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Reduced cortical inhibition in first-episode schizophrenia

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Abstract

Disturbances in cortico-cortical and cortico-subcortical circuits in schizophrenia have been described by previous neuroimaging and electrophysiological studies. Transcranial magnetic stimulation (TMS) provides a neurophysiological technique for the measurement of cortical excitability, especially of the motoneural system. Previous studies using paired-pulse TMS to investigate short-interval cortical inhibition (SICI) and intracortical facilitation (ICF), mainly involving chronic schizophrenia patients, have been inconsistent and only one study in first-episode patients has been conducted so far.

We assessed SICI (interstimulus interval, ISI, 3 milliseconds, ms) and ICF (ISI 7 ms) in 29 first-episode schizophrenia patients (FE-SZ) with limited exposure to antipsychotic treatment against measures of 28 healthy controls (HC). Amplitudes of motor evoked potentials (MEPs) were measured from the left and right first dorsal interosseus muscle (FDI). The conditioning stimulus was set at 80% intensity of resting motor threshold (RMT) and the test stimulus (TS) was set at an intensity that produced an MEP amplitude of about 1 mV.

For SICI conditions, FE-SZ demonstrated significantly higher MEP amplitudes from left motor cortex (right FDI) compared to HC, and for MEPs from right motor cortex (left FDI) a similar trend was observable (FE-SZ 41% vs. HC 21% of TS, $p=0.017$ for left motor cortex, and FE-SZ 59% vs. HC 31% of TS, $p=0.059$ for right motor cortex; Mann–Whitney U-test). No significant difference in MEPs could be detected for ICF on either hemisphere. In addition, there was no difference in left and right RMT comparing patients and control subjects.

Our result of a reduced SICI in a large sample of well characterized first-episode schizophrenia patients suggests that a GABAergic deficit may be involved in schizophrenic pathophysiology, already early in the disease course, supporting the intracortical dysconnectivity hypothesis.

Keywords: Schizophrenia; Cortical inhibition; Transcranial magnetic stimulation (TMS); Paired-pulse paradigm

1. Introduction

Transcranial magnetic stimulation (TMS) of the motor cortex has been utilized as a noninvasive approach for the in vivo evaluation of inhibitory and

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excitatory cortical circuits (Maeda and Pascual-Leone, 2003). In the primary motor cortex, TMS is thought to predominantly activate the pyramidal cells transsynaptically through excitatory interneuronal elements (Day et al., 1989).

With paired-pulse techniques, interactions between the first and the second pulse occur. Typically, a first subthreshold (conditioning) stimulus induces a short-term modulation of the motor evoked potential (MEP) evoked by a second suprathreshold (test) stimulus (Kujirai et al., 1993). Short interstimulus intervals (ISIs) of 2–5 ms inhibit, and longer ISIs of 7–20 ms facilitate the MEP amplitude. This TMS-induced modulation is at least in part generated cortically, presumably by intracortical interneurons modulating the activity of corticospinal neurons (Kujirai et al., 1993; Ziemann and Hallett, 2000). It is believed that in short-interval cortical inhibition (SICI), using ISIs of 2–5 ms, the subthreshold first pulse produces an inhibitory post-synaptic potential (IPSP) at the corticospinal neurons by means of activation of a low-threshold cortical inhibitory circuit. This in turn inhibits action potential generation by excitatory post-synaptic potentials (EPSPs) elicited by the suprathreshold second pulse (Kujirai et al., 1993; Ziemann, 2004). SICI is discussed to be mediated by GABAergic interneurons via $GABA_A$ receptors, which modulate the ligand-gated ion channels vital for most of the fast synaptic inhibition in the mammalian brain (Nakamura et al., 1997). Consistent with this hypothesis, $GABA_A$ agonists enhance SICI (Ziemann, 2004). On the other hand, intracortical facilitation (ICF), using ISIs longer than 7 ms, seems to be mediated by excitatory neuronal circuits in motor cortex, which are at least in part dissociable from the SICI network (Ziemann, 2004). ICF may represent a net facilitation consisting of prevailing facilitation and weaker inhibition. The onset latency of NMDA receptor-mediated EPSPs is in the order of approximately 10 ms, which is consistent with the time course of ICF, and points towards the importance of glutamatergic transmission for ICF. According to this assumption, NMDA receptor antagonists, and also $GABA_A$ agonists, mostly decrease ICF (Ziemann, 2004).

