Evidence for Impaired Cortical Inhibition in Schizophrenia Using Transcranial Magnetic Stimulation

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**Background:** Cortical inhibition (CI) deficits have been proposed as a pathophysiologic mechanism in schizophrenia. This study employed 3 transcranial magnetic stimulation (TMS) paradigms to assess CI in patients with schizophrenia. Paired-pulse TMS involves stimulating with a lower-intensity pulse a few milliseconds before a higher-intensity pulse, thereby inhibiting the size of the motor evoked potential produced by the higher-intensity pulse. In the cortical silent period paradigm, inhibition is reflected by the silent period duration (ie, the duration of electromyographic activity cessation following a TMS-induced motor evoked potential). Transcallosal inhibition involves stimulation of the contralateral motor cortex several milliseconds prior to stimulation of the ipsilateral motor cortex, inhibiting the size of the motor evoked potential produced by ipsilateral stimulation.

**Methods:** We measured CI using these 3 paradigms in 15 unmedicated patients with schizophrenia (14 medication-naive and 1 medication-free for longer than 1 year) (13 were in the transcallosal inhibition paradigm), 15 medicated patients with schizophrenia (11 taking olanzapine, 1 risperidone, 1 quetiapine, 1 methotrimeprazine + perphenazine, 1 quetiapine + loxapine), and 15 healthy controls.

**Results:** Unmedicated patients demonstrated significant CI deficits compared with healthy controls across all inhibitory paradigms whereas medicated patients did not (at all inhibitory intervals, paired-pulse TMS: controls = 59.9%, medicated = 44.3%, unmedicated = 28.7%; cortical silent period: controls = 55.0 milliseconds, medicated = 60.4 milliseconds, unmedicated = 39.7 milliseconds; transcallosal inhibition: controls = 33.6%, medicated = 23.7%, unmedicated = 10.4%; P < .05).

**Conclusions:** These results suggest that schizophrenia is associated with deficits in CI and that antipsychotic medications may increase CI.

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Several lines of evidence suggest that schizophrenia is a disorder associated with deficits in cortical inhibition (CI). These deficits have been demonstrated in cognitive, motor, neurophysiologic, and neuropathologic studies. First, cognitive studies suggest that patients with schizophrenia have impaired sensorimotor gating, inferred from their performance in prepulse inhibition tasks. Swerdlow and Koob\(^1\) posit that such impairment is due to excess activation of subcortical dopamine that leads to decreased activation of cortical inhibitory projections. Second, Walker et al\(^1\) posit that the motor abnormalities in schizophrenia, ranging from generalized incoordination to agitation and catatonia, are a corollary to disinhibition of cortical inhibitory neurotransmission. Third, neurophysiologic studies by Freedman et al\(^1\) demonstrate that patients with schizophrenia have impaired inhibition of event-related potential responses to paired auditory stimuli. Fourth, neuropathologic studies have shown that patients with schizophrenia have morphologic changes in cortical gamma-aminobutyric acid (GABA) inhibitory interneurons,\(^7\) which may in turn be linked to findings of reduced gray matter volume in these patients.\(^8\) Collectively, these results suggest that CI is dysfunctional in schizophrenia.

Transcranial magnetic stimulation (TMS)\(^9\) represents a noninvasive technique to measure CI. Conventionally, 3 inhibitory paradigms have been used: paired-pulse TMS (ppTMS), cortical silent period TMS (CSP), and transcallosal inhibition (TCI).\(^10,12\) In ppTMS, if a subthreshold pulse precedes a test pulse by 1 to 5 milliseconds, inhibitory interneurons are recruited and the motor-evoked potential (MEP) response is inhibited. In contrast, if a subthreshold pulse precedes the test pulse by 7 to 20 milliseconds, the MEP re-
SUBJECTS AND METHODS

