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Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study ☆

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Abstract

Background: Abnormalities in brain plasticity, possibly related to abnormal cortical inhibition (CI), have been proposed to underlie the pathophysiology of schizophrenia. Transcranial magnetic stimulation (TMS) provides a dynamic method for non-invasive study of plastic processes in the human brain. We aimed to determine whether patients with schizophrenia would exhibit an abnormal response to repetitive TMS (rTMS) applied to the motor cortex and whether this would relate to deficient cortical inhibition. *Methods*: Measures of motor cortical excitability and cortical inhibition were made before and after a single 15-min train of 1-Hz rTMS applied to the motor cortex in medicated and unmedicated patients with schizophrenia as well as healthy controls. *Results*: All three groups had equal motor cortical excitability prior to rTMS, although both patient groups had a shorter cortical silent period (CSP) and less cortical inhibition than the control group. Cortical excitability, as assessed by motor threshold levels, did not reduce in both medicated and unmedicated patients in response to rTMS as was seen in the control group. Significant differences were also seen between the groups in response to the rTMS for motor-evoked potential (MEP) size and cortical silent period duration. *Conclusions*: Both medicated and medication free patients with schizophrenia demonstrated reduced brain responses to rTMS and deficits in cortical inhibition.

Keywords: Repetitive transcranial magnetic stimulation; Cortical plasticity; Psychosis; Cortical inhibition; Schizophrenia; TMS

1. Introduction

It has been suggested that abnormalities of neural plasticity may underlie important neuropsychiatric disorders such as schizophrenia (Haracz, 1985). Neural and brain plasticity refer to the brain's ability to change structure and function in response to experience (Kolb and Whishaw, 1998). The mechanisms involved in these plastic responses include

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changes in synaptic activity, increases in dendritic length, changes in spine density, synapse formation, increased glial activity and neurogenesis (Kempermann et al., 2000). Two well-explored plastic mechanisms are long-term potentiation (LTP) and long-term depression (LTD). These are activity-dependent alterations in synaptic activity levels produced by repeated neuronal stimulation and are believed to be involved in learning and memory (Braunewell and Manahan-Vaughan, 2001; Miller and Mayford, 1999).

Several lines of research suggest that there are likely to be abnormalities of neural plasticity in patients with schizophrenia. First, several post mortem studies have found abnormalities in brain components required for adaptive cellular processes including GAP-43 (Benowitz and Routtenberg, 1997) and MAP-2 (Cotter et al., 1997) as well as abnormal axonal sprouting and abnormal axodendritic synapses (Uranova, 1996; Uranova et al., 1996). Second, evidence implicates dysfunction at *N*-methyl D-aspartate (NMDA) glutamate receptors in the pathogenesis of schizophrenia (Olney and Farber, 1995) and normal NMDA receptor function is crucial for a number of forms of synaptic plasticity including hippocampal LTP and LTD (Malenka and Nicoll, 1993). There is also evidence that adult patients with schizophrenia have an overrepresentation of the immature' NR2D subunit of the NMDA receptor in the prefrontal cortex (PFC) (Akbarian et al., 1996). This pattern of the NMDA receptor is associated with abnormal LTD and LTP (Okabe et al., 1998). Finally, several recent genetic studies suggest the involvement in schizophrenia of abnormalities in proteins, such as dysbindin and neuregulin 1 (NRG1), which are involved in NMDA receptor regulation and synaptic plasticity (Stefansson et al., 2002; Straub et al., 2002).