Post-mortem investigations have demonstrated reduced numbers of cortical GABAergic interneurons in the brains of schizophrenia patients (Benes, 1998), suggesting abnormalities in interneuro-pyramidal modulation. Reduced (levels of) glutamic acid decarboxylase (GAD67) mRNA expression – an enzyme that synthesizes GABA – in the dorsolateral prefrontal cortex is one of the most consistent findings in schizophrenia in post mortem studies (Knable et al., 2002). Furthermore, a dysfunction of subpopulations of gabaergic interneurons in dorsolateral prefrontal cortex, leading to alteration in the perisomatic inhibition of pyramidal neurons, is made responsible for deficits in working memory, a core syndrome in schizophrenia (Lewis et al., 2005).

Motor deficit is a known feature in patients with schizophrenia both with and without medication (Chen et al., 2000; Smith et al., 1999), and a cortical inhibition deficit has been suggested as one potential pathophysiological mechanism in schizophrenia (Freedman et al., 1983). In consequence, these considerations form the background for the investigation of cortical inhibition in schizophrenia by means of transcranial magnetic stimulation.

Previous studies using the paired-pulse paradigm in schizophrenia patients have revealed controversial results. Daskalakis et al. (2002) found reduced SICI in a small sample of unmedicated schizophrenic patients – but not in patients treated with antipsychotics – as compared to healthy controls, whereas another study reported reduced SICI and increased ICF in medicated but not in drug-naïve schizophrenic patients (Pascual-Leone et al., 2002). One research group observed reduced SICI in medicated schizophrenic patients compared to controls (and no difference in facilitation) (Fitzgerald et al., 2002a), but could not replicate this finding in a larger sample of patients (Fitzgerald et al., 2002b). A sample of neuroleptic-naïve first-episode patients, mainly consisting of patients with disorganized schizophrenia, showed no difference in SICI or ICF as compared to healthy gender- and age-matched control subjects (Eichhammer et al., 2004). However, this sample does not seem to be representative of first-episode patients, who mostly belong to the paranoid schizophrenia subtype. In addition, there is some evidence that the development of cerebral lateralization is disturbed in schizophrenia patients (e.g. Crow et al., 1989). Healthy subjects may have a lower resting motor threshold (RMT) in the dominant (left) hemisphere in correlation to handedness and increased use of the dominant (right) hand (Triggs et al., 1994). Schizophrenia patients apparently did not show this type of physiological lateralization in cortical motor representation in one study (Pascual-Leone et al., 2002).

In the present study, first-episode patients (FE-SZ) representative of this patient group and recruited from a hospital setting with minimal exposure to antipsychotics, were assessed using paired-pulse TMS, in order to examine their cortical excitability in comparison to healthy control subjects (HC). Additionally, motor thresholds in both hemispheres were compared.

2. Methods

2.1. Subjects

The study sample consisted of 57 subjects recruited from the University Hospital of the Saarland between 2003 and 2006. 29 patients suffered from first-episode schizophrenia (all paranoid subtype), and there were 28 healthy controls. Subjects suffering or having suffered in the past from dementia, neurological illnesses, severe brain injuries or brain tumors were excluded from the study. The following standardized examinations were performed on each subject biographical interview (Bassett et al., 1993), test of hand preference (Annett, 1970), assessment of psychopathology (Positive and Negative Syndrome Scale) (Kay et al., 1987), assessment of disease severity (Clinical Global Impressions) (Guy and Bonato, 1976) and assessment of social functioning (Global Assessment of Functioning) (Endicott et al., 1976). The diagnosis was based on a consensus of two independent psychiatrists performing SCID I and II interviews (Wittchen et al., 1997; Fydrich et al., 1997). Additionally, the duration of illness (DUI), counted from the beginning of initial prodromal symptoms, the duration of psychosis (DUP), counted from the onset of diagnostic/characteristic positive symptoms, and familial risk factors (psychosis in first degree relatives) were assessed. After a complete description of the study, written informed consent was obtained from each subject. The local ethics committee approved the protocol, which is in accordance with the Declaration of Helsinki.

None of the participants had a contraindication for TMS.

All 29 schizophrenic patients were treated with second generation antipsychotics (aripiprazole 2, olanzapine 18, quetiapine 2, risperidone 7, and two patients additionally treated with haloperidol). Yet, at the time of the study, no patient had been treated longer than 6 weeks continuously. To compare the cumulative and daily doses of the different antipsychotics and to explore the influence of this medication on TMS parameters, chlorpromazine equivalents were calculated as suggested by reviews and studies focusing on second generation antipsychotics (e.g. Woods, 2003). Duration, cumulative dose, and daily dose of the antipsychotic medication (expressed in chlorpromazine (CPZ) equivalents) are described in Table 1. There was no concomitant treatment with benzodiazepines, mood stabilizers, beta-blocking agents, or anticholinergics during the last week before TMS measurement.

