Motor Cortical Excitability in Schizophrenia

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Background: Transcranial magnetic stimulation (TMS) provides a method to examine cortico–cortical motor excitability and hemispheric asymmetry in unmedicated and medicated schizophrenia patients.

Methods: Fourteen right-handed schizophrenia patients (seven on conventional neuroleptics and seven medication-free) were compared with seven right-handed, age- and gender-matched normal control subjects. Motor threshold for induction of motor-evoked potentials (MEPs) and bihemispheric intracortical inhibition and facilitation were measured with single-pulse and paired-pulse TMS.

Results: Medicated patients showed an approximately 5% higher motor thresholds in both hemispheres than unmedicated patients and control subjects. Normal control subjects had a nearly 10% higher threshold for the left than the right hemisphere, whereas the opposite was true for the patient groups (5–10% higher threshold on the right than the left). Medicated patients showed significantly decreased intracortical inhibition relative to unmedicated patients and control subjects. This difference was more pronounced for the right than for the left hemisphere.

Conclusions: Treatment with conventional neuroleptics is associated with increased motor threshold and decreased intracortical inhibition, whereas unmedicated patients did not differ from normal control subjects on these measures; however, schizophrenia may be characterized by a reversed pattern of interhemispheric corticospinal excitability.

Key Words: TMS, motorcortex, cortical excitability, human, neuroleptic medications

Introduction

Motor abnormalities are frequently encountered in schizophrenia patients. Some abnormalities predate the onset of illness and may be part of the pathophysiology of schizophrenia (Walker et al 1994), whereas others may be a consequence of pharmacotherapy. Puri et al (1996) used transcranial magnetic stimulation (TMS) to compare the corticospinal excitability of nine unmedicated schizophrenia patients with that of age- and gender-matched control subjects. Motor threshold did not differ between groups; however, the latency of the motor-evoked potentials (MEPs) was significantly shorter in patients. In contrast, Abarbanel et al (1996) reported significantly lower motor thresholds in medicated schizophrenia patients compared with depressed patients and control subjects.

Motor threshold is thought to be a measure of membrane excitability in pyramidal neurons (Pascual-Leone et al 1998). Support for this claim comes from changes in motor threshold induced by antiepileptic medications with prominent sodium and calcium channel blocking activity (Ziemann et al 1996a). The paired-pulse TMS technique (Kujirai et al 1993) provides a direct measure of intracortical excitability. A conditioning stimulus (CS) is followed, at varying intervals, by a test stimulus (TS). Different neuronal circuits are recruited by different intensities of stimulation; the interstimulus interval (ISI) also influences recruitment because the time constant of neuronal circuits may differ. With differing ISIs, it is possible to investigate cortico–cortical inhibitory and facilitatory circuits selectively (Kujiral et al 1993; Nakamura et al 1997; Valls-Sole et al 1992; Ziemann et al 1996a).

It is also possible using TMS to compare measures of cortical excitability in the right and left hemispheres. Interhemispheric differences of motor function in schizophrenia are suggested by a variety of investigations. For example, functional magnetic resonance imaging revealed schizophrenia subjects to have a significantly lower laterality quotient while performing simple motor tasks (Matta et al 1997). In addition, a recent review of the handedness literature strongly supported the view that schizophrenia is characterized by a more variable and less completely lateralized pattern of manual performance than is found in the general population (Satz and Green 1999).

Methods and Materials

This study was approved by the local institutional review board and, after complete description of the study, written informed consent was obtained from all participants.
Subjects

Unmedicated schizophrenia patients (six men and one woman, aged 21 to 54 years) and schizophrenia patients on conventional neuroleptics (six men and one woman, aged 38 to 58 years) were recruited from an urban mental health center and diagnosed using the Structured Clinical Interview for DSM-IV (American Psychiatric Association 1994). Unmedicated patients had been off all neuroleptics for at least 6 months, and four of the seven patients were medication naïve. The medicated patients had been on the same regimen and doses of conventional neuroleptics for at least 8 weeks. Normal control subjects (six men and one woman, aged 21 to 54 years) were recruited from the hospital community. All subjects were right-handed according to the revised Edinburgh Handedness Inventory (Oldfield 1971), had normal neurological exams, and had no contraindication for TMS (Wassermann 1998). Subjects’ intelligence quotient (premorbid IQ in the case of the patients) was estimated using the National Adult Reading Test (Blair and Spreen 1989). Patients were assessed using the Positive and Negative Syndrome Scale (Kay et al 1987), and the Scale for the Assessment of Negative Symptoms (Andreasen 1983). Table 1 summarizes the demographic characteristics of all patients studied.