Transcranial magnetic stimulation (TMS) techniques can be used to study the excitability of motor systems and brain plastic processes in vivo. Single and paired pulse TMS techniques can be used to assess inhibitory activity in the motor cortex (Ferbert et al., 1992; Kujirai et al., 1993). Several studies have found that patients with schizophrenia exhibit deficits on TMS measures of cortical inhibitory activity (Daskalakis et al., 2002; Fitzgerald et al., 2002a,b, 2003). Repetitive TMS (rTMS) applied to the motor cortex can be used to alter cortical excitability in a way that persists beyond the time of the stimulation train (Chen and Seitz, 2001). For example, stimulation for 15 min at 1 Hz in normal subjects reduces cortical excitability as demonstrated by an increase in resting motor threshold (RMT) levels and decreased motor-evoked potential (MEP) size (Chen et al., 1997; Fitzgerald et al., 2002a,b). Although the mechanism underlying this reduction in excitability remains uncertain, the stimulation parameters utilized in these experiments are remarkably similar to those applied in basic cellular physiology experiments to induce LTD (Hoffman and Cavus, 2002).

The aim of this study was to investigate brain plasticity and cortical inhibition in schizophrenia utilizing the response to a prolonged period of low frequency rTMS. Although previous research has documented reduced inhibition in schizophrenia, no studies have directly explored rTMS-induced plasticity. We studied these in three groups, a group of unmedicated patients, a group of patients on stable antipsychotic medication and a group of normal volunteers. It was hypothesized that the patient groups would demonstrate less change in motor cortical excitability when stimulated with a low frequency rTMS train and reduced baseline cortical inhibition.

2. Methods

2.1. Subjects

The study included 26 patients with a diagnosis of schizophrenia (DSM-IV SCID) and 18 healthy controls recruited through newspaper advertisement. Of the 26 patients with schizophrenia, 10 had not been treated with any oral antipsychotic (or other) medication for at least 3 months or depot medication for at least 12 months. Sixteen were receiving treatment with a single antipsychotic medication for a minimum of 1 month (seven on olanzapine (mean dose: 11.8 ± 5.7 mg), four on risperidone (mean dose: 3.5 ± 1.0 mg), five on quetiapine (mean dose: 300.0 ± 100.0 mg)). The demographic and clinical characteristics are presented in Table 1. The three groups did not differ in age ($F(2,41) = 0.17$, $p = 0.68$) or sex ($p = 0.84$) and the two patient groups did not differ on any of the clinical variables or psychopa-

Table 1
Demographic characteristics of the groups and psychopathology scores

	Medicated patients	Unmedicated patients	Controls
Age	32.2 ± 8.8	32.6 ± 8.3	31.0 ± 5.5
Sex	6F/10M	2F/8M	3F/15M
Illness duration (years)	8.8 ± 10.4	6.4 ± 5.1	N/A
Number of admissions	2.7 ± 2.5	2.7 ± 1.9	N/A
Age of onset	25.4 ± 6.2	23.8 ± 6.3	N/A
PANSS Scores			
Total	54.6 ± 14.4	57.6 ± 12.2	N/A
Positive	13.4 ± 6.3	11.4 ± 2.8	N/A
Negative	11.6 ± 1.9	13.3 ± 4.6	N/A
General	29.6 ± 7.2	32.9 ± 6.9	N/A
SA	0.69 ± 1.01	0.40 ± 0.97	N/A
GAF	51.4 ± 15.8	50.5 ± 10.4	N/A

thology levels. There were two left-handed subjects in each group.

All normal volunteers were screened for past or current psychopathology by a trained clinician. Subjects in all groups were excluded with a co-morbid psychiatric, neurological or medical illness, concurrent substance or alcohol abuse or concurrent treatment with anticonvulsant medication or lithium. Subjects were also excluded who were regularly taking a benzodiazepine, who had taken any long acting benzodiazepine in the previous 3 days or a short acting benzodiazepine within 18 h of testing.

Written informed consent was obtained from all subjects on a form approved by the Human Research Ethics committee of Southern Health, Dandenong Hospital and The Alfred. No adverse events were reported following the TMS.

2.2. Study design

In all subjects, the study involved the measurement of parameters of motor cortical excitability before and after a period of repetitive TMS (rTMS) (Fig. 1). In the patient groups, an interview was conducted to confirm diagnosis (DSM-IV SCID) and for the measurement of symptom severity within 48 h of the testing procedure. Psychopathology was rated on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Simpson-Angus rating scale (SA) (Simpson and Angus, 1970) by a single trained rater. Handedness was rated with the Edinburgh Inventory (Oldfield, 1971).

