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Cortical motor neurophysiology of patients with schizophrenia: A study using transcranial magnetic stimulation

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ABSTRACT

Trancranial magnetic stimulation (TMS) provides a non-invasive means for exploring physiological alterations of central motor control in a variety of neuropsychiatric diseases. The present study aimed to assess the neurophysiological profile of muscle evoked responses to a standard TMS procedure in 51 medicated patients with schizophrenia and 51 age- and sex-matched healthy subjects. Motor evoked potentials (MEPs) from the abductor pollicis brevis muscle were elicited by stimulation of the contralateral motor cortex with a circular coil. The hot spot was marked, and the resting motor threshold (RMTh), the stimulus intensity for maximum MEP (SI-max), the post-stimulus silent period of voluntary muscle activity, and MEP latency and amplitude were measured. The main findings were the significantly higher than normal values for RMTh and SI-max, which are both indices of neuronal excitability. In particular, patients who had ziprasidone in their therapeutic regimen demonstrated the highest SI-max for both hemispheres, and the highest RMTh for the left hemisphere, patients receiving olanzapine demonstrated the lowest RMTh for the left hemisphere, and those on quetiapine showed intermediate values. The silent period was longer in the patients than in the controls when a RMTh-related SI was used and did not differ between the two groups when a fixed SI was used. We concluded that the observed TMS changes could be interpreted as primary alterations of intracortical motor excitability followed by defects of cortical inhibition and should be attributed to schizophrenia, antipsychotic medication or the interaction between the two factors.

1. Introduction

Motor performance and its deviation from normality in relation to the corresponding cortical–subcortical networks in patients with schizophrenia have been investigated with, for example, cytoarchitectural, neurochemical, neuroimaging and neurophysiological approaches (Schröder et al., 1995; Mattay et al., 1997; Benes and Berretta, 2001; Ferrarelli et al., 2008; Hashimoto et al., 2008; Rowland et al., 2008).

Over the last decade, several studies described differences in transcranial magnetic stimulation (TMS) motor measurements in patients with schizophrenia as compared with healthy subjects (Abarbanel et al., 1996; Eichhammer et al., 2005; Hoy et al., 2007; Daskalakis et al., 2008). These studies focused mainly on indices of inhibitory cortical circuits such as the silent period (SP), i.e. the period of suppression of tonic voluntary muscle activity after a TMS-evoked muscle response and transcallosal inhibition produced by paired pulses with short-stimulus intervals (Daskalakis et al., 2002; Fitzgerald et al., 2003). The prevailing view is that unmedicated patients with schizophrenia, as opposed to healthy subjects, demonstrate a shorter silent period and transcallosal inhibition, whereas the findings in medicated patients are quite variable (Davey et al., 1997; Boroojerdi et al., 1999; Daskalakis et al., 2002).

The minimum level of stimulus intensity (SI) required to elicit a small motor response of a given amplitude, and even more, the SI to elicit the maximal motor evoked potential (MEP), both measures of the excitatory status of motor neurons, have received little attention in previous investigations. However, SI is fundamental methodological element not only for MEP amplitude and latency measurements but also for the estimation of the silent period's duration, as was demonstrated in paradigms with application of TMS at different stimulus levels (Uozumi et al., 1992). Of equal concern is the question of sample size, which has ofteny been limited by difficulties in recruiting subjects and the time-consuming methods that are often used. The present study aimed to explore whether motor performance changes could be detected by using a standardized TMS procedure and

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measuring a battery of neurophysiological parameters of muscle responses in a considerable number of medicated schizophrenic patients.

2. Subjects and methods

2.1. Subjects

Fifty-one patients (33 men and 18 women; aged 21 to 54 years, mean age 34.4 ± 8.5 years) with a diagnosis of schizophrenia who were hospitalized for a brief period in the Psychiatry Department of the University Hospital of Patras Medical School were enrolled in the study. Fifty-one healthy volunteers, matched for age and sex, who were recruited from the hospital and university staff and had no first or second degree relatives with psychiatric illness, served as controls. All participants were unequivocally right-handed and their height varied from 160 to 185 cm; the mean height did not differ between patients and controls. No history of epileptic disorder; migraine attacks; head injuries; drug, alcohol or substance abuse; or systemic or neurological disease was recorded in any of the subjects.

