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The role of white matter microstructure in inhibitory deficits in patients with schizophrenia

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Abstract

Background—Inhibitory-excitatory (I-E) imbalance has increasingly been proposed as a fundamental mechanism giving rise to many schizophrenia-related pathophysiology. The integrity of I-E functions should require precise and rapid electrical signal transmission.

Objective/Hypothesis—We hypothesized that part of the I-E abnormality in schizophrenia may originate from their known abnormal white matter connectivity that may interfere the I-E functions.

Methods—We test this using short-interval intracortical inhibition (SICI) vs. intracortical facilitation (ICF) which is a non-invasive measurement of I-E signaling. SICI-ICF from left motor cortex and white matter microstructure were assessed in schizophrenia patients and healthy controls.

Results—Schizophrenia patients showed significantly reduced SICI but not ICF. White matter microstructure as measured by fraction anisotropy (FA) in diffusion tensor imaging had a significant effect on SICI in patients, such that weaker SICI was associated with lower FA in several white matter tracts, most strongly with left corona radiata ($r=-0.68$, $p=0.0002$) that contains the fibers connecting with left motor cortex. Left corticospinal tract, which carries the motor fibers to peripheral muscular output, also showed significant correlation with SICI ($r=-0.54$, $p=0.005$). Mediation analysis revealed that much of the schizophrenia disease effect on SICI can be accounted for by mediation through left corona radiata. SICI was also significantly associated with the performance of processing speed in patients.

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All other authors declare no conflict of interest.

Conclusion—This study demonstrated the importance of structural circuitry integrity in inhibitory signaling in schizophrenia, and encouraged modeling the I-E dysfunction in schizophrenia from a circuitry perspective.

Keywords

corona radiata; schizophrenia; intracortical inhibition; stimulation; white matter; diffusion tensor imaging

Introduction

An inhibitory - excitatory (I-E) imbalance has increasingly been investigated as a functional mechanism giving rise to many schizophrenia-related deficits ranging from working memory deficits, abnormal information processing, to social dysfunction [1-5]. However, the mechanisms underlying abnormal I-E vary greatly in these theories, ranging from disruptions of the inhibitory GABAergic [1,6] vs. excitatory glutamatergic systems [2], to synaptic disruptions in inhibitory post-synaptic potential (IPSP) vs. excitatory post-synaptic potential (EPSP) [3-5]. None of these can be easily assessed in schizophrenia patients, making clinical validation of these theories challenging.

One of the robust measurements of clinical I-E abnormality *in vivo* is the short-interval intracortical inhibition (SICI) vs. intracortical facilitation (ICF) elicited by paired-pulse transcranial magnetic stimulation (TMS). SICI refers to inhibition of motor response when two TMS pulses (a sub-threshold pulse followed by a super-threshold) are administered to motor cortex with short-intervals (1-6 ms). SICI has been interpreted as gamma-aminobutyric acid receptor alpha unit (GABAa) mediated [7-10]. On the other hand, ICF is obtained when the two pulses are delivered with longer intervals (9-25 ms), and is thought to be N-methyl-D-aspartate (NMDA) [11] and GABAa mediated [10,12]. The SICI-ICF paradigm provides one of the few cortical I-E functional assays that can be readily assessed in clinical patients.

Reduced SICI has been consistently replicated in schizophrenia, including in individuals at high risk for developing schizophrenia [13], in first-episode [14,15] and chronic patients [16-20]. In comparison, most studies did not show a significant deficit in ICF in schizophrenia patients [14,21-25]. These studies often referenced to abnormal GABAergic mechanisms as the explanation to the SICI deficit although direct evidence of a GABAergic abnormality in the motor cortex of schizophrenia patients is scarce. Nevertheless, the replicability of the SICI finding is intriguing, precisely because SICI is generated from stimulating the motor cortex, which is not a region commonly studied in the context of researching schizophrenia pathophysiology.

SICI should be sensitive to rapid neural information processing on a millisecond timescale as it is generated only within 1 to 6 ms interstimulus intervals. Any disruptions of the electrical signal processing in the involved circuitry could contribute to a SICI deficit. SICI also involves long-distance electrical signal traveling in the motor pathway from the motor cortex to the spinal cord. Myelinated axons provide the basic structure for rapid and precise

long-distance circuitry communication in the brain, and our basic hypothesis is that disruption in myelinated white matter may have a substantial impact on SICI.

