Cortical Inhibition, Excitation, and Connectivity in Schizophrenia: A Review of Insights From Transcranial Magnetic Stimulation

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Schizophrenia (SCZ) is a debilitating mental illness with an elusive pathophysiology. Over the last decade, theories emphasizing cortical dysfunction have received increasing attention to explain the heterogeneous symptoms experienced in SCZ. Transcranial magnetic stimulation (TMS) is a noninvasive form of brain stimulation that is particularly suited to probing the fidelity of specific excitatory and inhibitory neuronal populations in conscious humans. In this study, we review the contribution of TMS in assessing inhibitory and excitatory neuronal populations and their long-range connections in SCZ. In addition, we discuss insights from combined TMS and electroencephalography into the functional consequences of impaired excitation/inhibition on cortical oscillations in SCZ.

Key words: GABA/cortical inhibition/NMDA/connectivity

Introduction

Schizophrenia (SCZ) is a debilitating mental illness, which affects approximately 1% of the population.1 Despite a concerted effort over several decades, the pathophysiology underlying the symptoms of SCZ remains elusive. Abnormal dopaminergic signaling has been the prevailing theory due to the efficacy of dopaminergic antagonists in treating positive symptoms such as hallucinations.2 The ineffectiveness of these medications in treating negative symptoms such as flat affect and cognitive symptoms including impaired executive functioning, however, has led to new and modified theories on brain function in SCZ. Understanding the pathophysiology of these symptoms is particularly relevant, as cognitive symptoms are considered a core feature of the illness.3 A number of recent theories have focused on the role of cortical dysfunction, such as an altered excitation/inhibition balance in local cortical networks4 and impaired short- and long-range cortical connectivity.5 As a result, other fundamental neurotransmitter pathways such as the glutamate and γ-amino butyric acid (GABA) systems have been implicated.5,6 However, finding in vivo evidence for the role of these neurotransmitters in SCZ supporting some of these theories has been challenging. Transcranial magnetic stimulation (TMS) is a noninvasive technique for stimulating cortical neurons, particularly suited for probing cortical function in conscious humans. In this study, we provide an overview of several emerging theories on cortical dysfunction in SCZ and outline the contribution of TMS in directly testing these theories.

Mechanisms of TMS

TMS involves the use of a time-variable pulsed magnetic field to stimulate a small field of cortical neurons. When single pulses are applied to the motor cortex, a motor-evoked potential (MEP) in peripheral muscles controlled by the stimulated region is produced (see figure 1A for details). MEP amplitude is dependent on cortical, spinal, and peripheral neurons and is considered a basic measure of corticospinal excitability. Various additional TMS paradigms have been developed to assess specific intracortical excitatory and inhibitory populations within the motor cortex.8,9 Using these TMS paradigms, researchers have assessed multiple aspects of motor cortical function in SCZ as a proxy for inferring wider cortical dysfunction. The recent combination of TMS with other neuroimaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) has provided an additional perspective on neural network properties and cortical connectivity.10,11 Importantly, these new methods have allowed TMS to move outside of the motor cortex.
and directly assess cortical regions relevant to SCZ symptomatology including prefrontal cortex (PFC).

**Local Inhibitory and Excitability Networks in SCZ**

Postmortem studies have found abnormalities in both excitatory and inhibitory neuronal components in SCZ. Specific subclasses of cortical inhibitory interneurons expressing the protein parvalbumin show reductions in the 67-kDa isoform of glutamic acid decarboxylase (GAD67), an important precursor for GABA synthesis. The reductions in GAD67 are accompanied by reduced expression of specific N-methyl-d-aspartate (NMDA) subunits and decreased spine density in specific cortical layers in SCZ, suggesting altered excitatory drive on to interneurons. Although these findings have been largely reported in the PFC, reductions in GAD67 have been found at various other cortical sites such as visual, sensory, and motor cortices. Several single- and paired-pulse TMS paradigms exist that allow direct testing of specific inhibitory and excitatory populations in the motor cortex. Importantly, TMS allows assessment of cortical inhibition and excitability at different stages of illness, information that is difficult to obtain through postmortem studies.

