Cortical Neuronal Excitability and Transcallosal Inhibition in Schizophrenic Patients: Transcranial Magnetic Study

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ABSTRACT

Background: Transcranial Magnetic Stimulation (TMS) is a non-invasive method of stimulating the brain that is increasingly being used in neuropsychiatric research and clinical psychiatry. Some studies have suggested that the pathophysiology of schizophrenia may involve dysfunction of excitatory and/or inhibitory neural function. This study aimed to investigate the cortical neuronal excitability and the transcallosal inhibition in schizophrenic patients.

Material and Methods: The study included 26 schizophrenic patients and 13 healthy volunteers, clinical evaluation and determination of motor threshold (MT) at rest (RMT) and during active contraction (AMT), motor evoked potential (MEP) amplitude, input-output curve, cortical silent period (CSP) duration and transcallosal inhibition were done for each subject. Results: There was significant prolongation of duration and latency of TCI as well as lengthened transcallosal conduction time. (P< 0.001, 0.003 and 0.001 respectively) in schizophrenics compared with control group. Despite the absence of significant differences between schizophrenics and controls in other neurophysiological parameters (RMT, AMT, MEP or CSP), there was significant correlation between resting motor threshold and negative symptoms of schizophrenia (P = 0.003). There was significant positive correlation between the CSP duration and positive symptoms of schizophrenia (P = 0.001). There were no significant differences between paranoid and non-paranoid schizophrenia in cortical neuronal excitability or in transcallosal inhibition.


INTRODUCTION

Some histopathological and pharmacological studies have suggested that the pathophysiology of schizophrenia may involve dysfunction of excitatory and/or inhibitory neural function. In a number of recent studies, TMS of motor cortex has been used to evaluate both cortical excitability and inhibitory mechanisms in patients with schizophrenia. This research is still in its early days and most of these studies are limited to small sample sizes. Further more due to methodological differences it is often difficult to directly compare the results of different studies.

Researchers have utilized TMS of the motor cortex to study neuronal excitability, and cortical inhibitory mechanisms, both in patients and healthy subjects. This has mainly been achieved by examining EMG recorded motor evoked potentials. Transcallosal inhibition has also been used to investigate inter-hemispheric interactions of homologous brain areas by measuring the latency of the inhibition. In the first TMS study of transcallosal inhibition in schizophrenia, Boroojerdi et al., using a single pulse paradigm, found a significant delay in the onset of transcallosal inhibition in 10 medicated schizophrenia patients compared to 10 controls. However, other investigators did not report a significant delay in the onset of transcallosal inhibition or indications of increased transcallosal conduction time in patients with schizophrenia.

There is some agreement that positive symptoms of schizophrenia is related to excess...
dopaminergic transmission and negative symptoms are probably due to structural brain changes\cite{3,10}. Because of controversy and paucity of studies related to neuronal excitability, and cortical inhibition in patients with schizophrenia, the present study aimed to investigate the cortical neuronal excitability and the transcallosal inhibition in schizophrenic patients and correlated it with the clinical symptoms.

**MATERIALS AND METHODS**

**Subjects:**

The study included 26 patients and 13 healthy volunteers. Written informed consent was obtained from all subjects on a form approved by the ethics committee of Assiut University Hospital, Assiut/Egypt. All patients and controls were right handed. All patients met the DSM-IV criteria for schizophrenia. Exclusion criteria were a history of head injury, epilepsy, significant neurological and medical disorders and substance abuse. Sixteen patients were diagnosed as paranoid and ten patients were non-paranoid schizophrenia, (seven were undifferentiated and 3 were disorganized schizophrenia). Fifteen patients were males. Ten patients had family history of schizophrenia. The mean age of studied patients was 26.65 ± 4.5 years and the mean duration of illness was 3.5 ± 1.7 years. All schizophrenic patients were non-medicated for at least one month. The schizophrenic patients were evaluated through a Scale of Assessment of Negative Symptoms (SANS)\cite{11} and a Scale of Assessment of Positive Symptoms (SAPS)\cite{12}. The control group was recruited from the staff employed at the same hospital. A screening interview confirmed the absence of any medical or psychiatric illness.

