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# Inhibition of the cortex using transcranial magnetic stimulation in psychiatric populations: current and future directions

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Several lines of evidence suggest that deficits in  $\gamma$ -aminobutyric acid (GABA) inhibitory neurotransmission are implicated in the pathophysiology of schizophrenia, bipolar disorder, major depressive disorder and obsessive–compulsive disorder. Cortical inhibition refers to a neurophysiological process, whereby GABA inhibitory interneurons selectively attenuate pyramidal neurons. Transcranial magnetic stimulation (TMS) represents a noninvasive technique to measure cortical inhibition, excitability and plasticity in the cortex. These measures were traditionally specific to the motor cortex, which is an important limitation when nonmotor neurophysiological processes are of primary interest. Recently, TMS has been combined with electroencephalography (EEG) to derive such measurements directly from the cortex. This review focuses on neurophysiological studies related to inhibitory and excitatory TMS paradigms, linking dysfunctional GABAergic neurotransmission to disease states. We review evidence that suggests cortical inhibition deficits among psychiatric populations and demonstrate how each disorder has a specific neurophysiological response to treatment. We conclude by discussing the future directions of TMS combined with EEG, demonstrating the potential to identify biological markers of neuropsychiatric disorders.

## Introduction

Transcranial magnetic stimulation (TMS) is an important neurophysiological tool that allows researchers to noninvasively study the cortex of healthy individuals and patients with neuropsychiatric disorders.<sup>1</sup> It is used to understand the neurobiology of cognitive function, behaviour and emotional processing<sup>2</sup> by assessing neurophysiological markers of inhibition, excitation and plasticity.<sup>3,4</sup> In 1985, Barker and colleagues<sup>1</sup> introduced TMS as a tool for investigating the functional state of the motor pathways in patients with neurological disorders and healthy participants. It involves the generation of a magnetic field through the use of an electromagnetic coil connected to a TMS device, which induces an electrical current in the brain.<sup>5</sup> They demonstrated that a single TMS pulse applied to the motor cortex could activate cortical tissues associated with the hand or leg muscles, and this

activation could elicit motor evoked potentials (MEPs) at the periphery captured through electromyography<sup>1</sup> (Appendix 1, Figs. S1A and S2, available at [cma.ca/jpn](http://cma.ca/jpn)). Recently, TMS has been combined with electroencephalography (EEG; Appendix 1, Fig. S3) to evaluate the effects of electromagnetic induction on cortical oscillations.<sup>6–8</sup> This review emphasizes the neurophysiological evidence underlying psychiatric disorders through the application of TMS and demonstrates the functional consequences of disordered inhibition.

We performed a literature search using PubMed, MEDLINE, EMBASE Psychiatry and PsycINFO databases from January 1990 through December 2011. The following search terms were used: “transcranial magnetic stimulation,” “TMS,” “TMS-EEG,” “psychiatry,” “psychiatric disorder,” “neuropsychiatric disorder,” “schizophrenia,” “bipolar disorder,” “mania,” “depression,” “major depressive disorder,” “obsessive–compulsive disorder,” “cortical inhibition,” “cortical silent period,” “short

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interval cortical inhibition," "long interval cortical inhibition," "interhemispheric inhibition," "cortical excitability," "resting motor threshold," "active motor threshold," "intra-cortical facilitation," "motor evoked potential amplitude," "interhemispheric signal propagation," "plasticity," "paired-associative stimulation," "long-term potentiation" and "use-dependent plasticity."

## Evaluating cortical inhibition with TMS

Cortical inhibition refers to a neurophysiological process, whereby  $\gamma$ -aminobutyric acid (GABA) inhibitory interneurons selectively attenuate the activity of other neurons (e.g., pyramidal neurons) in the cortex.<sup>9</sup> Pyramidal cell activity is coordinated through a balance of inhibitory postsynaptic potentials (PSPs) and excitatory PSPs.<sup>10</sup> Inhibitory PSPs are generated by GABAergic interneurons terminating on the pyramidal cell.<sup>10</sup>  $\gamma$ -Aminobutyric acid is the main inhibitory neurotransmitter in the brain regulating the modulation of cortical excitability and neural plasticity.<sup>11,12</sup> We describe the following TMS paradigms implicating GABAergic inhibitory neurotransmission: cortical silent period, short interval cortical inhibition, long interval cortical inhibition and interhemispheric inhibition (Appendix 1, Table S1).