The patients were interviewed and the diagnosis was made by one of the authors (E.S.) using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association, 1994). In addition, acute extrapyramidal symptoms and tardive dyskinesia were initially evaluated at study entry using the Simpson and Angus Scale (Simpson and Angus, 1970) and the Abnormal Involuntary Movement Scale (Guy, 1976), respectively. Patients who had a score ≥1 on any item of either scale were excluded. The subtype of schizophrenia was found to be paranoid in 37 patients, undifferentiated in 10, and disorganized in 4, while the mean illness duration was 9.0 years (±7.7 SD, ranging from 1 to 29 years). At the time of investigation all 51 patients were receiving antipsychotic medication, which remained unchanged for type and doses for at least 2 months. Thirty-nine of them were treated with an atypical antipsychotic drug alone and 12 with a combination of a typical and an atypical drug. Specifically, 20 patients were taking 20 mg/day olanzapine; 8 patients 600 to 1200 mg/day quetiapine; 11 patients 240 mg/day ziprasidone; 4 patients 20 mg/day olanzapine and 20 mg/day haloperidol; 2 patients 600 mg/day quetiapine and 20 mg/day haloperidol; and 6 patients 240 mg/day ziprasidone and 20 mg/day haloperidol. None was receiving anticonvulsants or benzodiazepines. The study protocol was approved by the University Hospital of Patras ethics committee, and all patient and control subjects gave written informed consent after the study procedure was explained to them.

2.2. Experimental procedure

All tests were performed in the neurophysiology lab of the same institution during a morning session from 10 am to 12 am. The patients had received their morning medication 2 hours before the procedure. Each participant was seated comfortably with the examined hand relaxed and stabilized. We stimulated each hemisphere in an alternative order in consecutive participants using a Magstim 200 stimulator (The Magstim Company, Whitland, Dyfed, U.K.) equipped with a circular coil of 90 mm diameter, a 2.0 T maximum magnetic field strength and a stimulus frequency of 0.2–0.3 Hz. The current direction in the coil was counterclock-wise when viewed from above (side A visible) to preferentially stimulate the left hemisphere and clock-wise (side B visible) to activate the right hemisphere. MEPs were recorded with surface electrodes from the—contralateral to the stimulation side—abductor pollicis brevis (APB) muscle on a Dandec Key-point electromyographic (EMG) apparatus (Medtronic-Dantec Electronics, Skovlunde, Denmark) with a filter bandpass of 100 Hz to 2 kHz, a sensitivity of 0.1 to 1 mV/division, and a sweep speed of 10 ms/division.

2.3. Determination of TMS parameters

I. First, in order to determine the optimal stimulation position (hot spot) for each subject, the coil was held flat on the vertex of the scalp with the handle pointing backward and 45° laterally from middle line. Starting from Cz, zero–zero point (10–20 system), the coil was displaced in lateral and anterior-posterior directions in 1-cm steps until the largest MEP at rest was obtained. This point was marked with red ink to ensure that the coil would be held in the same position during all measurements. To estimate the lateralization of the hot spot in each participant, the vertical distance between midline and the center of the coil was defined as being more or less than 2 cm.

II. SI was initially set at 70–80% of maximum output; once the hot spot was determined, intensity was increased and decreased by 2% steps to ensure supramaximal stimulation. The lowest stimulus intensity required to produce maximum MEP (SI-max) was estimated.

III. Subsequently, following a 3-min interstimulus interval, the Resting Motor Threshold (RMTh) was defined as the lowest stimulus intensity able to evoke an MEP from a resting muscle with peak-to-peak amplitude >50 mV in at least three out of five consecutive trials. RMTh was estimated by increasing the stimulus intensity from sub-threshold level in steps of 2% of maximal output.