Indeed, disruption of cerebral white matter is another consistent biological finding in schizophrenia, supported by postmortem [26-30], genetic [31,32], and over one hundred diffusion tensor imaging (DTI) studies [e.g., 33,34]. There are several major white matter bundles subserving the motor cortex. The most prominent one is corona radiata, which is the fiber bundle carrying the axons exiting or entering multiple cortical structures including the motor cortex [35]. From the cortex, corona radiata passes through the internal capsule, then travels through the corticospinal tract to reach the spinal cord (Figure 1). Disruption of corona radiata and many other tracts have been observed in schizophrenia [36,37], which may interfere with the speed or precision of electrical transmission. Previous studies have combined DTI and TMS in normal controls and found an association between TMS measurements and white matter in some tracts [38-45], but not the corticospinal tract [46,47]. To our knowledge, this is the first study to test how SICI-ICF functions in schizophrenia could be related to white matter. Our hypothesis is that white matter microstructure might play an important role in the SICI abnormality in schizophrenia. This hypothesis can be further supported if findings of SICI and/or ICF relationship to white matter are primarily in fibers connecting to the TMS site at the motor cortex, particularly along the motor pathway from corona radiata to corticospinal tract.

Materials and methods

Participants

Patients with schizophrenia (n=26, age 20-57 years) and healthy controls (n=36, age 21-61 years) were recruited (**Table 1**). The Structured Clinical Interview for DSM-IV (SCID) was used to confirm the diagnoses in patients and no current DSM-IV Axis I diagnoses in controls. Major medical and neurological illnesses, history of head injury with loss of consciousness, substance abuse and taking clozapine more than 400 mg/day (per TMS safety guideline) were exclusionary [48]. Except for four medication-free participants, all schizophrenia patients were on antipsychotic medications, including 1 taking typical antipsychotics, 20 taking atypical antipsychotics, and 1 taking a combination of antipsychotic types. Cognitive function was assessed using the Digit Symbol Coding task [49] which assesses primarily processing speed and in part also executive function. All subjects gave their written informed consent approved by local Institutional Review Board.

TMS and electromyography procedure

Monophasic TMS pulses were given through a figure-of-eight coil (70 mm diameter) using Magstim 200 BiStim stimulators (Magstim Co., Whitland, UK). The coil was held pointing backward and rotated 45° away from the midline [50-52]. Each subject first underwent an anatomical MRI scan. Their structural images were imported into Brainsight™ Navigation system (Rogue Research Inc, Montreal, Canada) to allow individualized anatomic positioning of the coil. The stimulus target was left motor cortex (Figure 1) where TMS induced the maximum response from right first dorsal interosseous (FDI) muscle. Surface electromyography (EMG) was recorded from right FDI. EMG was recorded with NeuroScan

synamp^2 amplifier (Charlotte, NC) amplified (gain of 10) and sampled at 1000 Hz [53,54]. Peak-to-peak amplitude of the motor-evoked potentials (MEP) was measured. The EMG root mean squared (RMS) value from 50 to 5 ms prior to TMS pulse was verified to ensure appropriate resting levels for each trial.

Motor threshold and paired pulse paradigm

Resting motor threshold (RMT) was defined as the minimum intensity needed to elicit a MEP of >50 μV in at least 5 out of 10 consecutive stimuli [54]. For paired-pulse TMS (ppTMS), the intensities of the subthreshold conditioning stimulus (CS) and the testing stimulus (TS) were set to 80% and 120% RMT, respectively [55-57]. Typically, SICI protocols include 1 and 3 ms interstimilus intervals (ISIs) to induce inhibition [58-60] while ICF protocols include 9-21 ms ISIs to induce facilitation [61]. In order to detect these and other potential inhibitory and facilitatory ISIs, 14 ISIs were tested on each session: 1, 3, 6, 9, 12, 15, 18, 21, 30, 40, 80, 120, 200 and 500 ms. Single 120% RMT stimuli were delivered as a control condition (TS alone). The ppTMS effect was expressed as the ratio between responses of ppTMS and TS. Ratios less than 1 indicate inhibition and the smaller the ratio, the stronger the inhibition. A session included 6 trials for each ISI and 12 trials of TS alone. They were randomized and delivered in one session, with intertrial intervals jittered between 4 and 10 seconds. Participants were evaluated in two sessions about 4 weeks apart to ensure reproducibility of the SICI-ICF effects. The two sessions did not show significant differences in any ISIs (all paired t-test $p>0.05$). We then merged the two sessions to represent SICI-ICF. Therefore, data were from 12 trials for each ISI and 24 trials for TS alone for each subject.

Neuroimaging

All imaging was performed using a Siemens 3T TRIO MRI (Erlangen, Germany) system equipped with a 32-channel phase array head coil. Participants were scanned prior to TMS assessment. A high resolution T1-weighted image (0.8 mm isotropic) was obtained (TE/TR/TI=3.04/2100/785 ms, flip angle=11 degrees) for TMS localization. The structural images were aligned to anterior commissure-posterior commissure line (AC-PC). DTI data were collected using a single-shot, echo-planar, single refocusing spin-echo, T2-weighted sequence at 1.7×1.7×3.0 mm, TE/TR=87/8000ms, FOV=220mm, 50 slices and no gaps, five interleaved (every 10 volumes) b=0 volumes and 64 non-colinear distributed diffusion weighted directions with b=700 s/mm^2 [62]. These sequence parameters were calculated using an optimization technique that maximizes the contrast to noise ratio for FA measurements [63].