### *Cortical silent period*

The cortical silent period is measured by stimulating the contralateral motor cortex in a moderately tonically active muscle (i.e., 20% of maximum contraction) with TMS intensities of 110%–160% of resting motor threshold, resulting in the interruption of voluntary muscle contraction<sup>3,13</sup> (Appendix 1, Fig. S1B). The duration of the cortical silent period is measured from MEP onset to the return of any voluntary electromyography activity, ending with a deflection in the electromyography waveform.<sup>14</sup> Studies have demonstrated that the cortical silent period is related to GABA<sub>B</sub> receptor-mediated inhibitory neurotransmission, as it displays a similar time course to the GABA<sub>B</sub> receptor-induced inhibitory PSP, about 150–200 ms poststimulus.<sup>15–18</sup> For instance, administration of tiagabine, a GABA reuptake inhibitor, leads to an increased concentration of GABA in the synaptic cleft and predominantly activates GABA<sub>B</sub> receptors,<sup>19</sup> which has been reported to result in a dose-dependent prolongation of the cortical silent period.<sup>16</sup> Furthermore, baclofen, a potentiator of GABA<sub>B</sub> receptor-mediated inhibitory neurotransmission, has also been found to lengthen the cortical silent period.<sup>17</sup>

### *Short interval cortical inhibition*

Short interval cortical inhibition, first reported by Kujirai and colleagues,<sup>3</sup> involves a subthreshold conditioning stimulus set at 80% of the resting motor threshold that precedes a suprathreshold test stimulus, adjusted to produce an average MEP of 0.5–1.5 mV peak-to-peak amplitude in the contralateral muscle (Appendix 1, Fig. S2).<sup>3,13</sup> To measure short interval cortical inhibition, conditioning stimuli are applied to the motor cortex before the test stimulus at interstimulus inter-

vals (ISIs) between 1 ms and 4 ms, as the subthreshold conditioning stimulus suppresses the MEP produced by the test stimulus (Appendix 1, Fig. S1C). Research suggests that short interval cortical inhibition is related to GABA<sub>A</sub> receptor-mediated inhibitory neurotransmission,<sup>20</sup> as it has been demonstrated that short interval cortical inhibition is increased by medications, such as lorazepam, that facilitate GABA<sub>A</sub> neurotransmission.<sup>21</sup> Baclofen (a GABA<sub>B</sub> agonist) has also been shown to decrease short interval cortical inhibition,<sup>22</sup> possibly associated with presynaptic GABA<sub>B</sub> autoreceptors.<sup>23</sup> Moreover, short interval cortical inhibition is related to GABA<sub>A</sub> receptor-mediated inhibitory neurotransmission, as it displays a similar time course to the GABA<sub>A</sub> receptor-induced inhibitory PSP. For example, Wang and Buzsaki<sup>24</sup> showed through computer simulations that the synaptic time constant for GABA<sub>A</sub> receptors ranges from about 10 to 25 ms, confirming that short interval cortical inhibition is associated with activity of GABA<sub>A</sub> receptor-mediated inhibitory neurotransmission.

### *Long interval cortical inhibition*

Long interval cortical inhibition refers to the pairing of a suprathreshold conditioning stimulus followed by a suprathreshold test stimulus at long ISIs (e.g., 50–100 ms), resulting in inhibition of the MEP produced by the test stimulus (Appendix 1, Fig. S1D).<sup>25,26</sup> Studies have strongly suggested that long interval cortical inhibition is mediated by slow inhibitory PSPs via activation of GABA<sub>B</sub> receptors.<sup>22,27,28</sup> For example, 50 mg of baclofen orally administered to 9 healthy participants resulted in enhanced long interval cortical inhibition, implying that the increase in long interval cortical inhibition is likely a result of increased GABA<sub>B</sub> receptor-mediated inhibitory PSPs.<sup>22</sup> Also, long interval cortical inhibition is optimal when the conditioning stimulus precedes the test stimulus by 100–150 ms,<sup>28</sup> comparable to the time course of the GABA<sub>B</sub> receptor activation, which has been shown to typically peak at around 150–200 ms poststimulus.<sup>15</sup> More recently, a significant positive association has been shown between the suppression of MEP amplitudes in long interval cortical inhibition (with an ISI of 100 ms) and in the cortical silent period in healthy individuals,<sup>29</sup> providing evidence for the mediation of the GABA<sub>B</sub> receptor in both long interval cortical inhibition and the cortical silent period.

### *Interhemispheric inhibition*

Interhemispheric inhibition is measured using 2 magnetic stimulating coils, whereby a suprathreshold TMS pulse delivered to one hemisphere can inhibit the MEP response to a suprathreshold TMS pulse delivered within 6–50 ms to the opposite hemisphere.<sup>30,31</sup> Inhibitory GABAergic neurons mainly serve local circuits;<sup>32</sup> interhemispheric inhibition may be mediated through excitatory axons that cross the corpus callosum to act on local inhibitory neurons in the contralateral motor cortex.<sup>33</sup> Daskalakis and colleagues<sup>23</sup> demonstrated that short interval cortical inhibition is reduced in the presence of interhemispheric inhibition. Furthermore, interhemispheric

inhibition is reduced in the presence of long interval cortical inhibition when matched for test MEP amplitude, but no significant change is seen when matched for test stimulus intensity. These results demonstrate that interhemispheric inhibition may be related to GABA<sub>B</sub> activity. This is consistent with the findings of Ziemann and colleagues,<sup>21</sup> who showed that lorazepam increased short interval cortical inhibition but did not change interhemispheric inhibition, suggesting that the latter is not related to GABA<sub>A</sub> activity.

