased rsFC in distal DMN regions

whereas iTBS aftereffects in older adults (age \geq 60 yrs) were more local and limited to proximal DMN regions [176]. Importantly, older adults with “young-like” functional responses to iTBS had greater structural integrity in the brain (as measured by diffusion tensor imaging), higher education, and superior cognitive performance at baseline as well as less cognitive decline after 3 years [176]. These results suggest that iTBS measures of plasticity as measured by changes in rsFC can provide an index of the brain’s resilience in aging and enable the assessment of network plasticity, which may constitute a neurophysiological substrate of cognitive reserve [177,178].

A large-scale analysis of individual participant data from several TBS studies found a small, non-significant linear attenuation of iTBS- and cTBS-induced plasticity with age [99]. However, age had a significant non-linear effect, with young participants exhibiting increased iTBS-induced facilitation, and older adults exhibiting a steady drop-off in facilitation [99]. Because the data used in that analysis included very few participants in the 35–50 age group, further systematic investigations of changes in TBS measures of plasticity across the lifespan with adequate sampling from all age groups are warranted.

Effects of genetic variability in TMS-TBS measures

Genetic factors clearly influence the effects of TMS [179]. Brain-derived neurotrophic factor (*BDNF*) is one of the most important neurotrophins critically involved in the NMDA-type glutamate receptor-dependent LTP [180] and LTD [181]. The common single-nucleotide polymorphism (SNP) Val66Met in the *BDNF* gene influences the intracellular transport and packaging of the LTD-associated precursor peptide of BDNF (pro-BDNF), while the regulated secretion of the mature (m)BDNF protein is involved in LTP [182,183].

Several studies have shown the effects of *BDNF* Val66Met polymorphism on TMS measures of plasticity in humans, including reduced training-dependent facilitation of MEPs [184,185], reduced cTBS-induced suppression [141,153], and reduced iTBS-induced facilitation of MEPs [141,143,185,186]. Mori et al. [187] reported that individuals carrying the G allele in the GRIN2B rs1805247 SNP of the NR2B subunit gene of the NMDA receptor showed greater iTBS-induced cortical plasticity.

Other genetic influences on TMS measures of plasticity include reduced efficacy of the mechanism of cortical plasticity due to the presence of the ϵ 4 allele in the apolipoprotein

E (ApoE) gene [188–191] and reduced cTBS-induced suppression of MEPs in healthy older adults with the Val158Met SNP in the catechol-O-methyltransferase (COMT) gene [192]. The results from these small studies need to be replicated in larger studies before they can be considered reliable genetic determinants of TBS-induced plasticity.

TMS plasticity measures in disease

Autism spectrum disorder

Rodent models of autism spectrum disorder (ASD) and studies on genetic syndromes with a high prevalence of ASD symptoms in humans indicate altered mechanisms of synaptic plasticity, including use-dependent changes in synaptic strength [193–198] and aberrant LTP and LTD of excitatory synaptic strength [199–206].

Studies in adults with ASD have found greater and longer-lasting TBS-induced changes in MEP amplitude in adults with ASD compared to neurotypical (NT) adults, indicating an exaggerated, hyperplastic response to TBS in ASD [107,133,207]. Similarly, children and adolescents with high-functioning ASD (HF-ASD) show abnormally greater facilitatory responses to cTBS than typically developing children [208]. Moreover, children and adolescents with HF-ASD show a maturational trajectory of cTBS measures of plasticity, in which the extent or the maximum amount of cTBS-induced suppression of MEPs increases linearly with age [208,209]. These findings indicate the utility of cTBS measures of cortical plasticity as diagnostic biomarkers for individuals with ASD across the lifespan [210].

Schizophrenia

A pilot M1 cTBS study on five early-onset, first-episode, antipsychotic-naive schizophrenia patients found the duration of cTBS-induced aftereffects was noticeably shorter in patients with schizophrenia compared with their age- and gender-matched counterparts [211]. This finding suggested that the efficacy of the mechanisms of cortical plasticity is already reduced in the early stages of schizophrenia. A more recent study [212] compared M1 cTBS aftereffects in 10 schizophrenia patients under treatment by antipsychotics with 10 healthy controls and found fewer schizophrenia patients exhibited the expected plasticity response

induced by cTBS compared to healthy controls. These results suggest the reduced efficacy of the mechanism of plasticity induced by cTBS among patients with schizophrenia [212].

Depression

TMS studies in patients with depression have found evidence of decreased cortical excitability in the frontal cortex [213–219], interhemispheric imbalances in prefrontal and motor cortices in the form of reduced excitability in the left hemisphere [213–216,219] or increased excitability in the right hemisphere [220]. One study found that 1-Hz rTMS applied to the left M1 expectedly reduced cortical excitability in that hemisphere, but did not modulate the excitability in the right hemisphere, indicating loss of normal interhemispheric modulation in depression [221]. Subsequent studies found applying high-frequency rTMS to the left prefrontal cortex would increase cortical excitability (as indexed by lowered rMT) in the ipsilateral hemisphere [222] or reduce the interhemispheric difference in excitability [216] and was associated with lasting clinical improvements [223].

rTMS studies have found evidence of reduced modulation of cortical plasticity in patients with major depressive disorder (MDD), including reduced post-exercise MEP facilitation [224,225], and reduced plasticity induced by PAS [226], both in the motor cortex [227] and in the prefrontal cortex [228]. Consistent with these findings, drug-free patients with MDD showed reduced iTBS-induced facilitation of MEPs compared to healthy controls, suggesting that LTP-like mechanisms mediated by the glutamatergic NMDA receptor pathway are impaired in patients with MDD [229].