2.3. Measurement procedures

EMG was recorded from the right abductor pollicis brevis (APB) muscle using techniques that we have previously described (Fitzgerald et al., 2002a,b). Subjects were seated in a reclining chair with a headrest for stabilisation of the head. Single and paired pulse stimulation was administered with a figure-of-8 coil (70-mm diameter, peak magnetic field 2.2 T) using two Magstim 200 magnetic stimulators (Magstim, UK) linked with a Bistim module (Magstim). At the commencement of protocol, the optimal site for stimulation of the APB muscle was established using standard methods. The coil was held tangential to the scalp with the handle pointing back and away from the midline at 45°. The induced current flow was posterior to anterior in the cortex perpendicular to the central sulcus.

TMS measures of cortical excitability (motor thresholds, MEP size and cortical silent period) were made pre- and post-rTMS in the same order in all subjects (see Fig. 1) and were the dependent variables in the change with rTMS analysis. Paired pulse measures of cortical inhibition and facilitation were only recorded before the rTMS train.

2.4. Dependent measures

2.4.1. Resting and active motor threshold

The RMT was defined as the minimum stimulator intensity that evoked a peak-to-peak MEP of >50 μV in at least 5 out of 10 consecutive trials with the subject at rest. The active motor threshold (AMT) was the lowest intensity producing at least 1 MEP of 100 μV in five trials measured during a sustained low intensity contraction (5% of maximum). During the second measurement of the motor thresholds (after rTMS), determination of whether a particular stimulus intensity was above or below threshold was made blind to knowledge of the actual stimulation intensity applied. To do this, two investigators were involved. One investigator set and adjusted the stimulation intensity level. The second investigator, who was unaware of the current stimulation intensity level, read the size of the

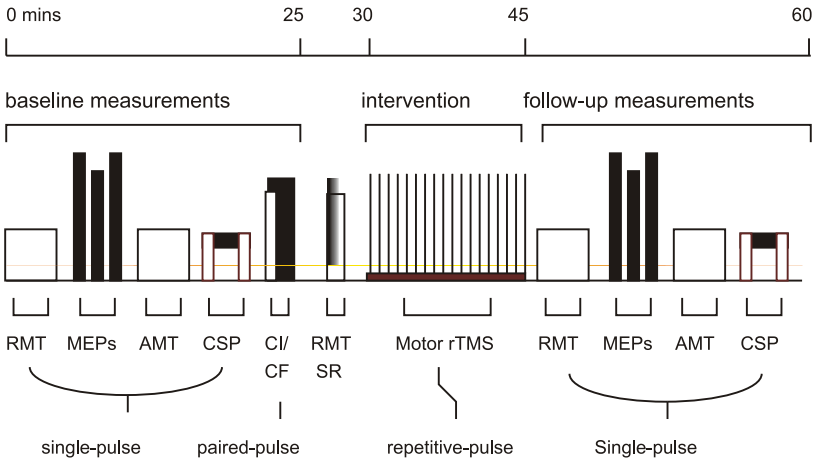

Fig. 1. Experimental design and time Line. RMT: Resting motor threshold, MEPS: motor-evoked potentials, AMT: active motor threshold, CSP: cortical silent period, CI: cortical inhibition, CF: cortical facilitation, RMT SR: resting motor threshold measured with the Magstim Superrapid.

evoked motor responses and decided whether a particular stimulation level was above or below threshold.

2.4.2. MEP size and cortical silent period

MEP size was measured at rest by recording 10 sweeps of data during stimulation at 120% of the RMT. MEP size was measured on individual rectified sweeps off-line as the area under the curve, which was then averaged for each subject and condition (pre- and post-rTMS). The cortical silent period (CSP) is a period of suppression of tonic motor activity following the induction of a MEP. The duration of the CSP was measured following the recording of 10 sweeps during sustained contraction of 5% of maximum with stimulation at 120% of the AMT. The CSP duration was measured on individual sweeps off-line and the results averaged. CSP duration was calculated from the time of stimulation to the return of spontaneous EMG activity. An investigator blinded to group of the subjects made all off-line measurements.