**GABA<sub>A</sub>-Mediated Inhibition**

Cortical inhibition is mediated by two classes of GABA receptor: GABA<sub>A</sub> and GABA<sub>B</sub> receptors. The ionotropic GABA<sub>A</sub> receptor is located postsynaptically and results in rapid (2–20 ms) hyperpolarization of the postsynaptic neuron. GABA<sub>A</sub>-mediated cortical inhibition can be measured using a paired-pulse TMS.

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**Fig. 1.** Transcranial magnetic stimulation (TMS) over motor cortex and TMS paradigms assessing various inhibitory and excitatory neuronal populations. (A) TMS generates a fast, time-varying magnetic field, which penetrates the skull, inducing an electric field in underlying tissue, and depolarizes cortical neurons. At high enough intensities, stimulation of motor cortical regions results in motor-evoked potentials (MEPs) in peripheral muscles controlled by these areas, which can be measured using electromyography. (B) Short-interval intracortical inhibition (SICI) involves comparing MEP amplitude of a single, suprathreshold test stimulus (TS) to a paired-pulse condition with a subthreshold conditioning stimulus (CS) and suprathreshold TS at 1–4 ms intervals. (C) Long-interval cortical inhibition (LICI) involves comparing a suprathreshold with a paired-pulse suprathreshold CS and TS at 50–200 ms intervals. (D) The silent period (SP) involves measuring the duration of absent muscle activity following a single, suprathreshold TS given during a muscle contraction. (E) Intracortical facilitation (ICF) involves comparing a suprathreshold TS with a paired-pulse subthreshold CS and suprathreshold TS at 10–15 ms intervals. (F) I-wave facilitation involves comparing a suprathreshold TS with a paired-pulse condition in which a subthreshold CS follows the TS at specific intervals of 1.3, 2.5, and 4.5 ms.
paradigm (short-interval intracortical inhibition [SICI]; figure 1B). The timing of SICI coincides with inhibitory postsynaptic potentials (IPSPs) resulting from GABA\textsubscript{A} receptor binding following electrical stimulation of the cortex in cortical slice experiments. Further supporting a role of GABA, SICI is increased in the presence of pharmacological agonists of the GABA\textsubscript{A} receptor.

Reduced SICI is the most consistently replicated TMS finding in SCZ. Abnormal SICI has been reported in patients at various stages of illness including people at risk of developing SCZ, first-episode patients, recent-onset patients, and chronic patients. Of the studies that have not found significant differences in SICI strength in SCZ, four have reported trend-level differences and only one no clear significant difference. The effect of medication on SICI is less clear with studies finding greater deficits in medicated compared with unmedicated patients and vice versa. Comorbid cannabis use may also impact on SICI circuitry with first-episode cannabis users displaying greater SICI deficits compared with nonusers. SICI abnormalities may relate to core symptoms of SCZ with several studies reporting correlations between positive symptoms and SICI strength. The persistence of SICI deficits throughout different stages of illness support deficient cortical inhibition in SCZ.

**GABA\textsubscript{A}-Mediated Inhibition**

The second class of GABA receptor is the metabotropic GABA\textsubscript{B} receptor, which is located pre- and postsynaptically and results in slower (50–500 ms) hyperpolarization of neurons. GABA\textsubscript{B}-mediated cortical inhibition can be assessed using two TMS paradigms: a paired-pulse paradigm deemed long-interval intracortical inhibition (LICI; figure 1C) and a single-pulse paradigm deemed the silent period (SP; figure 1D). The time course of both measures is similar to GABA\textsubscript{A}-mediated IPSPs measured in slice preparations following electrical stimulation of the cortex. The two measures likely reflect inhibition mediated by a similar population of interneurons; however, a relationship between these measures has not always been found. Importantly, the population of neurons responsible for GABA\textsubscript{B}-mediated inhibition appears different to that of SICI.

