Investigational and Therapeutic Applications of Transcranial Magnetic Stimulation in Schizophrenia

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Abstract

Purpose of Review—This current review summarizes the investigational and therapeutic applications of transcranial magnetic stimulation (TMS) in schizophrenia.

Recent Findings—Fairly consistent findings of an impaired cortical excitation-inhibition balance, cortical plasticity, and motor resonance have been reported in schizophrenia. Cortical connectivity impairments have also been demonstrated in motor and prefrontal brain regions. In terms of treatment, the best support is for 1-Hz TMS to the left temporoparietal cortex for the shortterm treatment of persistent auditory hallucinations. High-frequency TMS to the left prefrontal cortex improves negative and cognitive symptoms, but with inconsistent and small effects.

Summary—TMS combined with diverse brain mapping techniques and clinical evaluation can unravel critical brain-behavior relationships relevant to schizophrenia. These provide critical support to the conceptualization of schizophrenia as a connectopathy with anomalous cortical plasticity. Adaptive modulation of these aberrant brain networks in a neuroscience-informed manner drives short-term therapeutic gains in difficult-to-treat symptoms of schizophrenia.

Keyword

Brain stimulation; Neuromodulation; TMS; Connectivity; Treatment; Psychosis; Resistant schizophrenia

Introduction

Schizophrenia is a severe brain disorder with a lifetime prevalence of ~ 1% that typically begins in early adulthood, resulting in substantial disability, morbidity, and mortality, at considerable personal and societal costs [1, 2]. Antipsychotic medications discovered in the

1950s, which act via blocking dopamine receptors in the brain, are still the mainstay of treatment in schizophrenia [1]. They are effective in approximately 50% of patients [3] and help in correcting positive symptoms like hallucinations and delusions, with little impact on the more disabling negative and cognitive symptoms. It is therefore imperative to examine novel therapeutic avenues that not only target the resistant, positive symptoms but also improve negative and cognitive symptoms of schizophrenia. In order to develop new treatments, the current pathophysiological models need to be empirically examined using both in vivo and in vitro methods. It is here that the role of transcranial magnetic stimulation (TMS) plays a dual and vital role. First, TMS can be utilized as a neurophysiological probe to understand brain function, thus enabling better neurobiological characterization of disease processes and their evolution with treatment [4, 5••]. Next, when precisely delivered in trains of repeated pulses (rTMS), it can potentially have excitatory and inhibitory cortical network-level effects, depending on the pattern of stimulation. This property of TMS has been leveraged to drive short-term change in behavior based on prior understanding of the underlying cortical-level pathophysiological processes [6]. This current review will focus on both these applications of TMS—(a) an investigational probe for characterizing aberrant brain function in schizophrenia, and (b) a therapeutic tool for treating resistant symptoms of schizophrenia.

TMS as an Investigational Probe (Table 1)

The motivation behind the invention of TMS was primarily to use it as an investigational tool that could focally (and non-invasively) modulate brain activity [7]. Typically, a single stimulus (perturbation pulse) is applied over the scalp area corresponding to the motor cortex via a figure-of-eight coil that carries a large, brief pulse of current (~ 4000 A), generating a magnetic field, which passes effortlessly through a highresistance structure like the skull. Visible motor twitches in the contralateral limb arise from the resultant action potentials generated by ionic currents induced in the superficial brain by the rapid, time-varying magnetic field. Electromyography is typically used to measure the amplitude of this motor response.

Depending on the number, frequency, and interval between pulses, diverse brain physiological systems can be probed to reveal both correlative and causal mechanisms of the schizophrenia pathophysiology (Fig. 1). Single and paired-pulse TMS paradigms are used to study functional brain dynamics through cortical reactivity (excitation and inhibition) and connectivity (inter- and intrahemispheric) at resting or active/task states with high temporal (order of milliseconds) resolution. In contrast, longer-lasting trains of rTMS pulses are used to manipulate neuronal activity to produce transient/virtual lesions or neuroenhancement, based on long-term depression (LTD)– or potentiation (LTP)-like plasticity effects. When applied in an offline manner, paired with an informed examination of cortical/ behavioral after-effects that last over several minutes, this technique permits the study of causal contributions of specific brain networks towards specific behaviors [5••].

Motor Cortical Reactivity

Balance of excitatory and inhibitory post-synaptic potentials generated through the stimulation of gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) glutamate interneurons regulates pyramidal neuron firing. An optimal cortical excitation/inhibition balance is necessary for synchronized firing of neuronal networks that drive social behavior relevant to psychiatric disorders [8]. TMS can probe the functioning of these intracortical networks and their neurotransmitter systems using single/paired-pulse paradigms [4].