Table 1
Sociodemographic and clinical parameters

	HC (N=28)		FE-SZ (N=29)		df	F	p
	m	sd	m	sd			
Age (years) [a]	32.18	7.86	29.79	8.47	1, 55	1.21	0.28
DUP (weeks)	–	–	50.41	64.0	–	–	–
DUI (weeks)	–	–	183.17	157.1	–	–	–
PANSS total score	–	–	91.48	17.2	–	–	–
PANSS positive score	–	–	22.14	6.1	–	–	–
PANSS negative score	–	–	21.45	6.6	–	–	–
PANSS gen. psychop. score	–	–	47.90	9.4	–	–	–
CGI	–	–	5.96	0.6	–	–	–
GAF	–	–	28.6	10.5	–	–	–
Daily dose of antipsychotics (CPZ equivalents)			356.2	203.7			
Duration of antipsychotic medication (days)			21.0	14.4			
Cumulative dose of antipsychotics (CPZ equivalents)			7565.2	7886.8			

			df	Chi [2]	p
Gender (male/female) [b]	14/14	21/8	1	3.02	0.082
Handedness (right/left/both) [b]	28/0/0	25/0/4	1	4.15	0.042
Psychosis in first degree relatives, no. of subjects (%)	0 (0)	12 (41.3)	–	–	–

Legend: HC = healthy controls; FE-SZ = patients with first-episode schizophrenia; m = mean; sd = standard deviation; DUP = duration of psychosis; DUI = duration of illness (including initial prodrome); PANSS = Positive and Negative Syndrome Scale; gen. psychop. = general psychopathology; CGI = Clinical Global Impressions; GAF = Global Assessment of Functioning; no. = number; df = degrees of freedom; F = F-statistics; p = probability; CPZ = chlorpromazine.

[a] Analysis of variance (ANOVA).

[b] Chi-square test.

2.2. TMS procedure

Subjects were seated in a comfortable chair with their arms supported passively. Electromyographic (EMG) recordings from the right and left first dorsal interosseus muscle (FDI) were made with surface electrodes, using a commercial amplifier with a bandpass filter of 2 Hz to 10 kHz (Keypoint portable, Medtronic Co., Denmark). Each signal curve was manually analyzed off-line. Focal transcranial magnetic stimulation (TMS) was applied to the hand area of the left and right motor cortex using a figure-of-eight magnetic coil and a MagPro X 100 magnetic stimulator (Medtronic Co., Denmark).

For each subject, the optimal coil position – defined as the stimulation site that produced the largest MEP at moderately suprathreshold stimulation intensities (i.e. intensities that induce MEPs of about 0.5–2.0 mV) in the resting right and left FDI muscle – was determined by moving the coil in 0.5-cm steps over the presumed left and right motor cortex areas. Sites were marked to ensure constant coil position throughout the experiment. The coil was held tangentially to the head, with the handle pointing backwards and in an angle of 45° lateral to the midline. This ensured that the induced current pointed forwards and perpendicular to the central sulcus, which is optimal for producing transsynaptic activation of corticospinal neurons. The resting motor threshold (RMT), expressed as a percentage of maximum stimulator output, was defined as the lowest intensity that produced an MEP of >50 μV in five out of ten trials in the relaxed FDI (Ziemann et al., 1996a).

Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were obtained in accordance with previously published protocols (e.g. Maeda and Pascual-Leone, 2003; Eichhammer et al., 2004). The intensity of the first (conditioning) stimulus was always set at 80% of the RMT. The second (test) stimulus was delivered at an intensity that produced MEPs averaging 0.5–1.5 mV in the resting FDI. Since it is known from previous studies that short ISIs (2–5 ms) lead to inhibition and longer ISIs (7–20 ms) lead to facilitation of test stimulus MEP (Kujirai et al., 1993), we used an ISI of 3 ms in the inhibitory (SICI) and an ISI of 7 ms in the facilitatory (ICF) paired-pulse TMS paradigm. We performed a minimum of 10 trials with each ISI and 10 trials with the test stimulus alone. The effect of the conditioning stimulus on MEP amplitude of the test stimulus was determined as the ratio of the average amplitude of the conditioned ppTMS MEP (cMEP) to the average amplitude of the unconditioned test MEP (uMEP) (Eichhammer et al., 2004).