**Scale of Assessment of Negative Symptoms (SANS) and Scale of Assessment of Positive Symptoms (SAPS):**

SANS and SAPS are two scales developed by Andreasen\cite{11,12} for evaluation of negative and positive symptoms of schizophrenia. Each individual group of symptoms subdivided into different items. Each item is evaluated in a rating score of 0-5, where 0 means absence of the symptom and grade 5 means severe degree of the symptom.

**Devices:**

A commercially available stimulator, Dantec Maglite, TM Copenhagen, Denmark with a figure-of-eight coils (outer diameter of one wing 9 cm) was used for magnetic stimulation and produce a focal magnetic field that is greatest in magnitude under the crossing point of the coil. The current in the central axis had twice the magnitude of the current flowing in the two arms of the coil. Stimulation coordinates are given with reference to this point. The recording of the responses are performed with the Dantec Keypoint TM device, Copenhagen Denmark.

**Preparation**

The subjects were seated in a comfortable chair and instructed to be as relaxed as possible. Electromyography (EMG) recordings from right first dorsal interossus muscle (FDI) were acquired with silver–silver chloride surface electrodes, using a muscle belly-tendon setup, with a 3 cm diameter circular ground placed on the wrist. A Dantec keypoint EMG was utilized to collect the signal (Dantec, Skovlunde, Denmark). EMG parameters included a bandpass of 20–1000 Hz, and a recording time window of 200 ms. TMS was delivered using a figure-of-eight coil, with each coil wing having a 9 cm outer diameter. The coil was hand held in place by paying attention to keep orientation and position constant. Single pulse was applied using Maglite r 25 magnetic stimulator (Dantec, Skovlunde, Denmark).

**Determination of resting and active motor threshold (rMT and aMT)**

First, we determined the optimal scalp location for stimulation defined as scalp position from which TMS evoked MEPs of greatest amplitude in the FDI. We used constant suprathreshold stimulus intensity, as the figure of eight coil was systematically moved in 1-cm steps.
to determine the scalp position from where TMS evoked MEPs of maximum peak-to-peak amplitude in the target muscle. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at a 45 angle from the midsagittal line\textsuperscript{13,14}. Then, single pulse TMS was delivered to the optimal location starting at suprathreshold intensity and decreased in steps of 2\% of the stimulator output. Relaxation and EMG signals were monitored for 20 ms prior to stimulation and judged by audio-visual feedback. The rMT was defined, as the minimal intensity required eliciting MEPs of 50 UV peak-to-peak amplitude, in five out of 10 consecutive trails\textsuperscript{15,16}.

**Silent period (SP)**

The duration of the transcranially postexcitatory SP was determined for both hemispheres during isometric voluntary contraction of the contralateral FDI. The participants were asked to perform a maximum voluntary abduction of the Fifth finger as judged by audio-visual feedback. Voluntary contraction started several seconds before TMS. Stimuli were delivered not closer than one every 15 s to avoid fatigue. Six magnetic stimuli were applied at intensity 125\% of rMT. The EMG traced were rectified and averaged the length of the SP was determined from the start of the transcranially evoked response to the recurrence of at least 50\% of EMG background activity. MEPs size was also determined during voluntary contraction from peak-to-peak in mV.

**MEP input–output curves**

TMS was applied over the right and then over the left hemisphere while two responses were recorded at each of a range of different stimulus intensities. Stimulus intensity was increased in steps of 10\% of the individual rMT (from 110 to 150\% rMT). MEP size was measured peak-to-peak in signal trails and averages were calculated for each of the different intensities.

**Transcallosal inhibition (TCI):**

During the testing of a single pulse TCI, stimulation will be applied at a frequency of 0.2 Hz. The subject will instructed to make a contraction of maximal intensity on the side of stimulation. The contraction is sustained for approximately 1 s prior to the stimulus and 1 s after the stimulus with several seconds rest between stimulation. The stimulation intensity is set at 150\% of resting motor threshold. The onset and the offset of TCI is defined as the points where the EMG trace fell persistently below and where it returned persistently above the base line. The TCI duration is calculated as the time of offset of TCI minus the onset. TCI latency was calculated as the time of TCI onset minus the time of stimulation (this time equals the transcallosal and peripheral conduction times). The transcallosal conduction time was calculated as time of onset of TCI minus the time from stimulation to the time of the MEP in the contralateral hand\textsuperscript{17}.