Interestingly, recent studies have found that the extent of MEP modulation induced by 10-Hz rTMS applied to M1 predicts the clinical response to the standard 10-Hz rTMS treatment applied to the DLPFC in depressed patients [230,231]. If confirmed in larger multisite studies, these findings can help stratify patients with depression based on their likelihood of positive response to 10-Hz rTMS, support physicians in choosing the best therapeutic approach, and assist TMS clinics in prioritizing and allocating their resources. Accelerated protocols using iTBS instead of 10-Hz rTMS can alleviate some of these concerns, allowing for more eligible patients to be treated within the same time period and using comparable human and equipment resources [171,172]. For example, the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol delivered iTBS at 90% rMT in 10 daily sessions over 5 consecutive days to an individually targeted region in the left

DLPFC based on the strongest resting-state functional connectivity (negative correlation) with the subgenual anterior cingulate cortex and found remission in 90% of patients [172].

Traumatic brain injury

Traumatic brain injury (TBI) can cause several neurological symptoms including chronic pain [232], mood and sleep disturbances [233,234], as well as increased susceptibility to seizures and post-traumatic epilepsy [235,236], which can be attributed to impaired cortical inhibition. This notion is supported by animal studies that have found a post-TBI shift of cortical E:I ratio toward excess excitation due to loss of GABA-mediated synaptic inhibition and reduction in GABA-synthesizing enzymes in the cortical inhibitory synapses [237–239]. Evidence for loss of such cortical inhibitory tone after TBI was obtained *in vivo* in a rat fluid percussion injury model [240] using a form of ppTMS known as long-interval cortical inhibition (LICI) [241] that is an index of cortical GABA-mediated inhibition [242,243]. The results showed a reduction in LICI for up to 6 weeks following TBI [241]. Various studies using different ppTMS measures of intracortical inhibition have reported heterogeneous results including facilitation, suppression, and no effect on MEPs following mild traumatic brain injury (mTBI) [244].

Support for altered cortical plasticity after mTBI has been obtained by rTMS measures of plasticity. In one of the first rTMS studies in humans with mTBI, 1-Hz rTMS induced irregular shape alterations in the MEP waveform at 2 weeks after injury, which was normalized in 9 out of 15 patients when re-tested after 3 months [245]. Bashir and colleagues [246] used cTBS to assess changes in cortical plasticity following mTBI and found that, unlike control subjects, mTBI patients exhibited paradoxical MEP facilitation at week 2, at 0, 5, 10, and 20 min post-cTBS. The cTBS response in mTBI patients returned to the expected inhibition at week 6 post-injury [246]. Another evidence for abnormal TMS measures of plasticity in mTBI was reported in a proof-of-principle study [247], in which cTBS did not induce a significant suppression of MEPs two weeks after injury, but cTBS response was normalized at 6 weeks post-injury when most patients became asymptomatic.

Further evidence for altered mechanisms of cortical plasticity as measured by M1 cTBS was obtained in a TMS-EMG-EEG study [244], where patients with mTBI showed greater suppression of MEPs at 30 min post-cTBS relative to the controls. Moreover, mTBI

patients exhibited significant inhibition of TMS-evoked EEG potentials (TEPs) P30 and N45 at 30 min post-cTBS, while the corresponding TEPs in the control subjects were unaffected. These results provide evidence for enhanced cTBS-induced LTD-like plasticity up to approximately 4 months post-injury among patients with mTBI [244].

Alzheimer's disease

In Alzheimer's disease (AD), synaptic degeneration is strongly correlated with cognitive decline and plays a critical role in the development of dementia [248]. The results of preclinical studies have shown that soluble A β oligomers can block hippocampal LTP [249], which is an electrophysiological index of learning and memory [250] but enhance LTD [251]. These aberrations in the mechanisms of plasticity can induce conformational changes in the tau proteins, resulting in pathological consequences in synaptic plasticity and cognition [252,253]. Because iTBS-induced LTP-like plasticity is likely mediated by the strengthening of glutamatergic synapses via NMDA receptor, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and calcium channel [110], iTBS measures of M1 plasticity can be used as a tool for investigating alterations in cortical plasticity in early AD [254].

In a large group of newly diagnosed AD patients, Koch and colleagues found evidence for impaired iTBS-induced LTP-like cortical plasticity – with a paradoxical LTD relative to healthy controls – and impaired short-latency afferent inhibition (SAI), which is considered an index of central cholinergic impairment [255]. Based on the fact that impairment of cortical plasticity was not correlated with age of onset, it was argued that impairment in cortical LTP is a central mechanism of AD pathophysiology that is independent of the age of onset [256]. A study on the reproducibility of iTBS aftereffects in patients with AD [151] found that reproducibility was higher in AD patients than in individuals with healthy aging, which was attributed to the pathological rigidity of neurophysiological systems in AD.

Importantly, paradoxical LTD-like cortical plasticity in response to iTBS has been found to be associated with high tau in the cerebrospinal fluid and more rapid cognitive decline [257]. A subsequent study from the same group found the impairment in LTP-like plasticity was associated with less efficient verbal memory but not with other cognitive functions [258]. The association between reduced LTP-like cortical plasticity and faster cognitive decline in patients with AD was replicated in another study on 60 newly diagnosed

patients [259], which found iTBS aftereffects had excellent accuracy for differentiating between AD patients and healthy controls. A separate study on mostly medicated AD patients found the extent of M1 iTBS-induced plasticity at baseline predicted the change in patients' cognition following treatment with 10-Hz rTMS [260]. These findings collectively support the crucial role of synaptic degeneration in the pathophysiology of dementia [261] and indicate the diagnostic and predictive utility of rTMS measures of plasticity in assessing the AD pathophysiology and predicting clinical response to rTMS treatment [261].