Experimental Procedure

For each subject, we determined motor threshold and the paired-pulse modulation curve over both hemispheres using standard procedures (Rossini and Rossi 1998). The order of stimulation of each hemisphere was counterbalanced across subjects in each group. We performed TMS with a 70-mm figure-eight coil using Magstim 200 magnetic stimulators (Magstim Company, Dyfed, UK). A single magnetic stimulator was used for motor threshold determination; two magnetic stimulators connected through a Bistim module (Magstim Company, Dyfed, UK) to one coil were used for paired-pulse studies. For both studies, the stimulation coil was placed flat on the subjects’ scalps over the optimal scalp position for induction of MEPs of maximal peak-to-peak amplitude in the contralateral target muscle (first dorsal interosseus muscle; FDI). This optimal scalp position was defined and identified following recommended guidelines in each study subject at the beginning of the experiment (Rossini and Rossi 1998). The stimulation coil was held on the scalp with its handle pointing occipitally and rotated approximately at 45° to the sagittal axis (i.e., approximately perpendicular to the expected orientation of the central sulcus; Brasil-Neto et al 1992). In this position, the induced current flows in an
anterior–medial to posterior–lateral direction in the brain, approximately perpendicular to the orientation of the central sulcus, and predominantly activates corticospinal neurons transsynaptically (Werhahn et al 1994).

Motor Threshold Determination
The motor threshold was defined as the minimal intensity of stimulation required to induce MEPs of more than 50-µV peak-to-peak amplitude in at least 6 of 10 trials. The intertrial interval was 10 sec to prevent interaction effects of consecutive TMS stimuli on corticospinal excitability (Chen et al 1997). The threshold determination was made during complete muscle relaxation for at least 100 msec before the stimulation as monitored by electromyogram (EMG). Stimulation began at high intensity (approximately 90% of maximal stimulator output) and was decreased in 2% decrements until the highest TMS intensity that failed to induce MEPs of 50-µV peak-to-peak amplitude in at least 6 of 10 trials was identified.

The EMG was recorded using pairs of disposable, self-adhesive, surface electrodes (Nicolet Biomedical, Madison, WI) that were placed on the belly and tendon of the FDI muscle bilaterally. Two round ground electrodes with a diameter of 30 mm were placed on the forearm bilaterally and linked to a common ground. The MEPs were collected using a Dantec Counterpoint electromyograph with an amplification of 1.0 mV and a band pass of 20 to 1000 Hz (Dantec, Skovlunde, Denmark). Following preamplification, the signal was digitized using a CED 1401 interface (Cambridge Electronic Design, Cambridge, UK; sampling rate 2 kHz) and stored in a personal computer for offline analysis.

Paired-Pulse TMS Study
The CS was applied at 80% of the subject’s motor threshold and was confirmed to induce no MEPs by recording 10 consecutive trials at a sensitivity of 20 µV/div on the EMG monitor. The TS was applied at approximately 130% of the subject’s motor threshold. The test stimulus intensity was adjusted to evoke MEPs of approximately 1-mV peak-to-peak amplitude (±0.2 mV). The ISIs used in this study were 1, 3, 4, 6, 12, and 20 msec. Eight MEPs were recorded at each ISI. Interspersed with the collection of MEPs to paired stimuli, we collected eight MEPs to the TS alone on at least four occasions. The intertrial interval was 10 sec to prevent interaction between consecutive TMS stimuli on corticospinal excitability (Chen et al 1997). The order of the trials with different ISIs was randomized for each subject. In each subject, we rectified the MEPs evoked by the paired stimuli at each ISI and calculated the area under the curve for each MEP. We then calculated the mean area under the curve for the MEPs at each ISI and expressed them as percent of the average area under the curve for the MEPs induced by the TS applied alone.