Studies assessing GABA\textsubscript{B}-mediated inhibition in SCZ have produced varied results. For instance, in both chronic medicated and unmedicated SCZ patients, one study assessing LICI found no difference with controls, whereas in studies assessing SP, decreased, and comparable duration has been reported. Two studies assessing first-episode patients reported increased SP early in the illness. However, both first-degree relatives and individuals at risk of SCZ have similar SP durations to controls, suggesting abnormalities may develop with the illness. The disparity between findings in chronic patients is unclear and could reflect subtle differences in methodology. Alternatively, alterations in GABA\textsubscript{B}-mediated inhibition may reflect a compensatory mechanism for other primary deficits. Indeed, perhaps the most interesting finding on SP duration relates to the effect of clozapine, an effective antipsychotic medication. Patients treated with clozapine show increased SP duration relative to controls and patients treated with other antipsychotics, suggesting improved GABA\textsubscript{B}-mediated cortical inhibition may partially underline the therapeutic benefits of this drug. In support, a recent animal study found clozapine facilitates binding of GABA to GABA\textsubscript{B} receptors, whereas a separate study found baclofen, another GABA\textsubscript{B} agonist, normalizes cortical network behavior in a mouse model of SCZ.

**Cortical Excitability**

Two paired-pulse TMS paradigms exist to assess cortical excitability and glutamatergic functioning: intracortical facilitation (ICF; figure 1E) and I-wave facilitation (figure 1F), also called short-interval ICF. Pharmacologically and genetic evidence suggests ICF may partially represent excitation mediated by the NMDA glutamate receptor; however, a contribution of non-NMDA receptors is also possible. I-wave facilitation reflects glutamatergic activity of a different neuron population to ICF, most likely mediated by non-NMDA receptors. The neuronal population underlying I-wave facilitation is also dependent on cortical inhibition as GABA\textsubscript{A}-agonists decrease facilitation.

Majority of studies have failed to find significant differences in ICF in people at risk of SCZ, first-episode SCZ, and both medicated and unmedicated chronic SCZ. However, one study has reported increased ICF in chronic medicated SCZ, albeit in a small sample (n = 7). In addition, comorbid cannabis use in first-episode SCZ appears to increase ICF compared with nonusers. In contrast to ICF, I-wave facilitation is increased in both medicated and unmedicated SCZ compared with controls. Increased I-wave facilitation in SCZ may result from cortical disinhibition. This is plausible given the apparent cortical inhibitory deficits in SCZ.

**Summary**

Findings from paired-pulse TMS studies support reduced GABA\textsubscript{A}-mediated cortical inhibition in SCZ (figure 2). These deficits are present in people at risk of psychosis and persist throughout all phases of illness. Reduced SICI in the motor cortex is often related to SCZ symptomatology and appears indicative of a wider cortical inhibition deficit in SCZ. The role of GABA\textsubscript{A}-mediated cortical inhibition in SCZ is less clear. However, increased GABA\textsubscript{B}-mediated inhibition appears to partially underline the therapeutic benefit of certain medications and is a potential target for novel treatment paradigms.
facilitation is increased in SCZ, possibly reflecting deficits in cortical inhibition.

Cortical Connectivity in SCZ

The emergence of complex brain functions such as sensory processing and cognition is dependent not just on the integrity of local circuits, but on the coordination of distributed neural processes across the brain. Successful coordination requires widespread connectivity between brain regions. Dysfunctional network connectivity has been proposed to underlie the impairments in cognition and behavior seen in SCZ. In support, an abundance of neuroimaging studies have found abnormal connectivity in SCZ. However, the underlying cause of this dysconnectivity remains unclear, possibly reflecting deficits in synaptic transmission, a breakdown in anatomical connectivity or a combination of the two. In addition, the directionality of impaired connectivity (often called effective connectivity) is difficult to ascertain. Twin-coil TMS paradigms offer particular advantages in studying cortical connectivity, however, as connectivity can be tested in a causal manner and the specific neural populations within the motor cortex that brain regions project to can be determined.