Diffusion Tensor Imaging Processing

DTI data was processed using the ENIGMA-DTI analysis pipeline (http://www.nitrc.org/projects/enigma_dti) [64]. It uses a tract-based spatial statistics (TBSS) method for tract-based analysis of diffusion anisotropy [65]. Raw images were corrected for motion and eddy currents using eddy correction tool distributed as a part of FMRIB Software Library (FSL) package version 5.0.9 [66]. Fractional anisotropy (FA) images were created by fitting the diffusion tensor to the motion and eddy current corrected diffusion data. RMSDIFF [65] was used to estimate the root mean square movement distance between diffusion sensitized and

b=0 images. All data passed QA control of <3mm accumulated motion during the scan. All FA images were globally spatially normalized to the Johns Hopkins University (JHU) atlas [67] and then nonlinearly aligned to ENIGMA-derived, minimal-deformation target (MDT) brain using the FLIRT method [66]. The JHU atlas was used to separate white matter into the following tracts: the genu, body and splenium of corpus callosum and bilateral fornix, internal capsule (IC), external capsule (EC), corticospinal tract (CST), corona radiata (CR), thalamic radiation (TR), superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFO), superior fronto-occipital fasciculus (SFO), cingulate gyrus (CGC), and sagittal stratum (SS) (total 25 tracts). The tract of interests includes left CR, left IR and left CST (Figure 1). SLF should also contain some fibers from the left motor cortex that communicate with other cortical areas [35,68]. Those areas in left hemisphere were the *a priori* regions of interest, as we applied TMS to left M1. Whole brain averaged FA was also obtained to assessed whether SICI-ICF were related to whole brain white matter property in general.

Statistical analysis

Repeated measures ANOVA was used to evaluate whether inhibition/facilitation was present in any ISIs. ISIs identified to have the expected inhibition or facilitation effects in both groups were averaged to represent SICI and ICF, respectively. One-way ANOVA was applied to test group difference. Only TMS measures that showed significant group differences were applied for correlation analyses with white matter measures.

FA values of the 25 tracts were correlated with SICI and ICF with age as a covariate [69] to test if white matter microstructure would influence SICI and ICF. A correlation was significant after Bonferroni correction for correlation analyses on 25 tracts (corrected $p<0.05/25=0.002$) unless they were tracts on the left motor pathway for which Bonferroni correction based on 25 tracts was considered unnecessary. For tracts that showed significant correlation with SICI-ICF in either group, the correlation coefficients were Fisher's z-transformed, then compared between groups using Z test.

To further estimate whether group effects on SICI-ICF was mediated by white matter FA, the direct and indirect relationships between diagnostic groups, white matter FA and SICI-ICF were evaluated using mediation analyses from PROCESS marco for SPSS with age as covariate [70]. The white matters included in mediation analysis are those tracts that showed significant correlations with SICI-ICF and were significantly different between groups. Bootstrap method was used for estimating 95%CI with 10,000 resamples.

Results

Group difference on SICI and ICF

There was no significant difference between groups on resting motor threshold (RMT) ($F_{(1,60)}=0.01$, $p=0.93$) or MEP amplitude in response to single pulse TMS ($F_{(1,60)}=1.96$, $p=0.17$) (**Table 1**). There were significant effects of ISI in controls ($F_{(13,442)}=23.80$, $p<0.001$) and patients ($F_{(13,325)}=10.96$, $p<0.001$). Post-hoc tests showed that significant inhibition at 1 and 3 ms ISIs for both groups (all $p<0.001$); significant facilitation at 9 and 12

ms ISIs for controls (all $p<0.001$) and 9 ms ($t_{(25)}=2.66$, $p=0.01$) and 12 ms ISI ($t_{(25)}=2.88$, $p=0.008$) for patients (Figure 2A). No other ISI showed a group difference (all remaining $p>0.05$).

Therefore, SICI and ICF were observed independently in both groups in the same ISI ranges. Data were thus averaged from 1 and 3 ms ISIs to represent SICI, and from 9 and 12 ms ISIs to represent ICF. Patients with schizophrenia showed significantly reduced SICI ($F_{(1,60)}=6.13$, $p=0.02$) compared with controls (Figure 2B). There was no significant group difference in ICF ($F_{(1,60)}=0.56$, $p=0.46$).