Data Analysis
Analyses of variance (ANOVA) were performed on dependent variables with post hoc Fisher’s least significant difference test and Bonferroni–Dunn correction. All results are expressed as means ± standard deviation.

Results
All 21 subjects completed the procedure. None reported adverse effects; subjects were specifically queried about tinnitus, neck pain, and headache (Wassermann 1998).

Motor Threshold
There was a significant effect of group on motor threshold \( F = 6.0; df(2); p = .006 \) (Figure 1). Post hoc tests demonstrated that medicated patients had a significantly higher motor threshold than unmedicated patients \( p = .003 \) and control subjects \( p = .01 \). Control subjects and unmedicated patients did not differ.

A two-way analysis of variance (ANOVA) revealed no significant interaction of stimulated hemisphere (right or left) and group on motor threshold \( F = 0.8; df(2); p = .2 \); however, split by hemisphere, the results revealed a significant effect of subject group on motor threshold for the left hemisphere \( F = 4.9; df(2); p = .02 \), but not for the right \( F = 2.3; df(2); p = .12 \). Medicated patients had significantly higher motor thresholds in the left hemisphere than unmedicated patients \( p = .02 \) and control subjects \( p = .01 \).

There was also a significant effect of subject group on the interhemispheric motor threshold difference \( F = 6.2; df(2); p = .005 \). Post hoc tests revealed significant differences between control subjects and both the unmedicated \( p = .01 \) and medicated patients \( p = .02 \). Control subjects had a higher motor threshold in the right than the left hemisphere (Figure 2), whereas both patient groups exhibited the opposite pattern. These effects could not be accounted for by handedness differences. The revised Edinburgh Handedness Inventory (Schacter 1994) revealed no differences between control subjects, medicated or unmedicated patients. Furthermore, no correlation between score on the Edinburgh Handedness Inventory and

![Figure 1. Bar histogram of the motor thresholds (+SD) for all subjects according to group and hemisphere.](image)
motor threshold or interhemispheric motor threshold difference was found across groups of subjects.

**Paired-Pulse TMS study**

Control subjects showed a significant effect of ISI on the MEPs area under the curve for the right \( F = 18.9; df(5); p < .0001 \) and the left hemisphere \( F = 8.3; df(5); p < .0001 \) (Figure 3). Similarly, unmedicated subjects also showed a significant effect of ISI on the MEPs for the right \( F = 10.5; df(5); p < .0001 \) and the left hemisphere \( F = 4.2; df(5); p = .004 \); however, in medicated subjects the ISI significantly influenced MEP area for the left only \( F = 5.0; df(5); p = .002 \) and not for the right hemisphere \( F = 0.2; df(5) \).

As revealed in Figure 4, the variability of the paired-pulse study results was large in the medicated patients (note large standard error); however, we could not identify a relation between intracortical inhibition or facilitation and clinical ratings, length of time on medication, or medications taken. A study with larger numbers of patients on different medications might be most interesting in this context.

Two-way ANOVA for the interaction of group \( (df = 2) \) and ISI \( (df = 5) \) on MEP area was not significant for either hemisphere [left: \( F = 0.8; df(10); p = .6 \); right: \( F = 0.6; df(10); p = .8 \)]; however, we found a significant effect of group on the intracortical inhibition index \( [ICI; F = 11.8; df(2); p < .0001] \) and the intracortical facilitation index \( [ICF; F = 9.8; df(2); p = .0002] \). The ICI was defined as the average results of MEP modulation for the paired-pulse study at ISIs of 1, 3, and 4 msec (Pascual-Leone et al 1998; Ziemann et al 1996a). The ICF was defined as the average MEP modulation for the paired-pulse study at ISIs of 12 and 20 msec (Pascual-Leone et al 1998; Ziemann et al 1996a). Post hoc tests revealed that ICI was significantly lower in medicated subjects than in unmedicated subjects \( (p = .0002) \) and normal subjects \( (p < .0001) \). The ICF was significantly greater in medicated subjects than in unmedicated \( (p < .0001) \) and control subjects \( (p = .003) \). The ICI and ICF were not significantly different between unmedicated and control subjects. None of the groups showed significant interhemispheric differences in ICI or ICF.

