

The Relationship of the Change in Symptoms and Cognitive Functions with the Change in Cortical Inhibition Parameters Measured by Transcranial Magnetic Stimulation: An Eight-Week Follow-Up Study



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SUMMARY

Objective: Previous transcranial magnetic stimulation (TMS) studies have demonstrated cortical inhibition (CI) abnormalities in patients with schizophrenia. However, the relationship between changes in CI and changes in psychopathology and cognition resulting from antipsychotic treatment is not known. This is an 8 week follow up study which aims to evaluate the relation of the CI with the symptoms and cognitive functions of the patients who are switched to new atypical antipsychotic treatment, and to compare the TMS measurements of patients with those of controls.

Method: Thirteen patients and 13 control subjects matched according to age, sex, and educational level were included in the study. Patients were assessed with TMS, Positive and Negative Syndrome Scale (PANSS), and a neurocognitive battery at baseline and at 8 weeks post-treatment, while the control group was evaluated with the neurocognitive battery and TMS at baseline only. CI parameters evaluated by TMS include resting motor threshold, cortical silent period, ipsilateral silent period (ISP), short interval intracortical inhibition (SICI) and intracortical facilitation.

Results: Intracortical facilitation (ICF) was weaker and ISP was longer in patients relative to control subjects both at baseline and at the end of the eight weeks. Intracortical facilitation decreased following 8 weeks of antipsychotic treatment, indicating an increase in CI. The decrease in PANSS general psychopathology score was directly correlated with the decrease in ICF. SICI positively correlated with cognitive test performance in both cross-sectional and longitudinal analyses.

Conclusion: Our findings suggest that increase in CI is associated with the improvement in the symptoms and the action of the atypical antipsychotics.

Key Words: Transcranial magnetic stimulation, excitability, motor cortex, schizophrenia, cognitive symptoms

INTRODUCTION

Neuropathological and neurophysiological studies carried out with schizophrenia patients have suggested that deficits in cortical inhibition and in gamma-aminobutyric acid-ergic (GABAergic) inhibitory mechanisms may play a critical role in the pathophysiology of schizophrenia (Akbarian et al. 1995, Freedman et al. 2000). It is assumed that the functional changes in cortical dynamics underlying delusions and

hallucinations, the basic symptoms of schizophrenia, can be assessed directly in the motor cortex (George and Belmaker 2007).

Transcranial Magnetic Stimulation (TMS) is used to investigate cortical inhibitory and facilitatory circuits in schizophrenia (which respectively, reduce and increase neuronal excitability) and differences in these neuronal pathways have been reported between schizophrenia patients and healthy

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individuals (Eichhammer et al. 2004, Daskalakis et al. 2008, Radhu et al. 2013). In these studies, evaluation of cortical inhibition is based on measurements of the cortical silent period (CSP), short interval intracortical inhibition (SICI), and transcallosal inhibition (TCI). Evaluation of cortical excitability is based on resting motor threshold (RMT) and intracortical facilitation (ICF). RMT is the lowest stimulation intensity sufficient to evoke a small motor response with a defined amplitude in the targeted resting muscle (Rossini et al. 1994). ICF is a parameter thought to be produced by inter-neuron mediated increases in cortical excitability and is measured by the paired-pulse TMS method (Terao and Ugawa 2002). In the paired-pulse TMS technique a conditioning stimulus given before the test stimulus and after a defined time interval strengthens the muscular response given to the test stimulus, which is called “intracortical facilitation” or “paired-pulse facilitation”. This facilitation takes place when the effectiveness of the inhibitory circuits is relatively weaker than the facilitatory circuits. In addition, N-methyl-D-aspartate receptor (NMDA receptor) mediated glutamatergic neurotransmission has been shown to mediate facilitation (Schwenkreis et al. 1999), whereas GABA-A agonists have been shown to weaken this facilitation (Ziemann et al. 1996a). Suppression by the conditioning stimulus of the response to the test stimulus applied 1-6 ms later is called “short interval intracortical inhibition” or “paired-pulse inhibition” (Kujurai et al. 1993), which is believed to progress mainly by GABA-A receptor mediated neurotransmission (Sanger et al. 2001). CSP is the interruption of electromyographic (EMG) activity of a voluntarily contracting muscle secondary to the stimulus given to the contralateral motor cortex (Terao and Ugawa 2002). CSP duration is an indication of GABA-B mediated neurotransmission, and any lengthening of this duration reflects an increase in the level of cortical inhibition (Inghilleri et al. 1996). Another parameter indicating cortical inhibition is transcallosal inhibition, which is defined as the inhibition of the cortex in the contralateral hemisphere when a transcranial stimulation is given to the primary cortex in the ipsilateral hemisphere (Haraldsson et al. 2004).

Previous studies comparing schizophrenia patients and healthy controls using TMS have suggested the presence of CI deficits in schizophrenia patients, including decreased RMT (Daskalakis et al. 2002a, Eichhammer et al. 2004), CSP shortening (Fitzgerald et al. 2002a, Fitzgerald et al. 2002b), decreased SICI (Fitzgerald et al. 2002c, Daskalakis et al. 2002b, Wobrock et al. 2008, Hasan et al. 2012) and TCI (Daskalakis et al. 2002a, Fitzgerald et al. 2002a). However, other studies reported no significant differences in these parameters between schizophrenia patients and control subjects (Borojerd et al. 1999, Davey et al. 1997, Eichhammer et al. 2004, Hoy et al. 2007, Daskalakis et al. 2008, Li et al. 2009).

