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BRIEF REPORT

Cortical inhibition in first-degree relatives of schizophrenic patients assessed with transcranial magnetic stimulation

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Abstract

Although cortical inhibition deficit has been shown in schizophrenia patients by transcranial magnetic stimulation (TMS), some controversies remain, possibly due to confounding factors such as medication use and clinical state at the time of assessment. First-degree relatives of schizophrenia patients, who share various degrees of genetic vulnerability with the patients, but are free from confounds related to medication and/or florid psychosis, have not been studied to date. We compared 12 relatives with 14 controls on several paradigms with TMS. Three of the 12 healthy relatives lacked transcallosal inhibition (TI) in one or more of the stimulation levels. There were no significant differences in other parameters. The lack of TI in 25% of the relatives is an important finding that needs to be replicated in larger samples that are heterogeneous in terms of psychosis-proneness.

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Key words: Cortical inhibition, first-degree relatives, marker, schizophrenia, transcranial magnetic stimulation.

Introduction

Although the search for a schizophrenia marker has been the focus of many studies, one with high sensitivity and specificity is yet to be found. Cortical inhibition (CI) deficit has been suggested as one component of the possible pathophysiological mechanisms (Freedman et al., 1983) and transcranial magnetic stimulation (TMS) has been used in the assessment of CI since 1993 (Burt et al., 2002).

Many studies on CI in schizophrenia, as assessed by TMS (Daskalakis et al., 2002; Eichhammer et al., 2004; Fitzgerald et al., 2002a, 2003; Hoppner et al., 2001; Pascual-Leone et al., 2002) have clearly demonstrated deficits. However, controversies remain, possibly due to confounding factors such as medication use and clinical state at the time of assessment. In their study of medication-naive or medication-free patients, Daskalakis et al. (2002) reported inhibition deficits in paired pulse motor-evoked potential (MEP) inhibition, silent period duration (SP) and transcallosal inhibition (TI). Others could not find any significant differences in the SP or TI paradigms, although abnormalities were shown in the MEP thresholds or latencies (Eichhammer et al., 2004; Pascual-Leone et al., 2002).

Indeed, cortical excitability seems to change with the use of antipsychotics (Davey et al., 1997; Fitzgerald et al., 2002b). It also seems to be related to the clinical state and varies with the severity of psychotic symptoms (Daskalakis et al., 2002). The lack of a significant deficit in first-episode patients (Eichhammer et al., 2004) implies that the duration of the illness as well as a history of antipsychotic use might be important factors to be controlled for.

Genetic load is known to be one of the strongest determinants for the development of schizophrenia. Patients and their first-degree relatives, who on an average share 50% of their genetic material are also similar in terms for the presence of neurological signs, brain volume changes (Seidman et al., 2003) and indirect indicators of an inhibition deficit as shown in experiments of prepulse inhibition, P50 event-related potential suppression, or smooth-pursuit eye tracking (Cadenhead, 2002). Study of the putative illness markers in the healthy relatives of patients, who share

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various degrees of genetic vulnerability with the patients but are free from the effects of medication and/or florid psychosis might, therefore, prove to be a valuable method. To our knowledge, cortical inhibition has not been studied to date in healthy relatives.

We, therefore, aimed to assess cortical inhibition with the use of TMS in the healthy first-degree relatives of patients and compare them with another group of healthy subjects who lacked a family history of the illness.

Methods

Twelve first-degree relatives of schizophrenia patients (age 29.00 ± 10.50 yr; 5 men, 7 women) and 14 healthy volunteers (age 27.00 ± 8.27 yr; 9 men, 5 women) were assessed. The groups were not significantly different in terms of age or gender distribution. The schizophrenia patients had been at our follow-up programme for at least 6 months and their DSM-IV diagnoses were re-evaluated by three of the authors (M.C.S., E.C.A., H.D.O.) before the relatives were recruited. Two were parents and all others were siblings of the subjects studied. The protocol was approved by the Local Ethics Committee and written consent was obtained from all subjects after explanation of the complete procedure. The *Structured Clinical Interview for DSM-IV* (First et al., 1997) was used to rule out any psychiatric disorder. All subjects were right-handed as measured by Chapman Handedness Inventory (Chapman and Chapman, 1987). None of them had a history of serious head trauma or any neurological or serious medical disorder.