White matter and inhibition/facilitation in patients

Significant inverse relationship with SICI was found in multiple tracts (Figure 3). The highest correlation was at the left corona radiata (CR) ($r=-0.68$, $p=0.0002$) (Figure 4A), such that reduced FA was strongly associated with less inhibition (larger SICI ratio) in schizophrenia patients. The left CR was also the only tract that survived Bonferroni correction of 25 tracts (i.e., $p<0.002$).

Two other tracts known to contain fibers from the left motor cortex also showed significant correlation with SICI: left corticospinal tract (CST) ($r=-0.54$, $p=0.005$) and left superior longitudinal fasciculus (SLF) ($r=-0.53$, $p=0.006$).

The remaining tracts that showed nominally significant correlations with SICI were the right CR ($r=-0.53$, $p=0.007$), right CST ($r=-0.57$, $p=0.003$), body of corpus callosum (BCC) ($r=-0.49$, $p=0.01$), and right IR ($r=-0.50$, $p=0.01$) (not significant after Bonferroni correction) (Figure 3). There was a significant inverse relationship between whole brain average FA and SICI ($r=-0.60$, $p=0.002$).

Patients with schizophrenia had significantly lower whole brain white matter averaged FA values compared with controls ($F_{(1,57)}=7.69$, $p=0.008$). For those tracts that were significantly correlated with SICI, significant FA reduction in patients were found at left CR ($F_{(1,57)}=10.56$, $p=0.002$), right CR ($F_{(1,57)}=4.81$, $p=0.03$), left SLF ($F_{(1,57)}=4.75$, $p=0.03$), but not at bilateral CST, BCC, or right IR (all $p>0.05$), compared with controls. Only left CR was significant if Bonferroni corrections were applied.

To further test anatomic specificity, we divided the left CR into anterior (ACR), superior (SCR) and posterior (PCR) segments. Motor cortex fibers descend mainly through SCR. Significant correlations with SICI were found at SCR ($r=-0.72$, $p=0.0001$), ACR ($r=-0.58$, $p=0.002$), and PCR ($r=-0.45$, $p=0.02$).

Exploratory analysis on white matter and ICF showed that ICF showed no significant correlation with any tracts ($|r|<0.37$, $p>0.05$) except the left inferior fronto-occipital fasciculus ($r=-0.48$, $p=0.02$), which was non-significant after Bonferroni correction.

White matter and inhibition/facilitation in controls

SICI showed no significant correlation with any of the 25 tracts (all $|r|<0.3$, all $p>0.05$) in controls. ICF also showed no significant correlation with any tracts ($|r|<0.33$, $p>0.05$) except

left CST (r=−0.40, p=0.03) and bilateral sagittal stratum (left, r=−0.46, p=0.01; right, r=−0.51, p=0.004). None were significant after Bonferroni correction. Controls showed significantly weaker correlations between FA and SICI at left CR (Z=−2.04, p=0.04) and left CST (Z=−2.92, p=0.004) as compared with patients. Similar trend was shown at left SLF (Z=−1.94, p=0.05).

Mediation of SICI deficits in schizophrenia by white matter

Mediation analysis was conducted with diagnosis as the bivariate independent variable, SICI as the outcome variable, left CR as the potential mediator and age as a covariate. As in Figure 4C, the total effect of diagnosis on SICI was significant (path C; t=2.32, p=0.02; effect size=0.15). Adding left CR as mediator, the direct effect from diagnosis to SICI was no longer significant (path C'; t=0.63, p=0.53; effect size=0.04) while the indirect path via left CR was significant (Sobel test, p=0.01, bootstrap 95% CI=0.03 to 0.23). Therefore, the diagnosis effect on SICI was largely mediated by FA values of left CR.

Relationship between processing speed and SICI

Processing speed (PS) was slower in patients than controls ($F_{(1,57)}$=5.66, p=0.02). Faster processing speed was associated with stronger inhibition (r=−0.46, p=0.03) in patients but not in controls (r=−0.13, p=0.46) (Figure 4B). ICF was not significantly associated with processing speed in either group (all |r|<0.1, p>0.05). However, mediation analysis with SICI as independent variable, processing speed as outcome variable, FA value of left CR as mediator showed no significant mediation effect of left CR on SICI (Sobel test, p=0.54).

Discussion

Impaired short-interval intracortical inhibition (SICI) has emerged as one of the more reproducible biomarkers for schizophrenia [13,14,17-20,71-73]. This inhibitory dysfunction has been linked to intracortical and GABAergic mechanisms for explaining its abnormality in schizophrenia, largely derived from healthy control data [7-10]. Findings from this study suggested that a significant portion of the variance of SICI in schizophrenia patients is actually explained by white matter microstructures, especially those along the motor pathway. Mediation analysis further suggested that FA of the left corona radiata explained a significant portion of the schizophrenia-control differences in SICI.