Cortical Excitability—Resting motor threshold (RMT), motor evoked potential (MEP) amplitude, and intracortical facilitation (ICF) capture cortical excitability. Voltage-gated $Na+$ channels and ionotropic non-NMDA glutamate receptors govern the transsynaptic effects of the TMS pulse on the corticospinal pyramidal neurons and spinal motoneurons, thus regulating RMT [9]. Trans-synaptic activation of pyramidal neurons via excitatory/inhibitory interneurons, and the moderating effects of dopamine, serotonin, norepinephrine, and acetylcholine, contribute to the MEP amplitude [9]. ICF reflects predominant facilitation triggered by stronger excitatory (glutamatergic; primarily NMDA) and weaker inhibitory (GABAergic; primarily $GABA_A$) interneurons. A meta-analysis that examined pooled effect sizes in these excitability measures revealed no significant differences between schizophrenia patients and healthy comparison subjects [10•]. This indicates that the excitability of the motor cortex to an external perturbation TMS pulse is intact in schizophrenia.

Cortical Inhibition—Short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) are paired-pulse inhibitory TMS paradigms. Fast inhibitory post-synaptic potentials mediated by the rapid but less potent ionotropic $GABA_A$ receptors mediate SICI [11]. In contrast, slow inhibitory post-synaptic potentials mediated by the more potent metabotropic $GABA_B$ receptors mediate LICI [12]. $GABA_B$ receptor–driven motor cortical inhibition mediates the cortical silent period (CSP) [4]. While the observation of deficits in LICI and CSP (both mediated by $GABA_B$ receptors) was inconsistent, that of deficient SICI was consistent in schizophrenia (Hedge's g = 0.47) [10•]. Diminished SICI is related to the strength of the prefrontal to motor cortex functional connectivity and the integrity of the connecting white matter tracts [13], suggesting a dysregulated top-down frontal inhibitory mechanism. Importantly, a deficit in SICI is not specific to schizophrenia; it is also observed in marginally greater magnitude (Hedge's g ~ 0.6) in major depression and obsessive-compulsive disorder [10•]. SICI impairments in schizophrenia are related to deficits in both social [14] and non-social [15] cognition. A critical aspect of CSP in schizophrenia is that it is enhanced with clozapine treatment as compared to other antipsychotic medications [16, 17]; this not only provides insights into the mechanisms of clozapine but also provides a potential physiological marker of tracking symptom change. Recent studies in untreated patient populations [14, 18] have revealed that the balance between $GABA_a$- and $GABA_B$-mediated neurotransmission may differentiate schizophrenia (deficient $GABA_A$ and normal $GABA_B$) patients from those with mania (deficient $GABA_A$ and elevated $GABA_B$); however, these findings need replication.

Motor Resonance or Putative Mirror Neuron System Activity—The mirror neuron system (MNS) is a frontoparietal network of specialized nerve cells with dual properties— they discharge during action execution, as well as observation of the same action [19]. This dual property is thought to form an internal template to decode intentions underlying gestures, actions, and emotions in social interactions via an automatic reflexive mechanism referred to as embodied simulation [20]. Social behaviors like imitation and empathy are potential functional correlates of the MNS. TMS can be used to indirectly infer premotor MNS activity, via its posited connections with the motor cortex [21, 22]. Deficient MNS response was observed in un-medicated schizophrenia patients that had a significant association with the severity of their social cognition impairments [23, 24]. In contrast, an elevated MNS response (possible disinhibition) was demonstrated in unmedicated bipolar mania patients that correlated with hyperimitative behaviors (incidental echolalia) and manic symptom severity [25]. Evidence for such a deficit is not consistently reported in medicated schizophrenia patients [26, 27]. Recent investigations have attempted to examine MNS responses using more nuanced, social context–based action observation stimuli. Viewing actions within a context results in greater facilitation of motor cortical reactivity relative to neutral action observation in both patients and healthy subjects. However, this MNS response to context-based action observation was still blunted in schizophrenia patients treated with antipsychotic medications [28].

Cortical Connectivity

TMS-evoked cortical reactivity propagates to connected hubs of the network that is being stimulated. This propagation can inform about the integrity of the connecting white matter tracts, as well as examine functional properties (excitatory or inhibitory) of the stimulated networks.