Interhemispheric Cortical Connectivity

Interhemispheric connectivity can be assessed by placing a coil over each motor hemisphere and utilizing a paired-pulse paradigm in which one hemisphere is stimulated followed by the other. Using this approach, 2 periods of interhemispheric inhibition (IHI; also called transcallosal inhibition) have been identified, mediated by different neuronal populations (figure 3). The early period of inhibition occurs at intervals of ~10ms (IHI\textsubscript{10}). The latter period occurs at intervals of ~40ms and can also be assessed by measuring the SP during a muscle contraction of the ipsilateral hand (ipsilateral silent period [iSP]; figure 3). Evidence from lesion studies suggests that IHI is mediated via the corpus callosum as people with callosal lesions have absent or reduced IHI.

Abnormal IHI in SCZ has been observed in numerous studies. Reduced IHI\textsubscript{10} at rest has been a consistent finding in both medicated and unmedicated chronic SCZ. In contrast, studies have also consistently found increased iSP in medicated and unmedicated chronic SCZ, although not in first-degree relatives. As IHI\textsubscript{10} and iSP are mediated by different neuronal populations, these divergent findings are likely to reflect separate pathological mechanisms. Reduced IHI\textsubscript{10} likely reflects deficiency in the neuronal population that mediates inhibition in the target hemisphere (figure 4). Conversely, increased iSP is likely to reflect increased motor output from the conditioning hemisphere on to inhibitory populations in the target hemisphere. As iSP is influenced by the neuronal population mediating SICI in the conditioning hemisphere, hyperexcitability within this pathway may reflect disinhibition from impaired SICI (figure 4). Further supporting divergent mechanisms, IHI\textsubscript{10} and iSP are differentially altered in patients treated with olanzapine and risperidone. An important consideration is whether IHI deficits reflect dysfunction of the corpus callosum tracts or deficits in local neuronal populations involving long-range transmission. Transcallosal connectivity appears intact in SCZ. With the exception of 1 study, transcallosal conduction times, measured as the onset of the iSP, are similar between groups. Further confirming this observation, 1 study compared iSP with corpus callosal morphology using MRI. Despite reduced callosal thickness in SCZ, this study found no correlation between callosal thickness and iSP measures and no evidence for demyelination of callosal fibers in patients with SCZ. Disinhibition from abnormal IHI may also contribute to motor dysfunction in SCZ. Excessive motor overflow, the involuntary activation of resting muscles that occasionally accompanies voluntary activation of other muscles, is common in SCZ.
with chronic SCZ display altered interhemispheric conduction times, which is indicative of hyperexcitability. Together, these findings suggest abnormalities in local inhibitory neuronal populations in the output and target hemispheres underlie impaired IHI in SCZ.

In addition to inhibitory interhemispheric connections, facilitatory connections also exist between motor cortices. Interhemispheric facilitation (IHF) has proven difficult to measure, however, due the dominance of inhibition and occurs with large variability within and between participants. During a voluntary contraction, IHF can be observed with a suprathreshold conditioning pulse, low-intensity test stimulation, and ISIs between 4 and 5 ms. Hoy et al. assessed IHF in medicated patients with SCZ. There was no difference between SCZ and healthy controls at rest or during a weak voluntary contraction; however, considerable variability between participants was observed resulting in no mean facilitation in either group.

An alternative approach to assess interhemispheric connectivity is to apply a plasticity-inducing protocol over one hemisphere and assess changes in cortical excitability in the opposing hemisphere. One such protocol is transcranial direct current stimulation (tDCS). tDCS involves applying a small (~1 mA) current across the scalp and results in changes in cortical excitability for 1–2 hours following stimulation. These changes are thought to reflect altered neural membrane potentials and modulation of synaptic efficacy within the stimulated and connected regions. Typically, tDCS increases cortical excitability under the anode and decreases cortical excitability under the cathode. Hasan et al. applied cathodal tDCS to the left motor cortex of healthy controls and people with SCZ. In controls, tDCS reduced cortical excitability in both left and right hemispheres; however, this modulation was reduced in the left hemisphere and completely absent in the right hemisphere of medicated patients with SCZ, further supporting impaired interhemispheric connectivity.
Inter-regional Cortical Connectivity