SUBJECTS

The study included 30 right-handed patients with a DSM-IV diagnosis of either schizophrenia or schizoaffective disorder confirmed using the Structured Clinical Interview for DSM-IV (SCID).24 performed by a board-certified research psychiatrist (Z.J.D.). Patients were recruited through the Schizophrenia and Continuing Care Program at the Centre for Addiction and Mental Health (Toronto, Ontario). Fifteen patients were unmedicated (14 medication-naïve and 1 medication-free for longer than 1 year) and 15 were medicated with either typical or atypical antipsychotic medications (16.8±6.7 mg of olanzapine, 11 patients; 7 mg of risperidone, 1 patient; 1200 mg of quetiapine, 1 patient; 100 mg of quetiapine+10 mg of loxapine, 1 patient; and 50 mg of methotrimeprazine+16 mg of perphenazine, 1 patient). The control group consisted of 15 healthy, right-handed volunteers. For all subjects, handedness was confirmed using the Oldfield Handedness Inventory.25 Controls were recruited through advertisements in the community and postings within the hospital. Groups were similar across demographic variables (Table 1). Controls were screened for psychopathology with a modified SCID. Exclusion criteria included a self-reported comorbid medical illness or a history of drug or alcohol abuse. The University of Toronto ethics committee approved the study and written informed consent for each participant was obtained.

Before the neurophysiologic investigation, we used the Positive and Negative Syndrome Scale (PANSS) to index the severity of psychopathology.26 Most patients scored in the moderate range of symptom severity (Table 1). Motor abnormalities were assessed using the Abnormal Involuntary Movements Scale,27 Simpson-Angus Scale,28 and Barnes Akathisia Scale.29 None of the subjects demonstrated evidence of motor abnormalities.

RESULTS

CSP studies.11,15,22 Boroojerdi et al23 found that TCI was prolonged in a group of medicated patients with schizophrenia. The authors concluded that prolonged TCI was indicative of abnormal corpus callosum function, although it also implies greater CI in these patients.

The objective of the present study was to compare CI, using all 3 TMS inhibitory paradigms, in medicated and unmedicated patients with schizophrenia and healthy controls. It was hypothesized that unmedicated patients would demonstrate deficient CI compared with healthy controls and that medicated patients would demonstrate greater CI compared with their unmedicated counterparts.

All subjects except 2 completed the protocol. These 2 unmedicated subjects withdrew from the TCI experiment because they felt uncomfortable with the double coil placement on their heads. Therefore, they were dropped from the unmedicated group in the analysis for this paradigm. A total of 44 of 9036 trials recorded in the entire sample were discarded. In the control group, 11 trials were discarded compared with 22 trials in the medicated and 11

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The CSP was obtained in moderately tonically active FDI by stimulating the motor cortex with intensities of 10%, 20%, 30%, and 40% above AMT. For each intensity, 15 trials were performed. The CSP duration was defined as the time from the MEP onset to the return of any voluntary EMG activity. This is referred to as the absolute CSP and ends with a deflection in the EMG waveform. At each intensity, the mean MEP size and CSP duration for all 15 trials was calculated separately.

Paired-pulse inhibition and facilitation was also obtained according to previously published protocols. In short, a subthreshold conditioning stimulus (CS), set at 80% of RMT, preceded a suprathreshold test stimulus (TS). The TS was adjusted to produce an average MEP of 0.5 to 1.5 mV peak-to-peak amplitude in the contralateral FDI muscle. Conditioning stimuli were applied to the motor cortex prior to the TS at 1 of 5 random interstimulus intervals. Four blocks of trials were performed, each consisting of 6 randomly intermixed conditions presented 3 times each: the TS alone and 5 conditions with the CS preceding the TS at different intervals (2, 4, 10, 15, and 20 milliseconds). The time between trials was 5 seconds. Peak-to-peak MEP amplitudes were measured for each condition and conditional averages were obtained from these. Changes in the TS MEP amplitude at each interstimulus interval were expressed as a percentage of the mean unconditioned MEP amplitude. Surface EMG activity was monitored from the FDI at all times to ensure relaxation, and auditory feedback was given to subjects through a loudspeaker. This was important since muscle activation has been shown to result in less inhibition and facilitation in this paradigm. Trials contaminated by an increase in background EMG activity were discarded from further analysis.