It should be noted, however, that AD-related alterations in LTP-like plasticity as indexed by iTBS are not necessarily uniform across all stages of the disease. For example, Buss and colleagues [262] used iTBS to assess LTP-like cortical plasticity in patients with amnesic mild cognitive impairment (aMCI), which is considered a prodromal stage of AD [263,264]. The patients with aMCI showed a lack of LTP-like plasticity unrelated to the quantitative A β burden on positron emission tomography. Unexpectedly, greater LTP-like response to iTBS was associated with worse memory function in aMCI patients, underlining the complexity of alterations in neuroplasticity in the prodromal stages of AD [262].

Diabetes

Rodent models of type-2 diabetes mellitus (T2DM) show aberrant synaptic plasticity in the hippocampus resulting in cognitive deficits [265] and less likelihood of post-stroke recovery due to impaired neuroplasticity [266]. Consistent with those findings, individuals with T2DM showed reduced iTBS-induced plasticity, indicating altered efficacy of neuroplastic mechanisms in the cortex [267]. Interestingly, those alterations were associated with cognitive impairment as indexed by lower learning scores on the Rey auditory verbal learning test (RAVLT) and fewer correct trials of the Digit Span Backwards test [267]. Those results were in line with mouse models of T2DM that showed impaired object discrimination, hippocampal LTP, and impaired spatial memory [268–270].

Considering that iTBS aftereffects, RAVLT, and working memory performance in humans have all been shown to be NMDA-dependent [104,271–274], the association between reduced verbal learning and working memory and reduced LTP-like plasticity in T2DM may be due to a brain-wide reduction in the density or efficacy of NMDA receptors [267]. A subsequent study found that reduced iTBS measures of cortical plasticity in T2DM patients were already present in individuals with pre-diabetes, and reduced corticomotor

plasticity in T2DM, but not in prediabetes, was associated with lower cortical glutamate concentration [275].

Translational studies of TMS-TBS measures – Insights and challenges

In each of the sections above on specific disease states, we have cited the key evidence from animal models that form a foundation for investigating pathophysiological changes in plasticity using human rTMS measures. Here, we summarize some of the parallel TMS-TBS studies in animal models that can be translated to human studies using the same protocols (**Figure 4**).

LTP as a use-dependent enhancement of excitatory synaptic strength was first identified in the hippocampus of an anesthetized rabbit in 1973 [276] and subsequently replicated in rodent brain slices [277,278]. LTD as a homeostatic mechanism was first identified in rat hippocampal slices in 1992, is reliably reproducible *in vitro* in numerous laboratories, and appears to be due to the reversal of the LTP-related molecular mechanisms [279]. Translational research in this field ideally involves *in vivo* experimental rTMS [280]TBS studies in animals that can help elucidate the mechanisms of TBS-induced plasticity in humans.

Extrapolating from animal LTP/LTD studies to human brain stimulation protocols is not without challenges. For instance, the rate at which synaptic plasticity matures varies in different regions of the rodent brain [281,282]. Similarly, the capacity for LTP in mice varies by age; it is greater in the visual cortex of adult mice (older than 6 months) than in 4–5-week-old mice [283]. In contrast, younger rats exhibit a lower threshold for LTD induction and a greater magnitude of hippocampal LTD than older rats [283,284].

An iTBS study in rats found functional modification of cortical GABAergic parvalbumin-positive (PV+) interneurons only after 32 days of life (human age: 4–11 years), which peaked by postnatal day 40 (human age: 12–18 years). This result may be due to a lack of enough synaptic connections in immature PV+ cells that prevents them from receiving the level of excitatory input required to be influenced by iTBS [285].

Another important issue to consider when extrapolating from results of *in vitro* studies of synaptic plasticity is that most of the results of those studies are obtained by precise

electrical stimulation of isolated pathways, whereas *in vivo* brain stimulation protocols such as TMS have much coarser localization and lower spatial resolution, and activate entire neuronal networks and their supporting glial cells [279].

A major challenge of implementing translational rTMS studies in rodent models is the low focalization of stimulation due to the large size of the coil relative to the rodent's brain. To overcome this challenge, Hsieh and colleagues developed a *cortical electrical stimulation* (CES) technique for iTBS and cTBS protocols in rats [286], which is both less invasive and has higher accuracy and spatial resolution than TMS for targeting a specific area of the motor cortex. The authors used direct CES over the motor cortex using conventional iTBS and cTBS patterns and found CES-TBS protocol induced both LTP- and LTD-like plasticity effects for at least 30 min post-TBS, similar to those obtained in human TBS studies [286]. Because the rats were under anesthesia to suppress major stress, the stimulation intensity was set to 80% of rMT, instead of the lower intensity of 80% of active aMT commonly used in human TBS protocols. The facilitation of MEPs by CES-iTBS and suppression of MEPs by CES-cTBS were replicated in a subsequent study [287]. These results indicate that CES-TBS animal models can be useful for investigating the mechanisms of cortical plasticity and bridging the human and animal studies for establishing new diagnostic and therapeutic applications for neurological disorders [286,288–291].