### TMS as a method to measure excitability

Glutamate and aspartate are the main excitatory neurotransmitters within the central nervous system.<sup>34</sup> Excitatory PSPs in neurons of the rat sensorimotor cortex are mediated by  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA) and kainate receptors.<sup>35</sup> Voltage-gated sodium channels are vital in regulating axon excitability,<sup>36</sup> whereas nonionotropic non-NMDA glutamate receptors are responsible for fast excitatory synaptic neurotransmission within the neocortex.<sup>37</sup> We discuss the following excitatory paradigms: resting motor threshold, active motor threshold and intracortical facilitation (Appendix 1, Table S1).

#### *Resting motor threshold*

Transcranial magnetic stimulation permits assessment of the resting motor threshold, defined as the minimal intensity that produces an MEP greater than 50  $\mu$ V in 5 of 10 trials in a relaxed muscle.<sup>3</sup> The resting motor threshold is a global measure of corticospinal excitability and depends on the excitability of axons activated by the TMS pulse and the excitability of synaptic connections at both the cortical and spinal level.<sup>38</sup> The resting motor threshold depends on glutamatergic synaptic excitability.<sup>38</sup> It has been shown that drugs that block voltage-gated sodium channels, in particular anti-convulsants, such as carbamazepine, lamotrigine and losigamone, increase the resting motor threshold;<sup>20</sup> by contrast, NMDA antagonists, such as ketamine, reduce it.<sup>39</sup> Lastly, drugs with GABAergic properties, such as vigabatrin (GABA analogue), baclofen (GABA<sub>B</sub> receptor agonist) and gabapentin (GABA analogue) do not affect motor threshold.<sup>20</sup>

#### *Active motor threshold*

The active motor threshold is defined as the first intensity that produces an MEP of greater than 100  $\mu$ V in 5 of 10 trials in an isometrically moderately active muscle.<sup>40</sup> The active motor threshold is measured during muscle contraction, where corticospinal neurons and spinal motor neurons are very close to firing threshold.<sup>38</sup>

#### *Intracortical facilitation*

Intracortical facilitation is a paired pulse paradigm that can be used to index excitability of the excitatory circuits in the motor cortex, whereby conditioning stimuli are applied to

the motor cortex before the test stimulus at ISIs usually between 7 and 20 ms (Appendix 1, Fig. S1E). It has been shown that intracortical facilitation originates from excitatory PSPs transmitted by glutamatergic NMDA receptors.<sup>41</sup> In fact, the latency of onset of the excitatory PSP mediated by the NMDA receptor is about 10 ms, which is consistent with the time course of intracortical facilitation.<sup>3,42</sup> This is supported by most pharmacological studies, which demonstrate that NMDA receptor antagonists, such as dextromethorphan and memantine, decrease intracortical facilitation.<sup>43,44</sup> Benzodiazepines, such as lorazepam (GABA<sub>A</sub> agonist), also decrease it,<sup>21</sup> and baclofen (GABA<sub>B</sub> agonist) increases it.<sup>20</sup> Lastly, it has also been suggested that intracortical facilitation is not exclusively mediated by excitatory interneurons, but rather by a net balance between inhibition and excitability.<sup>45</sup>

### Motor cortex inhibition in psychiatric populations

Several lines of evidence suggest that deficits in GABA functioning are implicated in the pathophysiology of schizophrenia, bipolar disorder, major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). The integration of TMS with electromyography is a valuable tool for the assessment of the pathological processes associated with psychiatric disorders.

#### *Schizophrenia*

Schizophrenia is a severe psychiatric illness characterized by delusions, hallucinations, disorganized thinking and often lifelong disability.<sup>46</sup> It exacts enormous personal, social and economic costs.<sup>46</sup> Cortical inhibition may represent an important mechanism responsible for the symptoms observed in patients with schizophrenia. Several lines of evidence suggest that abnormalities in cortical inhibition are an important neurophysiological mechanism in schizophrenia, and these impairments have been shown to be related to GABAergic deficits. Benes and colleagues<sup>47</sup> first reported that patients with schizophrenia have morphologic changes in cortical GABA interneurons by demonstrating a decreased density of nonpyramidal cells (i.e., interneurons) in anterior cingulate layers II–VI and in prefrontal cortex layer II.