Transcallosal Connectivity—The ipsilateral silent period (ISP) is a function of corpus callosum integrity [29] since it reflects transcallosal inhibition of the contralateral preactivated motor area by the motor area stimulated by TMS. This can also be evaluated by applying TMS pulses in close temporal approximation to both hemispheres. This transcallosal inhibition (TCI) is also cortical in origin and mediated by transcallosal motor fibers, thus providing a direct measure of optimal corpus callosum maturation/integrity [29]. TCI at shorter interstimulus intervals (7–10 ms) does not correlate with that at longer intervals (40 ms). However, the 40-ms TCI correlates with ISP duration, indicating both common and shared mechanisms [30]. Transcallosal facilitation (TCF) is the percentage of MEP facilitation relative to suprathreshold test pulse MEP from one hemisphere when a low-intensity conditioning pulse is delivered over the contralateral hemisphere 4–5 ms before the test pulse [31]. In schizophrenia, there is consistent evidence of diminished TCI and ISP [32–34], indicative of aberrant corpus callosum functioning. However, there is inconclusive evidence about interhemispheric facilitation in schizophrenia [33].

Motor Cortical Connectivity—Ipsilateral subthreshold parietal stimulation facilitates the MEP obtained from the motor cortex [35]. This twin-coil, paired-pulse TMS paradigm can provide a robust estimation of functional connectivity within the brain. This *parieto-motor connectivity,* structurally supported by the superior longitudinal fasciculus, is found to be

deficient in patients with schizophrenia and has behavioral correlates with severity of the disabling negative symptoms [36]. On similar lines, *premotor-motor connectivity* is also found to be impaired in schizophrenia [37]—a subthreshold conditioning stimulus produces diminished facilitation of MEP elicited by a suprathreshold test pulse in the contralateral hemisphere in schizophrenia as compared to healthy subjects. Lastly, the inhibitory influence of the cerebellum on the motor cortex (via Purkinje cells) can also be examined with TMS, informing about the integrity of *the cerebellar-thalamo-cortical connectivity.* In schizophrenia, a diminished cerebellar inhibition of MEP was reported in a small study [38]. This is, however, in keeping with more recent findings of an association between negative symptom severity and aberrant cerebellar-prefrontal connectivity in schizophrenia [39•]. Delivering single TMS pulses to the motor cortex and examining the change in resting-state fMRI BOLD signals in the thalamus can reveal cortico-thalamic connectivity. The strength of this TMS-evoked fMRI response in the thalamus is significantly diminished in schizophrenia as compared to healthy subjects [40].

Motor Cortical Plasticity

Dysplasticity is a core pathophysiology of schizophrenia, which encompasses hypoplastic cognitive and volitional neural systems, as well as hyperplastic salience detection and emotion processing systems [41]. With the advent of diverse neuromodulatory techniques, we can now quantify and compare cortical plasticity in schizophrenia and healthy individuals [42–44]. TMS can be employed as both a *neuromodulator*—to induce plastic change, and, as a *neurophysiological probe*—to quantify the degree of plastic change, in combination with EMG, EEG, or fMRI. In schizophrenia, both TMS and transcranial electrical stimulation perturbation protocols have been used to study in vivo transitory cortical reactivity increases or decreases [45] that are thought to parallel the commonly observed in vitro longterm potentiation/depression (LTP/LTD)–like experience-dependent synaptic plasticity [46]. A recent meta-analysis of 16 datasets yielding data from 189 schizophrenia patients and 187 healthy controls [47•] to quantify the magnitude of such cortical plasticity impairments in schizophrenia revealed effect sizes ranging from 0.66 (LTP-like plasticity) to 0.68 (LTD-like plasticity). The consistency of these findings, despite the known clinical heterogeneity of schizophrenia, encourages the use of these biomarkers to characterize illness trajectories and treatment response. Future studies can also examine how the cortical excitation-inhibition balance influences cortical plasticity outcomes to the different neuromodulatory techniques [48]. Connectivity of the motor cortex to distinct premotor and parietal cortices can also be examined using such perturbation protocols. Delivering 1-Hz TMS to the premotor cortex resulted in suppression of motor cortical excitability in healthy individuals, but facilitation in schizophrenia patients [49]. In contrast, delivering 20-Hz TMS to the premotor/inferior frontal gyrus area enhanced MNS responsiveness in healthy individuals [50, 51]. This application of TMS has both heuristic (understanding the behavioral aftereffects of enhancing MNS activity) and translational (poten-tial treatment of social cognition deficits) applications when tested in patients with schizophrenia.