Although TMS evaluation of CI parameters in schizophrenia patients generally support the presence of CI deficits in the disease, differences in stimulation parameters, psychopathological severity of the cases, duration of the illness, and, most importantly, the effects of the antipsychotic agents used have resulted in widely conflicting CI data in the available literature. The use of antipsychotic drugs is believed to have significant effects on the CI. Previous studies have reported conflicting data regarding CI parameters measured in the motor cortex of schizophrenia patients who were taking antipsychotic drugs. Controlled cross-sectional studies of cortical excitability in schizophrenia patients have reported CI deficits among patients not on drug therapy relative to controls while the data of schizophrenia patients on drug therapy is conflicting (Davey et al. 1997, Borojerd et al. 1999, Daskalakis et al. 2002a). In a cross sectional TMS study, CSP duration was significantly greater in schizophrenia patients on clozapine treatment relative to control subjects, although no difference in SICI was detected (Daskalakis et al. 2008). In another study, clozapine treated schizophrenia patients exhibited longer CSP and lower SICI levels compared to the healthy controls, whereas CSP was shorter among patients on antipsychotics other than clozapine or patients not taking an antipsychotic relative to control subjects (Liu et al. 2009). A single dose of haloperidol and olanzapine given to healthy individuals did not change CI relative to placebo (Daskalakis et al. 2003), although CSP was significantly lengthened following a single dose of quetiapine (Langguth et al. 2008). Many studies have concluded that longitudinal studies are a necessity in the investigation of the effects of antipsychotic agents on CI.

Apart from the conflicting results of the studies on the effects of antipsychotic drugs on CI, the relationship of the estimated changes in the CI parameters resulting from antipsychotic treatment and the parallel changes in the psychopathology and cognitive functions of schizophrenia is unclear. Some studies have suggested a correlation between schizophrenia symptoms and CI deficits, and between the severity of positive symptoms and SICI levels (Daskalakis et al. 2002a, Daskalakis et al. 2008). However, cross-sectional designs have limited the interpretation of these studies. One prior study has investigated the relationship between CI and cognitive impairments in schizophrenia patients (Takahashi et al. 2013). In this study, lower SICI levels were found to be associated with poor working memory performance (Takahashi et al. 2013).

No previous study has investigated changes in CI parameters secondary to antipsychotic treatment and the association of this change with the change in psychopathology and cognitive functions in schizophrenia using TMS. These type of studies are expected to clarify the relationship between motor cortical inhibition abnormalities and the pathophysiology of positive symptoms, as well as cognitive symptoms and the

negative symptoms that are observed to change less change with treatment.

The present study aimed to investigate the changes in CI parameters in schizophrenia patients who were placed on a new, atypical antipsychotic treatment due to exacerbation of symptoms using TMS over an 8 week follow up period to determine the relationship between changes in CI and the parallel changes in symptom severity and cognitive functions assessed by the neuropsychological tests. Furthermore the CI parameters of matched healthy control subjects were measured and compared to those of patient group both at baseline and at the end of the follow-up to identify any differences in cortical inhibition associated with schizophrenia and the response to antipsychotic treatment.

METHODS

Sample

Thirteen patients between the ages of 17 and 65 years undergoing follow up at Hacettepe University Faculty of Medicine Psychiatry Clinic with a diagnosis of schizophrenia were included in the study after being switched to new atypical antipsychotic treatments due to exacerbation of the symptoms. All patients provided written informed consent. A group of 13 healthy individuals matched to the patient group according to age, sex, and educational background were also enrolled in this study. The study was reviewed and approved by the Hacettepe University Medical School Medical, Surgical and Pharmacological Research Ethical Committee's decision, number LUT 06/19 dated 20.07.2006.

Diagnosis of schizophrenia was confirmed through structured clinical interview for DSM-IV axis I disorders (SCID-I) (First et al. 1997, Çorapçıoğlu et al. 1999). Patients were switched to a new antipsychotic drug treatment by the physician in charge. Criteria for inclusion in the study group included a total score of > 60, with ≥ 4 for at least two positive items, in the Positive and Negative Syndrome Scale (PANSS). SCID-I was applied to exclude any axis I disorder among the healthy control subjects. Exclusion criteria included diagnosis with another DSM-IV axis I disorder, left hand preference on the basis of the Edinburgh Handedness Inventory (EHI) (Oldfield 1971), a history of substance or alcohol dependence, epileptic seizures, major head trauma, brain surgery and/or cerebrovascular accident, and presence of cardiac pace maker or neural implants.