Interhemispheric connectivity between dorsal premotor cortex and motor cortex can be assessed using a similar approach to IHI. At intervals of 8–10 ms and subthreshold conditioning intensities, stimulation of the left dorsal premotor cortex results in inhibition of MEPs and reduced SICI in the contralateral motor cortex. At shorter ISIs of 8 ms and lower conditioning intensities, dorsal premotor stimulation results in facilitation of the contralateral motor cortex. Connectivity between ventral premotor cortex and motor cortex can also be indirectly tested using an action observation paradigm, where MEP amplitude is facilitated when movements involving the test muscle are observed. This phenomenon is thought to result from connections between the motor cortex and “mirror neuron” populations in the ventral premotor cortex. Mirror neurons were first observed during single cell recordings in monkeys and are activated both during execution of a movement and the observation of another individual performing the same movement. Finally, premotor-motor connectivity can be assessed using a plasticity-inducing TMS protocol. In this approach, 1-Hz repetitive TMS (rTMS) is applied to the premotor cortex, and modulation of cortical excitability following stimulation is assessed in the motor cortex. Abnormal premotor-motor connectivity has been observed in people with SCZ using all three approaches. Medicated patients with SCZ showed less motor cortex facilitation following dorsal premotor stimulation compared with healthy controls and unmedicated SCZ. Reduced facilitation was associated with increased negative symptoms and was not correlated with medication dosage. There was no difference in inhibition following dorsal premotor stimulation suggesting that transcallosal connectivity was intact between the groups. Although unmedicated patients did not show any impairment in dorsal premotor facilitation, this may have resulted from lower symptom severity in this group. Concurrently, medicated patients with SCZ and schizoaffective disorder also showed reduced facilitation following action observation compared with healthy controls. Whether this finding reflects abnormal mirror neuron activation, impaired premotor-motor facilitation, or a combination of the 2 remains unclear. Regardless, abnormal connectivity within this network may contribute to impaired social cognitive function in SCZ. Finally, 1-Hz rTMS over premotor cortex suppressed motor cortical excitability in controls, however facilitated motor cortical excitability in medicated patients with SCZ, further supporting abnormal connectivity and interactions between these regions.

Subcortical-Cortical Connectivity

The recent combination of TMS with other neuroimaging techniques such as fMRI has allowed direct assessment of connectivity between the motor cortex and subcortical structures such as the thalamus. In this approach, significant changes in the hemodynamic response in nonmotor regions following stimulation of the motor cortex are taken as evidence for connectivity between
these regions. Guller et al.\textsuperscript{86} stimulated the motor cortex of medicated patients with SCZ and found reduced activation of the thalamus compared with healthy controls. Other regions such as the superior frontal gyrus and the insula also showed reduced activation in SCZ, possibly as a result of impaired thalamic function disrupting propagation of the neural signal. Impaired thalamic activity in SCZ was further confirmed following performance of a simple motor task, which activated similar motor networks to TMS.

**Cerebellar-Cortical Connectivity**

Stimulation of the cerebellar hemisphere with a double-cone coil results in inhibition of MEPs from the contralateral motor cortex at intervals of 5–7 ms.\textsuperscript{87} This inhibition is thought to be mediated by cerebello-thalamo-cortical pathways. The dentate nucleus in the cerebellum exerts tonic facilitatory drive on the contralateral motor cortex via a synaptic relay in the ventral thalamus. The conditioning TMS pulse is thought to stimulate Purkinje cells in the cerebellar cortex, which inhibit the dentate nucleus, resulting in disinhibition of the motor cortex. Projections from the cerebellum also terminate on inhibitory interneurons as SICI is decreased in the presence of cerebellar inhibition.\textsuperscript{88} Cerebellar inhibition is decreased in medicated patients with SCZ.\textsuperscript{89} The deficit in inhibition may result either from abnormal cerebellar output, impaired thalamic functioning, or from altered connectivity between structures. Given that the cerebellum provides projections to both excitatory and inhibitory neurons in the motor cortex, disrupted cerebello-thalamo-cortical pathways may contribute to the abnormalities in SICI observed in SCZ.