Cortical Reactivity and Connectivity in Non-motor Brain Regions

Earlier TMS investigations focused on the motor cortex. This limitation is overcome partly by the advent of TMS-EEG, which has ushered a new era of examining brain states and their dynamics in motor and non-motor regions [52••]. Cortical reactivity and effective connectivity can be recorded with EEG following a TMS pulse [53]. These responses are thought to reflect a summation of excitatory and inhibitory cortical pyramidal and inteneuron post-synaptic potentials [54]. Despite the tremendous challenges that come with the technique (especially handling artifacts and analyzing large data dimensions), there are important inferences from current TMS-EEG experiments that could be consolidated in the future. Schizophrenia patients demonstrated diminished TMS-evoked EEG gamma oscillations in the site of frontal stimulation; its propagation (connectivity) to other cortical regions was also restricted as compared to healthy subjects [55]. Slowing of the TMS-evoked EEG frequency in the prefrontal (and not in the parietal) cortex was associated with symptom severity and cognitive deficits in schizophrenia [56]. Similar aberrations in prefrontal reactivity were described in first-episode psychotic patients as well [57]. In a related investigation, schizophrenia patients demonstrated waves of recurrent excitation propagating throughout the cortex, as compared to a faster fading away in healthy subjects [58].

Further advances have been made in examining cortical inhibitory processes within the prefrontal cortex using TMS-EEG. SICE LICI, and ICF can now be determined in nonmotor areas, thus providing measurements of various excitatory and inhibitory intracortical circuit functioning. Inhibition or facilitation is measured as suppression or facilitation of specific positive (e.g., P30) and negative (e.g., N100) peaks of the TMS-evoked potentials (TEP) [59] or as a change in the average EEG amplitude [60]. Schizophrenia patients demonstrate diminished prefrontal LICI as compared to their unaffected relatives and healthy subjects [61]. They also revealed deficits in prefrontal SICI and ICF as compared to healthy subjects in some of the positive and negative peaks of the TEP [62]. Lastly, another inhibitory paradigm that has been examined using TMS-EEG is the short-latency afferent inhibition (SAI). Here, a somatosensory conditioning (electrical stimulation of a peripheral nerve) stimulus delivered at a short latency (20 ms) inhibits the MEP (motor cortex) or TEP (prefrontal cortex). This process is thought to be mediated by both cholinergic and GABAergic inputs [63]. The prefrontal (and not motor) SAI is seen to be deficient in schizophrenia and is related to their cognitive performance [64]. Nevertheless, these TMS-EEG results are very preliminary findings that require replication in future studies.

TMS in the Treatment of Schizophrenia

TMS has been used in the treatment of difficult-to-treat symptoms of schizophrenia, like persistent auditory hallucinations, negative symptoms, and cognitive deficits. There is a need for exploring alternative, neuroscience-informed treatments of these symptoms. Administering repetitive TMS treatment successively for several days can leverage the unique focal neuromodulatory property of TMS in bringing about behavioral change based on the site and pattern of stimulation, guided by our current understanding of the neurobiology of these symptom dimensions.

Conventional TMS can either increase or decrease cortical activity depending on the frequency used to administer magnetic pulses. High-frequency TMS (10 or 20 Hz) enhances cortical activity while low-frequency TMS (1 Hz) reduces it. Recently introduced theta burst stimulation (TBS) uses bursts of very high frequency (50 Hz) repeatedly in either intermitted or continuous pattern to bring about stimulation or inhibition of cortical neiuons, respectively [65]. TBS has advantages of being brief and has longer-lasting neuroplasticity changes and a theoretically lower risk of inducing seizures compared to conventional TMS.

Positive Symptoms

Apart from its effects on resistant auditory hallucinations, the utility of TMS in treating other positive symptoms like delusions, made phenomena, or formal thought disorder is limited, with the current stimulation site and parameters. Speech processing brain regions in the bilateral temporal lobes are hyperactive during ongoing auditory hallucinations [66]. Therefore, low-frequency (1-Hz) rTMS has been used to reduce this cortical hyper-activation to treat auditory hallucinations [67]. Recent meta-analyses on the therapeutic effects of rTMS for auditory hallucinations reveal significant benefits as compared to sham stimulation, with varying effect sizes: 0.29 [68•], 0.44 [69], 0.49 [70], and 0.51 [71••]. However, these come with several caveats. The effect sizes observed in more recent metaanalyses, which include larger samples, are lower than those reported in earlier analyses with smaller samples but stronger effects of 0.8 [72] to 1 [73]. There is a high degree of variability in the stimulation parameters, brain region targeted, the degree of treatment resistance, and duration of treatment. Concerns of publication bias, where negative trials may not have been published and unstable results on sensitivity analyses by removing individual trials [68•], also require consideration. The most common and perhaps most effective among all stimulation protocols is the low-frequency (1-Hz) stimulation over the left temporoparietal cortex [69]. This protocol, however, has limited benefits for other psychotic symptoms [69, 71••]. Interestingly, within-group (before and after treatment) effects of placebo (sham) treatment are also significant (effect size of 0.29) [74]; however, it must be noted that the effect sizes reported in the meta-analyses quoted above are for between-group differences (true versus sham). The durability of beneficial effects is short-lasting (4–6 weeks), and this underlines the importance of continued medical treatment with antipsychotics [69], as well as a systematic study of pragmatic maintenance treatment strategies [75].