Procedure

The schizophrenia patients included in the study were switched to a new antipsychotic drug by the physician according to standard treatment procedures. Dose adjustments were made accordingly throughout the 8-week study. On the

fourth day of the new drug therapy, the patients were examined using the PANSS (Kay et al. 1987, Kostakoğlu et al. 1999) to evaluate the positive and the negative symptoms of schizophrenia. Subsequently, TMS procedures were carried out to assess CI parameters on the same day. On the fifth day of the new drug therapy, a cognitive test battery was applied to evaluate neurocognitive function. At eight weeks after the initiation of the study, the evaluation of CI parameters by TMS, the PANSS interview and the cognitive test battery were repeated with the 11 patients who remained on antipsychotic treatment. Two patients were evaluated at the start of the study only: one patient had been unable to comply with the clozapine treatment, and the other patient on risperidone did not attend follow up consultations. The control group was evaluated once using neurocognitive battery and TMS at the start of the study.

The cognitive test battery used with both the patient and the control groups consisted of the Rey-Auditory Verbal Learning Test (R-AVLT) to assess verbal learning and memory performance (Rey 1958, Açıkgöz 1995), the Controlled Verbal Recall Test and Category Tests (CVRCT-CT) (Lezak 1995, Bingöl et al. 1994) to assess verbal fluency, the digit symbol test (Wechlers 1987, Lezak 1995) and the Digit Span (Wechlers, 1987, Lezak 1995) subtests of Wechlers Adult Intelligence Scale-Revised (WAIS-R) to assess attention, the Trail Making Test-Part B and the Stroop Test (Spreen and Strauss, 1998, Stroop, 1935) to assess executive functions and visual motor tracking performance, the Auditory Trigram Consonant Test (Peterson and Peterson, 1959, Anıl et al. 2003) to assess working memory, and the Wechsler Memory Scale-Revised (WMS-R)- Visual Reproduction subscale tests 1-2 (Wechsler, 1987, Karakaş et al. 1996) to assess visual memory performance.

Measurements of CI and cortical excitability parameters were carried out using TMS equipment and techniques. Surface recording electrodes were placed on the right hand I. dorsal interosseus (IDI) muscle according to the central core (endonion) principle, and responses were recorded using an EMG device (Medtronic Keypoint, Denmark). Using the Medtronic MagPro device the left motor cortex was stimulated by TMS to determine the optimal position on the scalp skin yielding the maximum motor evoked potential (MEP) amplitude. The stimulation coil was fixed at this position and the parameters listed below were measured:

1. Resting Motor Threshold (RMT): The minimum TMS intensity required to evoke an MEP of more than 50 μ V peak to peak amplitude in at least 5 of 10 sequentially applied stimulations was recorded as the RMT.
2. Cortical Silent Period (CSP): CSP is the suppression of EMG activity in the IDI muscle after the application of supra-threshold TMS to achieve a 120% increase in RMT in

the contralateral left motor cortex during voluntary contraction of the right IDI muscle. The CSP duration was determined by the time difference between the initiation of EMG suppression and the termination of the suppression measured at 10 successive TMU applications.

3. Short Interval Intracortical Inhibition (SICI) and Intracortical Facilitation (ICF): While implementing paired-pulse TMS, a sub-RMT stimulation is delivered followed by a supra-RMT stimulation. The ratio of the MEP amplitude obtained by the paired-pulse TMS to that obtained after the single test TMS was calculated. When the interval between the control and the test stimulations, i.e., the 'inter stimulus interval' (ISI), is 1-6 ms, the decrease in the MEP amplitude is known as the "short interval intracortical inhibition" (SICI) (Kujurai et al. 1993, Ziemann et al. 1996b). When ISI is determined to be 7-30 ms, the increase in the MEP amplitude known as "intracortical facilitation" (ICF) is detected. In this study the 1-6 ms interval was used to measure SICI and the 7,8,9,10,12, and 14 ms intervals were used to measure ICF. For each stimulation the negative peak amplitude of MEP was measured. The mean test response values obtained from 10 different paired pulse stimulation measurements applied for each ISI was calculated. The mean MEP response obtained from 10 different single stimulus trials was calculated. Numeric values of SICI and ICF parameters for each ISI are calculated as shown below:

$$(\text{mean MEP amplitude after paired-pulse TMS} \times 100 / \text{mean MEP amplitude after single pulse TMS})$$

The increase in the calculated percentage values for the inhibitory ISI's indicate a decrease in the CI, whereas and the increase in the calculated percentage values for the facilitating ISI's corresponds to an increase in intracortical facilitation (Kujurai et al.1993).

4. Transcallosal Inhibition (TCI): Transcallosal inhibition measured by single pulse TMS technique is measured as the duration of the ipsilateral silent period (ISP). Suppression of voluntary EMG activity was observed during the contraction of the right IDI muscle, following the application of a supra-threshold TMS equivalent to 155% of the RMT to the right ipsilateral motor cortex. The ISP duration obtained from 10 different TMU trials was calculated as the time interval between the initiation of the suppression of EMG activity and the end of EMG suppression. The increase in the duration of ISP indicates increasing TCI.