Therapeutic implications of TMS measures of plasticity and brain state

As reviewed above, at a system level, rTMS modulates excitability and plasticity in a targeted cortical region [6,292–294] and exerts broader effects across networks connected to that region [30,295–298]. Additionally, the putative mechanism of action of the therapeutic effects of rTMS is thought to be the modulation of dysfunction within and between functional networks [299–302]. Thus, targeting the rTMS based on structural and/or functional networks has become a prominent focus for optimizing the efficacy of rTMS for therapeutic purposes. That being said, the stimulation location is only one factor influencing the clinical and physiological impact of rTMS. The therapeutic benefit of such neuromodulation is also impacted by how the stimulation is received and processed in the brain. In other words, the impact of applying a pulsed magnetic field to an electrically charged region of the cortex is influenced by both the degree and direction of the magnetic field itself as well as the state of excitability of the targeted cortical region and the broader functional network [43,179,303,304] (**Figure 5**). Thus, to optimize the induced changes in plasticity and

modulation of the putative mechanism underlying the clinical symptom, it is important to characterize the current brain state in terms of local cortical excitability and network connectivity in order to determine the optimal treatment protocol for a given patient.

Impact of pharmacology on brain state

For both safety and feasibility, most rTMS treatments have allowed participants to continue their current medications [305]. Safety reviews suggest that rTMS in those receiving stable doses of antidepressant medication does not increase the risk of adverse events [13] but nonetheless increases within-group variability in neurochemical state and decreases statistical power. To control for variability due to medications, investigators could enroll only participants who have been withdrawn from all psychotropic medications; however, withdrawing symptomatic patients from their medications introduces safety concerns of increased suicidal ideation and withdrawal-related side effects, and it demands close medical monitoring. A more feasible approach would be to require participants to maintain a steady medication dose and to apply a within-subject model controlling for baseline severity as the primary outcome measure. While this would not eliminate variability across participants, it reduces the effects of neurochemical brain state on the primary outcome measure. Combining rTMS and pharmacological treatment is another novel multimodal intervention being developed in adults and adolescents with depression [306,307].

Impact of concurrent behavioral task on brain state

To increase the tolerability of rTMS sessions (especially those that may last several minutes to hours, in the case of long research study visits), clinics and research studies have allowed patients to read, watch TV, or listen to music during rTMS sessions. However, factors such as attention, arousal, and mood state have been shown to affect the modulation of excitability by rTMS [55,308–310]. The difference in behavioral engagement/arousal this causes is another potential source of within-group variability and suboptimal therapeutic efficacy. To control and optimize brain state, some studies have the participant watch or listen to specific stimuli or engage in a behavioral or cognitive task that engages the same brain networks as the rTMS target, thus amplifying the impact of the rTMS on the targeted network [304]. Studies of rTMS for post-traumatic stress disorder (PTSD), smoking cessation, and obsessive-compulsive disorder (OCD) have shown increased treatment

response when the participant's symptoms were provoked (e.g., by asking questions about thoughts, images, or impulses related to their obsessions or compulsions or asking the patient to perform a task related to their symptoms [311] immediately before rTMS stimulation [312–314]. Others are beginning to pair rTMS with concurrent behavioral interventions such as cognitive-behavioral therapy (CBT) [315]. This is a burgeoning field with many groups seeking to harness the power of plasticity provided by the rTMS and appropriately guide it toward the ultimate functional network and clinical target (**Figure 6**).

Individualizing rTMS protocols based on brain state

The degree of modulation at the brain network level can be quantified using functional magnetic resonance imaging (fMRI) as well as quantitative EEG. Previous research has shown that high-frequency rTMS (as is often used for therapeutic protocols in depression and other neuropsychiatric disorders) leads to synchronization of EEG activity primarily in alpha and beta frequency bands, both at the targeted site as well as distant areas [63,316–325]. It has been proposed that rTMS may act through triggering and inducing long-term entrainment of oscillations to the stimulation frequency. In doing so, rTMS may reset cortical and thalamocortical oscillators and facilitate more stable intrinsic oscillatory activity [316,318,319]. Alpha frequency (8-13 Hz), in particular the upper alpha band (10-12 Hz), seems to be well-suited to coordinating activities over distance in the brain both at the cortical and the cortico-subcortical (e.g., thalamic) level [326,327]. Standard rTMS protocols often apply stimulation at a standard 10-Hz frequency, but there is large variability in response, perhaps partially due to interindividual variability in intrinsic alpha frequency and its proximity to 10 Hz [328]. There is some evidence to support that individualizing the frequency of stimulation to match the individual's intrinsic alpha frequency results in better clinical efficacy for both schizophrenia and depression [329–332].

Most recently, in this area of research, “closed-loop EEG-rTMS” devices have been developed to record EEG and process it in real-time such that rTMS pulses can be applied not only at a specific frequency, but also at a specific time-point within the oscillation [70,71]. Using this device, Zrenner and colleagues found that TMS applied at the trough (or negative peak) of the alpha rhythm induced greater LTP-like facilitation in the primary motor cortex than pulses applied at the positive peak of the alpha rhythm [70]. They extended these findings to DLPFC and found that closed-loop rTMS applied at the trough of the individual's alpha rhythm, compared to random alpha phase stimulation, leads to reduced left frontal

resting-state alpha power and increased TMS-induced beta oscillations over medial frontocentral EEG channels [71]. The therapeutic potential of closed-loop EEG-rTMS has yet to be established, however, and a clinical trial is ongoing [333].

Funding

AP-L was partly supported by the National Institutes of Health (R24AG06142 and P01 AG031720) and received funding from MagStim, Inc. AR was partly supported by the National Institutes of Health (NIH R01 MH100186, R01 NS088583), and The Boston Children's Hospital Translational Research Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard University and its affiliated academic health care centers, the National Institutes of Health, or any of the other listed granting agencies.

Conflicts of Interest Statement

AJ is an employee of Linus Health. AP-L is a cofounder of Linus Health and TI Solutions AG; serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., and MedRhythms; and is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. AR is a founder and advisor for Neuromotion and PrevEP, serves on the medical advisory board or has consulted for Cavion, Epihunter, Gamify, Neural Dynamics, NeuroRex, Otsuka, Roche, and is listed as an inventor on a patent related to integration of TMS and EEG. The authors declare no other financial relationship that could be construed as a potential conflict of interest.