Younger age, female gender [76], higher co-prescribed antipsychotic dose, short (< 3-week) trial duration [71 ••], shorter scalp-to-temporal cortex distance [77], and increased regional cerebral blood flow at the site of stimulation before treatment are associated with better response [78]. High emotional salience to die hallucinations predicts a better response to rightsided 1-Hz rTMS [79]. While some of these predictive findings are plausible from a neurophysiological perspective, others (e.g., shorter trial duration and greater improvement) are indeed counterintuitive, requiring more systematic investigation. Given the promising but variable results, investigators have attempted to examine means to enhance the efficacy and durability of rTMS effects. High-frequency (20-Hz) rTMS to the left temporoparietal cortex [80], high-frequency primed 1-Hz rTMS [81], structural [82] and functional [83] MRI guided or neuronavigational rTMS, theta burst stimulation [84], bilateral sequential rTMS

[85], and deep TMS [86] have been used to enhance treatment outcomes, with mixed results. Indications other than treatment resistance are under-represented. For example, the potential benefits during early-course treatment of schizophrenia, its utility in children, pregnancy, and maintenance therapies have not been evaluated sufficiently.

Negative Symptoms

TMS is typically administered to enhance the "hypofrontality" of the dominant prefrontal cortex for improving negative symptoms. Results from two recent meta-analyses [71••, 87••] suggest a small-to-moderate benefit of true TMS over sham in improving negative symptoms (effect sizes 0.49 to 0.64). A third meta-analysis included studies examining only 10-Hz rTMS with more stringent selection criteria and did not show any significant benefit of true TMS [68•]. In a sensitivity analysis that excluded two studies with unusually high effects of true TMS, the overall benefits of true TMS over sham TMS persisted at a much lower (effect size 0.31) magnitude [87••]. Higher pulse frequency (10–20 Hz), stronger stimulus intensity (100–110% RMT), longer treatment duration (> 3 weeks), younger age (< 39 years), and shorter duration of illness (< 13 years) were associated with better outcomes [71••, 87••]. However, there was also a trend suggesting a worsening of positive symptoms with this treatment protocol for negative symptoms, thus necessitating stringent monitoring [71••]. Structural plasticity of the left hippocampus and precuneus also predicts negative symptom improvement following left prefrontal stimulation [88•].

Nevertheless, these are short-term effects, from small trials and influenced by heterogeneity in the recruited patients and the technique of TMS administration. Not all studies control for the moderating effects of improvement in depression since the stimulation protocol is similar [89]. Interestingly, sham stimulation also resulted in a significant within-group improvement with an effect size of 0.31 [87••]. Moreover, an adequately powered multi-center trial failed to demonstrate any beneficial effects of true left prefrontal TMS over sham in improving negative symptoms immediately post-treatment and at the 3-month follow-up [90•].

These observations have led to the investigation of stimulating newer sites (e.g., cerebellum) with different parameters. Prefrontal TBS [91], deep prefrontal TMS [92], and bilateral prefrontal TMS [93] are modifications of stimulation technique that have been examined for negative symptoms, with limited and mixed results. One promising alternative approach is to target prefrontal activity by stimulating its connections within the cerebellum. In a recent study, the functional connectivity of the cerebellum with the right prefrontal cortex was inversely associated with negative symptom severity; modulating the cerebellum using intermittent theta burst stimulation (iTBS) resulted in improvement of negative symptoms and reversal of this functional dysconnectivity in schizophrenia [39•]. These emerging findings provide further scientific rationale to explore cerebellar iTBS in the treatment of negative symptoms [94, 95]. A recent study from our facility randomized 60 patients to active and sham groups of intermittent TBS at 90% of RMT over the cerebellar vermis administered twice daily for 5 days. Both groups demonstrated a significant improvement in negative symptoms at the end of treatment and at the 6-week followup, but only the hue TMS group revealed a significant engagement of the cerebellar-prefrontal resting-state

functional connectivity [96]. Future studies may examine more prolonged and potent activation of this neural circuit.