If the RMT or AMT changed after rTMS, the stimulation intensity used for measuring the MEP size and CSP after rTMS was adjusted so that it remained 120% of the threshold intensity (Fitzgerald et al., 2002a,b). This adjustment was conducted as MEP size is dependent on the level of stimulation intensity above motor threshold (Devanne et al., 1997) and the adjustment allowed these measurements to remain as independent dependent variables.

2.4.3. Cortical inhibition and facilitation

The procedure for measuring cortical inhibition (CI) and facilitation (CF) followed that described in the literature for paired pulse TMS measures (ppTMS) (Kujirai et al., 1993). All measurements were conducted at rest with continuous EMG monitoring. Sweeps contaminated with tonic EMG activity that can result in reduced inhibition (Ridding and Rothwell, 1999) were discarded. The initial or conditioning stimulus was set at 5% below the AMT. The second stimulus (test stimulus) was adjusted to produce MEPs of 0.5–1.0 mV. Ten trials were recorded for each of three conditions in a pseudo-random order; a control single test stimulus and 2- and 15-ms interstimulus intervals (ISIs). Pairs of stimuli were delivered 5 s apart. For each sweep, the peak-to-peak MEP size was measured and the average MEP size was calculated for each ISI and the control condition. CI and CF were then expressed as percentages of the mean control condition.

2.5. rTMS train

A single 15-min rTMS train was applied to the motor cortex in each subject at 110% of the RMT. rTMS was applied with a Magstim Super Rapid stimulator (Magstim) and a 70-mm figure-of-8 coil. The coil orientation and position was identical to that used for single and paired pulse stimulation. As the RMT produced with the Magstim Super Rapid and Magstim

200 vary, the RMT was remeasured with the Magstim Super Rapid prior to the rTMS and the stimulus intensity used for the rTMS was based on this measurement.

2.6. Statistical analysis

One-way analysis of variance models (ANOVA), *t*-tests and chi-squared tests were used to investigate differences between the three groups on demographic variables and between the two patient groups on the clinical variables. ANOVA tests were also used to test for differences between the three groups in the baseline values of the dependent measures. Log transformation was used to normalize MEP scores prior to analysis.

Change in RMT, MEP size and the CSP were calculated by subtraction of the post-rTMS scores from the pre-rTMS scores. Differences between the three groups on these change scores were calculated with analysis of variance (ANOVA) models. Where a significant effect of group was found in the ANOVA model, post hoc pair-wise comparisons between the three groups were made using the Bonferonni procedure to control for multiple comparisons. In addition, where significant differences were seen in the ANOVA models, analysis of covariance (ANCOVA) models were subsequently calculated to control for baseline differences in the dependent variables.

Correlational analysis was used to explore the relationship between significant alterations in the dependent variables and baseline measures of cortical inhibition (CSP and ppTMS CI). Correlational analysis was also used to investigate the relationship between the change scores and the measures of psychopathology for the patient groups (pooled). All procedures were two-tailed and significance was set at an α level of 0.05. All statistical analysis was conducted with SPSS 10.0 (SPSS for Windows. 10.0 Chicago: SPSS; 2000).

3. Results

The full protocol was completed in all subjects except for three control subjects in whom it was not possible to measure CI and CF with paired pulse TMS because of technical difficulties with the functioning of one of the Magstim 200 devices. A total of 17 sweeps were excluded prior to analysis from the ppTMS measures (0.72% of total sweeps) because of the presence of tonic motor activity.

3.1. Baseline measures

Baseline scores on the dependent variables are presented in Table 2. There was a significant difference in CSP duration ($F(2,41)=12.78$, $p<0.001$). The CSP was longer in the control group than in the medicated group ($p=0.001$) and the unmedicated group ($p<0.005$) with no differences between the patient groups. There was also a significant difference in CI ($F(2,38)=3.2$, $p<0.05$). CI was significantly greater in the control group than the medicated patient group ($p=0.01$). The difference between the control group and the unmedicated patient group and the difference between the two patient groups were not significant. No significant baseline differences were seen in the other measures.