**Discussion**

We found intracortical and corticospinal excitability in unmedicated schizophrenia patients to be largely normal except for interhemispheric motor threshold differences; however, patients treated with conventional neuroleptics showed several striking abnormalities relative to control and unmedicated subjects. Medication-free patients are not the same as medication-naive patients, and indeed most of our unmedicated patients had been exposed to neuroleptic medication in the past. Therefore, we cannot exclude
long-term neuroleptic-induced changes in cortical excitability that may persist even after drug withdrawal. Furthermore, our study was conducted on a relatively small number of subjects and should be regarded as preliminary and in need of confirmation in future investigations. Nevertheless, several interesting findings warrant attention and discussion.

Unlike the study by Puri et al (1996), we did not find shorter latency of the MEPs induced by TMS in the target muscle in unmedicated schizophrenia patients; however, the subjects in the Puri et al study voluntarily activated the target muscles, whereas we tested the TMS-induced MEPs in the relaxed target muscle. Voluntary activation of the target muscle shortens the latency and increases the amplitude of the MEPs to TMS (Hess et al 1986). The physiologic basis for these effects is complex and may include a reduced threshold for indirect activation of corticospinal neurons but not for direct stimulation of their axons (Mazzocchio et al 1994), enhanced excitability of spinal motoneurones (Di Lazzaro et al 1998), and shortening of the peripheral conduction time (Izumi et al 1996). Consistent with these possibilities, Puri et al (1996) proposed three explanations for their findings: 1) relative lack of corticospinal inhibition in the schizophrenic patients, 2) direct rather than indirect activation of corticospinal neurons, and 3) peripheral nerve or neuromuscular function abnormalities in schizophrenia. The results of our paired-pulse TMS experiment provide novel insights into these proposed explanations.

Our results regarding interhemispheric differences in motor threshold are consistent with and expand the results of Puri et al (1996) in that they suggest a left hemispheric abnormality in schizophrenia patients. Our results also agree with and extend the findings of Puri et al (1996) with regard to the lack of differences in motor threshold between unmedicated schizophrenia patients and control subjects.

**Interhemispheric Differences**

Both groups of schizophrenia patients significantly differed from control subjects on the index of interhemispheric differences in motor threshold. In normal subjects the dominant (left) hemisphere had a lower motor threshold. This is consistent with previous reports (Triggs et al 1994) and has been interpreted as a correlate of handedness and increased use of the dominant hand. Schizophrenia patients showed the opposite pattern; the left hemispheric threshold was higher than the right despite right-handedness in all patients and regardless of medication status.

Abarbanel et al (1996) failed to find interhemispheric differences in motor threshold in their study of medicated schizophrenia patients; however, they did not report the patients’ handedness, nor did they describe whether they calculated individual interhemispheric threshold differences or compared group differences for right and left motor threshold. Given the effects of handedness on hemispheric differences in motor threshold and the large interindividual variability in motor threshold, their results are difficult to interpret. Furthermore, Abarbanel et al (1996) determined motor threshold using intensity decrements of 5% of stimulator output and may therefore have failed to detect small interhemispheric differences.

Our findings of interhemispheric differences in motor threshold in the schizophrenia patients suggest a relative hypoxcitability of the left or hyperexcitability of the right motor cortex. A possible interpretation of this finding is that schizophrenia patients fail to show the normal laterality in physiologic differences in corticospinal tract function or cortical motor representation secondary to anomalous handedness (Triggs et al 1994). Schizophrenia patients demonstrate inconsistent manual superiority and
preference (Manoach 1994; Satz and Green 1999). Hand-
edness is an index of cerebral lateralization, and these findings are thought to reflect a neurodevelopmental abnormality that renders both hemispheres incapable of assuming consistent motor dominance. Some investigators have hypothesized that schizophrenia more broadly dis-
rupts the development of cerebral lateralization and therefore affects the complex behaviors that depend on lateral-
ized systems (Crow et al 1989; Pearlson et al 1996). This is still a subject of intense debate and study. In several studies, evidence of structural abnormalities have been more pronounced on the left side, such as enlargement of cerebral ventricles (Crow et al 1989) and diminished size of the superior temporal gyrus (Shenton et al 1992). A recent review of functional imaging studies of brain metabolism and blood flow also implicates the left hemi-
sphere as abnormal (Gur and Chin 1999). Our findings of interhemispheric differences in cortical excitability sug-
gest left hemispheric hypoactivity. Longitudinal evalua-
tion of such measures in schizophrenia patients both off medications and during successful treatment will allow us to clarify the relation of lateralized dysregulation to motor dysfunction and symptom presentation in schizophrenia.