Author Contributions

AP-L and AJ contributed to the conception and design of the manuscript. AJ drafted the manuscript with contributions from LMO. All authors contributed to the revising and the final approval of the manuscript and agreed to be accountable for the content of the manuscript.

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Figure legends.

Figure 1. Common metrics of applying TMS to motor cortex. (A) Resting motor threshold (rMT) for the APB muscle is calculated by identifying the minimum stimulus strength, measured in percent machine output (% MO), that evokes an MEP of a fixed amplitude (typically $\geq 50 \mu\text{V}$) in the APB at rest in a majority of trials. Stimulus strength is indicated in the left panel, with resulting MEPs shown in the right panel, where red arrows indicate the time of stimulation and percent stimulator output is proportional to the arrow length. (B) ppTMS paradigms where a subthreshold conditioning stimulus (short red vertical line) followed by a supra-threshold test stimulus (longer red vertical line). At short inter-stimulus-intervals (ISIs) (1–5 ms) short interval intracortical inhibition (SICI) is seen with inhibition of the test MEP by the antecedent conditioning stimulus. At longer ISIs (10–20 ms), test MEP amplitude is enhanced relative to the control MEP, such that ICF is seen. (C) Still longer ISIs (50–300 ms) are applied with two suprathreshold stimuli in LICI protocols where the MEP resultant from the test stimulus is predictably lower in amplitude than the preceding MEP resulting from the conditioning stimulus. ICF = intracortical facilitation; ISI = interstimulus interval; LICI = long-interval intracortical inhibition; ppTMS = paired-pulse transcranial magnetic stimulation; rTMS = repetitive transcranial magnetic stimulation; spTMS = single-pulse transcranial magnetic stimulation (adapted from [336]).

Figure 2. cTBS and iTBS measures of plasticity. Evaluation of corticospinal excitability by comparing MEPs recorded from the peripheral muscle in response to a single pulse to M1. TBS involves applying triplet pulses at 50 Hz repeated at intervals of 200 ms. MEPs are recorded at baseline and following either cTBS or iTBS, providing an index of local cortical plasticity. Following iTBS, MEPs typically show increased amplitude for ~30 mins, whereas cTBS induces a suppression MEPs for approximately the same amount of time [93]. Post-TBS enhancement or suppression of cortical activity is considered an index of LTP- or LTD-like mechanism of plasticity in the targeted brain area. Applying paired pulses to M1 at an ISI of either 3 or 100 ms can be used to evaluate intracortical inhibition. cTBS = continuous theta-burst stimulation; ISI = interstimulus interval; iTBS = intermittent theta-burst stimulation; LTD = long-term depression; LTP = long-term potentiation; M1 = primary motor cortex; MEP = motor evoked potential; TBS = theta-burst stimulation (adapted from [106]).

Figure 3. Neurophysiological effects of plasticity-inducing TMS protocols. (A) Epidural volleys recorded at baseline (black trace) and after excitatory (red traces) and inhibitory

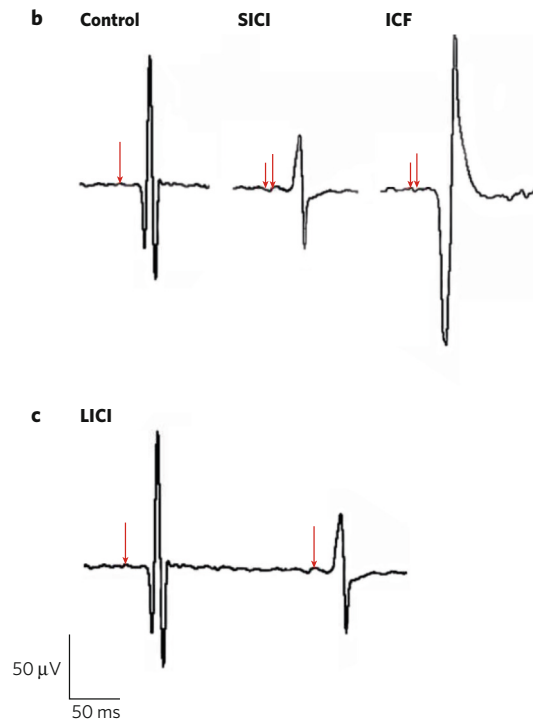
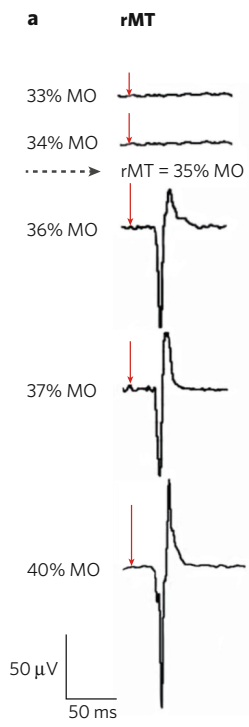
(green traces) plasticity protocols. Each trace is the average of the responses to 10–25 TMS pulses. 5 Hz rTMS increases the amplitude of the proximal D wave and all I waves. Paired associative stimulation at a 25-ms ISI (PAS25) selectively facilitates the late I waves without changing the I1 wave. cTBS leads to suppression of the amplitude of the I1 wave. 1 Hz rTMS causes a selective suppression of late I waves with no change in the I1 wave. **(B)** Corticospinal volleys and MEPs evoked by single TMS pulses in baseline conditions and after iTBS. Each trace is the average of 20 sweeps. Three descending waves can be observed in the epidural recording. iTBS facilitates the amplitude of I2 and I3 waves without affecting the amplitude of the I1 wave. The amplitude of MEP is slightly (but, in this case, nonsignificantly) increased following iTBS. **(C)** It is proposed that 5 Hz subthreshold rTMS suppresses the excitability of superficial inhibitory circuits, including superficial (L1) cortical neurons, and that most of the protocols (iTBS, PAS25, PAS10, 1 Hz rTMS, TDCS) modulate bursting neurons of layer 2 and 3 (L2/L3) that project upon PTNs and generate the late I waves. It is proposed that cTBS selectively suppresses the excitability of monosynaptic connections to PTNs. 5 Hz rTMS may produce its *excitatory* effects by enhancing the excitability of PTNs. cTBS = continuous theta-burst stimulation; ISI = interstimulus interval; iTBS = intermittent theta-burst stimulation; MEP = motor evoked potential; PAS = paired associative stimulation; PTNs = pyramidal tract neurons; rTMS = repetitive transcranial magnetic stimulation. TDCS = transcranial direct current stimulation (adapted from [123,128]).