**Statistical analysis:**

Comparisons between schizophrenics and controls were made by means of an unpaired t-test (for rMT, and aMT, SP, TCI values) and ANOVA for repeated measures (for the input–output curve). Due to the abnormal distribution of data, Spearman’s correlation coefficient test was used to study correlations between, neurophysiological data (rMT, aMT, CSP, TCI) and clinical parameters (age, duration of illness, positive and negative symptoms of schizophrenia).

**RESULTS**

The demographic and the clinical data represented in table 1. There was no significant difference in age or male/female ratio between patients and controls (P>0.05). No adverse effects were recorded following TMS. Details of negative and positive symptoms were illustrated in the first table. There were no significant differences between paranoid and undifferentiated schizophrenia in cortical neuronal excitability or
in transcallosal inhibition (P<0.05). No significant differences between patients with and without family history of psychotic disorders in different neurophysiological parameters or between males and females.

There were no significant differences between schizophrenics and controls in RMT (47.2±9.9, 42.7±9.1 respectively, P = 0.186), AMT (31.9±4.6, 30±7.4.1 respectively, P = 0.426) (Fig. 1). Despite the higher MEP amplitude in schizophrenics compared with normal volunteers but insignificant (1.9±2.4, 1.2±0.67 respectively, P = 0.126). No significant differences in MEP latency between schizophrenics compared with normal volunteers (P>0.05). There were no significant differences between schizophrenics and controls in CSP (137.05±41.46, 132±35.54 respectively, P = 0.906).

While there was significant prolongation of duration of TCI in schizophrenics compared with controls (40.2±9.7, 28.3±6.9 respectively, P = 0.001), and latency of TCI (41.2±7.4, 35.5±4.2 respectively, P = 0.003), as well as lengthened transcallosal conduction time in schizophrenics compared with normal control group (21.8±5.6, 16.2±3.5 respectively, P = 0.001) (Fig. 2).

There was no significant difference between schizophrenics and control in input output curve, despite the rapid increase in amplitude of MEP with increased intensity of stimulation in schizophrenics compared with control group (df = 0.99, F =0.607 and P = 0.534) (Fig. 3).

Concerning the relation between the severity of symptoms of schizophrenia and neurophysiological data: there was a significant positive correlation between resting and active motor threshold and negative symptoms of schizophrenia: global rating of Anhedonia-Asociality, attention, and avolitional-apathy (r = 0.62, P = 0.003; r = 0.442, P = 0.02; r = 0.62, P = 0.002 respectively) (Fig. 4). On the other hand there was significant positive correlation between the CSP duration and positive symptoms of schizophrenia (global rating of severity of bizarre behavior) r = 0.62, P = 0.001) (Fig. 5). While there was no significant correlation between the TCI data and other symptoms rated on the SANS and SAPS.

### Table 1. Demographic and clinical data of the studied groups.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients (26)</th>
<th>Control (13)</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>26.65 ± 5.8</td>
<td>28.3 ± 4.9</td>
<td>NA</td>
<td>NS</td>
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</table>

| Duration of illness (years) | 3.5 ± 1.7 | NA |

<table>
<thead>
<tr>
<th>Positive symptoms</th>
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<tr>
<td>Global rating of severity of hallucinations</td>
<td>2.6±2.0</td>
<td>NA</td>
</tr>
<tr>
<td>Global rating of severity of delusions</td>
<td>3.4±1.5</td>
<td>NA</td>
</tr>
<tr>
<td>Global rating of severity of bizarre behavior</td>
<td>3.9 ± 1.1</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Negative symptoms</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Global rating of affective flattening</td>
<td>3.1±1.39</td>
<td>NA</td>
</tr>
<tr>
<td>Global rating of alogia</td>
<td>2.6±1.8</td>
<td>NA</td>
</tr>
<tr>
<td>Global rating of avolitional-Apathy</td>
<td>3.4±1.0</td>
<td>NA</td>
</tr>
<tr>
<td>Global rating of Anhedonia-Asociality</td>
<td>3.3 ± 1.4</td>
<td>NA</td>
</tr>
<tr>
<td>Global rating of attention</td>
<td>3.1 ± 1.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = Not Applicable

NS= Non Significant
Fig. (1): AMT/RMT (Data are represented as means). There was no significant differences in resting or active motor threshold in both groups.