Cognitive Symptoms

Cognitive deficits across social and non-social domains are a significant hallmark of schizophrenia [97]. They persist during symptom remission [98] and are an important determinant of real-world functioning [99]. With the advent of rTMS as a viable therapeutic option for depression [100], there was an active call for monitoring its cognitive safety [101]. Over the years, it became apparent that TMS had limited detrimental effects on cognition, and could perhaps be leveraged to enhance cognition when delivered under strictly monitored conditions [102, 103]. Also, trials that examined the benefits of TMS for negative symptoms noticed improvements in cognition in the active TMS group [104]. Subsequently, trials have been designed with specific aims of evaluating the cognitive benefits of rTMS in schizophrenia. Given the critical role of the prefrontal cortex in cognitive dysfunction of schizophrenia [105], and the ease with which it can be targeted, most studies have attempted to deliver high-frequency rTMS to the left or bilateral prefrontal cortices.

A pilot randomized controlled trial of 20-Hz bilateral prefrontal rTMS over 4 weeks demonstrated significant improvement in working memory as compared to sham rTMS in schizophrenia [106]. Modulation of task-related frontal gamma oscillatory activity may drive this response [107]. Another trial examined 10-Hz bilateral prefrontal rTMS at subthreshold doses (90% RMT), but longer train duration (10 s); cognition improved only in one (verbal fluency) of the seven domains assessed [93]. Similar improvements in overall neurocognitive performance were observed in a more recent trial with a small sample receiving a similar bilateral 20-Hz stimulation, but for 2 weeks [108]. The improvement persisted even at the 2-week follow-up, and baseline left frontal cortical thickness correlated with treatment response. However, a large, multi-center study involving 156 schizophrenia patients found no benefits of 3-week left prefrontal 10-Hz stimulation as compared to sham stimulation [109]. Interestingly, 2-week left prefrontal 10-Hz stimulation improved a measure of social cognition (facial emotion recognition) in schizophrenia as compared to sham stimulation, thus opening a window of opportunity to explore newer neuromodulatory techniques to improve the disabling social cognition deficits in schizophrenia [110]. A recent meta-analysis of cognitive benefits with rTMS in schizophrenia reported a beneficial effect size of 0.34 in improving working memory as compared to sham stimulation [111•]; these benefits persisted when reassessments were performed approximately 1 month after stopping treatment.

Nevertheless, the modest degree of improvement in limited cognitive domains requires the study of novel stimulation patterns, targeting different brain networks. In this regard, hippocampal-functional connectivity–guided stimulation of the lateral parietal cortex has shown improvements in associative memory in healthy individuals [112•]; this technique holds promise for exploration in schizophrenia. Lastly, combining rTMS with other known therapies for cognitive enhancement may be able to yield more potent therapeutic gains [113]; future studies may explore this avenue. This field is still nascent, and important

challenges regarding matching the best stimulation parameters for the specific cognitive deficits a given patient experiences still remain. In addition, safety, durability of benefits, their generalizability to real-world functioning, and dissemination to a larger community patient population require more refined study [114].

Conclusions and Future Directions

With its immense potential of (a) *evoking brain responses* with precision temporal resolution and (b) *targeted modulation of cortical activity* and therefore behavior with successive trains of stimulation, TMS is an invaluable tool for both neuroscientists and psychiatrists. Future studies must focus on consolidating the critical leads derived in the last three decades.

As for investigational applications, the field has gradually moved to incorporate multimodal strategies that combine TMS with functional neuroimaging [115] and high-density EEG [52••] studies. While these methods are technologically challenging, they have the potential to reveal brain dynamics in schizophrenia at rest and during tasks, with much better spatiotemporal accuracy. This may result in more accurate diagnostic and prognostic biomarkers. Important methodological challenges and variability in responses still remain, especially in terms of the stimulation parameters to elicit cortical reactivity/ connectivity. Systematic studies to ascertain the reliability and validity of these measurements will go a long way in bridging the translational application gap of these techniques [13, 116].

Therapeutic use of rTMS in schizophrenia has not achieved success as in depression. Larger, high-quality, multi-center studies are very few, and they do not support its unequivocal clinical utility. Nevertheless, meta-analyses suggest small to modest effect size benefits of rTMS over placebo treatment for all three symptom dimensions described above. The clinical applicability of small effect treatments appears discouraging. However, it must be noted that most of these trials have been conducted on patients with resistant or difficult-to-treat symptoms. This also emphasizes an urgent need to strategize and identify key thrust areas for research. Clinicians must work in tandem with basic neuroscientists and engineers to refine stimulation parameters (site, dose, duration, etc.) that would improve clinical benefits without compromising safety. The clinical effectiveness of newer treatments must be examined in large, multi-center trials that are sufficiently powered to yield reliable and consistent results. Clinical trials need to be supplemented by mechanistic studies that identify key processes driving clinical benefits. Lastly, future studies should explore demographic, clinical, genomic, and brain physiological reasons for variable treatment response. This could help identify the category of patients responding well to rTMS, and set the platform to explore next-generation personalized treatment approaches catered to a given person's symptoms based on individualized biological markers.