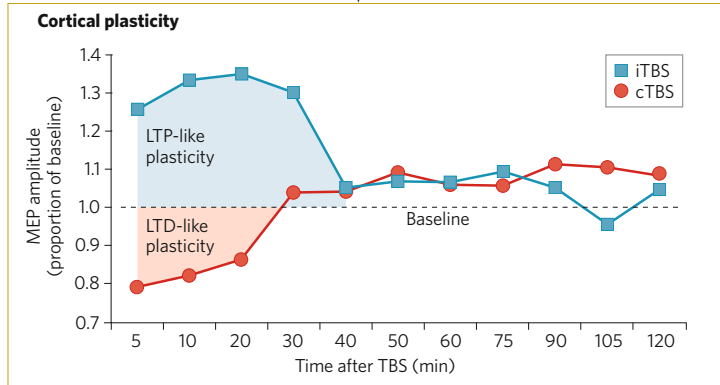
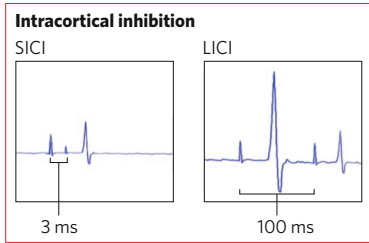
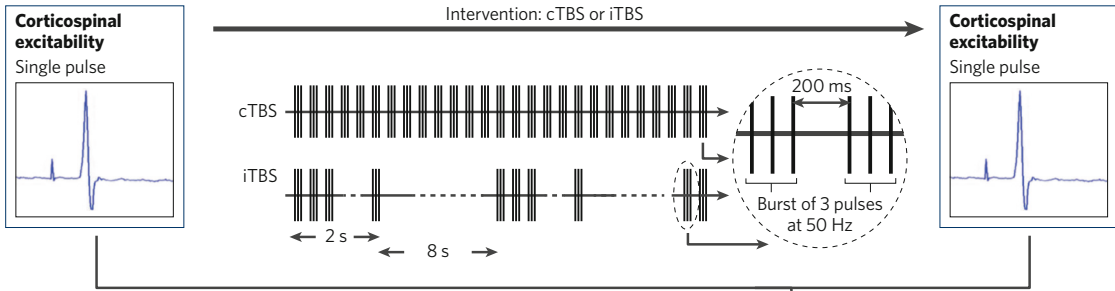
Figure 4. Translational TMS studies in rats. (A) TMS-MMG setup. An unanesthetized rat is restrained on a platform with 4 straps with minimal discomfort. A figure-of-8 TMS coil is centered over the dorsal scalp at the interaural line. The MMG is obtained by two 3-axis accelerometers on each ventral surface of the foot while the rat is under brief isoflurane anesthesia before placement into the restraint. **(B)** Representative data during spTMS (left) or ppTMS (right) obtained with ISIs of 50, 100, and 200 ms in rats. ppTMS traces show long-interval intracortical inhibition of the test-evoked MMG. Arrow indicates the onset of the test stimulus. **(C)** Examples of MEP changes following sham stimulation, iTBS, and cTBS in anesthetized rats. Representative MEP traces following TBS show no obvious change after sham stimulation, whereas MEP traces show increased amplitude after iTBS and reduced amplitude after cTBS. cTBS = continuous theta-burst stimulation; ISI = interstimulus interval; iTBS = intermittent theta-burst stimulation; MEP = motor evoked potential; MMG = mechanomyogram; ppTMS = paired-pulse transcranial magnetic stimulation; spTMS =