IV. According to previously described procedures (Abarbanel et al., 1996) and in order to account for MEP variability (Zanette et al., 1995), a train of 10 responses to SI-max were recorded from each muscle and the MEP with the highest amplitude, which was most often the one with the shortest latency as well, was selected for analysis. The MEP amplitude was measured peak to peak and MEP latency from stimulus artifact to onset of negative peak.

V. SP was determined while the subject exerted isometric contraction at 80% of maximal voluntary contraction, as previously estimated by a dynamometer, at two levels of SI: SI1, 130% of RMTh and SI2, 90% of maximal output. For each of the two intensities, three trials were averaged (Uozumi et al., 1992) and the duration of SP1 and SP2, respectively, were measured from the stimulus artifact to the re-occurrence of continuous EMG activity. Throughout the study, muscle condition (resting or contraction) was ensured by audiovisual EMG feedback.

2.4. Statistical analysis

The Mann–Whitney test was used for comparisons of neurophysiological data between patient and control groups, and the Wilcoxon test was used for evaluation of side-to-side differences. The effect of disease type and medication on the neurophysiological measurements was analyzed by means of the Kruskal–Wallis test for multiple samples. Level of significance was set at 5%. All analyses were completed using SPSS version 15 (SPSS, Inc., Chicago, IL, USA).

3. Results

The TMS protocol was successfully completed, and clear-cut MEPs were recorded from both sides in all patients and controls. The hot spot was detected in symmetrical positions over the left and right hemispheres in all subjects. The lateralization of this spot differed significantly between the two groups, being at least 2.0 cm lateral to midline in 48 controls and 23 patients, while in the remaining 3 controls and 28 patients the spot was located at midline or less than 2.0 cm laterally ($p = 0.000$).

The findings of TMS parameters in patients and controls are presented in Table 1. SI-max and RMTh to either left or right

Table 1
Results of TMS parameters, mean ± SD (range), in patients with schizophrenia compared with control subjects.

Parameter	Left cortex			Right cortex		
	Patients	Controls	*p*	Patients	Controls	*p*
SI-max (%max. output)	68.9 ± 6.7 (55–80)	61.3 ± 5.8 (50–75)	**0.000**	69.3 ± 6.9 (55–90)	62.0 ± 6.9 (50–75)	**0.000**
RMTh (%max. output)	47.2 ± 9.2 (28–75)	38.8 ± 6.2 (28–57)	**0.000**	47.0 ± 9.2 (30–75)	38.3 ± 7.1 (28–55)	**0.000**
SP1 (ms)	184.9 ± 47.7 (93–323)	158.2 ± 54.0 (38–292)	**0.035**	197.7 ± 48.4 (107–358)	160.9 ± 56.4 (35–270)	**0.003**
SP2 (ms)	249.0 ± 47.0 (160–400)	232.7 ± 54.9 (71–365)	0.240	258.5 ± 47.8 (165–380)	241.8 ± 52.9 (120–379)	0.082
MEP-lat (ms)	21.9 ± 1.8 (17.0–25.6)	21.3 ± 1.6 (18.3–24.8)	**0.024**	21.9 ± 1.5 (18.9–25.5)	21.1 ± 1.6 (18.0–24.7)	**0.011**
MEP-amp (mV) (mV)	2.13 ± 1.47 (0.1–6.5)	2.88 ± 2.39 (0.2–9.0)	0.281	1.88 ± 1.45 (0.2–7.0)	2.49 ± 1.40 (0.4–10.0)	0.304

SI-max: stimulus intensity required to produce maximum motor evoked potential; RMTh: resting motor threshold; SP1: silent period obtained by SI at 130% of RMTh; SP2: silent period obtained by SI at 90% of maximum output; MEP-lat: motor evoked potential latency; MEP-amp: MEP amplitude. *p* in bold: statistically significant.