Research using TMS has shown cortical inhibition abnormalities in patients with schizophrenia. For example, Daskalakis and colleagues<sup>48</sup> measured resting motor threshold, short interval cortical inhibition, intracortical facilitation, cortical silent period and interhemispheric inhibition in 15 unmedicated patients with schizophrenia (14 medication-naive and 1 medication-free for more than 1 yr), 15 medicated patients and 15 healthy controls. The study found that unmedicated patients had significantly lower cortical inhibition than healthy controls in measures of short interval cortical inhibition, cortical silent period and interhemispheric inhibition, providing TMS evidence for deficient GABAergic neurotransmission in patients with schizophrenia. Similarly, Fitzgerald and colleagues<sup>49</sup> found comparable results in 22 medicated patients with schizophrenia compared with 21 healthy controls. They demonstrated significantly lower

short interval cortical inhibition and cortical silent period in the schizophrenia group than in healthy controls. Fitzgerald and colleagues<sup>50</sup> also evaluated interhemispheric inhibition in 25 patients with schizophrenia and 20 healthy controls. They similarly demonstrated a significant decrease in interhemispheric inhibition in patients independent of medication dose. More recent studies using TMS have also demonstrated deficits in cortical inhibition in patients with schizophrenia. For example, Daskalakis and colleagues<sup>51</sup> reported that 10 clozapine-treated patients with schizophrenia had significantly longer cortical silent periods than 6 unmedicated patients and 10 healthy controls. A subsequent study by Liu and colleagues<sup>52</sup> with a large sample of 78 patients with schizophrenia and 38 healthy controls confirmed that clozapine-treated patients demonstrated longer cortical silent periods and lower short interval cortical inhibition than healthy controls. However, patients treated with other antipsychotics and unmedicated patients demonstrated significantly shorter cortical silent periods. These findings suggest that cortical inhibition is involved in the pathophysiology of schizophrenia and that clozapine may potentiate GABA<sub>B</sub> receptor-mediated inhibitory neurotransmission. Additionally, across all patients in the study by Liu and colleagues,<sup>52</sup> the cortical silent period was inversely related to negative symptoms, whereas short interval cortical inhibition was inversely associated with positive symptoms, highlighting the role of both GABA<sub>B</sub> and GABA<sub>A</sub> receptor-mediated inhibitory neurotransmission in patients with schizophrenia. This finding is consistent with recent neurochemical evidence demonstrating that there is a direct link between clozapine and the GABA<sub>B</sub> receptor.<sup>53</sup> Furthermore, Wobrock and colleagues<sup>54</sup> examined 12 patients with first-episode schizophrenia with a history of comorbid cannabis use and 17 without. They found that patients with a history of comorbid cannabis use had lower short interval cortical inhibition and increased intracortical facilitation, but no significant differences were found in resting motor threshold or the cortical silent period. Comorbid cannabis abuse was suggested to potentiate the reduced short interval cortical inhibition and enhanced intracortical facilitation observed in patients with first-episode schizophrenia. This finding is consistent with a those of a previous study by Fitzgerald and colleagues<sup>55</sup> reporting that heavy and light users of cannabis demonstrated significantly decreased short interval cortical inhibition compared with healthy controls. Taken together, these studies provide evidence that schizophrenia is associated with cortical inhibition deficits in the motor cortex. Future studies are needed to identify biological markers of both illness and treatment response and develop a deeper understanding of the neurophysiological mechanisms underlying schizophrenia.

### *Bipolar disorder*

Bipolar disorder is a serious psychiatric illness with prevalence estimates of 2.4% worldwide.<sup>56</sup> It is characterized by periods of mania or hypomania alternating with phases of depression<sup>57</sup> and is associated with an early age at onset, usually between 16 and 26 years.<sup>58,59</sup> Suicide and suicide attempts are

important contributors to premature mortality and disability.<sup>60</sup> Relatively little work has been done to understand the neurophysiological underpinnings of this disease. Limited neuroanatomical evidence demonstrates that patients with bipolar disorder have impaired cortical inhibitory neurotransmission.<sup>61</sup> Benes and Berretta<sup>62</sup> found that the density of cortical GABA interneurons, which mediate cortical inhibition, is reduced in the anterior cingulate cortex among patients with bipolar disorder, and they also found a 30% decrease in cortical inhibitory GABAergic interneurons in patients with bipolar disorder versus a 16% decrease in those with schizophrenia.<sup>62</sup> The data suggest a loss of GABAergic interneurons in both groups of patients. However, there is little *in vivo* neurophysiological evidence supporting such impairments in those with bipolar disorder. Levinson and colleagues<sup>63</sup> used TMS to evaluate short interval cortical inhibition, the cortical silent period and interhemispheric inhibition in 15 patients with bipolar disorder (13 medicated with a single mood stabilizer and 2 unmedicated) and 15 healthy controls. They found that patients with bipolar disorder demonstrated significant deficits in short interval cortical inhibition, the cortical silent period and interhemispheric inhibition compared with healthy individuals. The authors concluded that GABAergic inhibitory neurotransmission was deficient in the motor cortex of patients with bipolar disorder. Furthermore, most patients were medicated, and the evidence suggested that these inhibitory deficits were attenuated with treatment. Nevertheless, additional studies are needed with large, unmedicated samples and more severely ill patient populations. It would be hypothesized that any inhibitory deficits would be magnified under these conditions.