We replicated the findings that patients with schizophrenia had decreased SICI but no significant change in ICF [13,15,18]. The primary role of myelination of white matter fibers in the brain is to ensure speed and fidelity of the transmission of the electric signals. In the patients, reduced inhibition as indexed by SICI was associated with lower FA values at white matter tracts most likely contributing to SICI signal transmission, such as the corona radiata and the corticospinal tract. Interestingly, most tracts that showed nominally significant correlations with SICI also carry fibers from motor cortex, for example the right CR, CST, IC, and the left SLF. One possibility is that these tracts shared motor-related functions and thus should share myelination properties as the left CR. Importantly, left CR is the only white matter bundle that is significantly associated with SICI (p=0.0002) and exhibits significant reduction in FA in patients compared with controls (p=0.002) after correction for

multiple comparisons. Further support of the idea came from subdividing CR and showed that the superior CR, which is the portion of the CR most directly under the motor cortex, carries the strongest association with SICI (r=−0.72). The overall pattern is consistent with the hypothesis that myelinated fibers provide pivotal support for inhibitory signals that may require rapid electrical transmission. Therefore, impaired white matter microstructures should contribute to the deficits of SICI in schizophrenia. In a recent TMS-EEG-imaging-genetic study, Lett et al. found that white matter microstructure in the prefrontal cortex mediates the effects of the glutamic acid decarboxylase 1 (GAD1) gene, which is a major determinant of GABA, on working memory performance [74]. Consistent with our results, their findings also demonstrated the important role of white matter in mediating the effects of neurochemicals or genetics on cognitive performance.

However, white matter does not show strong correlations on SICI in healthy controls. This is unlikely due to small sample size as we included a larger sample of healthy controls. Pharmacological studies showed that SICI is associated with the GABAa receptor-mediated inhibitory neurotransmission in healthy subjects [7-10,12]. Our finding does not necessarily dispute this mechanism and in fact suggests that when white matter is relatively intact as in healthy controls, white matter contribution to the I-E signaling as measured by this TMS paradigm, if any, is likely negligible.

Further support of this conclusion can also be found in studies on TMS and white matter in healthy subjects, where non-significant to modest relationships between TMS measurements and FA were observed [38, 40,41,45, 75], but none found significant correlations between TMS motor threshold and corticospinal tracts [46,47,75]. Therefore, it appears that only in clinical populations like schizophrenia, SICI might interact with the pathophysiology of that disease and explicit disease-specific relationship with white matter microstructures.

One limitation of the study is that we only measured upper motor pathway white matter at and above the brainstem corticospinal tract but not spinal cord white matter and peripheral nerve. However, Di Lazzaro and colleagues used direct epidural recording on descending corticospinal volleys evoked by TMS pulse(s) [76,77] and have observed the SICI effects at spinal cord, which suggests that the origin of SICI started before transferring from brain white matter to spinal cord white matter. Therefore, measuring white matter up to the corticospinal tract above the brainstem level is anatomically justified. Another limitation is that most of the patients were taking antipsychotic medications which may modulate parameters of cortical inhibition [12,22]. However, such a medication effect, if present, is likely distributed and unlikely to be limited to the motor cortex fibers. Adding chlorpromazine equivalent (CPZ) as a covariate, we found no substantial change in the correlation between left CR FA and SICI (r=−0.67 without CPZ and r=−0.60 with CPZ) or correlation between the whole brain averaged FA and SICI (r=−0.60 without CPZ and r=−0.66 with CPZ). Finally, without directly examination on how GABAa mechanism may also impact SICI in schizophrenia patients, we cannot conclude whether and the extent of GABAa mechanism or its interaction with the white matter mechanism may still be involved in the SICI deficit in patients.

Conclusions

This study found that patients with schizophrenia had decreased SICI and this inhibition deficit was associated with and mediated by the white matter of left corona radiata and perhaps other white matter in the motor path where the SICI signals are travelling. Findings from this study potentially challenge the exclusively cortical neuronal or synaptic transmission view of the inhibitory-excitatory mechanism dysfunction in schizophrenia, and suggest that larger scale structural circuitry may also contribute, especially in patients with structural deficits at the white matter connectivity level. Evaluating brain circuitry contribution to SICI biomarker should help reveal additional I-E neural mechanisms underlying schizophrenia.

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- Patients with schizophrenia showed deficits in short-interval intracortical inhibition (SICI) and white matter integrities, but not cortical facilitation (ICF) as compared with healthy controls.
- Only in patient group, SICI was significantly associated with white matter microstructure.
- Mediation analysis suggested that the deficit of SICI in schizophrenia was largely mediated by white matter microstructure.