Effect of Conventional Neuroleptics

Davey et al (1997) studied the effects of antipsychotic medications on motor threshold and silent period (SP) to TMS by comparing a group of medication-free and treated schizophrenia patients. In their study, unlike ours, patients maintained a weak isometric voluntary contraction of the target muscle. The investigators found no difference in motor threshold or in the latency of the evoked MEPs between drug-naïve and medicated patients. During the early component of the SP, there was a weaker suppres-
sion of EMG in the medicated patients compared with the drug-naïve patients. These results support the notion of disrupted intracortical inhibition by antipsychotic drugs. Consistent with these findings, we found a significant reduction in intracortical inhibition and an excessive intracortical facilitation in medicated schizophrenia patients.

In Parkinson’s disease, the dopamine deficiency is associated with reduced cortico–cortical inhibition; dopa-
mimetic drugs have been shown to enhance cortico–
cortical inhibition in control subjects and Parkinsonian patients (Berardelli et al 1996; Priori et al 1994; Ridding 1995). Intracortical facilitation (ICF) appears related to a balance between GABAergic and glutamatergic activity. Medications that enhance GABAergic activity (Inghilleri et al 1996; Ziemann et al 1996) and those that antagonize glutamatergic activity (Ziemann et al 1998) markedly decrease the degree of cortico–cortical facilitation evoked by paired-pulse TMS. Conventional neuroleptics block dopaminergic function and, consistent with our results, would be predicted to reduce intracortical inhibition. In addition, we found an increase in intracortical facilitation that might be related to glutamatergic effects or may be secondary to the reduced cortico–cortical inhibition. Conven-
tional antipsychotic agents have complex effects on glutamatergic activity (Goff 2000) including enhanced release of glutamate in striatum (Yamamoto and Cooper-
man 1994; See and Lynch 1996), direct agonist effects on glutamatergic N-methyl-D-aspartate receptors (Banerjee et al 1995; Fletcher and MacDonald 1993; McCoy and Richfield 1996) and antipsychotics can alter the subunit composition of glutamatergic receptors (Fitzgerald et al 1995; Healy and Meadowoodruff 1997; Meadowoodruff et al 1996; Riva et al 1997). Each of these effects on glutamate release or receptor dynamics might affect cor-
tical activation, either at the level of pyramidal neurons or inhibitory interneurons (Grunze et al 1996).

Our findings reveal a reversed pattern of hemispheric asymmetries in unmedicated schizophrenia patients, in whom corticospinal and intracortical excitability is other-
wise found to be normal. In contrast, treatment with conventional neuroleptics was associated with abnormal cortical excitability suggestive of antidopaminergic ef-nets. These results have to be considered preliminary and require replication in a larger patient population. Furth-
more, we studied the excitability of the motor cortex, and our findings may not necessarily generalize to other cortical areas. Currently we are investigating the effects of atypical neuroleptics on these parameters of cortical ex-
citability to determine whether changes in cortical excitabil-
ity correspond with therapeutic effects or, in the case of conventional agents, with motor side effects. Such studies might help elucidate the mechanisms of action of different classes of psychoactive drugs.

The authors thank Zoe Stinchfield, Cornelia Brenninkmeyer, and Edward Amico for their help during the project and Julian P. Keenan for assistance with data analysis. Supported in part by Grants from the Stanley Vada NAMI Foundation (AP-L, DSM), the National Alliance for Research in Depression and Schizophrenia (AP-L, DSM), and the National Institutes of Mental Health (AP-L, Grant No. RO1-MH5790; DCG, Grant No. RO1-MHS4245, and Grant No. MH57708).

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