The measurements were performed by an experienced investigator (T.W.), controlled by another experienced investigator (M.S.), and corrected for outliers and extreme values. The stimuli were ordered differently and randomly for each subject, and they were counterbalanced across groups.

2.3. Statistics

For statistical analyses, SPSS for Windows 14 was used. All tests were two-tailed. Level of significance was set at $\alpha = 0.05$. Dependent variables were RMT, SICI (ISI 3 ms), and ICF (ISI 7 ms) in both hemispheres. The independent variable was diagnosis (HC, FE-SZ). Kolmogorov–Smirnov tests were applied to test the assumption of normal distribution for all dependent variables. As the normality assumption was violated for SICI and ICF, non-parametric tests were performed for these variables.

One-way analysis of variance (ANOVA) was used to analyze age differences between the two diagnostic groups. Chi ^{2}-tests of independence were performed to analyze (potential) group differences in the distributions of gender and hand difference.

For the control sample, correlations between age and dependent variables were computed (RMT: Pearson product moment correlations, SICI and ICF: Spearman rank correlations), and effects of the gender factor on dependent variables were analyzed (RMT: one-way ANOVA, SICI and ICF: Mann–Whitney *U*-test). Since all controls were right-handed, hand preference effects were analyzed in the FE-SZ sample (RMT: one-way ANOVA, SICI and ICF: Mann–Whitney *U*-test).

These preliminary calculations regulated the main analyses. An analysis of covariance (ANCOVA, factor diagnostic group, covariate age) was computed on RMT measures, since age correlated significantly with RMT. Furthermore, a repeated measures MANOVA (within-subject factor hemisphere, between-subject factor diagnostic group) was performed to test the hypothesis that in right-handed subjects RMT is lower in the left vs. right motor cortex. Group differences in SICI and ICF variables were assessed with the Mann–Whitney *U*-test. For the FE-SZ patients, Spearman rank correlations between dependent variables and total PANSS, GAF, CGI, DUP and DUI scores were performed.

3. Results

3.1. Sociodemographic and clinical characteristics

First-episode patients and healthy controls did not differ significantly in age (mean age 29.8 ± 8.5 years vs.

Table 2
TMS parameters

	HC (N=28)		FE-SZ (N=29)		df	F	p
	m	sd	m	sd			
RMT left motor cortex (%) [a]	47.82	6.5	46.93	6.9	1, 54	0.0	0.88
RMT right motor cortex (%) [a]	49.58	10,0	48.25	8.0	1, 51	0.1	0.73
					df	Z	p
ppTMS ISI 3 ms left motor cortex (ratio cMEP/uMEP) [b]	0.20	0.1	0.41	0.3	1	−2.39	0.017
ppTMS ISI 7 ms left motor cortex (ratio cMEP/uMEP) [b]	0.96	0.5	1.12	1.0	1	−0.22	0.83
ppTMS ISI 3 ms right motor cortex (ratio cMEP/uMEP) [b]	0.31	0.2	0.59	0.9	1	−1.89	0.059
ppTMS ISI 7 ms right motor cortex (ratio cMEP/uMEP) [b]	1.14	0.7	1.48	1.4	1	−0.41	0.68

Legend: HC = healthy controls; FE-SZ = patients with first-episode schizophrenia; m = mean; sd = standard deviation; ppTMS = paired-pulse transcranial magnetic stimulation; ISI = interstimulus interval; mV = millivolt; N = number; df = degrees of freedom; F = F-statistics; Z = Z-value; p = probability; cMEP = conditioned motor evoked potential; uMEP = unconditioned motor evoked potential; RMT = resting motor threshold.
[a] Analysis of covariance (ANCOVA, factor diagnostic group, covariate age). Percentage of maximum stimulator output.
[b] Mann–Whitney U-test.

32.2±7.9 years, p=0.28). The percentage of male patients tended to be higher in the FE-SZ group (p=0.082). While all HC subjects were right-handers, 4 patients of the FE-SZ group were ambidexters (p=0.042). No subject fulfilled the criteria for borderline or antisocial personality disorder (according to the SCID II interview, DSM-IV axis II, personality disorders), which include abnormally high impulsivity potentially linked to reduced inhibition processes. In addition, no HC subject fulfilled the criteria of any axis II disorder.