Transcallosal inhibition was obtained according to the methods outlined by Ferbert et al. Short interstimulus intervals (2 and 4 milliseconds) produced inhibition of the response at each inhibitory interstimulus interval—served as the dependent variable. In the CSP experiment, the CSP duration served as the dependent variable. Motor threshold differences were analyzed using a 1-way analysis of variance. Group membership (ie, unmedicated, medicated, and control) was entered as a between-group independent variable. The percentage above AMT were entered as the within-group independent variables in the ppTMS and TCI, and CSP experiments, respectively. In the ppTMS and TCI experiments, the change in MEP size—expressed as a ratio of the MEP amplitude of each conditioned response to the unconditioned response at each inhibitory interstimulus interval—served as the dependent variable. In the CSP experiment, the CSP duration served as the dependent variable.

ppTMS

The overall excitability curve was comparable with previously published reports. Short interstimulus intervals (2 and 4 milliseconds) produced inhibition of the test response (Table 2) whereas long interstimulus intervals (10, 15, and 20 milliseconds) produced facilitation. On measures of inhibition, a significant main effect of group (ie, unmedicated, medicated, and healthy controls) was obtained (F<sub>2,42</sub> = 4.90; P = .01), with no significant group-by-ISI interaction (F<sub>2,42</sub> = 0.24; P = .79). Post hoc tests (least significant difference [LSD]) revealed significant differences between the unmedicated and healthy control groups (P = .003) (effect size: Cohen d = 0.69) and trended toward significantly greater inhibition between the medicated and unmedicated groups (P = .12) and between the healthy control and medicated groups (P = .12). Averaged across all inhibitory ISIs (ie, 2, 4 milliseconds) unmedicated patients demonstrated 31.2% less inhibition compared with healthy controls whereas medicated patients demonstrated 15.64% less inhibition compared with healthy controls. There were no group differences on measures of cortical facilitation (ie, measurements at ISI 10, 15, 20) (F<sub>2,42</sub> = 0.39; P = .67).

CORTICAL SILENT PERIOD

Two raters (1 blind to diagnosis and 1 not) measured CSP durations for all subjects independently. An intraclass correlation coefficient was calculated to determine the interrater reliability for this measure. We obtained an average intraclass correlation coefficient of 0.96 (F<sub>.05,.09</sub> = 56.56; P = .001). A significant main effect of group (ie, unmedicated, medicated, and healthy controls) (F<sub>2,42</sub> = 4.42; P = .02) and a significant group-by-intensity interaction (F<sub>2,42</sub> = 4.63; P = .02) was obtained (Table 2). Post hoc tests (LSD) revealed significant differences between the unmedicated patient and healthy control groups (P = .04) (Cohen d = 0.58) and between the medicated and unmedicated patient groups (P = .01) (Cohen d = 0.70) but no difference was found be-
tween medicated patient and healthy control groups (P = .46). One-way analysis of variance showed significant group differences for 30% above the AMT (F2,42 = 3.90; P = .03) and 40% above the AMT (F2,42 = 4.79; P = .01). Post hoc tests (LSD) demonstrated that unmedicated and medicated patients were significantly different at 30% and 40% above the AMT (P = .01 in both) whereas unmedicated patients differed from healthy controls at 40% above the AMT (P = .03). Averaged across all intensities (ie, 10%-40% above the AMT), the CSP was 15.26 milliseconds shorter in unmedicated patients compared with healthy controls whereas it was 5.38 milliseconds longer in medicated patients compared with healthy controls.

Examples of EMG recordings from unmedicated and medicated patients and healthy controls are shown in Figure 1. It has been demonstrated that MEP size influences the duration of the CSP. Therefore, we compared MEP size and found no significant group differences (F2,42 = 0.38; P = .69), excluding this as a potential confound.