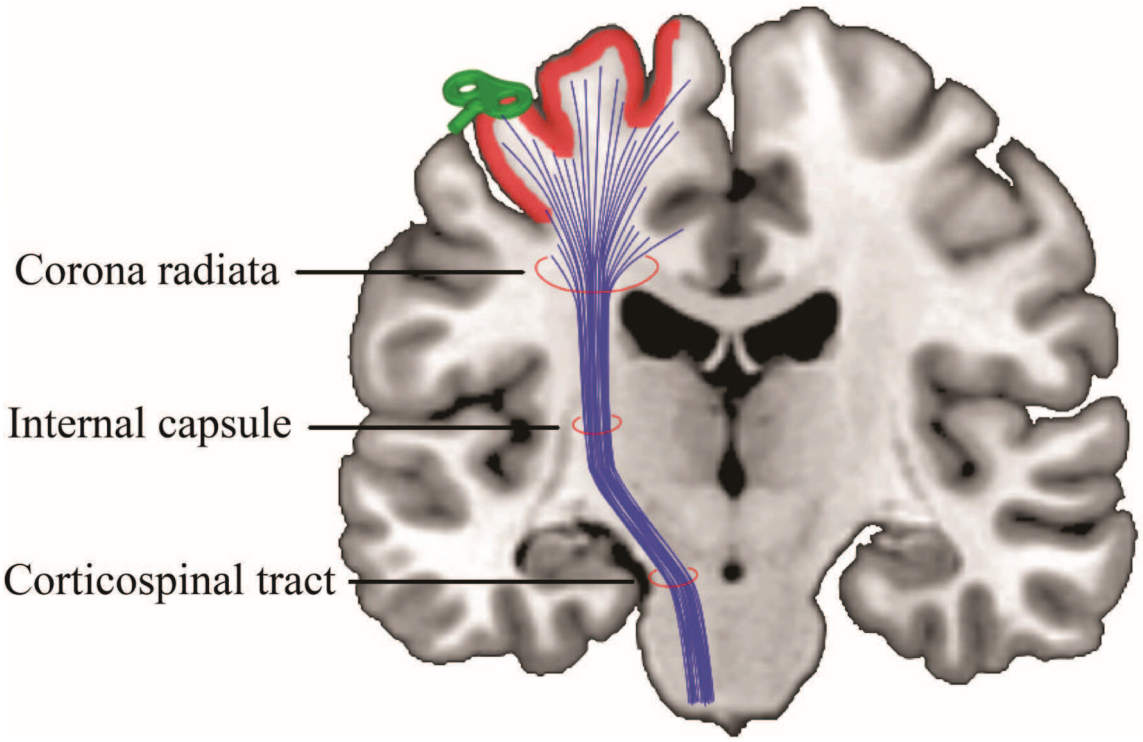

Figure 1.
Illustration of TMS site and major motor related white matter tracts to generate SICI and ICF. Green coil represents the TMS site over the left motor cortex. Upper limb related motor cortex was marked in red.

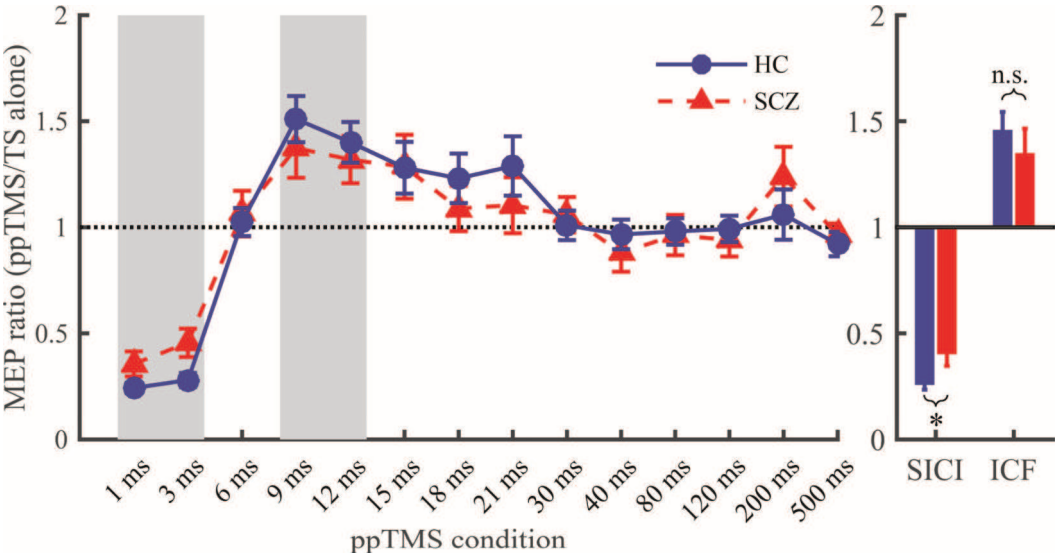

Figure 2.