The FE-SZ patients suffered from moderate to severe positive and negative symptoms according to the PANSS, accompanied by a severe degree of illness (CGI), and severe impairment of social functioning (GAF). For details see Table 1.

More severely ill patients received higher medication dosages (expressed in CPZ equivalents): the cumulative doses and total PANSS scores correlated positively at a trend level (rho=−0.65, p=0.062), and the correlation of cumulative dosage and CGI was significant (rho=0.65, p<0.0005).

3.2. Influence of sociodemographic characteristics on TMS parameters

A positive correlation was found between age and RMT in both hemispheres in the HC group (r=0.36, p=0.04, left motor cortex; r=0.41, p=0.04, right motor cortex). Furthermore, a significant influence of gender on cortical facilitation (ISI 7 ms, right side) was observed in the HC group (male controls displayed enhanced facilitation; p=0.004). In FE-SZ, no significant differences between right-handers and ambidexters were observed in any of the dependent variables.

3.3. Resting motor threshold (RMT)

RMT was similar in FE-SZ and HC subjects in both hemispheres (46.9% in FE-SZ vs. 47.8% in HC, p=0.88 for left motor cortex, and 48.3% in FE-SZ vs. 49.6% in HC; p=0.73 for right motor cortex; for details see Table 2). When only the right-handed subjects were included in the analysis, RMT was significantly lower in the left compared to the right motor cortex in both subgroups (p=0.039).

3.4. Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)

With an inhibitory ISI of 3 ms, there were significantly higher MEP ratios (cMEP/uMEP) in FE-SZ vs. HC subjects following left motor cortex stimulation (MEP ratio 41% in FE-SZ vs. 21% in HC; p=0.017; see Fig. 1 and Table 2), reflecting lower SICI in the patient group. This group difference remained significant (p=0.033) when only right-handed FE-SZ data (MEP ratio 40%) were analyzed. Following right motor cortex stimulation, this reduced SICI in FE-SZ (ISI 3 ms) was marginally significant (MEP ratio 59% in FE-SZ vs. 31% in HC; p=0.059).

For the MEP ratio of the facilitatory ISI of 7 ms (ICF), no significant differences between the two groups could be observed for either hemisphere (for details see Table 2).

3.5. Correlation with clinical parameters

There was a positive correlation between total PANSS score and RMT of the left motor cortex (rho=0.395, p=0.034; Spearman rank correlations)

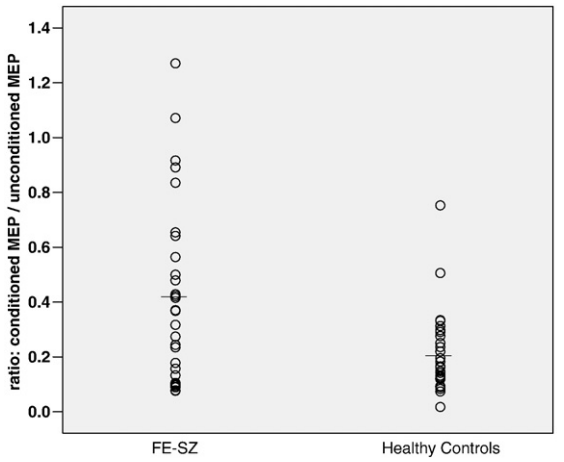

Fig. 1. Scattergram for paired-pulse inhibition in diagnostic groups. *Legend:* First-episode patients showed significantly less decreased MEP amplitudes (higher ratio: conditioned MEP) at the inhibitory ISI of 3 ms compared to healthy controls following left motor cortex stimulation (Z = -2.39; p = 0.017; Mann-Whitney-U-test). *Abbreviations:* MEP= motor evoked potential; ISI = interstimulus interval; FE-SZ = patients with first-episode schizophrenia.

and a negative correlation between total PANSS score and cortical inhibition (MEP ratio at 3 ms) in the left motor cortex in first-episode schizophrenia (rho = −0.403; $p=0.030$; Spearman rank correlations). These correlations could not be found with the PANSS positive or negative subscores, but between RMT of the left motor cortex and the PANSS general psychopathology score (rho = 0.385, $p=0.039$; Spearman rank correlations). The detected correlations were, however, non-significant after Bonferroni correction and thus have to be interpreted with caution. No other significant correlations between clinical parameters (GAF, CGI, DUP, DUI) and TMS parameters were observed.