TCI

The overall excitability curve was comparable with that previously published.11,12 Our results suggest that inhibition begins at an interstimulus interval of 6 milliseconds and continues for as long as 20 milliseconds. A sig-

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### Table 1. Demographic and Clinical Characteristics of the Sample*

<table>
<thead>
<tr>
<th></th>
<th>Unmedicated (n = 15)</th>
<th>Medicated (n = 15)</th>
<th>Controls (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID diagnosis</td>
<td>14 With schizophrenia (8 paranoid, 6 undifferentiated)</td>
<td>14 With schizophrenia (7 paranoid, 7 undifferentiated)</td>
<td>No psychiatric illness</td>
</tr>
<tr>
<td>Age, y</td>
<td>33.1 ± 9.3</td>
<td>32.4 ± 9.0</td>
<td>28.4 ± 8.6</td>
</tr>
<tr>
<td>Sex, No. of subjects</td>
<td>7 F, 8 M</td>
<td>5 F, 10 M</td>
<td>5 F, 10 M</td>
</tr>
<tr>
<td>Illness duration, y</td>
<td>8.5 ± 7.2</td>
<td>3.9 ± 5.8</td>
<td>NA</td>
</tr>
<tr>
<td>PANSS scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77.5 ± 8.5</td>
<td>66.1 ± 22.8</td>
<td>NA</td>
</tr>
<tr>
<td>Positive</td>
<td>20.3 ± 2.8</td>
<td>15.9 ± 7.0</td>
<td>NA</td>
</tr>
<tr>
<td>Negative</td>
<td>20.7 ± 4.8</td>
<td>18.7 ± 6.2</td>
<td>NA</td>
</tr>
<tr>
<td>Global</td>
<td>36.5 ± 4.4</td>
<td>31.5 ± 10.7</td>
<td>NA</td>
</tr>
<tr>
<td>AIMS scores</td>
<td>0.9 ± 1.6</td>
<td>0.4 ± 0.7</td>
<td>NA</td>
</tr>
<tr>
<td>SAS scores</td>
<td>1.8 ± 2.9</td>
<td>1.1 ± 2.9</td>
<td>NA</td>
</tr>
<tr>
<td>BAS scores</td>
<td>0.0 ± 0.3</td>
<td>0.0 ± 0.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise indicated. SCID indicates Structured Clinical Interview for *DSM-III-R*. PANSS, Positive and Negative Syndrome Scale; NA, not applicable; AIMS, Abnormal Involuntary Movement Scale; SAS, Simpson-Angus Scale; and BAS, Barnes Akathisia Scale.

### Table 2. Results From ppTMS Inhibition and Facilitation and CSP and TCI Measures in Unmedicated and Medicated Patients With Schizophrenia and Healthy Controls*