**Summary**

Findings from twin-coil and TMS-fMRI studies support widespread dysconnectivity in SCZ. Impairments in connectivity are not limited to the cortex and also affect subcortical and cerebellar connectivity. Dysconnectivity between premotor and motor cortices appear relevant to social cognitive function in SCZ, whereas disinhibition between primary motor cortices may underlie excessive motor overflow. Interestingly, the propagation of TMS activity from distant regions to the motor cortex appears intact. This finding argues against a strong contribution of anatomical disruptions to dysconnectivity in SCZ, instead favoring either disrupted synaptic transmission or abnormalities in key neuronal populations that mediate connectivity, such as cortical inhibitory interneurons. Finally, it should be noted that the relationship between neural communication, which is presumably reflected in complex, patterned spike trains that differ from one fiber to the next, and the large, unnatural neural volleys evoked by TMS remains unclear. Therefore, the applicability of dysconnectivity measured using TMS to functional dysconnectivity in SCZ requires further investigation.

**Cortical Oscillations in SCZ**

Disruptions involving either inhibition, excitation, or a combination of both, expressed either locally or between connected regions, are likely to have significant impact on cortical oscillatory dynamics detectable by EEG and MEG.\textsuperscript{90} For instance, recent studies using optogenetics revealed γ band oscillations (25–100 Hz) require fast spiking, parvalbumin-positive inhibitory interneurons organized in particular network arrangements with excitatory pyramidal cells.\textsuperscript{91–93} The same PV-positive interneurons and networks are disrupted in postmortem studies of SCZ.\textsuperscript{94} Accordingly, abnormal γ oscillations across a range of brain states have been a consistent finding in EEG and MEG studies of SCZ.\textsuperscript{94} Abnormalities in brain oscillations are not necessarily restricted to the γ band, as nearly all frequency bands have been implicated in SCZ pathophysiology.\textsuperscript{95}

**TMS-Evoked Oscillations**

The recent combination of TMS with EEG offers a unique perspective on the properties of neural networks and cortical oscillations.\textsuperscript{10,96} TMS provides an external input directly to the cortex, bypassing sensory and attentional processes. As these processes are implicated in SCZ, this approach offers an alternative measure of cortical function independent of confounding deficits in early processing systems.\textsuperscript{97} TMS-evoked potentials provide a basic measure of cortical excitability of the stimulated network (figure 5A),\textsuperscript{98} and measurement of the propagation of the TMS-evoked signal provides a measure of effective connectivity between the stimulated regions and other distant regions.\textsuperscript{99} In the frequency domain, TMS-evoked oscillations provide a measure of the preferred frequency at which specific networks oscillate, also called the resonant frequency (figure 5B).\textsuperscript{100}

Several recent studies have assessed TMS-evoked oscillations over different cortical regions in SCZ using TMS-EEG. Over motor cortex, patients with SCZ show reduced amplitude and propagation of TMS-evoked oscillations within the first 100 ms following stimulation compared with healthy controls,\textsuperscript{101,102} supporting an abnormal excitation/inhibition balance as suggested by previous studies. Interestingly, TMS-evoked oscillations at longer time intervals (400–700 ms) following motor cortex TMS appear to be increased in SCZ.\textsuperscript{103} Excessive propagation of γ oscillations was related with positive symptom severity, whereas negative symptom severity was related with excessive δ and θ propagations. This excessive spread of activation following TMS in SCZ may be related to disinhibition of the motor cortex and could reflect a potential mechanism for SCZ symptomatology.
The real power of TMS-EEG is in assessing the neural properties of nonmotor regions more relevant to SCZ. When stimulated over premotor cortex, patients with chronic SCZ showed a marked decrease in $\gamma$ amplitude and synchronization at the site of stimulation compared with healthy controls. The same research team recently replicated this finding and compared several other sites between the parietal cortex and PFC. In healthy participants, different cortical regions displayed different resonant frequencies, increasing from low $\beta$ (~20 Hz) over parietal cortex to $\gamma$ (~31 Hz) over PFC. However, patients with chronic SCZ did not show this same pattern, displaying lower resonant frequencies over motor, premotor, and particularly PFC. For patients, lower resonant frequency over PFC was associated with higher positive symptoms and slower reaction time on a word memory task, suggesting an inability to sufficiently generate $\gamma$ rhythms may contribute to SCZ pathophysiology.

