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Research report

Impairments in motor-cortical inhibitory networks across recent-onset and chronic schizophrenia: A cross-sectional TMS Study

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HIGHLIGHTS

- TMS-investigation in the largest cross-sectional sample of schizophrenia patients.
- Schizophrenia patients show impairments in intracortical inhibitory networks.
- These impairments seem to be pronounced in chronically-ill patients.
- Results of this work have implications for the timing of schizophrenia treatment.
- Especially regarding the application of non-invasive brain stimulation.

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ABSTRACT

Transcranial magnetic stimulation is an established method to probe inhibitory and facilitatory networks within the human motor cortex. Reduced motor-cortical inhibition is a common finding in schizophrenia patients. Based on neuropathological findings, the reduced cortical inhibition in schizophrenia has been linked mainly to alterations in GABAergic neurotransmission. The aim of this study was to investigate the impact of disease state on intracortical inhibitory and facilitatory networks measured by TMS in schizophrenia. Cortical excitability was investigated in a pooled cross-sectional sample of recent-onset-schizophrenia (RO–SZ), chronically-ill schizophrenia patients (CH–SZ) and healthy controls (HC) using single- and paired-pulse TMS applied to the left primary motor cortex. The sample included 41 RO–SZ, 42 CH–SZ and 59 HC. Analyses were focused on resting motor threshold (RMT), short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and cortical silent period (CSP). There was a significant difference regarding the mean CSP durations across our three study groups ($p = 0.002$). Subgroup comparisons revealed a shorter CSP in HC compared to RO–SZ ($p < 0.001$). Three group comparisons of SICI ($p = 0.098$) and RMT ($p = 0.075$) showed differences at a trend-level. An overall comparison between HC and all patients showed a significantly reduced SICI ($p = 0.031$) and prolonged CSP ($p = 0.003$) in schizophrenia patients. This is the largest and first cross-sectional investigation of various excitability parameters in schizophrenia patients. These findings indicate general alterations of cortical inhibition, with differences between recent-onset and chronically-ill schizophrenia patients.

1. Introduction

Impaired GABAergic neurotransmission and reduced cortical inhibition are established pathobiological models for schizophrenia. In humans, transcranial magnetic stimulation (TMS) has been used successfully to probe noninvasively such inhibitory, as well as facilitatory, networks in the primary motor cortex (M1). Three main TMS paradigms have traditionally been applied to assess cortical inhibition and facilitation in schizophrenia patients: measurement of $GABA_A$-mediated short-interval cortical inhibition (SICI), measurement of intracortical facilitation (ICF) and the assessment of $GABA_B$-mediated cortical silent period (CSP) [1–4]. In brief, TMS paradigms can provide information about the activity of both different neurotransmitter systems and intracortical networks at the system level of the human cortex (for review see [1,5]).

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Several studies have demonstrated impaired motor-cortical excitability as a common, yet not fully understood, observation in patients suffering from schizophrenia. A reduction in SICI has been the most consistent result, with findings related to ICF, CSP and motor thresholds being more varied (for review see [6,7]). It has been suggested that disturbances in GABAergic and glutamatergic neurotransmission may explain these reduced inhibitory functions in schizophrenia. Neuropathological findings support these hypotheses, with substantial alterations having been found in GABAergic interneurons, GABA-synthesizing enzyme glutamic acid decarboxylase (GAD67) and GABA-related gene expression in various parts of the schizophrenia brain, including M1 [8–12].

There remains a lack of clarity relating to the factors underlying the inconsistent observations made across TMS studies conducted in schizophrenia patients. One already identified contributor to the inter-study variability is antipsychotic medication. For example, clozapine administration leads to a prolonged CSP compared to unmedicated patients and healthy controls [13,14]. On the other hand, one early study conducted in drug-naïve, first-episode schizophrenia patients demonstrated lower RMTs, but no other differences in cortical excitability compared to healthy controls [15].

However, aside from medication, neurobiological factors relating to different disease states have to be included in any discussion that aims to explain the heterogeneous findings across studies. Unlike neuroimaging studies, the impact of disease course on cortical excitability and inhibitory networks has gained minimal attention in the field. Recent meta-analyses confirm a progressive brain volume loss in schizophrenia [16,17], and longitudinal imaging studies stress the importance of a recurring disease course for increasing brain pathology [18]. Furthermore, reduced inhibitory interneuron activity and excessive excitatory pruning appear to increase through disease progression [19] with a subsequent alteration to excitatory/inhibitory network balance in neural circuits in schizophrenia [20].