### *Major depressive disorder*

Major depressive disorder is one of the most prevalent psychiatric disorders and is estimated to affect 16.6% of individuals in their lifetime.<sup>64</sup> It not only affects physical and cognitive functions, but also has a profound impact on psychosocial well-being.<sup>64</sup> Preclinical work has demonstrated that chronic stress induces compensatory changes in the GABAergic system in animal models.<sup>65</sup> Evidence suggests that MDD may be associated with abnormalities in cortical excitability and, more specifically, deficits in cortical inhibition. For example, Fitzgerald and colleagues<sup>66</sup> assessed cortical excitability before a trial of repetitive TMS (rTMS) treatment in patients with MDD. This study included 60 patients with treatment-resistant depression, of whom 46 were medicated during the trial (antidepressants, mood stabilizers and antipsychotics). The authors found a decreased short interval cortical inhibition of the right motor cortex (1 ms ISI) and reported that an increased cortical silent period in the left motor cortex predicted a poorer response to rTMS treatment. Bajbouj and colleagues<sup>67</sup> assessed 20 patients with MDD who had been off of medication for at least 4 weeks and 20 healthy participants. They found reduced short interval cortical inhibition and cortical silent periods in patients with MDD, consistent with the hypothesis of deficient GABAergic tone in depressed patients. Similarly, Lefaucheur and colleagues<sup>68</sup>

demonstrated that patients with MDD showed a reduced excitability of both excitatory (resting motor threshold, intracortical facilitation) and inhibitory (cortical silent period, short interval cortical inhibition) processes in the left hemisphere compared with healthy controls. More recently, Levinson and colleagues<sup>69</sup> examined cortical inhibition in 25 medicated individuals with treatment-resistant depression, 19 medicated euthymic participants, 16 unmedicated depressed patients and 25 healthy controls and found that all patients with MDD, regardless of symptom or medication state, demonstrated significant cortical silent period deficits compared with healthy participants. Patients with treatment-resistant depression also demonstrated significant deficits in short interval cortical inhibition compared with healthy participants. These findings all held true after controlling for benzodiazepine use, which has been shown to affect TMS parameters.<sup>69</sup> Since all patients with MDD showed cortical silent period abnormalities, but only patients with treatment-resistant depression also demonstrated short interval cortical inhibition reductions, the authors concluded that the depressed state overall may be associated with GABA<sub>B</sub> deficits; however, severe symptomatology, as seen in patients with treatment-resistant depression, may be associated with greater deficits in both GABA<sub>A</sub> and GABA<sub>B</sub> neurotransmission. Taken together, these findings suggest that MDD is associated with deficits in GABAergic inhibitory neurotransmission and abnormalities in inhibitory functions of the motor cortex. Future studies are needed to explore these findings further in cortical regions that are more closely associated with the pathophysiology of MDD (e.g., the dorsolateral prefrontal cortex [DLPFC]).

### *Obsessive-compulsive disorder*

Obsessive-compulsive disorder is a serious psychiatric illness characterized by the presence of recurrent, intrusive thoughts, impulses or images (obsessions) that are often also accompanied by repetitive rituals or behaviours (compulsions) designed to counteract the associated anxiety. As obsessive thoughts and/or rituals may cause great distress and take up substantial time during the day, OCD often leads to pronounced psychosocial impairment.<sup>70</sup> It is estimated to affect up to 2.5% of the world's population.<sup>64,71</sup> Although, its pathophysiology remains to be fully elucidated, research suggests that OCD may involve inhibitory deficits in orbitofrontal striatal circuits.<sup>72</sup>

One preliminary study found decreased short interval cortical inhibition in 12 patients with OCD without a history of comorbid tics or Tourette syndrome compared with 12 healthy controls,<sup>73</sup> implicating a role for GABA<sub>A</sub> inhibitory neurotransmission in patients with OCD. These results were expanded with 9 medicated and 7 unmedicated patients with OCD compared with 11 healthy controls.<sup>74</sup> In this case, both the resting and active motor thresholds were found to be significantly lower in patients with OCD than in controls. Similarly, short interval cortical inhibition was significantly lower in patients with OCD than controls, and this difference remained significant even when the same comparison was

made with only unmedicated patients; no differences were found for short interval cortical inhibition between unmedicated and medicated patients with OCD. By contrast, there were no differences in intracortical facilitation or cortical silent period detected between patient and control groups. Furthermore, patients with OCD with tics had significantly less short interval cortical inhibition than those without tics. The authors concluded that OCD, in the presence or absence of comorbid tics, was characterized by deficient short interval cortical inhibition.