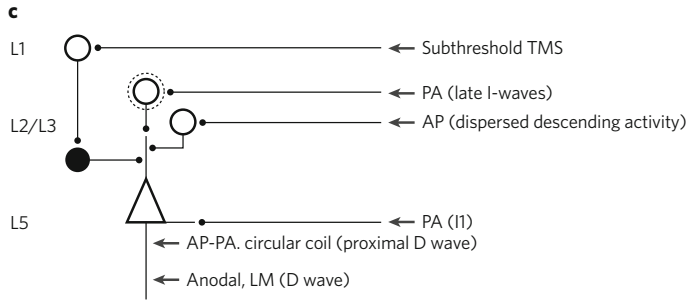
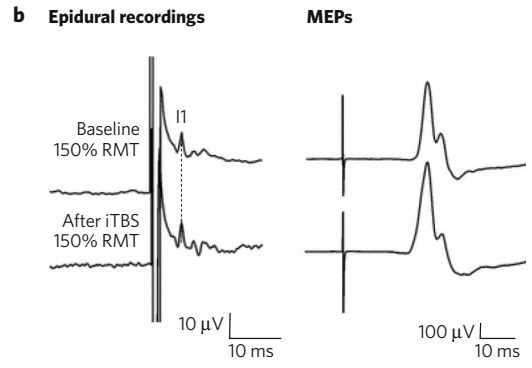
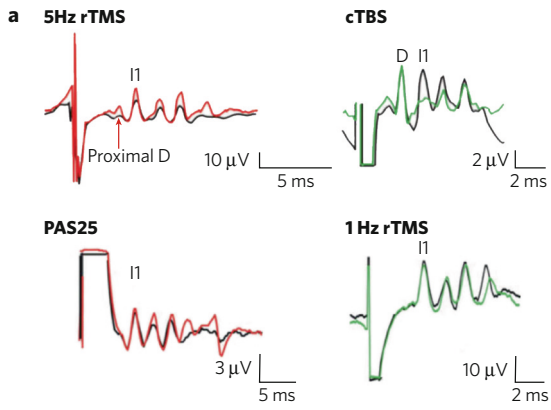
single-pulse transcranial magnetic stimulation; TMS = transcranial magnetic stimulation (adapted from [243,286]).

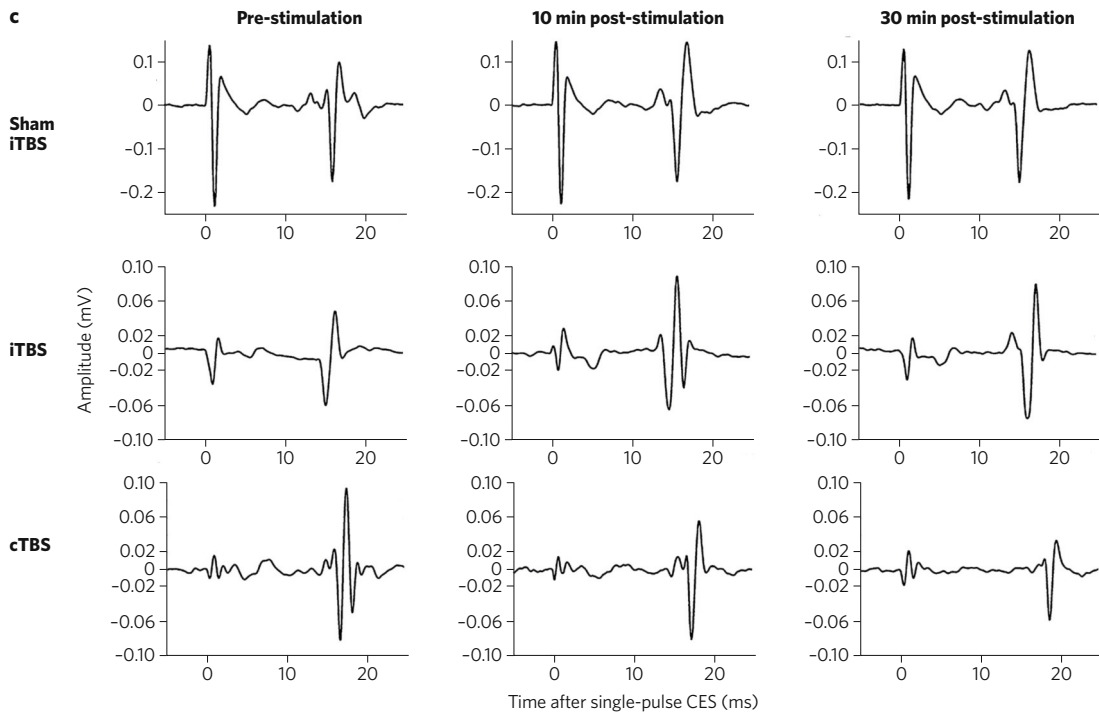
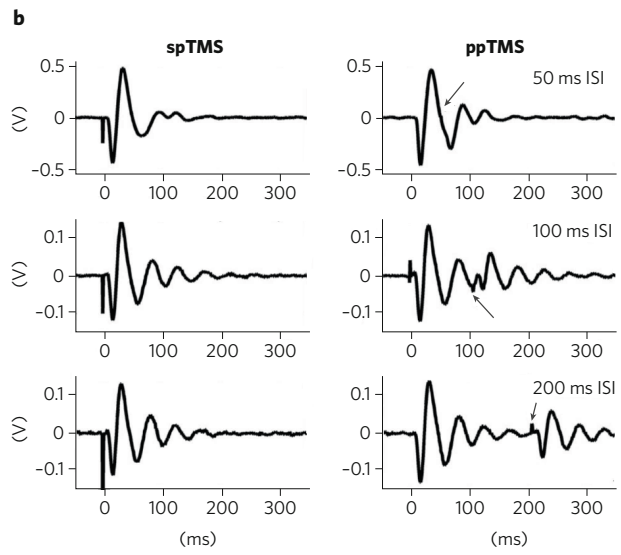
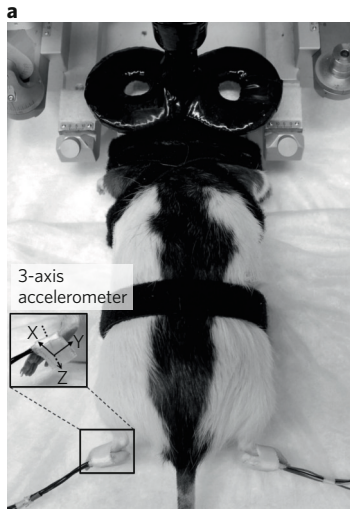
Figure 5. Antidepressant response to repetitive transcranial magnetic stimulation is associated with functional connectivity (FC) between the stimulation site and the subgenual cingulate cortex (SGC) across different cohorts. The intrinsic spontaneous activity of the SGC (A) can be compared with that of other regions of the brain to identify regions of strong positively or negatively correlated FC. The dorsolateral prefrontal cortex (DLPFC) (B) includes regions of positive (red) and negative (blue) FC with the SGC. Stronger negative FC with the SGC occurs at more anterolateral sites. (C) Illustration of negative (anticorrelated) time course between the DLPFC (green) and SGC (red). (D, E) Greater treatment outcome (% change in clinical score) was associated with more negative SGC FC at the individual DLPFC stimulation site across Boston (D) and Melbourne (E) cohorts. For the Boston cohort, the green and red circles in panel (D) highlight individual participants with good and poor clinical outcomes, corresponding to circled cortical sites of negative and positive SGC FC, respectively, displayed in panel (B). BDI, Beck Depression Inventory; BOLD, blood oxygen–level dependent; HCP, Human Connectome Project; MADRS, Montgomery–Åsberg Depression Rating Scale (adapted from [337]).