3.6. Influence of antipsychotic medication on TMS parameters

Because the duration, cumulative dose, and daily dose of the antipsychotic medication (expressed in CPZ equivalents) were not normally distributed, we performed non-parametric correlations to assess the influence of these variables on TMS parameters. No significant correlations were observed. At a trend level, there was a positive correlation between the cumulative dosage (CPZ equivalents) and RMT of the left motor cortex (rho = 0.34, $p=0.068$), and a negative correlation between the cumulative dosage (CPZ equivalents) and the MEP ratio at ISI 7 ms (ICF) following left motor cortex stimulation (rho = −0.32, $p=0.085$). There were no significant correlations of dosage (CPZ equivalents) with RMT of the right motor cortex (rho = 0.17, $p>0.2$), MEP ratio at ISI 7 ms following right motor cortex stimulation (rho = 0.20, $p>0.2$), or MEP ratios at ISI 3 ms following either left (rho = −0.21, $p>0.2$) or right motor cortex stimulation (rho = 0.01, $p>0.2$).

4. Discussion

The main result of the present study is that first-episode patients demonstrated increased MEP amplitudes evoked by paired-pulse TMS at the inhibitory interstimulus interval (ISI) of 3 ms, as compared to healthy control subjects. No significant differences at the facilitatory ISI of 7 ms could be detected between the diagnostic groups. These findings reflect reduced short-interval cortical inhibition (SICI) but equivalent intracortical facilitation (ICF) in patients with first-episode schizophrenia compared to healthy controls.

Evidence for reduced cortical inhibition in schizophrenic patients as demonstrated by paired-pulse TMS is not conclusive to date. For instance, one study reported reduced SICI in a small sample of unmedicated schizophrenic patients, but not in patients treated with antipsychotics (Daskalakis et al., 2002). In another study, reduced SICI and increased ICF was shown in medicated, but not in drug-naïve schizophrenic patients (Pascual-Leone et al., 2002). One research group observed reduced SICI in medicated schizophrenic patients and no difference in ICF (Fitzgerald et al., 2002a), but could not replicate this finding in a larger sample of patients (Fitzgerald et al., 2002b). In the only study investigating neuroleptic-naïve first-episode patients (mainly disorganized subtype), schizophrenia patients showed no difference in cortical inhibition or facilitation as compared to healthy control subjects (Eichhammer et al., 2004). Differences between these results may be partially explained by different patient populations, often consisting of multi-episode patients with chronic disease, and the influence of various antipsychotic medications. Patients with first-episode schizophrenia have rarely been investigated. However, although the literature is still inconsistent, our finding of reduced cortical inhibition in a large sample of medicated first-episode patients with limited exposure to antipsychotic medication strongly supports the hypothesis that inhibitory intracortical deficits may be part of the schizophrenic pathophysiology. Several other neurophysiological studies using other tools than TMS have provided evidence for inhibitory deficits in schizophrenia. For instance, schizophrenia patients showed reduced P50 wave suppression in an event-related potential auditory

conditioning test paradigm (Adler et al., 1982), potentially reflecting reduced inhibition in a cortico-subcortical loop. We could not detect significant differences in ICF between medicated first-episode patients and comparable healthy control subjects. Besides reduced SICI, schizophrenia patients could have presented increased ICF, but in our study this was not the case.