**Inhibitory Modulation of TMS-Evoked Oscillations**

In addition to generating brain oscillations, control of these oscillations is also highly important for brain function. The LICI paradigm has been successfully adapted to TMS-EEG providing a putative measure of $\text{GABA}_\text{B}$-mediated inhibition of TMS-evoked oscillations (figure 5C). Using the LICI paradigm, inhibition of TMS-evoked potentials has been demonstrated over motor, prefrontal, and parietal regions, with specific oscillatory bands preferentially inhibited in different cortical regions. Farzan et al demonstrated that patients with SCZ have specific deficits in inhibition of $\gamma$ band oscillations over PFC. Deficits in $\gamma$ inhibition appear specific to the pathophysiology of SCZ as $\gamma$ inhibition was intact in patients with bipolar disorder. The functional consequences of this deficit remain unclear; however, LICI over PFC is associated with working memory performance in healthy participants, suggesting a possible link with working memory deficits in SCZ.

**Summary**

Findings from TMS-EEG studies support cortical oscillation abnormalities in SCZ. In particular, patients show reduced generation and control of $\gamma$ oscillations over PFC that appear important for both positive and cognitive symptoms. The relationship between abnormal $\gamma$ oscillations and anatomical findings of deficient PV-positive interneurons in postmortem studies remains to be seen. In line with paired-pulse TMS studies, TMS-evoked potentials are also altered over the motor cortex in SCZ. Finally, abnormalities in propagation of the TMS-evoked response from different cortical regions in SCZ support the dysconnectivity findings of twin-coil studies. In particular, late propagation of the TMS-evoked response can be excessive in SCZ supports the notion of impaired control within cortical networks due to deficient cortical inhibition.

**Conclusions**

TMS has provided important insights into the pathophysiology of SCZ. Using paired-pulse paradigms, TMS has revealed $\text{GABA}_\text{A}$-mediated cortical inhibitory deficits
in people at high risk of psychosis through to chronically ill patients. These inhibitory deficits may lead to hyperexcitability in glutamatergic pathways and other network abnormalities. Widespread abnormalities in long-range cortical, subcortical, and cerebellar connectivity in SCZ have also been revealed by TMS. Importantly, some aspects of long-range transmission are intact, arguing against a strong contribution of anatomical dysfunction. Instead, evidence from TMS suggests impairment in specific local neuronal populations that interact with long-range connections underlie cortical dysconnectivity in SCZ. TMS-EEG studies have revealed deficiencies in generating and modulating cortical oscillations within motor and nonmotor regions of people with SCZ, providing further evidence of impaired excitation/inhibition balance. Finally, TMS has informed novel targets for therapeutic intervention, such as increasing GABA_{\alpha}^-mediated cortical inhibition.

Despite the progress made in understanding SCZ pathophysiology using TMS, several important questions remain. First, do motor cortical deficits translate to other brain regions relevant to SCZ? Further research investigating the role of specific neural populations (ie, SICI) in TMS-evoked oscillations over motor cortex will inform the understanding of underlying mechanisms relating to oscillatory deficits in nonmotor regions measurable by TMS-EEG. The development of new TMS-EEG paradigms to assess specific mechanisms such as IHI in nonmotor regions will allow researchers to more specifically address this issue. Second, do local and long-range deficits in cortical function revealed with TMS change through different stages of the illness and are these changes effected by medications? To address this question, longitudinal, within-subject studies are required. This approach will also aid in identifying potential TMS biomarkers for SCZ. With the development of new techniques, TMS will continue to offer a unique and valuable perspective on cortical function in the pathophysiology of SCZ.

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