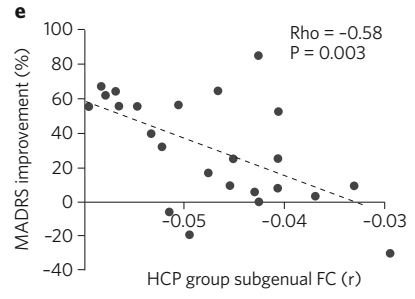
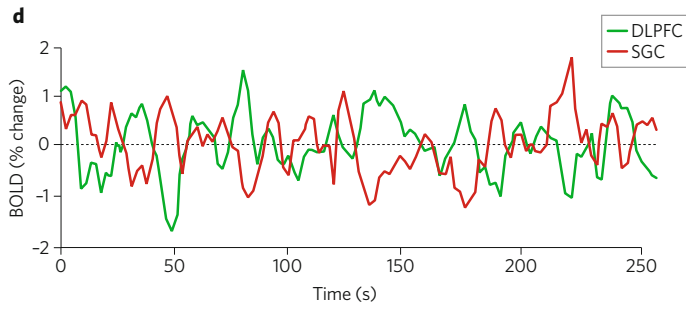
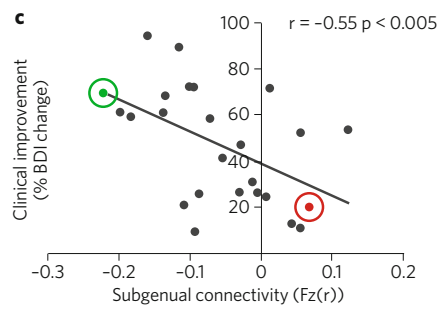
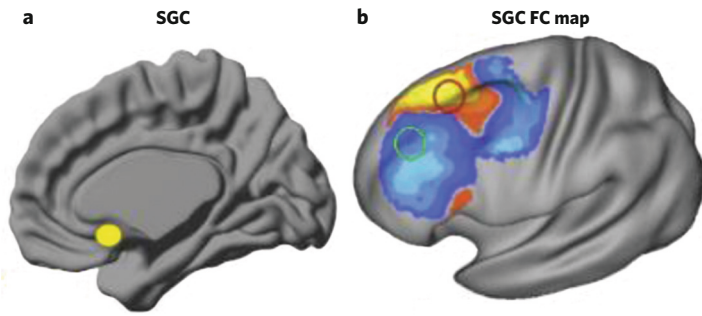
Figure 6. Precision neurostimulation. The stimulation can be adapted to individual patient needs by achieving specificity in the key elements of dosing (spatial, temporal, and contextual). Spatial precision can be achieved through individual imaging-guided targeting, electric field modeling, and focal or multifocal coils/electrodes. Temporal precision can be achieved by optimizing the pulse waveform, frequency, and train characteristics and by coupling it to endogenous oscillations via closed-loop techniques. Contextual precision can be achieved by controlling brain state during stimulation via online cognitive task performance, synchronizing to endogenous neural oscillations, or combination therapies such as simultaneous brain stimulation and pharmacotherapy. (adapted from [338]).



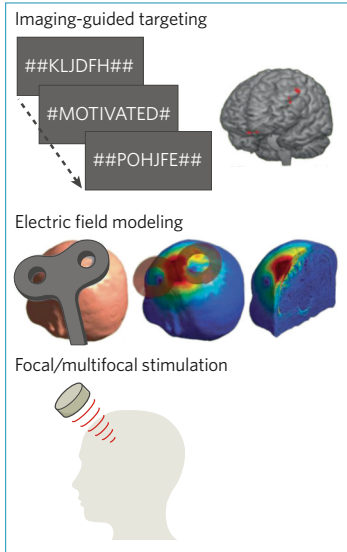




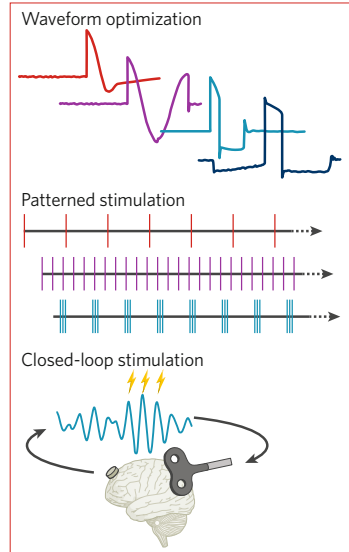




Spatial precision



Temporal precision



Contextual precision