SICI is linked to the GABAergic system and the function of cortical GABAergic interneurons (Ziemann, 2004). In healthy subjects, $GABA_A$ agonists and also glutamate antagonists enhance SICI; the latter effect may be best explained by a decrease of facilitatory effects (Ziemann, 2004). Recent investigations were able to segregate different GABAergic inhibitory circuits in human motor cortex and to show that SICI is probably mediated via the α2- or α3-subunit rather than the α1-subunit of the $GABA_A$ receptor (Di Lazzaro et al., 2007). The α2-subunit is found in only about 15% of cortical GABA receptors, but in more than 95% of inhibitory synapses connecting onto initial segments of pyramidal neuron axons, especially in the superficial layers of the human cerebral cortex. Also, the α2-subunit seems to be related to higher affinity for GABA, which results in faster activation and slower deactivation times than the more common α1-subunit of the $GABA_A$ receptor (Lewis et al., 2005). On the other hand, there are pharmacological studies suggesting that GABAergic activation (e.g. by benzodiazepines) mainly influences ICF rather than SICI in healthy controls (Ziemann et al., 1996b). Dopamine and noradrenaline agonists increase SICI, while dopamine antagonists like haloperidol decrease SICI (Ziemann, 2004). Interestingly, the selective serotonin re-uptake inhibitor citalopram increased SICI in subjects who were homozygotic for the long variant of the 5-HT transporter gene (Eichhammer et al., 2003). This finding also suggests an involvement of serotonin in cortical inhibition, dependent on genetic polymorphism. On the other hand, neither single nor chronic administration of paroxetine seems to result in SICI changes in schizophrenic patients, while a single dose of paroxetine can decrease ICF; in contrast, chronic paroxetine administration enhances ICF in healthy volunteers (Gerdelat-Mas et al., 2005). These opposite effects on ICF emphasize the different pharmacological actions of a drug at the cortical level, depending on its acute or long-term administration. For ICF the majority of pharmacological studies on healthy subjects demonstrated a decrease of ICF by NMDA antagonists (Ziemann, 2004). In contrast, another study found an increase of ICF after application of ketamine, an NMDA antagonist, potentially mediated by activation of non-NMDA glutamatergic transmission via AMPA and kainate receptors (Di Lazzaro et al., 2003). In conclusion, our results of decreased SICI and unchanged ICF compared to healthy controls fit best with the hypothesis of GABAergic dysfunction in schizophrenia, although the dysbalance of other neurotransmitters like glutamate, dopamine, and serotonin involved in SICI reduction may also be of relevance. The reader should bear in mind, however, that the cited findings in healthy subjects are not necessarily comparable to the results and conditions in schizophrenia patients, and neuronal networks in schizophrenia, including adaptive processes during the course of the disease and long-term medication, may be responsible for observed differences.

We found no significant differences in resting motor threshold (RMT) between schizophrenia patients and healthy controls. This is in line with the literature. Summing up the results of previous studies investigating RMT in schizophrenic patients, more than half of the studies (8 out of 15) demonstrated no significant differences between patients and control subjects (Wobrock et al., 2007). In 3 studies, a decreased RMT in schizophrenic patients was observed, as it should be expected if assuming reduced cortical inhibition and increased excitability of motor neurons (Abarbanel et al., 1996; Daskalakis et al., 2002; Eichhammer et al., 2004). In an other study, a significantly increased RMT in patients treated with antipsychotics compared to medication-free patients and normal controls was detected (Pascual-Leone et al., 2002), and in addition, a higher RMT in the left, dominant vs. right hemisphere was observed in medicated and unmedicated patients. This is remarkable given the observation that in some investigations healthy controls display a lower RMT on the left, dominant side in interhemispheric comparisons (Triggs et al., 1994). In our study, we found no difference in laterality between controls and first-episode patients. In two studies investigating the effect of low frequency rTMS on RMT, no increase of RMT after rTMS was found in schizophrenic patients compared to healthy controls (Oxley et al., 2004; Fitzgerald et al., 2004). This was attributed to reduced cortical neuroplasticity or missing cortical inhibition in schizophrenia.

Furthermore, we found evidence for a correlation between overall symptom severity, expressed by total PANSS score, and increased RMT, as well as decreased cortical inhibition. This means that reduced cortical inhibition is inversely associated with symptom severity, which seems rather counterintuitive. An explanation may be that more severely ill patients receive higher dosages of antispsychotics (CPZ equivalents), as they did in our study, and therefore the cortical inhibition

deficits could be "overcorrected". However, the above-mentioned negative correlation between left motor cortex SICI and total PANSS score could not be replicated with the PANSS positive and negative subscores. This may indicate that there is no stable correlation between symptom severity and cortical inhibition deficits at all. Furthermore, our findings of decreased cortical inhibition in schizophrenia may reflect a more general vulnerability factor (i.e. a trait marker) rather than a characterization of psychopathology (i.e. a state marker).

Our study has several limitations. First of all, antipsychotic medication could be a considerable confounding factor in using TMS paradigms (Davey et al., 1997). For instance, one study found a difference in RMT between patients treated with risperidone (increased RMT) and olanzapine (decreased RMT; Fitzgerald et al., 2002c). We did not find a differential influence of the used antipsychotics in our patient sample. This corroborates the result of another study with healthy control subjects, in which an effect on resting motor threshold (RMT) after olanzapine or haloperidol administration could not be detected (Daskalakis et al., 2003). This was explained by the fact that RMT is conventionally regarded as a measure of the membrane excitability of corticospinal neurons and interneurons in the motor cortex, increased by drugs that block voltage-gated sodium channels and not affected by drugs that alter GABA, glutamate, or dopamine transmission, like olanzapine or haloperidol (Di Lazarro et al., 2003; Liepert et al., 1997; Werhahn et al., 1999; Ziemann et al., 1996 a,b, 1997, 1998).