<table>
<thead>
<tr>
<th>ISI/Intensity</th>
<th>Unmedicated (n = 15)†</th>
<th>Medicated (n = 15)</th>
<th>Controls (n = 15)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppTMS, conditional MEP/control MEP Inhibition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI 2</td>
<td>0.61 ± 0.46</td>
<td>0.48 ± 0.32</td>
<td>0.34 ± 0.20</td>
<td>F2,42 = 4.90‡</td>
</tr>
<tr>
<td>ISI 4</td>
<td>0.82 ± 0.30</td>
<td>0.64 ± 0.29</td>
<td>0.47 ± 0.23</td>
<td>P = .01</td>
</tr>
<tr>
<td>Facilitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI 10</td>
<td>1.28 ± .53</td>
<td>1.32 ± .42</td>
<td>1.31 ± .51</td>
<td></td>
</tr>
<tr>
<td>ISI 15</td>
<td>1.22 ± .50</td>
<td>1.23 ± .57</td>
<td>1.05 ± .51</td>
<td></td>
</tr>
<tr>
<td>ISI 20</td>
<td>1.21 ± .44</td>
<td>1.03 ± .42</td>
<td>0.98 ± .39</td>
<td></td>
</tr>
<tr>
<td>CSP duration, milliseconds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMT + 10</td>
<td>25.20 ± 11.68</td>
<td>33.18 ± 12.66</td>
<td>29.45 ± 16.69</td>
<td>F2,42 = 4.14§</td>
</tr>
<tr>
<td>AMT + 20</td>
<td>32.04 ± 13.93</td>
<td>45.50 ± 18.39</td>
<td>43.49 ± 15.89</td>
<td></td>
</tr>
<tr>
<td>AMT + 30</td>
<td>44.03 ± 16.87</td>
<td>70.38 ± 35.73</td>
<td>61.70 ± 22.77</td>
<td>P = .02</td>
</tr>
<tr>
<td>AMT + 40</td>
<td>57.61 ± 20.46</td>
<td>92.41 ± 39.77</td>
<td>85.23 ± 34.20</td>
<td></td>
</tr>
<tr>
<td>TCI, conditioned MEP/control MEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI 2</td>
<td>1.21 ± .44</td>
<td>1.03 ± .42</td>
<td>0.98 ± .39</td>
<td>F2,42 = 3.16‡</td>
</tr>
<tr>
<td>ISI 6</td>
<td>1.02 ± .42</td>
<td>0.83 ± .19</td>
<td>0.69 ± .19</td>
<td></td>
</tr>
<tr>
<td>ISI 10</td>
<td>0.81 ± .34</td>
<td>0.65 ± .33</td>
<td>0.60 ± .33</td>
<td>P = .05</td>
</tr>
<tr>
<td>ISI 15</td>
<td>0.82 ± .36</td>
<td>0.65 ± .26</td>
<td>0.59 ± .25</td>
<td></td>
</tr>
<tr>
<td>ISI 20</td>
<td>0.73 ± .27</td>
<td>0.64 ± .26</td>
<td>0.56 ± .26</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise indicated. ppTMS indicates paired-pulse transcranial magnetic stimulation; CSP, cortical silent period; TCI, transcallosal inhibition; ISI, interstimulus interval; MEP, motor evoked potential; and AMT, active motor threshold.
†In the TCI paradigm, there were 13 unmedicated patients.
‡Unmedicated patients significantly different from healthy controls.
§Unmedicated patients significantly different from medicated patients.

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significant main effect of group (ie, unmedicated patients and healthy controls) was obtained ($F_{2,40}=3.16; P = .05$) (Cohen $d=0.73$), with no significant group × ISI interaction ($F_{2,40} = 0.92; P = .41$). Post hoc tests (LSD) revealed a significant difference between unmedicated patient and healthy control groups ($P = .02$) but no significant difference between unmedicated and medicated groups ($P = .16$) or between medicated patient and healthy control groups ($P = .27$). Averaged across all inhibitory ISIs (ie, 2-20 milliseconds), unmedicated patients demonstrated 23.25% less inhibition compared with healthy controls whereas medicated patients demonstrated 9.92% less inhibition compared with healthy controls.

**CI AND CLINICAL SYMPTOM SEVERITY**

Paired-pulse TMS inhibition correlated with psychotic symptom severity in patients with schizophrenia across PANSS total (inhibition × PANSS total: $r=0.50$, $P = .01$; 95% confidence interval, 0.17-0.73), Positive (inhibition × PANSS Positive: $r=0.46$, $P = .01$; 95% confidence interval, 0.12-0.70), and Global dimensions (inhibition × PANSS Global: $r=0.53$, $P = .001$; 95% confidence interval, 0.21-0.75), and trended toward significance for the PANSS Negative dimension (inhibition × PANSS Negative: $r=0.35$, $P = .06$) (Figure 2). For this calculation, ppTMS inhibition was averaged over the results obtained at the 2 inhibitory ISIs (ie, 2 and 4 milliseconds). Because the PANSS may not represent a true linear scale, we also correlated these measures using a Spearman rank correlation and found similar results (inhibition × PANSS Total: $\rho=0.53$, $P = .003$; inhibition × PANSS Positive: $\rho=0.53$, $P = .003$; inhibition × PANSS Negative: $\rho=0.35$, $P = .06$; inhibition × PANSS Global: $\rho=0.56$, $P = .001$). There was no significant correlation between other measures of inhibition (ie, TCI and CSP) and severity of psychotic symptoms. All subjects demonstrated minimal motor abnormalities (Table 1) that may have precluded our ability to correlate CI with the severity of these symptoms.