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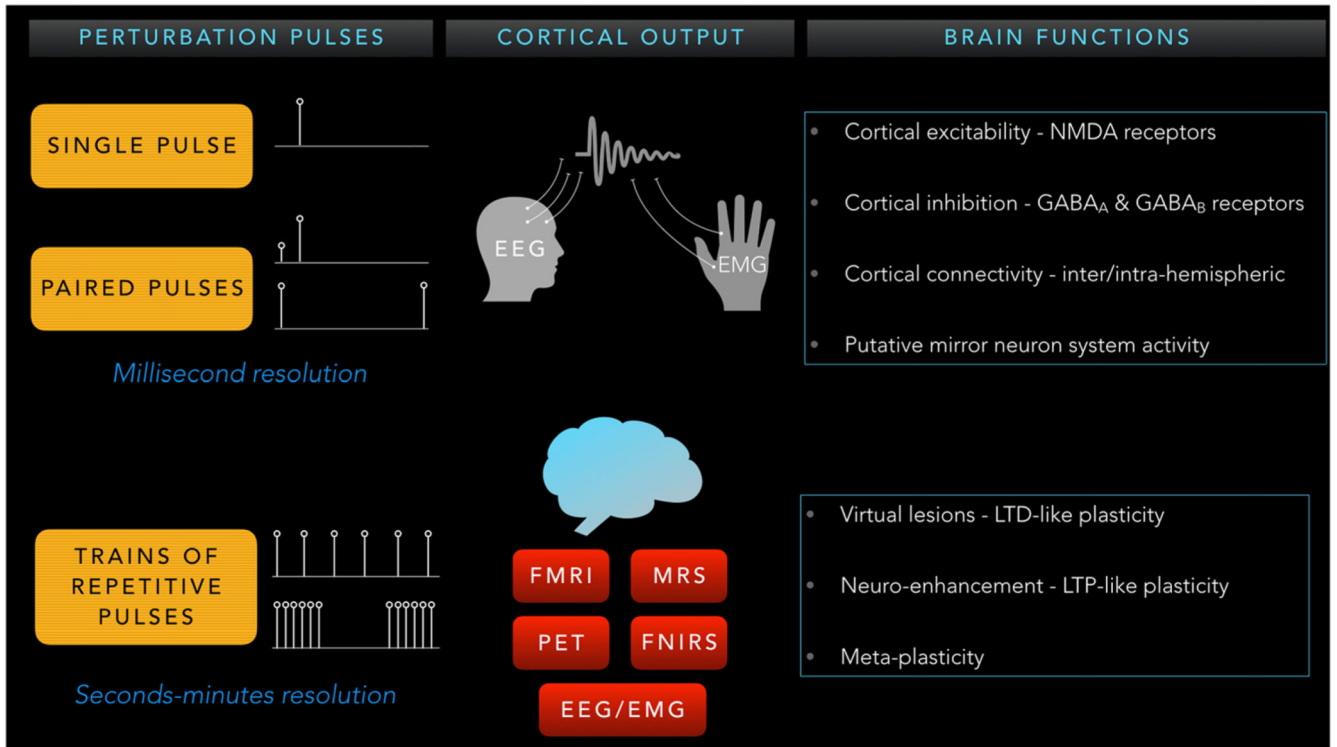
Fig. 1. Schematic representation of different investigational TMS approaches