Fig. (2): Duration and latency of TCI as well as transcallosal conduction time in schizophrenics and controls (Data are represented as means). There was significant prolongation of duration and delayed in latency in schizophrenics compared with controls. Also there is significant prolongation of transcallosal conduction time in schizophrenics compared with controls groups.
Fig. (3): Input–output curve of the primary motor cortex in Schizophrenic patients and control group. Data correspond to the amplitude of MEP expressed as mean at different intensities.

Fig. (4): There was a significant positive correlation between resting and active motor threshold and negative symptoms of schizophrenia: global rating of Anhedonia-Asociality, attention, and avolitional-apathy (r=0.62, P = 0.003; r = 0.442, P = 0.02;  r = 0.62, P = 0.002 respectively).
Overall, TMS studies provide little evidence for significant abnormalities in cortical excitability in patients with schizophrenia. Most investigations have failed to show any significant difference in motor threshold, MEP size or paired pulse facilitation between patients and healthy subjects. One exception is a study by Abarbanel et al., which demonstrated larger MEP size and lower motor thresholds in 10 medicated patients with schizophrenia compared to 10 depressed and 10 healthy subjects.

In the present study we failed to find any significant changes between patients of schizophrenia patients and controls neither in resting, active motor threshold nor in MEP amplitude, despite the presence of significant positive correlation between some global rating scales of negative symptoms of schizophrenia and the resting and active motor threshold. With increasing the score of negative symptoms increasing the resting motor threshold that is meaning decrease cortical excitability. The increased excitability in schizophrenia patients in the previous studies may have been due to increased muscle tonus secondary to extrapyramidal side effects from neuroleptic medications. However, our patients were drug free for at least one month and this explanation could not applied to our sample.

TMS research has provided inconclusive results concerning corticospinal conductivity in schizophrenia. In the first study of motor function in schizophrenia using TMS, Puri et al. detected a significantly shorter latency of MEPs in nine unmedicated patients with schizophrenia compared to nine healthy subjects. However, further studies measuring MEP latency did not find a difference between medicated schizophrenia patients and normal controls. In the present study we support the absence of alteration of corticospinal conductivity.
Several findings indicate that a lack of cortical inhibitory control may be involved in the pathophysiology of schizophrenia\(^{20}\). Abnormal motor function such as incoordination, involuntary movements and impaired fine motor skills, which are not related to antipsychotic drug treatment, have been detected in approximately 80% of patients with schizophrenia\(^{21}\). These motor deficits could be explained by disturbances in central inhibition and fine-tuning of motor responses\(^{18}\).

In the present study TMS has been employed to investigate cortical inhibitory mechanisms by focusing on two main paradigms: (1) Cortical Silent Period, (2) Single Pulse Transcallosal Inhibition. Our results suggest that despite the presence of significant correlation between the CSP duration and positive symptoms of schizophrenia there was no significant alteration in cortical silent period, which may be related to the small sample size or the alteration, reported by others was related to medication which is not the case in our sample. Four recent studies have found the silent period duration to be significantly shorter in medicated schizophrenic patients compared to healthy controls\(^{6,7,17,22}\). One of these studies also included a group of unmedicated patients\(^{22}\), and found that these patients had a significantly shorter silent period duration than the medicated group. Only one smaller study failed to report a significant difference in silent period duration between patients on conventional antipsychotics and healthy controls\(^{23}\). The differences between the results of our study and previous studies may be partially related to illness (shorter duration) or may be attributed to absence of medication, our patients were free of medication for at least one month.

**Transcallosal inhibition**

Single pulse transcallosal inhibition is observed when one stimulates the motor cortex with TMS while the subject performs a steady contraction of hand muscles on the same side as the stimulation. The TMS pulse triggers a volley of action potentials that pass through the corpus callosum and inhibit the corticospinal neurons controlling the contralateral hand muscles, which are voluntarily activated. In this way, transcallosal inhibition of voluntary muscle contraction can be measured.