Statistical Evaluation

Statistical analyses of the data were performed using SPSS 12.0 for Windows. PANSS scores indicating the symptoms of schizophrenia, scores obtained from the cognitive test battery

and the measured CI parameters obtained by the TMS techniques were all evaluated as numeric (quantitative) variables. CI parameters and cognitive test scores of the patient group at the initiation and at the end of the study were compared with those of the control group using the Mann Whitney U test. The statistical significance of any change in PANSS scores, cognitive test scores and the CI parameters among the patient group between the start of the trial and the 8th week time points were evaluated using the Wilcoxon signed rank test. Spearman correlation analysis was used to evaluate the correlation between PANSS and cognitive function tests with CI parameters as measured by TMS at each time point.

RESULTS

Sociodemographic Characteristics of the Sample

The mean age of the patient and the control groups was 37.69 ± 9 years. The study group included 8 female and 5 male patients. Both groups included 2 primary school graduates, 1 secondary school graduate and 10 high school graduates.

Clinical Characteristics of the Patients

The mean age at the onset of illness was 25.46 ± 6.69 years, and the mean duration of the disease was 12.31 ± 6.68 years. The dose of the antipsychotic medication used by the patients throughout the 8-week study was determined by the attending physician based on the clinical response to the treatment. The patients were on different doses of several atypical antipsychotic agents. When CI parameters were assessed at the end of the 8-week follow up, the mean chlorpromazine equivalent dose of the antipsychotic medications was determined to be 586.36 ± 258.93 mg. During the 8-week follow-up 6 patients (46.2%) were on clozapine, 3 (23.1%) were on olanzapine, 3 (23.1%) were on risperidone and 1 (7.6%) was on quetiapine. Drug usage among these patients differed greatly in the period prior to the start of the study, such that 3 patients had not used any medication, 2 were on olanzapine, 3 were on risperidone, 2 were on quetiapine, 1 on ziprasidone, 1 on aripiprazole, and 1 on combined aripiprazole and quetiapine.

Changes in Psychopathology and Cognitive Functions of Patients after 8 Weeks of Follow-up

Out of the 13 patients tested at the start of the trial, 11 patients underwent repeat measurements at the end of the 8th week. The PANSS scores recorded at the initiation of the study were compared with the scores obtained following 8 weeks of treatment with the new antipsychotic therapy (Table 1). PANSS total scores the positive symptom subscores obtained and the general psychopathology subscales were significantly lower relative to the initiation of the trial. However,

Table 1. Comparison of baseline and 8th week scores of PANSS and cognitive tests

	Baseline (visit 1)	8th Week (visit 2)	
	Mean (sd)	Mean (sd)	z, p ^a
PANSS scores			
Total	90.3 (19.66)	72.3 (18.27)	z=-2.357 p=0.018
Positive	24.5 (7.22)	15.2 (4.96)	z=-2.763 p=0.006
Negative	20.7 (6.42)	19.7 (5.8)	z=-0.719 p=0.472
General Psychopathology	45.1 (9.86)	37.5 (9.29)	z=-2.193 p=0.028
Cognitive Test Scores			
Controlled word association test	18.7 (9.24)	19.8 (11.4)	z= -.513 p=0.608
Digit Symbol Test	35.6 (10.5)	37.4 (12.08)	z=-0.816 p=0.415
Digit Span Test-Total	10.18 (3.03)	9.82 (2.23)	z= -0.303 p= 0.762
Auditory Consonant Trigram Test-Total	34.8 (9.07)	32.7 (11.75)	z=-1.248 p= 0.212
R-AVLT-Immediate Memory	5.6 (1.08)	6.7 (1.95)	z=-1.373 p=0.17
R-AVLT 1-5 Cumulative Learning	42.6 (6.79)	44.3 (8.13)	z=-0.561 p=0.575
R-AVLT 7 Delayed Recall	7.22 (3.46)	7.78 (2.78)	z=-0.905 p= 0.366
WMS- Visual Reproduction-1	32.6 (12.09)	34.3 (7.06)	z=-0.70 p=0.944
WMS-Visual Reproduction-2	27.9 (12.41)	29.8 (11.40)	z=-1.307 p=0.191
Trail Making Test B-total time	238.4 (152.9)	233.7 (96.26)	z=-0.357 p=0.721
Stroop word	55.3 (10.53)	54.3 (7.85)	z= -0.357 p= 0.721
Stroop colour	98.1 (29.47)	91.6 (18.45)	z= -0.918 p= 0.359
Stroop Word-colour	190.3 (62.25)	171.7 (32.83)	z= -0.714 p= 0.475

a: Wilcoxon signed-rank test, PANSS: Positive and Negative Syndrome Scale, sd: standard deviation, R-ISCOT: Rey Auditory Verbal Learning Test, WMS: Wechsler Memory Scale

no significant difference in negative symptom subscale or cognitive test score was observed at the end of the trial.

Changes in CI Parameters at the end of the 8-Week follow up period

Among the CI parameters, RMT, CSP and ISP values did not change significantly over the 8-week study (Table 2). Despite the absence of significant changes in SICI values after 8 weeks, the ICF value at ISI of 14 ms was significantly decreased relative to the start of the trial (Table 3). The most prominent SICI in both the patient and the control group was seen with ISI of 3 ms (Figure 1; Table 3). Both patient

and control group SICI and the ICF data are shown in the cortical excitability curve given in Figure 1.