3.2. Response to rTMS

Change scores for the dependent variables for each group before and after rTMS are presented in Table 3. There was a significant difference in change in RMT levels between the groups ($F(2,41)=26.1$, $p<0.001$, effect size: $\eta^2=0.56$). rTMS produced an increase in RMT in the control group but no increase in the two patient groups with a significant difference between the control group and the unmedicated patient ($p<0.001$) and medicated patient ($p<0.001$) groups. There was no difference between the two patient groups. The change score differences remained significant when controlling for baseline RMT levels ($F(2,40)=21.3$, $p<0.001$). There was also a significant difference between the groups in change in AMT size ($F(2,41)=4.8$, $p<0.05$, $\eta^2=0.19$). There was an increase in AMT level in the control and medication treated group but not the unmedicated patients (controls—unmedicated patients, $p<0.05$). These differences remained after controlling for baseline AMT levels ($F(2,40)=5.6$, $p<0.01$).

There was a significant difference in change in MEP size (rest) ($F(2,41)=4.4$, $p<0.05$, $\eta^2=0.18$) which remained significant controlling for baseline

Table 2
Mean scores (± S.D.) for each dependent variable before rTMS

	Controls	Unmedicated patients	Medicated patients	*F*	Sig
RMT (%)	41.9 ± 6.7	47.0 ± 10.4	48.0 ± 10.2	2.17	0.12
AMT (%)	31.83 ± 5.2	36.10 ± 7.3	34.63 ± 9.1	0.15	0.85
MEP (area)	5598.1 ± 7668.8	4999.4 ± 4855.2	5969.8 ± 5267.7	0.07	0.93
CSP (ms)	135.0 ± 50.4*^	91.7 ± 16.1*	89.9 ± 18.0^	8.54	0.001
CI (%)	65.5 ± 19.3^	50.8 ± 20.9	37.9 ± 41.3^	4.71	0.01
CF (%)	159.0 ± 98.8	158.8 ± 81.2	219.7 ± 141.7	1.38	0.26

Statistical results are presented for the between group differences (ANOVA) in the baseline variables. Significant post hoc differences are indicated between the control and unmedicated groups (*) and between the control and medicated patient groups (^).

MEP size ($F(2,40) = 7.9$, $p = 0.001$). There was a difference between the control and medication group but this difference did not remain significant when controlling for multiple comparisons.

There was a significant difference in change in CSP length ($F(2,41) = 6.2$, $p = 0.005$, $\eta^2 = 0.23$) which remained significant controlling for baseline CSP duration ($F(2,40) = 3.8$, $p < 0.05$, $\eta^2 = 0.16$). There was a significant difference between controls and medicated patients ($p < 0.01$) and between controls and unmedicated patients ($p < 0.05$). There was a significant decrease in CSP duration in the control group ($t(17) = 2.57$, $p < 0.05$). There was an increase in CSP duration in both patient groups but this was not significant for either group ($p > 0.05$). There were no significant differences in any of these analyses when they were repeated excluding the left-handed subjects.

3.3. Correlations

There was a significant relationship of change in RMT with baseline CSP duration ($r = 0.40$, $p = 0.007$) and baseline CI at a trend level ($r = 0.30$, $p = 0.05$). Subjects with a shorter CSP duration demonstrated significantly less change in RMT. Significant relationships were not seen with change in MEP size. Significant relationships were not seen between the baseline and change scores of the dependent variables and psychopathology measures.

4. Discussion

The results of our study indicate that patients with schizophrenia have reduced plastic responses to rTMS stimulation trains applied at 1 Hz. In particular, cortical excitability as assessed by motor threshold levels did not reduce in both medicated and unmedicated patients in response to rTMS as was seen in the control group. There was also a difference in responses in MEP size and CSP levels. In addition, we found a difference between patients and controls in two measures of baseline cortical inhibition and a relationship between the degree of cortical inhibition and plastic responses to rTMS. Differences in cortical plasticity and inhibition were seen in both medicated and unmedicated patients and do not appear to result from a confounding effect of medication treatment.