Inhibition and facilitation of ppTMS. ppTMS effects were represented as ratios to TS alone. Therefore, ratios below (above) 1 indicates inhibition (facilitation). Both healthy controls (HC; blue, circle) and patients with schizophrenia (SCZ; red, triangle) showed inhibition at 1 and 3 ms ISIs and facilitationat 9 and 12 ms interstimulus intervals (ISIs) (covered by gray bars). Further, as in previous literature, ppTMS effects were merged at 1 and 3 ms ISIs to indicate inhibitory effect and at 9 and 12 ms ISIs to indicate facilitatory effect. Patients with schizophrenia showed deficit of inhibition but not facilitation as compared with healthy controls.SICI: short-interval intracortical inhibition; ICF: intracortical facilitation. Error bar indicates S.E.. *$p<0.05$. n.s., non-significant.

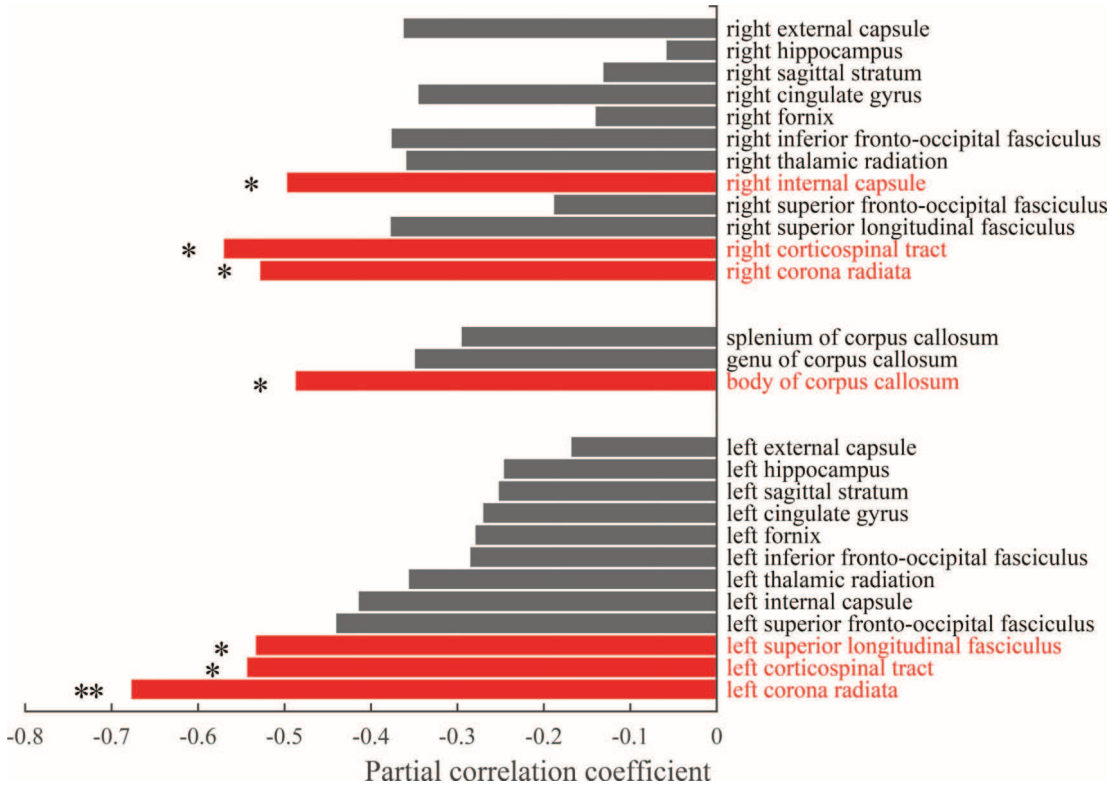

Figure 3.

Relationship between short-interval intracortical inhibition (SICI)and the fractional anistropy (FA) of white matter tracts in patients. X-axis are partial correlations after controlling for age. *p<0.05; **significant after Bonferroni correction for multiple comparisons.