Transcallosal inhibition has also been used to investigate inter-hemispheric interactions of homologous brain areas by measuring the latency of the inhibition. In the first TMS study of transcallosal inhibition in schizophrenia, Boroojerdi et al.\(^{5}\), using a single pulse paradigm, found a significant delay in the onset of transcallosal inhibition in 10 medicated schizophrenia patients compared to 10 controls which was consistent with our findings. However, other investigators did not report a significant delay in the onset of transcallosal inhibition or indications of increased transcallosal conduction time in patients with schizophrenia\(^{5,7,8}\). In the present study, there was a significant prolongation of the duration of transcallosal inhibition. Our results consistent with previous four studies, in which they reported that; the duration of transcallosal inhibition was significantly longer in schizophrenics than in healthy subjects\(^{5,6,7,8}\).

However, three studies found a reduction of the magnitude of transcallosal inhibition in schizophrenic patients\(^{7,17,22}\). In one of these studies, the difference was seen between unmedicated patients and healthy subjects but a group of medicated patients did not differ significantly from the control and unmedicated groups\(^{22}\). The significant abnormalities of TCI could support the hypothesis of an abnormally functioning corpus callosum in schizophrenia. There is clear evidence that TCI is mediated through corpus callosal pathways rather than via other interhemispheric tracts or via an effect on the descending unilateral tracts\(^{17}\). These conclusions are supported by the absence of TCI in patients with corpus callosum lesions\(^{24}\) and the persistence of TCI in patients with lesions of unilateral descending corticospinal pathways\(^{5}\). The correlation between severity of negative and positive symptoms and cortical inhibition (CI) deficit as indexed by resting and active motor potential. Theses findings are similar to those of Daskalakis et al.\(^{22}\), who found that paired pulse (pp) TMS paradigm of CI deficit was correlated with the severity of psychosis by using the PANASS scoring and severity is not correlated to other measures of cortical inhibition deficit (CI).
They explained that there is some evidence suggests that these CI measure may reflect different inhibitory neural pathway. For example, ppTMS inhibition may be mediated by GABA_A interneurons^25 as opposed to CSP inhibition, which may be mediated by GABA_B interneurons^26,27.

In summary, this study indicates that there is a trend toward greater cortical inhibition as detected by the correlation between clinical symptoms in one hand and resting motor threshold and cortical silent period on the other hand. This is beside the significant alterations in transcallosal inhibition in schizophrenia as demonstrated by a number of parameters that confirm the presence of abnormality in the corpus callosum functions in schizophrenia.

REFERENCES


الملخص العربي

استثارة الأنشطة العصبية والتثبيط عبر الجسم الثقى في مرضى الفصام
دراسة مطاقيطية خلال الجمجمة

تعتبر الاستثارة المغاقيطية عبر الجسم الثقى من الوسائل غير المختارة في استثارة الدم وقد أنشئ استخدامها في أبحاث أعراض المخ والأعصاب والطب النفسي زائدة ملحوظة وقد فلاح النظر بعض الدراسات إلى أن التغيرات الفسيولوجية والбиولوجية في مرضى الفصام ربما تشمل خلل في وظيفة الاستثارة والتثبيط العصبي وقد هدفت هذه الدراسة إلى فحص الاستثارة العصبية للبشرة المخية والتثبيط عبر الجسم الثقى.

وقد انتشرت الدراسة على 26 مريضاً بالفصام وأيضاً 13 شخص من المتطوعين كمجموعة ضابطة. وقد تم عمل فحص أكليبيكي للمرضى والمجموعة الضابطة وتتم حساب قيمة التأثير المرئي عند السكن وأثناء الاتقاط النشط ، ومدى الجهد المستمر للمرضى ومخرج داخل الخارج، ومدة فترة سكون القشرة المخية والتثبيط عبر الجسم الثقى.

وقد أظهرت النتائج أنه لا توجد فروق ذات إحساسية بين مرضى الفصام من النوع الشكسيكي والأدوات الأخرى في الاستثارة العصبية العاجية أو التثبيط عبر الجسم الثقى. كما وجد أنه لا يوجد فروق بين أي حصل في المجموعة الظاهرة في قيمة التأثير السكاكي والتشخيص والجهد المستمر للمرضى، ومدة فترة سكون القشرة المخية، بينما وجدت زيادة في فترة وحالة الكمون ذات إحساسية في التثبيط وفي مدة التوصل عبر الجسم الثقى، ونستخلص من النتائج أن التغيرات غير طبيعية ذات المغزى بين مدة وزمن التثبيط عبر الجسم الثقى ربما تدعم الفرض الذي يعتبر وجود خلل في الجسم الثقى في مرضى الفصام.