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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.
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.

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1. 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.

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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 1–6 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 (Fig. 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.

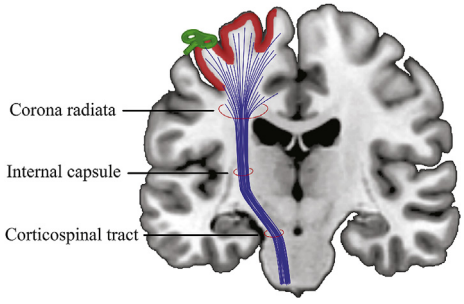

Fig. 1. Illustration of TMS site and major motor related white matter tracts to generate SICI and ICF. Green coil represents the TMS site over the left motor cortex. Upper limb related motor cortex was marked in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Materials and methods

2.1. 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.

2.2. 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 (Fig. 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.

2.3. 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 interstimulus 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 s. 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.