Reduced plastic responses were seen in the patient groups in regards to modulation of RMT, AMT and to

Table 3
Change scores for the dependent variables (post–pre rTMS scores)

	Controls	Unmedicated patients	Medicated patients	*F*	Sig
RMT (%)	2.4 ± 1.8*^	− 0.9 ± 1.4*	− 2.4 ± 2.4^	26.1	< 0.001
AMT (%)	0.8 ± 1.0*	− 0.9 ± 1.3*	0.94 ± 2.1	7.89	0.001
MEP (area)	− 1002.2 ± 3987.9^	− 2702.3 ± 3263.4	873.0 ± 3144.6^	4.4	< 0.05
CSP (ms)	− 12.2 ± 20.1*^	8.2 ± 14.9*	8.5 ± 20.3^	6.2	< 0.01

Statistical results are presented for the effect of subject group on change score (ANOVA). Significant post hoc differences are indicated between the control and unmedicated groups (*) and between the control and medicated patient groups (^).

a lesser degree MEP levels. As we have adjusted stimulation intensity for the measurement of MEP size post-rTMS for any change in RMT, the findings related to RMT levels and MEP size are independent of one another. Although the physiology of the RMT and MEP measures is not completely clear, they appear to be differing phenomena. MEP size appears to reflect global corticospinal pathway excitability and the RMT is determined in part by membrane related aspects of cellular excitability (Ziemann et al., 1996). Alterations in RMT and MEP levels with 1 Hz rTMS also occur through differing mechanisms as they respond differently to sub-threshold stimulation and differing stimulation train duration (Fitzgerald et al., 2002a,b; Muellbacher et al., 2000). It is of note that differences between both patient groups and the control group were seen for change in threshold levels, whereas abnormal responsively was only seen in MEP size for the medicated patients. Therefore, the differences in change in thresholds seem to relate to illness factors but the abnormality in MEP responses could well have arisen from medication effects. However, there was considerable variability in the MEP data making interpretation of these results problematic. MEP responses are highly variable at stimulation intensities relatively close to motor threshold and the measurement of MEP 'response curves' could be used in future studies to avoid this difficulty (Wassermann et al., 1998).

Interestingly, the reduction in excitability produced with 1-Hz rTMS does not seem to arise through an increase in cortical inhibition as assessed by change in CSP duration. In the controls, rTMS decreased CSP duration consistent with an increase rather than decrease in excitability. This is consistent with one previous report (Fierro et al., 2001) although other studies have failed to find alterations in CSP duration with 1-Hz stimulation (Fitzgerald et al., 2002a,b; Romeo et al., 2000). In contrast, stimulation at higher frequencies increases CSP duration (Berardelli et al., 1999; Romeo et al., 2000) as well as increasing excitability (Berardelli et al., 1998; Jahanshahi et al., 1997; Pascual-Leone et al., 1994). Therefore, 'opposing' effects of rTMS on excitability and inhibition can be seen with both high and low frequency stimulation suggesting that differing responses to rTMS may occur in excitatory and inhibitory circuits. The differences in responses between the patients and controls in both excitatory and inhibitory measures suggests that the disruption of plastic responses in the patient group may not be not restricted to a neurotransmitter or neuronal element only active in a single part of cortical motor networks.