For paired-pulse measurements, medication influencing GABA, glutamate, serotonin, or dopamine transmission could be potentially relevant, because the interneuronal-pyramidal circuits are mediated via these pathways. However, according to the literature, one would expect that antipsychotics should compensate for the reduced inhibition and not produce it, because there are no studies available showing increased cortical inhibition in unmedicated or medicated schizophrenia, and only one study demonstrating reduced cortical inhibition exclusively in medicated patients (Pascual-Leone et al., 2002). Studies of the medication effect on cortical inhibition performed on healthy people (mostly giving single dose) do not necessarily reflect the effect of the same psychopharmacological drugs administered chronically to schizophrenic patients with a potentially different neuronal network. For future studies in schizophrenia research, it may be helpful to include other comparison groups, patients with bipolar disorder treated with atypical antipsychotic drugs for instance, to control for effects of these drugs and to compare these effects with disease specific alterations.

The strength of our study is that we were able to investigate a sample of first-episode patients that is both well characterized and relatively large, and also seems representative for this patient group in a clinical setting. Due to disease severity and the clinical necessity for medication, it was not possible to measure these patients in a neuroleptic-naïve setting.

The origin of reduced cortical inhibition in schizophrenia as measured by TMS is still speculative. In one model, reduced cortical inhibition in schizophrenia is assumed to reflect a disorder of altered dopaminergic inputs from pyramidal to non-pyramidal neurons in the cortex (Benes, 1998, 2000). In support of this hypothesis, it was demonstrated that in schizophrenia dopaminergic projections to the cortex erroneously terminate on non-pyramidal cells (i.e. interneurons) to inhibit their function. Such connectivity would result in decreased activity of inhibitory interneurons and increased excitatory output in the cortex. Another explanation may be related to the finding of decreased numbers of inhibitory (GABAergic) interneurons in the postmortem brains of schizophrenic patients, which could also lead to reduced cortical inhibition (Benes et al., 1991). There is an increasing literature pointing towards a GABAergic dysfunction in schizophrenia (Lewis et al., 2005). For example, an increased density of $GABA_A$ receptors in schizophrenics has been found in ligand binding studies, probably indicating a local upregulation in response to a reduction in perisomatic inhibitory input from chandelier and wide arbor neurons (Lewis et al., 2005). In addition, post mortem findings of reduced glutamic acid decarboxylase (GAD67) mRNA expression in dorsolateral prefrontal cortex constitutes convincing evidence for decreased GABA synthesis in schizophrenia (Knable et al., 2002). This reduced synthesis of GABA in a parvalbumin-containing subpopulation of inhibitory GABA neurons may be caused by a deficiency in signaling via tyrosine kinase receptor B, the receptor for brain-derived neurotrophic factor (BDNF) (Lewis et al., 2005). One of the consequences of reduced GABAergic transmission may be a deficit in synchronization of pyramidal cells, for example resulting in working memory deficits, a core syndrome of schizophrenia (Lewis et al., 2005; Stone et al., 1998). Our finding of reduced SICI contributes to the hypothesis of GABAergic dysfunction in schizophrenia. However, it has to be kept in mind that histopathological studies demonstrating a reduced number of GABAergic interneurons in the primary motor cortex of schizophrenia patients are not available.

A reduced SICI detected by TMS has been found in other neuropsychiatric disorders, i.e. unipolar depression (Bajbouj et al., 2006), attention-deficit/hyperactivity disorder (ADHD; Richter et al., 2007), and obsessive-compulsive disorder (OCD; Greenberg et al., 2000). With regard to these findings, intracortical inhibition deficits do not seem to be specifically restricted to schizophrenia.

Future studies combining different modalities and investigational tools (e.g. TMS, event-related potentials, magnetencephalography, structural and functional magnetic resonance imaging) may enable us to gain new insights into neuronal networks and both intracortical and cortico-subcortical connectivity.

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Contributors

T.W. wrote the manuscript. T.W. and M.S. designed the study. T.W., M.S., and D.K. performed the measurements and the ratings, and generated the source data. T.S.-A. undertook the statistical analysis. U.E. added references, streamlined and proof-read the manuscript. W.R., M.R., and P.F. contributed to the literature searches and the interpretation of the data. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest directly or otherwise related to the submitted work.

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