More recently, Richter and colleagues<sup>75</sup> assessed a larger sample of patients with OCD, comparing 34 patients (23 medicated and 11 unmedicated) with 34 healthy individuals. In contrast to the previous study, no overall difference was found in resting motor threshold between the OCD and control groups; however, resting motor threshold was significantly lower in the medicated compared with the unmedicated OCD population. Additionally, the cortical silent period was also found to be significantly shorter in patients with OCD, but no further differences were detected between the medicated and unmedicated patients. Finally, although the study failed to detect differences in short interval cortical inhibition between the OCD and control groups, patients with OCD were found to have a significantly greater intracortical facilitation, regardless of medication status. No correlations were found between illness severity and TMS parameters in either the medicated or unmedicated patients. In this case, the results suggest that OCD is associated with deficient cortical silent period and excessive intracortical facilitation, regardless of medication state, reflecting abnormalities in GABA<sub>B</sub> and NMDA-mediated neurotransmission, which is consistent with the results of several genetic studies of this disorder.<sup>76-81</sup> The authors suggested that differences between their results and those previously published could be owing to the greater number of unmedicated patients and elevated symptom severity in their sample or to the different stimulation intensities used to elicit measures. The discrepant findings in the limited number of studies highlight the need for further research to better characterize the potential abnormalities seen in patients with OCD.

### **What are the implications of these findings?**

There is compelling evidence to suggest that GABAergic inhibitory deficits are closely involved in the pathophysiology of schizophrenia, MDD, OCD and bipolar disorder. However, each disorder has a specific neurophysiological response profile to treatment distinguishing it from the rest. For example, research has suggested that unmedicated patients with schizophrenia have demonstrated impairments in short interval cortical inhibition, cortical silent period and interhemispheric inhibition.<sup>48</sup> Moreover, 2 studies have shown that clozapine-treated patients with schizophrenia demonstrated significantly longer cortical silent periods, implicating the role of the GABA<sub>B</sub> receptor in clozapine treatment and showing a specific response profile of treatment in this disorder.<sup>51,52</sup> By contrast, Levinson and colleagues<sup>69</sup> found that all patients with MDD showed cortical silent period abnormalities, but only

patients with treatment-resistant depression demonstrated short interval cortical inhibition reductions. Treatment with antidepressants had no apparent effects on either measure, though other research has shown that selective serotonin reuptake inhibitors normalize GABAergic deficits in depressed patients through enhanced short interval cortical inhibition and decreased intracortical facilitation.<sup>82,83</sup> Patients with OCD have decreased short interval cortical inhibition and cortical silent periods and enhanced intracortical facilitation independent of medication status.<sup>73–75</sup> Lastly, patients with bipolar disorder treated with antipsychotics or anticonvulsant mood stabilizers have shown impairments in short interval cortical inhibition, the cortical silent period and interhemispheric inhibition.<sup>63</sup> In Appendix 1, Table S2, we summarize these TMS findings for each neuropsychiatric disorder. Further research is needed to replicate these findings and develop these measures further as biomarkers of either illness, treatment or both.

### Applications beyond the motor cortex

The neurophysiological studies mentioned previously demonstrate the conventional approaches to measuring cortical inhibition and excitability of the motor cortex. Such approaches have been used to demonstrate important neurophysiological findings in both healthy and diseased states. However, the restriction of such recordings over the motor cortex is of limited interest since the pathophysiology of many psychiatric disorders is associated with nonmotor brain regions. As a result, it is important to evaluate the neurophysiology of brain regions that are more proximal to the underlying phenotype (e.g., the DLPFC). Recently, TMS has been combined with EEG to derive inhibitory measurements directly from the DLPFC and the motor cortex in healthy individuals.<sup>29,84,85</sup> Long interval cortical inhibition can be measured using a combination of paired-pulse TMS and EEG to study how GABA<sub>B</sub> receptors modulate oscillations in the brain in both the motor cortex and DLPFC with high test–retest reliability.<sup>29,84,85</sup> Long interval cortical inhibition using TMS-EEG is defined using the area under rectified unconditioned and conditioned waveforms for averaged EEG recordings between 50 and 150 ms post-test stimulus. This interval was chosen as it represents the earliest artifact-free data (i.e., 50 ms post-test stimulus) and reflects the duration of GABA<sub>B</sub> receptor-mediated inhibitory PSPs (i.e., 250 ms post-conditioned stimulus).<sup>86</sup>  $\gamma$  Oscillations (30–50 Hz) in the cortex are generated as a result of rapid firing of output pyramidal neurons. Inhibitory interneurons exert fine control over the firing of pyramidal neuronal networks, which translates into high-frequency  $\gamma$  oscillatory activity on EEG.<sup>87</sup> Several reports also suggest that different GABA receptor subtypes are active during different phases of  $\gamma$  oscillations. It has been shown that GABA<sub>A</sub> inhibitory PSPs contribute to generation of  $\gamma$  oscillations and GABA<sub>B</sub> inhibitory PSPs contribute to the modulation of  $\gamma$  oscillations.<sup>88,89</sup>