Comparison of the CI Parameters between patients and control subjects at the initiation and the end of the Study

When the baseline CI parameters of the patients were compared with the baseline CI parameters of the control group, ISP duration was found to be significantly longer among the patient group compared to the control group (Table 2). ICF with ISI of 9 ms was significantly lower among the patient group relative to the control subjects (Table 3, Figure 1). CSP duration was significantly longer in the patient group after 8 weeks antipsychotic therapy relative to the baseline measurements in the control subjects. Although the ISP duration of the patient group at baseline was significantly longer relative to controls, the difference at the end of the study was only close to significance (Table 2). SICI did not differ between the patients and controls at the end of the study (Table 3, Figure 1). ICF values at ISI's of 7, 8, 9, 10 and 12 ms were significantly reduced in the patient group relative to the controls (Table 3, Figure 1).

Relationship Between the Antipsychotic Drug Dose and CI Parameters at the end of the Study

Spearman correlation analysis was used to evaluate the correlation between CI parameters and chlorpromazine equivalent antipsychotic doses at the conclusion of the study as assessed by TMS. Decreased SICI at 3 ms ISI was significantly correlated with increasing chlorpromazine equivalent dosage. ($r=0.66$, $p=0.028$).

Relationship Between CI parameters and PANSS and the Cognitive Test scores at the Initiation of the Therapy

The correlation between PANSS scores and CI parameters at the start of the study period was evaluated using the Spearman correlation test. PANSS total scores ($r= -0.582$, $p= 0.037$) and the general psychopathology scores ($r= -0.758$, $p=0.003$) were significantly correlated with reduced SICI (ISI 3 ms). SICI (ISI: 3 ms) and cognitive test battery scores were positively correlated with Visual Reproduction 1 and 2 test scores ($r= 0.637$, $p= 0.019$; $r= 0.558$, $p= 0.048$, respectively), the animal and name subtests of the Category Fluency Test ($r= 0.620$, $p= 0.031$; $r= 0.645$, $p= 0.024$, respectively), Stroop Test scores on the word-colour subtest time ($r= -0.588$, $p= 0.035$) and mistakes ($r= -0.742$, $p= 0.004$), performance on the R-AVLT test with respect to the R-AVLT 1-5 cumulative learning test scores ($r=0.613$, $p=0.026$), R-AVLT 6 ($r=0.647$, $p=0.017$), R-AVLT 7 delayed recall scores ($r=0.591$, $p=0.033$), R-AVLT correct recognition scores ($r= 0.566$, $p= 0.044$), R-AVLT wrong recognition scores ($r=-0.670$, $p= 0.012$); and the R-AVLT discrimination scores ($r= 0.734$, $p=0.004$).

Table 2. Comparison of RMT, CSP and ISP duration between patients and controls

Test	Control	Patient (visit 1)	Patient(visit 2)	Statistical analysis		
	mean (sd)	mean (sd)	mean (sd)	control/ visit1 ^a	control/ visit2 ^a	visit1/ visit2 ^b
RMT	51.78 (9.55)	48.8 (5.63)	51 (6.91)	z=-0.858 p=0.391	z=-0.383 p=0.702	z= -1.193 p=0.233
CSP duration	107.35 (54.83)	148.2 (80.78)	163.1 (88.36)	z=-1.410 p=0.158	z=-1.999 p=0.046	z=-1.245 p=0.213
ISP duration	15.64 (5.72)	27.16 (14.35)	23.07 (10.97)	z=-2.59 p=0.01	z=-1.854 p=0.064	z=-0.445 p=0.657

a: Mann Whitney U test b: Wilcoxon signed-rank test, ss: standard deviation, RMT: Resting Motor Threshold CSP:Cortical Silent Period, ISS: Ipsilateral Silent Period

Table 3. Comparison of percentage values calculated for short interval intracortical inhibition observed at inhibitory ISI's and intracortical facilitation observed at facilitatory ISI's