It is of note that the patients in our study demonstrated deficient baseline cortical inhibition (CI and CSP) and that reduced inhibition was correlated with reduced plasticity. Due to similarities in time course and stimulation parameters, it has been suggested that the effects of 1-Hz rTMS stimulation may be related to the actual induction of LTD (Hoffman and Cavus, 2002). There are also considerable similarities in the relationship between inhibition and plastic responses to rTMS and LTD in cellular models. In particular, normal inhibitory GABAergic function has been shown to be required for cellular LTD with blockade of inhibitory activity enhancing the induction of LTP over LTD (Gustafsson and Wigstrom, 1990; Steele and Mauk, 1999). Similarly, the patients in our study exhibited a reduction in inhibition coupled with a 'reversed' responsiveness (decreasing RMT levels rather than an increase or no change). Although this model is speculative, these similarities suggest that abnormal inhibitory activity may have functional implications in regards to the capacity of brain systems in these patients to respond to new stimuli.

The notion of reduced plasticity could have a number of important implications for the pathogenesis of schizophrenia and it could potentially draw together several disparate lines of research. For example, deficient synaptic regulation, rather than a specific alteration in a particular neurotransmitter, could explain the failure of studies to clearly demonstrate consistent alterations in particular neurotransmitter levels or receptor numbers (Haracz, 1985). It could also provide a basis for regional intra-individual and inter-individual heterogeneity with deficient plasticity potentially producing difficulties with the maintenance of cellular integrity, perhaps explaining volumetric regional changes. At a symptom level, as LTD and LTP are both important for normal memory processes (Bear, 1999; Malenka and Nicoll, 1997), abnormal plasticity could provide a direct explanation for the deficits of working and other forms of memory (Gold and Harvey, 1993) found in this patient group. Finally, although highly speculative, it is possible that dysfunctional plastic processes could underlie the

pathogenesis of psychotic symptoms. In particular, reduced plasticity could undermine the capacity of the brain to fine tune neural networks in a manner that results in pathogenic alterations of the signal-to noise ratio (Spitzer, 1995).

There are several limitations to interpretation of the results of our study. First, although we included a medication free group, they were not medication naïve. Therefore, it is possible that there are delayed effects of antipsychotic medication that contribute to these findings although this is unlikely as the unmedicated patients were studied well beyond a time at which they would be expected to have any significant residual receptor occupancy from previous treatment. Although one study has found an effect of haloperidol on CI (Ziemann et al., 1997), atypical antipsychotics as taken by the patients in this study do not seem to have these effects (Daskalakis et al., 2003). A second issue with the study is that we have no information as to the time course of these effects or their specificity to patients with schizophrenia. Changes in cortical inhibition have been reported in several disorders (for example, obsessive compulsive disorder (Greenberg et al., 2000)) although different populations have not been tested within the one study. The response to 1-Hz rTMS in patient groups has been explored only in a minimal way, in patients with migraine and writer's cramp (Brighina et al., 2002; Siebner et al., 1999) but this effect has not been tested to date in patients with other schizophrenia spectrum or depressive disorders. Further studies are required to explore the nature of the response to 1-Hz rTMS in these clinical groups and in differing stages of the evolution of schizophrenia. Finally, we did not include a sham control condition for each subject group. Although this would have provided additional support to the findings, it would have required a doubling of the sample size, or for all subjects to be tested twice which would have delayed the commencement of antipsychotic medication in the medication free group. The addition of the sham control was not thought to add sufficient value to justify this imposition given that the primary analysis is of between group differences in response.

In summary, in this preliminary investigation, patients with schizophrenia demonstrated reduced plastic responses to 1-Hz rTMS and deficient cortical inhibition that do not seem to be secondary to the effects of antipsychotic medication. The notion of abnormal plasticity in schizophrenia has considerable explanatory potential although these initial findings require clarification with further exploration of the basic physiology of these rTMS responses. The findings may also have implications for the design of clinical trials that utilize rTMS methods in patients with schizophrenia, such as in the treatment of auditory hallucinations (Hoffman et al., 2003). One-hertz rTMS targeting left temporoparietal cortex has been proposed as a potential treatment option for patients with persistent auditory hallucinations based on the notion that this may lead to a reduction in abnormally increased local activity (Hoffman and Cavus, 2002). The findings of the current study imply that we cannot assume a simple translation of rTMS effects from studies conducted in normal controls to patients with schizophrenia, and that therapeutic actions of rTMS may occur through alternate mechanisms.

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