The only available cross-sectional TMS study showed that first-episode schizophrenia patients had a prolonged CSP compared to subjects at-risk of developing psychosis, but that both groups had reduced SICI compared to healthy controls [21]. However, to the best of our knowledge, investigations of human cortical excitability that focus on different states later in the course of schizophrenia are lacking. Therefore, the aim of the present study was to investigate the impact of disease state on cortical excitability in the largest cross-sectional sample of schizophrenia patients available to-date. We hypothesized that patients with recent-onset and chronic schizophrenia would differ with regards to impairments of cortical excitability measured by motor-cortex TMS.

2. Methods

2.1. Subjects

A cross-sectional data-sample was acquired by analyzing samples from available published and unpublished datasets of our groups (2002–2012, Homburg and Goettingen). Participants in this study were healthy controls (HC) as well as patients with a diagnosis of recent-onset-schizophrenia (RO–SZ, defined by less than 2 years disease-duration, one psychotic episode), and chronic schizophrenia (CH–SZ). The pooled sample consisted of 41 RO–SZ, 42 CH–SZ and 59 HC, providing a total sample size of 142 participants. To account for expected differences in age, a subject-by-subject matched sample (age, gender and handedness) was assembled, resulting in a total of 72 participants and an age-independent control condition for three-group comparisons. Subjects with contraindication to TMS, such as neurological illness, severe brain injury, brain tumors, or a history of dementia and patients with concomitant benzodiazepine or mood stabilizer treatment were excluded. The initial studies were all approved in accordance with the declaration of Helsinki by the local ethics boards, and the presented analyses were approved by the LMU ethics board. All participants had given written informed consent. Diagnoses were confirmed by two independent board-certified psychiatrists. All participants underwent a standardized test of hand preference [22,23] and all patients received an assessment of psychopathological symptoms (PANSS; [24]), of disease severity (CGI; [25]) and of social functioning (GAF; [26]). To investigate the influence of antipsychotic medication on TMS-parameters, chlorpromazine equivalents (CPZ) were calculated from daily doses of antipsychotics [27]. Furthermore, the impact of the main antipsychotics in monotherapy (aripiprazole/clozapine/olanzapine/quetiapine/risperidone) and the main chemical classes ("5-HT/D2-antagonists" (risperidone) and "dibenzdiazepines" (olanzapine, quetiapine, clozapine)) [14] on cortical excitability was investigated.

2.2. TMS procedure

The full procedure-protocol was described previously [28,29]. Briefly summarized, subjects were examined in a comfortable sitting position with arms supported passively. Electromyographic activity (EMG) was recorded by surface electrodes on the right dorsal interosseus muscle (FDI). Raw signals were amplified, bandpass-filtered (2 Hz–10 kHz) and digitized using a standard amplifier (Keypoint portable, Medtronic Co., Denmark). TMS was performed over the left motor cortex with a standard 70 mm TMS figure-of-eight magnetic coil and a MagPro × 100 magnetic stimulator (Medtronic Co., Denmark). Throughout all experiments, the coil was held tangentially to the head, with the handle pointing backwards and in a 45° angle lateral to the midline. The stimulation site that produced the largest motor evoked potential (MEP) at moderately suprathreshold stimulation intensities was defined and marked as the optimal coil position.

2.3. Cortical excitability

RMT was defined as the lowest intensity that produced a minimum MEP of 50 μV in the relaxed FDI in at least 5 of 10 trials. SICI and ICF were recorded with a standardized paired-pulse protocol (conditioning stimulus: 80% RMT, test stimulus: intensity that produced resting MEPs averaging 0.5/0.7–1.5/1.3 mV, ISIs: 3, 7, 12 and 15 ms). CSP was obtained by recording from the FDI muscle under voluntary contraction while stimulating the contralateral M1 with 120% RMT. CSP duration was defined as the time from MEP onset to the return of voluntary EMG activity.

2.4. Statistics

For statistical analysis, SPSS 20 for Windows was used. Level of significance was set at $\alpha = 0.05$. Data measurements exceeding 2.5 standard deviations from the mean were excluded from further data analysis ($n = 13$, 142 remained for analyses). One-way analysis of variance (ANOVA) and χ^2-tests were used to analyze differences between the study groups on demographic variables (age, gender, handedness). Independent t-tests were used to compare clinical measures. Dependent variables were unconditioned RMT, S 1 mV, CSP, SICI/ICF (3, 7, 12, 15 ms), and the independent variable was study group (healthy controls, recent-onset schizophrenia, chronically-ill schizophrenia patients). Further analyses were based on different medication types and chemical classes of the antipsychotics. As most of the variables' data were not normally distributed (Kolmogorov–Smirnov test $p < 0.05$), multiple-group/two-group comparisons were conducted