Intracortical inhibition (SICI) *	Control	Patient visit 1 (baseline)	Patient visit 2 (8. week)	Statistical Analysis		
	mean (sd)	mean (sd)	mean (sd)	control/visit1 ^a	control/visit2 ^a	visit1/visit2 ^b
ISI 1 ms	37.22 (32.16)	37.23 (25.42)	34.68 (21.03)	z=-0.308 p=0.758	z=-0.377 p=0.706	z=-0.663 p= 0.507
ISI 2 ms	36.76 (25.38)	43.68 (28.32)	38.91 (25.2)	z=-0.617 p=0.537	z=-0.232 p=0.816	z= -.0830 p=0.407
ISI 3 ms	37.12 (28.46)	37.47 (23.80)	33.76 (22.82)	z=-0.590 p=0.555	z=-0.232 p=0.817	z= -0.561 p=0.575
ISI 4 ms	49.82 (37.18)	35.53 (19.73)	35.81 (24.61)	z=-0.359 p=0.719	z=-0.551 p=0.582	z= -0.153 p= 0.878
ISI 5 ms	56.6 (31.97)	49.05 (35.01)	41.23 (24.33)	z=-0.385 p=0.70	z=-1.246 p=0.213	z=-0.255 p=0.799
ISI 6 ms	85.67 (46.04)	64.23 (51.96)	60.95 (34.31)	z=-0.592 p=0.554	z=-1.537 p=0.124	z=-0.178 p= 0.859
Intracortical facilitation (ICF)*						
ISI 7 ms	125.2 (50.37)	97.05 (62.90)	77.24 (46.35)	z=-1.259 p=0.208	z=-2.406 p= 0.016	z=-0.801 p=0.423
ISI 8 ms	138.63 (45.89)	107.55 (32.66)	105.01 (38.6)	z=-1.438 p=0.150	z=-2.057 p= 0.04	z=-0.089 p=0.929
ISI 9 ms	144.32 (51.16)	198.47 (42.63)	104.47 (34.39)	z=-1.976 p=0.048	z=-1.914 p=0.056	z=-0.089 p=0.929
ISI 10 ms	164.55 (58.22)	118.74 (47.95)	92.3 (31.78)	z=-1.796 p=0.072	z=-3.129 p=0.002	z=-0.968 p=0.333
ISI 12 ms	161.26 (55.74)	143.45(39.68)	115.6 (36.31)	z=-0.924 p=0.356	z=-2.144 p= 0.032	z=-1.478 p= 0.139
ISI 14 ms	146.15 (57.77)	154.6 (48.6)	105.02 (49.28)	z=-0.180 p=0.857	z=-1.739 p=0.082	z=-1.957 p=0.050

a: Mann Whitney U test, b: Wilcoxon signed rank test, sd: standard deviation, ISI: inter stimulus interval, ms: milliseconds

Relationship between the Change in Psychopathology Severity and Cognitive Functions with the Change in the CI Parameters

Decreased PANSS general psychopathology subscale scores were correlated with decreased ICF (ISI: 7 ms) ($r = 0.62$, $p < 0.05$). Since a statistically significant change in the cognitive tests scores was not observed at the end of the 8-week therapy, and only SICI (ISI: 3 ms) was found to be related to cognitive

test scores at the initiation of the study, a correlation analysis was carried out for the SICI parameter only (ISI: 3 ms). The change in SICI (ISI: 3 ms) after 8 weeks of new antipsychotic drug treatment was correlated with the changes in the auditory verbal memory performance, as indicated by R-AVLT 7 scores ($r = 0.724$, $p < 0.05$) and the Stroop Test- word-colour subtest scores (calculated on the basis of the time taken to complete the test) ($r = -0.758$, $p < 0.05$).

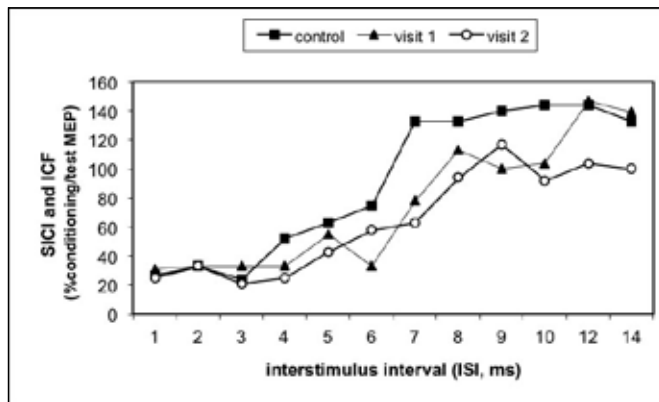


Figure 1. Cortical excitability curves showing SICI and ICF of patients and controls. Data from patient (visit 1 and visit 2) and control groups related to SICI and ICF are shown in the graphic. All the measurements are expressed as percentage values (conditioned MEP amplitude $\times$ 100/unconditioned test MEP amplitude). Values below 100 show short interval intracortical inhibition (SICI) while values above 100 show intracortical facilitation (ICF). Percentage values are calculated as the means of the values obtained from 10 different trials for each ISI. MEP: motor evoked potential

DISCUSSION

In this study the CI parameters of the patients evaluated by TMS at baseline and after 8 weeks of antipsychotic therapy were compared with healthy controls to examine the relationship between the change in CI parameters and change in psychopathological symptoms and cognitive functions. Although previous studies have investigated individual CI parameters, investigations which incorporate a wide range of CI parameters are few and generally rely on cross-sectional study designs.

Baseline CI parameters differed between patients and control subjects. ISP was significantly longer and ICF (ISI: 9 ms) was lower relative to controls. After 8 weeks of antipsychotic therapy, CSP duration was significantly longer and ISP was modestly increased in patients relative to the control subject baseline while ICF (ISI's of 7, 8, 9, 10 and 12 ms) was significantly lower. ICF (ISI: 14 ms) values at the end of the study were reduced relative to the start of the study. Cumulatively, these results suggest increased efficacy of the cortical inhibitory circuits after 8 weeks of antipsychotic therapy.