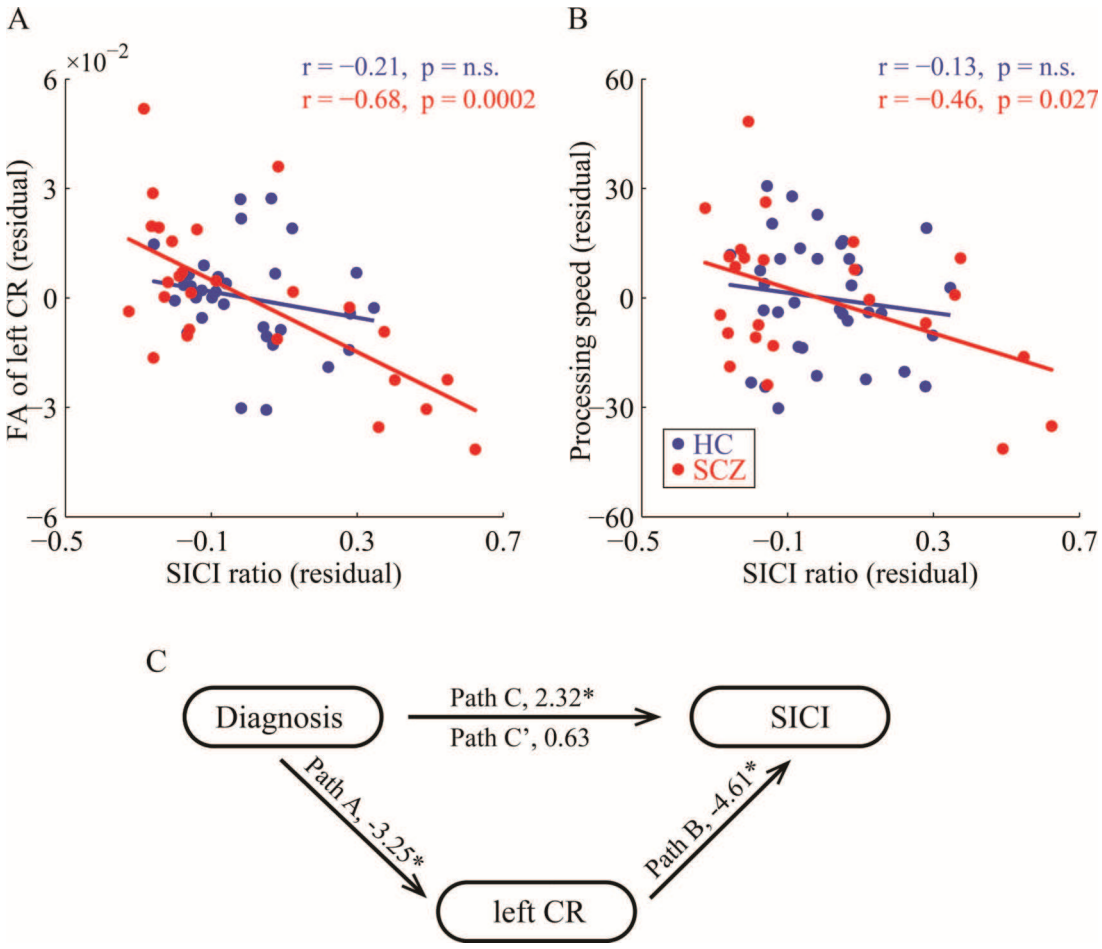

Figure 4.

The relationship between short-interval intracortical inhibition (SICI) and fractional anisotropy (FA) of anterior corona radiata (CR) and processing speed (PS), controlling for age. For schizophrenia patients (SCZ, red dot and red line), but not healthy controls (HC, blue dot and blue line), less left corona radiata microstructure was associated with less intracortical inhibition (A). SCZ patients with slow processing speed showed less inhibition (B). Mediation of white matter microstructure of left corona radiata (CR) on the relationship between diagnosis and SICI (C). The significant effects (path C) of diagnosis on SICI was largely removed with left CR as a mediator (path C'). Specifically, the effects of disgnosis on FA of left CR (path A) and left CR on SICI (path B) were significant. T scores were shown on each path. *p<0.05.

Table 1

Demographic, clinical characteristics, and group differences in paired-pulse TMS effects.

	Healthy control n=36	Schizophrenia n=26	Statistics F or χ^2	P value
Age (years) (±sd)	41.13±14.11	36.77±13.37	1.23	0.23
Male/Female	19/17	19/7	2.62	0.11
RMT (%)	47.89±7.29	47.71±7.99	0.01	0.93
Single pulse MEP (mV)	1.14±0.74	0.89±0.61	1.96	0.17
SICI ratio	0.26±0.16	0.41±0.30	6.13	0.02*
ICF ratio	1.46±0.53	1.35±0.61	0.56	0.46
Processing speed	72.74±16.19	61.33±20.57	5.66	0.02*
Averaged FA	0.46±0.01	0.44±0.03	7.69	0.01*

Note: resting motor threshold (RMT) was reported as a percentage of the maximum stimulator output. SICI: short-interval intracortical inhibition; ICF: intracortical facilitation; FA: fractional anisotropy. Single pulse MEP: Peak-to-peak amplitude of the EMG motor-evoked potential (MEP) amplitude when single pulse TMS delivered at 120% of RMT.

*Statistically different between schizophrenia patients and healthy controls.