In order to assess the degree or severity of psychosis-proneness and to control for dyskinesia and parkinsonism, a detailed neuropsychiatric assessment was performed with the use of the Magical Ideation Scale (Eckblad and Chapman, 1983), the Scale for Physical and Social Anhedonia (Chapman et al., 1976), the Perceptual Aberration Scale (Chapman et al., 1978), the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989), the Abnormal Involuntary Movement Scale (Guy, 1976) and the United Parkinson's Disease Rating Scale – Motor Evaluation (Fahn et al., 1987).

MEPs were recorded from first dorsal interosseus (FDI) muscles bilaterally by surface electrodes attached to the second finger. A 10 Hz–2 kHz bandpass filter was used for recordings. EMG recordings were made during rest and moderate activity (holding a cylinder between the thumb and the index finger). Background EMG activity was monitored during recordings made during rest and audio feedback was given to subjects to ensure sustained moderate activity of the FDI muscle.

Magnetic stimulus was given using a MagLite magnetic stimulator (Medtronic, Inc. Minneapolis, MN, USA) and a coil 5.2 inches in diameter. Subjects were seated in a reclining chair with a headrest (without immobilization) in order to ensure minimal head movement during assessment. The coil was held tangential to the head with the handle pointing backward and 45° away from the midline. The induced current is postero-anterior in the cortex, perpendicular to the line of the central sulcus (Kaneko et al., 1996). The optimal stimulation point was determined by moving the coil over the presumed innervation area for the right FDI using a suprathreshold stimulus. The point where the largest MEP could be recorded was labelled with a non-toxic red marker in order to ensure stimulation of the same site throughout the experiment.

Motor threshold was determined by using a suprathreshold stimulus and decreasing it by 1% in each successive step. The smallest intensity that could elicit a MEP amplitude higher than 50 μV in resting and 100 μV in moderately active FDI in at least five of the 10 trails were determined as the resting and active motor thresholds (RMT, AMT) respectively (Chen et al., 1998).

Cortical silent period (CSP) is the temporary loss of muscle contraction after a MEP has been elicited. CSP duration was measured from the point of the complete disappearance of the muscle potential (where the MEP ends) to the point of reappearance of the muscle electrical activity at 0.5 mV/D sensitivity in the moderately active FDI (absolute silence) (Matsumoto, 1996). CSP was measured in the moderately active FDI. Stimulation intensities of 10, 20, 30 and 40% over the AMT were used. The test was repeated 15 times at each stimulus intensity with a minimum of 5-s interstimulus interval and on average sweeps for each level the MEP amplitude, CSP latency and duration were calculated.

TI is defined as the temporary loss of voluntary contraction of ipsilateral FDI, on stimulation of the contralateral FDI with a suprathreshold stimulus. Three levels of stimulation intensities (40, 50 and 60% over the RMT) were used, each for 15 times and with a minimum of 5-s interstimulus interval. TI duration, TI latency (time from the stimulus to the beginning of TI) and transcallosal conduction time (TCT; the difference between the beginning of contralateral MEP and TI) were averaged for each level. Where TI could not be detected (three subjects), measurements were repeated twice more, giving the same results.

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Table 1. Clinical and TMS parameters compared between the two groups