Previous studies on the duration of CSP contain conflicting data. Some have reported reduced CSP duration among schizophrenia patients relative to controls (Fitzgerald et al. 2002a, 2002b). This has been interpreted as an indication of CI deficits. On the other hand, additional studies, have reported that CSP is longer in schizophrenia patients relative to controls, in concordance with the present study (Bajbouj et al. 2004, Daskalakis et al. 2008). CSP is shortened in patients with Parkinson's disease, a pathology known to include dopamine deficiency in the nigrostriatal system, and some dopaminergic drugs tended to shorten CSP in the Parkinson patients and

healthy controls. This suggests that CSP duration, although fundamentally determined by GABA-B mediated neurotransmissions, may also be influenced by dopaminergic activity (Priori et al. 1994, Valzania et al. 1997). Further, reports that dopaminergic drugs increase CSP length support this hypothesis (Priori et al. 1994, Valzania et al. 1997). The finding by Bajbouj et al. (2004) that CSP is longer in schizophrenia patients relative to control subjects attributed to relatively low doses of antipsychotics drugs compared to other published reports. The authors have proposed that this interpretation is also supported by their finding that the duration of the CSP was negatively correlated with antipsychotic drug dosage. In the present study, however, no correlation between the CSP duration and therapeutic drug dose was observed. On the other hand, the study by Daskalakis et al. (2008) indicates that CSP duration was longer among patients on clozapine than in patients not receiving treatment or control subjects. These authors, in contrast to Bajbouj et al. (2004), have proposed that antipsychotic drug use lengthens the CSP, meaning that CI is increased, and that clozapine accomplishes this effect by increasing GABA-B mediated neurotransmission (Daskalakis et al. 2008). This apparent conflict in the results of the two groups may have been due to the use of conventional antipsychotic drugs by more than 50% of the patients of Bajbouj et al. (2004). These drugs exhibit an enhanced antidopaminergic effect as compared to atypical antipsychotic agents. At the end of the present study, when the CSP of the patient group was observed to be longer than that of the control group, 5 of the 11 patients all of which were using atypical antipsychotic drugs were on clozapine therapy. Baseline CSP duration did not differ significantly between patients and controls. Therefore, the observed increase in CSP length after 8-weeks of atypical antipsychotic therapy may be explained by the increasing effect of these drugs on GABA-B mediated cortical inhibition in CI.

Similar to the results of the present study, previous studies have shown that ISP is longer in schizophrenia patients relative to control subjects (Boroojerdi et al. 1999, Fitzgerald et al. 2002b, Bajbouj et al. 2004). TCI is thought to share mechanistic similarities with CSP. However, TCI parameter is affected by the functional level and the integrity of the corpus callosum as well as CI parameters such as CSP. In previous studies reporting shortened CSP, prolongation of the ISP has also been observed. Abnormalities of the corpus callosum of schizophrenia patients may contribute to this pathology (Meyer 1995, Boroojerdi et al. 1999, Bajbouj et al. 2004). ISP is not demonstrable when there is agenesis or injury after surgery in the corpus callosum, indicating that the integrity of the corpus callosum is necessary for the formation of the ISP (Meyer et al. 1998). Functional anomalies of the corpus callosum may contribute to the lengthening of ISP in schizophrenia patients (Bajbouj et al. 2004). The positive

correlation of drug dosage with ISP duration suggests that antipsychotic drugs may lengthen ISP duration (Fitzgerald et al. 2002a). In the present study, no relationship between antipsychotic drug dose at the time of TMS measurements and the duration of the ISP was observed. Our observation that ISP was longer in patients both at the initiation and at the end of the present study than in the controls suggests that the existing pathological processes, and particularly the possible corpus callosum pathology and malfunction, may account for these results. The function of the corpus callosum has not been evaluated by neuroimaging techniques simultaneously with the evaluation of TCI. Such studies may clarify the relative significance of the CI or transcallosal conduction in the lengthening of ISP in schizophrenia.

Baseline ICF levels were lower in patients than in controls in the present study, and this difference became more distinct at the end of the 8-weeks of antipsychotic drug treatment. Several prior studies have reported no difference in ICF levels between patient and control groups (Daskalakis et al. 2002a, Fitzgerald et al. 2002b, 2002c, Eichhammer et al. 2004, Daskalakis et al. 2008, Liu et al. 2009, Hasan et al. 2012), while other studies have reported higher patient ICF levels were higher than those of the controls (Pascual-Leone et al. 2002, Fitzgerald et al. 2003). In the present study, more severe psychopathology was associated with ICF that was reduced relative to control subjects. Following the reduction of symptoms over the course of the 8 week treatment period ICF remained reduced relative to control subjects. Decreased ICF indicates that inhibitory intracortical circuits have dominance over the intracortical facilitatory circuits. At the end of the 8-week treatment, overall CI was increased compared relative to the start of the study. Intracortical facilitation may be associated with the balance between GABAergic and the glutamatergic activity. Drugs that induce GABAergic activity or decrease the glutamatergic activity have been shown to reduce ICF, as measured by paired pulse TMS (Inghilleri et al. 1996, Ziemann et al. 1998a and 1998b). The importance of GABA-A mediated inhibition for intracortical facilitation has been demonstrated (Ziemann, 1998b).

Atypical antipsychotic agents such as clozapine have been reported to increase the GABA-A mediated neurotransmission in animal studies (Farnbach-Prolong 1998). However, reduced activity of the N-methyl-D-aspartate (NMDA) receptor could be corrected experimentally and selectively on the cellular and behavioral level by acute or chronic administration of atypical antipsychotic agents. (Abi-Dargham and Laruelle 2005). Decreased ICF following atypical antipsychotic drug therapy may be attributable to the effects of these drugs in increasing GABAergic inhibition.

