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High-frequency repetitive transcranial magnetic stimulation in schizophrenia: a combined treatment and neuroimaging study

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ABSTRACT

Background. Repetitive transcranial magnetic stimulation (rTMS) of frontal brain regions is under study as a non-invasive method in the treatment of affective disorders. Recent publications provide increasing evidence that rTMS may be useful in treating schizophrenia. Results are most intriguing, demonstrating a reduction of negative symptoms following high-frequency rTMS. In this context, disentangling of negative and depressive symptoms is of the utmost importance when understanding specific rTMS effects on schizophrenic symptoms.

Method. Using a sham-controlled parallel design, 20 patients with schizophrenia were included in the study. Patients were treated with high-frequency 10 Hz rTMS over 10 days. Besides clinical ratings, ECD-SPECT (technetium-99 bicisate single photon emission computed tomography) imaging was performed before and after termination of rTMS treatment.

Results. High-frequency rTMS leads to a significant reduction of negative symptoms combined with a trend for non-significant improvement of depressive symptoms in the active stimulated group as compared with the sham stimulated group. Additionally, a trend for worsening of positive symptoms was observed in the actively treated schizophrenic patients. In both groups no changes in regional cerebral blood flow could be detected by ECD-SPECT.

Conclusions. Beneficial effects of high-frequency rTMS on negative and depressive symptoms were found, together with a trend for worsening positive symptoms in schizophrenic patients.

INTRODUCTION

Schizophrenia is a devastating illness affecting approximately 1% of the population. Despite growing insights into the neurobiological mechanisms involved, treatment of psychotic symptoms remains only partially successful for many patients (Schultz & Andreasen, 1999). To date, several studies suggest a therapeutic efficacy of repetitive transcranial magnetic stimulation (rTMS) in patients with schizophrenia (Cohen *et al.* 1999; Hoffman *et al.* 2000; Rollnik *et al.* 2000; Yu *et al.* 2002). Since its beginning in 1985 as a diagnostic tool (Barker *et al.* 1985), the use of TMS has progressed to a therapeutic application in a variety of neuropsychiatric diseases (Grisaru *et al.* 1998; Rosenberg *et al.* 2002), particularly focusing on affective disorders (McNamara *et al.* 2001; Burt *et al.* 2002). With respect to schizophrenia, early investigations found modest improvement of psychotic symptoms (Feinsod *et al.* 1998; Geller *et al.* 1997). Meanwhile, two placebo-controlled studies reported demonstrable beneficial effects in schizophrenia (Hoffman *et al.* 2000; Rollnik *et al.* 2000). However, one controlled trial failed to

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show improvement of psychotic symptoms (Klein *et al.* 1999). Analysis of these studies reveals that successful rTMS of schizophrenia may be linked to stimulation frequency as well as to the constellation of psychotic symptoms. In particular, positive symptoms, preferentially auditory hallucinations, seem to be improved by 1Hz low-frequency rTMS (Hoffman *et al.* 2000), whereas negative symptoms seem to respond to high-frequency rTMS (Cohen *et al.* 1999; Nahas *et al.* 2000; Rollnik *et al.* 2000; Hoffman & Boutros, 2001; Yu *et al.* 2002). This selective effect of stimulation frequency on distinct aspects of psychotic symptoms underscores the different neurobiological qualities of low- and high-frequency rTMS. As pointed out by Hoffman & Cavus (2002), low-frequency rTMS at a rate of 0·3–1·0 Hz may reduce cortical excitability, whereas high-frequency rTMS with stimulation frequencies greater than 1 Hz has been shown to increase dopamine turnover in cortical nigrostriatal and mesolimbic systems (Strafella *et al.* 2001; Keck *et al.* 2002). Thus, in terms of positive and negative symptoms, low-frequency rTMS seems to be an ideal tool to correct activity of disinhibited orbitofrontal and limbic structures associated with auditory hallucinations as core positive symptoms (Silbersweig *et al.* 1995). In contrast, high-frequency rTMS may selectively activate mesolimbic structures which are thought to play a key role in generating negative symptoms such as anhedonia and loss of interest (Heimer *et al.* 1997).

Focusing on the treatment of negative symptoms in schizophrenic patients, a considerable overlap with depressive symptoms has to be considered (Hausmann & Fleischhacker, 2002). In this context, improvement of negative symptoms by rTMS may be due to a selective modulation of depressed mood. Support for this hypothesis comes from a current study treating patients with post-traumatic stress disorder (PTSD) which shows that rTMS has antidepressant efficacy without changing symptoms of PTSD (Rosenberg *et al.* 2002).