Table 1

Summary of investigational TMS approaches in schizophrenia

TMS paradigm	Definition	Putative neurophysiology	Findings in SZ	
			Consistent	Emerging
Cortical excitability				
Resting motor threshold (RMT)	The minimal stimulator intensity that produces a motor evoked potential of 50 µV in 5 of 10 trials in a relaxed muscle	Neuronal membrane activity regulated by voltage-gated Na^+ channels & ionotropic non-NMDA glutamate receptors	≈ *	–
Motor evoked potential (MEP) amplitude	The mean amplitude of hand muscle contraction evoked by a series of pulses applied at a consistent TMS intensity	Neuronal membrane activity governed by the excitation/inhibition balance through various neurotransmitter systems	≈ *	–
Intracortical facilitation (ICF)	The % of MEP facilitation relative to suprathreshold test pulse MEP, elicited by pairing a subthreshold conditioning pulse (80% of RMT) 7-20 ms before the test pulse	NMDA-glutamate receptor-mediated excitability	≈ *	–
Cortical inhibition				
Short-interval intracortical inhibition (SICI)	The % of MEP inhibition relative to suprathreshold test pulse MEP, elicited by pairing a subthreshold conditioning pulse (80% of RMT) 1-5 ms before the test pulse	$GABA_A$ receptor-mediated inhibitory neurotransmission	↓ *	Non-specific to SZ, but related to cognitive dysfunction
Long-interval intracortical inhibition (LICI)	The % of MEP inhibition relative to suprathreshold test pulse MEP, elicited by pairing a suprathreshold conditioning pulse 50-200 ms before the test pulse	$GABA_B$ receptor-mediated inhibitory neurotransmission	≈ *	↑LICI in mania—differential biomarker
Cortical silent period (CSP)	Time from MEP offset to the return of any voluntary EMG activity when a suprathreshold pulse is delivered to the motor cortex contralateral to a voluntarily contracted hand muscle	First 50 ms of the silent period is mediated by spinal mechanisms; the later part is mediated by $GABA_B$ receptor-driven motor cortical inhibition	≈ *	Increases with clozapine treatment
Putative MNS activity Motor resonance	The degree of motor cortical reactivity facilitation during action observation, relative to static image viewing	Driven by premotor MNS activity, possibly through premotor-motor connections	↓ in untreated SZ, related to social cognition deficits	↑ in untreated mania, modulated by context, but less so in SZ
Cortical connectivity				
Ipsilateral silent period (ISP)	Time from MEP offset to the return of any voluntary EMG activity when a suprathreshold pulse is delivered to the motor cortex ipsilateral to a voluntarily contracted hand muscle	Corpus callosum functional integrity	↓	–
Transcallosal inhibition (TCI)	The % of MEP inhibition relative to suprathreshold test pulse MEP from one hemisphere, when a suprathreshold conditioning pulse is delivered over the contralateral hemisphere 7-20 ms before the test pulse	Corpus callosum functional integrity	↓	–
Transcallosal facilitation (TCF)	The % of MEP facilitation relative to suprathreshold test pulse MEP from one hemisphere, when a low-intensity conditioning pulse is delivered over the contralateral hemisphere 4-5 ms before the test pulse	Corpus callosum functional integrity	≈	–

TMS paradigm	Definition	Putative neurophysiology	Findings in SZ	
			Consistent	Emerging
Parieto-motor connectivity	A subthreshold conditioning pulse applied to the posterior parietal cortex 4 and 15 ms prior facilitates the MEP obtained by administering a test pulse to the motor hand area on the same side	Superior longitudinal fasciculus functional integrity	–	↓
Premotor-motor connectivity	A subthreshold conditioning stimulus to the premotor cortex (8 ms prior) facilitates the MEP elicited by a suprathreshold test pulse in the contralateralmotor cortex	Transcallosal premotor-motor connectivity	–	↓
Cerebellar-cortical connectivity	A subthreshold conditioning stimulus to the cerebellum 5-15 ms prior to a suprathreshold test stimulus to the contralateral motor cortex inhibits the output of the test stimulus	Inhibitory influence of the cerebellum on the motor cortex through the cerebello-thalamo cortical connectivity		↓
Cortical plasticity				
Motor cortical plasticity	The degree of facilitation or inhibition of cortical reactivity (most often measured as the MEP amplitude) with TMS/TES perturbation protocols	Long-term potentiation/depression (LTP/LTD)-like experience-dependent synaptic plasticity	↓ LTP- and LTD-like plasticity*	–
Non-motor cortical reactivity and connectivity				
TMS-evoked potential (TEP)	ATMS pulse when administered to the cortex elicits an immediate response of positive and negative deflections visible on EEG	Cortical reactivity	–	↓ prefrontal reactivity
Cortical connectivity	ATMS pulse when administered to the cortex elicits a delayed intra- and interhemispheric spread of activation that follows in spatial, temporal, and frequency domains	Effective connectivity		↓ prefrontal connectivity

μV microvolts, ms milliseconds, NMDA N-methyl-D-aspartate, SZ schizophrenia, MNS mirror neuron system, TMS transcranial magnetic stimulation, TES transcranial electrical stimulation, EEG electroencephalography, EMG electromyography

*Consistent findings are highlighted if data is available from meta-analyses (if available) or from at least two studies; emerging findings reflect more recent findings that are not replicated

≈ Not different from healthy

↓ Diminished as compared to healthy)

↑ Enhanced as compared to healthy