Lower levels of CI was associated with higher psychopathology severity at baseline among schizophrenia patients in the present study. After the 8-week antipsychotic drug therapy,

decreased ICF, reflecting the increase in CI, was related to the reduction in general psychopathology subscale PANSS scores. No previous TMS study has investigated the change in paired pulse facilitation following antipsychotic treatment in schizophrenia. Previous studies have been cross-sectional in design and it has not been previously possible to demonstrate a relationship between intracortical facilitation and psychopathology severity in cross-sectional TMS studies (Eichhammer et al. 2004, Wobrock et al. 2008, Hasan et al. 2012). Baseline ICF levels were lower among patients compared to the controls and were further decreased by the treatment in correlation with decreased psychopathological severity. This suggests that the therapeutic effect of the drugs may be mediated through decreased ICF, or increased CI. Hence, we could make an inference that ICF increase, an indicator of a decrease in cortical inhibition, may be associated with the pathophysiology of schizophrenia.

In order to clarify the role of increased ICF in the pathophysiology of schizophrenia independent of the the confounding effects of the antipsychotic drugs on the CI level, ICF and psychopathology severity needs to be investigated longitudinally in drug naive first episode schizophrenia patients who begin new antipsychotic drug treatment.

In the present study no significant improvement in cognitive functions occurred following 8 weeks of antipsychotic treatment. However, decreased SICI, measured at ISI of 3 ms, was identified among the patient group at the initiation of the study and was associated with deficits in visual memory, verbal fluency, verbal learning and memory, visual motor tracking, and executive function performances. After the 8-week antipsychotic drug treatment, CI found to be positively correlated with verbal learning and memory and visual motor tracking and the executive function performances. These results suggest that the decrease in the CI is related to the decrease in verbal fluency, verbal learning and memory, immediate and continuous visual memory, and the visual motor tracking and executive function performances. SICI at ISI of 3 ms is a significant CI function parameter for evaluating the association between CI and cognitive function.

Only one previous study has investigated the relationship between various cognitive functions and motor cortical inhibition parameters in a cross-sectional design, demonstrating a relationship between the reduction of SICI level with the working memory impairment (Takahashi et al. 2013). There are other studies in the literature demonstrating the association between sensory motor gating (another CI parameter) deficits and cognitive dysfunction in schizophrenia (Erwin et al. 1998, Cullum et al. 1993, Bitsios and Giakoumaki 2005). The two paradigms for evaluating CI are both associated with GABAergic inhibitory mechanisms (Freedman et al. 2000) but originate from different cortical regions (Möller et al. 2007). The extent to which CI level measured at the

motor cortex reflects the activity of the inhibitory mechanisms in cortical regions such as the prefrontal cortex remains unknown. Clarification of the relationship between motor cortical excitability and the inhibition of the prefrontal cortex is essential in order to explain the relationship between motor CI measured by TMS and the pathophysiology of various cognitive dysfunctions observed in schizophrenia.

The present study differs from many others in its approach, measuring RMT, CSP, TCI (ISP), SICI and ICF parameters together in to assess cortical excitability and CI in schizophrenia patients. Although all of these parameters are affected directly by CI, it is thought that different physiological processes contribute to the formation of each process. The wide disparity in the present literature regarding CI level evaluated through measurement of different parameters demonstrates the necessity of evaluating changes in these parameters individually in order to determine their relationship with the pathophysiology of schizophrenia and the mechanisms of action of antipsychotic drugs.

In conclusion, baseline ICF level was lower in patients relative to controls and was further reduced following an 8-week antipsychotic treatment. The remaining CI parameters did not change following antipsychotic drug treatment. Decreased ICF reflects the dominance of cortical inhibitory circuits over cortical facilitatory circuits. Decreased ICF after antipsychotic treatment was associated with decreased severity of psychopathology. These findings suggest that the therapeutic effects of atypical antipsychotic drugs are associated inhibition of ICF.

Small sample size is a significant limitation of the present study. Initial TMS measurements were made on the 4th day of the new therapeutic regime. This period may not have been sufficient to avoid the adverse or corrective effects of the drugs used previously on a long term basis by some of the patients on CI parameters. Therefore, low baseline ICF values in the presence of normal values for other CI parameters may be a result of the chronic corrective effect of antipsychotic drugs used by the patients prior to this study. Future studies should include first episode, drug-naïve schizophrenia patients to clarify the relationship between the therapeutic effect of antipsychotic drugs and ICF decrease.

To our knowledge, this is the first study investigating the relationship between the changes in the CI parameters measured by TMS and the concurrent changes in the psychopathology severity and cognitive functions brought about by antipsychotic drug treatment in schizophrenia. Such studies are expected to contribute to the understanding of the relationship between the CI abnormalities detected with TMS and pathophysiology of the positive psychotic symptoms of schizophrenia as well as the cognitive symptoms and negative symptoms known to improve less with antipsychotic treatment.

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