**MT**

The RMT over the left cortex was significantly lower in unmedicated patients with schizophrenia (mean [SD], 34.40 [6.51]) compared with medicated patients (mean [SD], 40.13 [6.47]) and healthy controls (mean [SD], 40.47 [7.13]) ($F_{2,40}=3.87; P = .03$) (Figure 3). Post hoc tests (LSD) revealed significant differences between unmedicated patient and healthy control groups ($P = .02$) and unmedicated and medicated groups ($P = .02$) but not between medicated patient and healthy control groups ($P = .90$). In the analysis of CI (ie, ppTMS, TCI), baseline MT differences are included as a part of the calculation for CS and TS and therefore, controlled for in all subjects.

**COMMENT**

Our results demonstrate that unmedicated patients with schizophrenia have significant deficits in CI compared with healthy controls across all 3 TMS paradigms. Medicated patients had significantly greater CI compared with unmedicated patients in the CSP paradigm and a trend toward greater inhibition in the ppTMS and TCI paradigms. The similarity between the results obtained from these 3 separate inhibitory paradigms is of note (Table 2). That is, unmedicated patients consistently demonstrated deficient CI compared with healthy controls while...
 Walker et al posit that the motor abnormalities in schizophrenia exist in multiple cortical and subcortical regions. First, our findings are consistent with those of Adler et al and several studies have confirmed such phenomena. Future research efforts directed at measuring inhibition in multiple cortical areas, using TMS and neuroimaging, may shed light on the complex interplay between inhibition, medication, and disease progression.

Several neurophysiologic studies have provided evidence for inhibitory deficits in schizophrenia. For example, Adler et al, in an auditory conditioning-test paradigm, showed that healthy controls suppress the amplitude of the P50 wave response to the second or TS, whereas patients with schizophrenia had loss of suppression of this response. Several studies have confirmed such findings. Although the relationship between event-related potentials and TMS inhibition has yet to be elucidated, several comparisons exist. First, both forms of inhibition seem to be enhanced with the addition of atypical antipsychotic medications. Second, the magnitude of inhibitory deficits in schizophrenia is similar. Thus, our findings are consistent with those of Adler et al and bolster the evidence for deficient CI as a pathophysiologic feature of this illness.

Several lines of evidence suggest that inhibitory deficits exist in multiple cortical and subcortical regions. First, Walker et al posit that the motor abnormalities in schizophrenia are a corollary to the increased activity of subcortical dopaminergic neurons that results in disinhibition of cortical inhibitory neurotransmission. Second, Benes et al reported that patients with schizophrenia have inhibitory deficits due to fewer GABAergic interneurons in the prefrontal, anterior cingulate, and hippocampal formation. Third, Freedman et al demonstrated that P50 inhibitory dysfunction in patients with schizophrenia may arise out of hippocampal interneuron abnormalities. Fourth, Swardlow and Koob posited that inhibition deficits in sensorimotor gating are the result of excess activation of subcortical dopamine that results in decreased activation of cortical inhibitory projections. It remains unclear, however, if these different inhibitory measures represent a unified inhibitory process across different contexts or separate inhibitory phenomena. Future research efforts directed at measuring inhibition in multiple cortical areas, using TMS and EEG, will be helpful in this regard.

Our results demonstrate that CI deficits, as indexed with ppTMS, were correlated with the severity of psychosis. In contrast, no other measure of CI was correlated with the degree of psychosis. Some evidence suggests that these CI measures may reflect different inhibitory neural pathways. For example, ppTMS inhibition may be mediated by GABA_A interneurons as opposed to CSP inhibition, which may be mediated by GABA_A interneurons. This evidence, albeit preliminary, suggests that GABA_A inhibitory abnormalities may, in part, underlie psychotic symptomatology in this illness. On close inspection of Figure 2, it seems that the 3 subjects with the lowest PANSS scores drive the estimated correlation. By removing these subjects, however, our PANSS ratings become restricted to moderate and severe scores, thus limiting our ability to find a correlation. Future research efforts aimed at replicating this finding and exploring this relationship are necessary.