#### *TMS-EEG studies of inhibition*

Two studies have used combined TMS and EEG to examine

the pathophysiology of schizophrenia. Farzan and colleagues<sup>90</sup> demonstrated that overall long interval cortical inhibition using TMS-EEG in patients with schizophrenia did not differ significantly in any region compared with patients with bipolar disorder and healthy controls. However, when the evoked EEG response was filtered into different frequency bands, they found a significant deficit in the inhibition of  $\gamma$  oscillations in the DLPFC of patients with schizophrenia relative to those with bipolar disorder and healthy controls, but no inhibitory deficit was found within the motor cortex. The authors concluded that this selective deficit in the inhibition of  $\gamma$  oscillations demonstrates that the DLPFC is a region in the brain closely related to the pathophysiology of schizophrenia. Along with the specificity of these findings, additional data also suggest high test–retest reliability<sup>29</sup> and trait stability<sup>90</sup> of this neurophysiological marker, implying that frontal  $\gamma$  inhibition deficits may represent a candidate endophenotype for schizophrenia. Deficits in frontal  $\gamma$  inhibition of the DLPFC are consistent with neurophysiological evidence of frontal impairments implicated in schizophrenia as deficits in cognitive functions, such as working memory, a major feature of this disorder.<sup>91</sup> An earlier study also provided supports this finding: Ferrarelli and colleagues<sup>92</sup> demonstrated a decrease in EEG-evoked responses in the  $\gamma$  band when TMS was applied directly to the frontal cortex, suggesting frontal  $\gamma$  deficits in patients with schizophrenia. Taken together, these studies point to important new directions in which TMS-EEG can provide new insights into the neurophysiological underpinnings of schizophrenia. Evaluating the diagnostic specificity and heritability of this trait in patients with schizophrenia is vital to identifying an adequate endophenotype for this disorder.<sup>93</sup>

#### *Assessing connectivity with TMS and EEG*

Current pathophysiological theories of schizophrenia emphasize the role of altered brain connectivity.<sup>94,95</sup> This disconnection may manifest anatomically, through structural changes of association fibres at the cellular level, or functionally through aberrant control of synaptic plasticity.<sup>95</sup> Transcranial magnetic stimulation combined with EEG can be used to evaluate the connectivity between and within hemispheres,<sup>96</sup> providing potential to ascertain functional connectivity between cortical regions.<sup>97,98</sup> Voineskos and colleagues<sup>96</sup> examined the association between microstructural integrity of subdivisions of the corpus callosum with TMS-induced interhemispheric signal propagation using a single-pulse paradigm. They found a significant inverse association between microstructural integrity of the genu fibres of the corpus callosum and TMS-induced interhemispheric signal propagation from the left to the right DLPFC. Further, they found a significant inverse association between microstructural integrity of callosal motor fibres with TMS-induced interhemispheric signal propagation from the left to the right motor cortex. The authors concluded that the examination of corpus callosum microstructure in relation to TMS-induced interhemispheric signal propagation may provide novel insight into the neurobiological mechanisms of severe psychiatric

disorders, such as schizophrenia. Research has shown that during early cortical development, reelin plays an important role in lamination of the cortex. Reelin is a protein that regulates cortical pyramidal neurons, interneurons and Purkinje cell positioning.<sup>99,100</sup> In patients with schizophrenia, reelin has been found to be decreased in layers I and II of the prefrontal cortex.<sup>101</sup> Furthermore, Costa and colleagues<sup>102</sup> found a downregulation of reelin expression and attenuated dendritic spine expression that in turn reduced corticocortical connectivity and glutamic acid decarboxylase 67 expression in patients with schizophrenia. These findings may explain the deficits in GABAergic inhibitory neurotransmission and the subtle disruptions in connectivity found in these patients. Future research may consider evaluating the association between long interval cortical inhibition and interhemispheric signal propagation, hypothesizing a strong correlation between deficits in frontal  $\gamma$  inhibition and a lack of TMS-induced interhemispheric signal propagation in patients with schizophrenia.

### Functional consequences of disordered inhibition

Plasticity in the human cortex involves the functional reorganization of synaptic connections in an effort to change or adapt throughout life and is characterized by processes involved in learning, memory and neural repair.<sup>103</sup> Evidence suggests that neural plasticity may also be a corollary of cortical inhibition, as mechanisms mediating plasticity include unmasking existing corticocortical connections<sup>12</sup> by removing cortical inhibitory neurotransmission.<sup>104</sup> For example, in humans, administration of a GABAergic agonist disrupts plasticity.<sup>105</sup> Abnormalities in brain plasticity, possibly related to abnormal cortical inhibition, have been proposed to underlie the pathophysiology of schizophrenia.<sup>106,107</sup> We discuss paired associative stimulation (PAS) and use-dependent plasticity as a way of measuring plasticity in the cortex. The evidence suggests that decreased neural plasticity is even more pronounced in patients with schizophrenia with impaired cortical inhibition.