	Relatives ($n=12$) [Mean ± S.D. (range)]	Controls ($n=14$) [Mean ± S.D. (range)]	Statistics (Mann–Whitney test)
AIMS	3.17 ± 3.01 (0–9)	2.14 ± 2.00 (0–6)	$z=-0.65$, $p=0.51$
UPDRS-ME	1.83 ± 2.37 (0–6)	2.29 ± 2.05 (0–7)	$z=-0.97$, $p=0.33$
NES	8.70 ± 3.65 (5–17)	6.36 ± 2.62 (3–12)	$z=-1.60$, $p=0.11$
Magical Ideation	4.42 ± 3.34 (1–13)	5.57 ± 2.98 (0–7)	$z=-1.24$, $p=0.21$
Perceptual Aberration	1.45 ± 2.11 (0–6)	2.29 ± 2.52 (0–8)	$z=-0.82$, $p=0.41$
Physical and Social Anhedonia	14.09 ± 8.20 (2–29)	15.86 ± 7.38 (4–26)	$z=-0.60$, $p=0.55$
RMT, % of maximal output	36.36 ± 10.20 (27–46)	35.14 ± 5.63 (26–63)	$z=-0.33$, $p=0.74$
AMT, % of maximal output	27.41 ± 7.64 (18–44)	26.50 ± 4.91 (18–36)	$z=-0.08$, $p=0.93$
MEP amplitude, mV	1.07 ± 0.84 (0.19–2.23)	0.84 ± 0.76 (0.11–3.00)	$z=-0.96$, $p=0.34$
CSP duration, ms	34.98 ± 29.08 (14.58–119.12)	33.13 ± 15.19 (13.50–63.72)	$z=-0.51$, $p=0.61$
TCT, ms (no TI in three subjects in one or more experiments)	13.62 ± 5.00 (7.80–25.07) ($n=9$)	15.58 ± 4.70 (8.90–24.13)	$z=-0.90$, $p=0.37$
TI duration, ms	19.14 ± 7.95 (0.00–28.73)	21.15 ± 4.40 (13.53–26.60)	$z=-0.36$, $p=0.72$

AIMS, Abnormal Involuntary Movement Scale; AMT, active motor threshold; CSP, cortical silent period, MEP, motor-evoked potential; NES, Neurological Evaluation Scale; RMT, resting motor threshold, TCT, transcallosal conduction time; TI, transcallosal inhibition; UPDRS-ME, United Parkinson's Disease Rating Scale – Motor Evaluation.

Preliminary analysis revealed non-significant differences for all the stimulation intensities studied. Therefore, the CSP, TCT and TI durations that were reported and statistically analysed are the arithmetic means of the values obtained at different stimulation intensities.

Results

There were no significant differences between the two groups in terms of the clinical, psychiatric or neurological assessments (Table 1).

Although TI was detected as expected in all healthy volunteers, three of the 12 healthy relatives lacked TI in one or more of the stimulation levels (one in 40% and two in 40% and 50% over the RMT). Resting and active motor thresholds were not different across groups. There were no significant differences for the MEP amplitude, CSP duration, TI duration, latency, or the TCT (Table 1).

Discussion

Previous studies with medication-naive or medication-free patients did not report a significant difference in the CSP or TI measurements (Eichhammer et al., 2004; Pascual-Leone et al., 2002) with the exception of the study by Daskalakis et al. (2002). Our results also show no significant differences between groups when the mean TI duration or the TCT are compared. However, the finding that three (25%) of the healthy relatives lacked TI deserves interpretation.

TI has not been studied in large samples of healthy subjects before, with or without a family history of schizophrenia. However, it is noteworthy that Hoppner et al. (2001) reported a lack of TI in 25% of schizophrenia patients.

The dysfunction of the corpus callosum leading to incomplete transmission of cortical stimulation may be an explanation for the lack of TI, however, the relevant transcallosal measurements (TCT and TI duration) were not different across the two groups in our study. Previous studies of corpus callosum in patients with schizophrenia (Innocenti et al., 2003) or their relatives (Chua et al., 2000) have not shown a robust dysfunction.

The exact nature of CI deficit in schizophrenia is not clear. It might be dependent on the clinical state or a stable marker of the illness (Daskalakis et al., 2002, Eichhammer et al., 2004). Neurological soft signs and schizotypal features are known to be associated with psychosis-proneness, as well as changes in some electrophysiological variables like P300 amplitude and latency. A group with many schizotypal features, neurological soft signs or other electrophysiological findings may be more likely to show deficits in CI as measured by the TMS. This argument, however, remains to be studied experimentally.

The lack of TI in 25% of the relatives is an important finding, since these individuals share the genetic load

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with the patients but are free from the effects of psychosis, antipsychotic treatment, or even the indirect indicators of psychosis-proneness. This study is the first to show the lack of TI in healthy relatives of patients with schizophrenia. Our finding implies that further study of TI or other indicators CI deficit in the first-degree relatives or schizotypal individuals might be necessary. Future studies should employ larger samples that are heterogenous in terms of psychosis-proneness.

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Statement of Interest

None.

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