Our results also demonstrate that patients with schizophrenia have deficits in TCI. There is considerable evidence that TCI is mediated by neuronal pathways that travel through the corpus callosum. First, in our experiments as well as others, inhibition begins at an interstimulus interval of 6 milliseconds. This is consistent with estimates of callosal conduction time (approximately 10 milliseconds) in humans. Second, in patients with bona fide corpus callosum abnormalities (eg, patients with agenesis of the corpus callosum as well as multiple sclerosis), TCI was profoundly impaired. Therefore, deficits in TCI may be related to disrupted corpus callosum pathways that mediate inhibition. In schizophrenia, there is considerable evidence of corpus callosum abnormalities (for review see Woodruff et al), which imply that TCI deficits are likely due to disruption of these crossed pathways. Animal evidence suggests that these pathways are excitatory and terminate on local inhibitory GABAergic interneurons to mediate inhibition. Therefore, our finding of TCI deficits in patients with schizophrenia may reflect either a disruption in crossed pathways mediating inhibition or deficient local inhibitory neurons. Given the consistency of our findings in all 3 inhibitory paradigms, our results support the latter.

Medicated patients demonstrated a trend toward enhanced CI compared with unmedicated patients, making it unclear what effects antipsychotic medications have on CI, particularly in patients with schizophrenia. In healthy volunteers, Ziemann et al demonstrated that antipsychotic haloperidol resulted in significantly less CI in the ppTMS paradigm compared with baseline. In contrast, Boroojerdi et al demonstrated that patients with schizophrenia, treated primarily with olanzapine and clozapine, possessed increased TCI and hence, enhanced CI compared with healthy controls. It is possible, given that baseline dopaminergic tone may be different in patients with schizophrenia compared with healthy controls, that haloperidol-induced changes to CI may act to correct these baseline abnormalities. In addition, olanzapine has been shown to cause a down-regulation of GABA_A receptors in animal studies, suggesting enhanced inhibitory GABAergic neurotransmission. However, the effect of antipsychotic medications on CI in schizophrenia needs further investigation.

Figure 3. Resting motor threshold in controls (n=15), medicated (n=15), and unmedicated patients (n=15) with schizophrenia. Resting motor threshold was defined as the first intensity that produced a motor evoked potential of more than 50 µV in 5 of 10 trials with the first dorsal interosseus muscle relaxed.

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further substantiation with these and other inhibitory experiments.

Unmedicated patients with schizophrenia had lower RMT compared with medicated patients and healthy controls. The MT is conventionally regarded as a measure of the membrane excitability of corticospinal neurons and interneurons in the motor cortex.65 It is increased by drugs that block voltage-gated sodium channels66,67 but is not affected by drugs that alter GABA,66 glutamate,68,69 or dopamine transmission.61 Two previously published reports20,23 suggest that patients with schizophrenia have no differences in MT compared with healthy controls. Puri et al20 reported this finding in unmedicated patients with schizophrenia. Abaranel et al,60 however, demonstrated a lower MT in patients with schizophrenia treated with a variety of antipsychotic medications compared with controls and patients with depression. Our findings suggest that membrane excitability is lower in unmedicated patients with schizophrenia compared with medicated patients and healthy controls.

There are several limitations to these initial experiments. First, CI differences between unmedicated and medicated patients with schizophrenia were not significant across all measures, likely due to small effects, limited sample size, and large variance in these measures. Second, we are uncertain if the differences observed between unmedicated and medicated patients were truly the result of medication effects or related to other confounding variables (eg, duration of illness). Third, it is unclear if differences in CI in the medicated group were related to the effects of medications on GABA, dopamine, or through some other neurotransmitter system.

In summary, unmedicated patients with schizophrenia demonstrated deficits in CI compared with healthy controls. Moreover, medications seemed to reduce CI deficits in these patients. We contend that disrupted CI may represent an important neurophysiologic mechanism responsible for the symptoms seen in patients with schizophrenia.

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