Paired associative stimulation represents a neurophysiologic paradigm that involves peripheral nerve stimulation of the median nerve, followed by TMS of the contralateral motor cortex. It has been shown to result in long-term potentiation if peripheral nerve stimulation precedes TMS by 25 ms (PAS-25).<sup>108</sup> Rajji and colleagues<sup>109</sup> demonstrated MEP potentiation after PAS-25 that was associated with enhanced motor learning at 1 week post-PAS in healthy participants. Moreover, Frantseva and colleagues<sup>110</sup> demonstrated that patients with schizophrenia showed deficits in MEP facilitation, indicating disrupted long-term potentiation-like plasticity associated with impaired motor skill learning compared with healthy participants. This study highlighted the role of PAS-TMS in the motor regions to assess synaptic plasticity in patients with schizophrenia. The authors concluded that these patients demonstrated impaired long-term potentiation-like plasticity, which may be associated with deficits in learning and memory.

Use-dependent plasticity involves the use of a TMS para-

digim that can measure neural plasticity in the cortex.<sup>4</sup> The spontaneous direction of TMS-induced thumb movements is measured in 2 axes ( $x$  and  $y$ ). As a result, use-dependent plasticity is assessed using a task in which individuals are trained to perform a simple motor task opposite to the direction of TMS-induced thumb movement. Transcranial magnetic stimulation is then reapplied to the cortex while evaluating the direction of the induced thumb movement over time. Classen and colleagues<sup>4</sup> found that immediately after training, the direction of TMS-induced movements followed the direction of training. Both GABA and NMDA receptor-mediated neurotransmission play an important role in use-dependent plasticity.<sup>105</sup> Daskalakis and colleagues<sup>111</sup> evaluated use-dependent plasticity in 14 medicated and 6 unmedicated patients with schizophrenia and 12 healthy participants. A significant reduction of use-dependent plasticity was demonstrated in those with schizophrenia compared with healthy participants. That is, patients with schizophrenia demonstrated significantly small angular deviations in the 5–10 minutes of post- versus pretraining periods compared with controls. The authors concluded that such abnormalities may be related to dysfunctional neurophysiological brain processes, including long-term potentiation-like activity, that exist as a result of disturbances of GABA, NMDA and dopamine neurotransmission. These findings potentially account for the aberrant motor performance demonstrated in patients with schizophrenia. Taken together, these studies provide preliminary evidence for a diminution of the neurophysiological processes that mediate neural plasticity in patients with schizophrenia.

### Limitations

The aforementioned studies relating to deficits in cortical inhibition in patients with schizophrenia, bipolar disorder, MDD and OCD are limited in several ways. Several studies are limited to measuring the motor cortex, as the exact mechanism underlying the generation and modulation of the TMS-evoked MEPs remains unclear. Additional limitations include small samples, differences in the TMS methodologies between research groups, heterogeneous populations and an overall lack of diagnostic specificity. Several lines of evidence demonstrate motor cortex cortical inhibition deficits in patients with schizophrenia, bipolar disorder, MDD and OCD, although they reveal very different clinical phenotypes demonstrated as a limitation of the TMS-electromyography findings. However, TMS combined with EEG is an important technique used to investigate candidate endophenotypes, allowing for assessments of the neurophysiology of the DLPFC. Lastly, it has been shown that medication may affect outcomes of TMS measures. As such, the inclusion of medicated individuals on various classes of psychotropic agents in these studies may be an important confounder of results. Addressing these issues systematically in future research by assessing large samples of unmedicated psychiatric populations will allow for a greater confidence in results and provide a more stable evidence base for elucidating biological markers involved in psychiatric illnesses.

There are several methodological limitations to using combined TMS and EEG paradigms that should be considered when measuring the cortex in human participants. Transcranial magnetic stimulation-evoked EEG responses may be contaminated by muscular activity, indirect cranial reflexes and somatosensory evoked potentials,<sup>112-114</sup> producing artifacts in the recordings.

## Where do we go next?

Transcranial magnetic stimulation has provided us with the ability to evaluate cortical processes, such as inhibition, excitation and plasticity, in healthy participants, which has led to invaluable evidence in elucidating the pathophysiology of neuropsychiatric disorders. Taken together, the literature has demonstrated that disorders, such as schizophrenia, bipolar disorder, MDD and OCD, are characterized by abnormalities in cortical inhibition, highlighting the lack of GABAergic inhibitory neurotransmission. It is important to assess the neurophysiology of brain regions (e.g., the DLPFC) that are more proximal to the underlying phenotype. Additionally, the ability to evaluate the response profiles of different oscillatory frequency bands via EEG in response to TMS may ultimately serve as a key method to identify endophenotypes of psychiatric illness. Endophenotypes are valuable as they are presumably upstream in the pathophysiology of the illness and closer to the genetic variation underlying complex psychiatric disorders.<sup>93</sup> Compared with current subjective clinical diagnoses, endophenotypes are objective, quantifiable and heritable, and they allow for measurement of aberrant neural circuitry.<sup>93,115</sup>

## Conclusion

There is a great need to better understand the neurobiological underpinnings of psychiatric disorders for more objective diagnosis and for the potential of treatment discovery.

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