Based on the evidence of these findings, we designed a sham-controlled study to preferentially investigate the effects of high-frequency rTMS on negative and depressive symptoms in patients with schizophrenia. For this reason, we additionally used the Calgary Depression Scale for Schizophrenics (CDSS) in order to distinguish between depression, and negative and extrapyramidal symptoms (Addington *et al.* 1994). Moreover, ECD-single photon emission computed tomography (SPECT) imaging was performed before and after termination of rTMS treatment to investigate whether rTMS causes changes in regional cerebral blood flow (rCBF) in brain regions. Changes in rCBF were shown after rTMS treatment of affective disorders (Teneback *et al.* 1999; Zheng, 2000).

METHOD AND MATERIALS

Patients

In the light of the results of Rollnik *et al.* (2000), which demonstrated a clinical improvement in 12 schizophrenic patients under low-frequency rTMS using the Brief Psychiatric Rating Scale (BPRS), an effect size of about 1·20 was to be expected. Restricting the type 1 error to alpha = 0·05 and the type 2 error to beta = 0·20 (equivalent to a power of 0·8) a total sample size of 19 subjects was required. Therefore, 20 in-patients meeting DSM-IV criteria for schizophrenia ($n = 14$) or schizoaffective disorder ($n = 6$) as diagnosed with the Structured Clinical Interview (SCID) were enrolled in the study. After detailed explanation of the study, written informed consent was obtained through a protocol approved by the local ethics committee.

Exclusion criteria included alcohol or substance dependence disorder in the past four years, focal neurological findings, systemic neurological illness, a history of brain trauma or seizures, or electroconvulsive therapy within the last 12 months. All patients were on stable antipsychotic medication at least 2 weeks prior to entering the study without evidencing sufficient improvement. Using a parallel group design, upon entering the study patients were randomized to receive active or sham rTMS. Both groups, each consisting of 10 patients, did not differ with respect to demographic and clinical characteristics (Table 1) and received stable-dose neuroleptic treatment for the duration of the trial.

Treatment

Repetitive TMS was performed with a Magstim Rapid Pro stimulator (Magstim Company Ltd, Whiteland, UK) using a figure-of-eight coil with

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Table 1. *Demographic and clinical characteristics of the two study groups*

	Active TMS ($n=10$)	Sham TMS ($n=10$)	Significance test
Age	37·9 ± 7·7	41·7 ± 10·3	N.S.
Sex (F/M)	8/2	6/4	N.S.
Handedness (R/L)	10/0	8/2	N.S.
Age at onset	23·1 ± 6·3	27·5 ± 14·2	N.S.
Duration of illness (years)	14·8 ± 7·9	14·2 ± 9·3	N.S.
No. of hospitalizations	10·6 ± 10·0	7·2 ± 6·1	N.S.
Concomitant medication			
Atypical antipsychotics (Y/N)	4/6	5/5	N.S.
Anticholinergics (Y/N)	1/9	2/8	N.S.
Mood stabilizers (Y/N)	3/7	2/8	N.S.
Antidepressants (Y/N)	3/7	3/7	N.S.
Clinical ratings			
PANSS (baseline)	82·2 ± 15·6	82·0 ± 17·9	N.S.
MADRS (baseline)	27·9 ± 8·1	25·0 ± 4·4	N.S.
CDSS (baseline)	12·7 ± 4·9	9·4 ± 3·5	N.S.

PANSS: Positive and Negative Syndrome Scale; MADRS: Montgomery–Asberg Depression Scale; CDSS: Calgary Depression Scale for Schizophrenics.

an inner diameter of 7 cm per wing. Prior to treatment, motor threshold of the right abductor pollicis brevis muscle was determined. Stimulation site was the left dorsolateral prefrontal cortex, defined as 5 cm anterior and in a parasagittal plane from the point of maximum stimulation of the abductor pollicis muscle. Stimulation intensity was at 110% of motor threshold. The treatment protocol consisted of 10 daily sessions. On each treatment session 1000 stimuli resulting from 20 trains at a rate of 10 Hz for 5 s were applied, leading to a total number of 10 000 pulses. Sham stimulation occurred in the same manner by using a sham coil system (Magstim, UK) that mimics the popping sound of the discharge without induction of magnetic fields. This sham procedure elicited no tactile sensation at the site of stimulation but guaranteed that no substantial cortical stimulation occurred which was shown to be produced by sham conditions tilting an 'active' coil 45° off the scalp (Lisanby *et al*. 2001). Therefore, in analogy to recent published studies combining rTMS treatment with functional imaging (Siebner *et al*. 2003), we decided to use a sham-coil system to absolutely exclude effective stimulation induced by sham-rTMS treatment.

Clinical ratings

Clinical ratings were assessed at baseline before treatment and after the last treatment session (2 weeks). The Positive and Negative Symptoms Scale (PANSS) was used to assess schizophrenic symptomatology, the Montgomery–Asberg Depression Rating Scale (MADRS) was used to assess depressive symptoms in general, and the CDSS was used to selectively disentangle negative, depressive and extrapyramidal symptoms. A psychiatrist who was blinded to the nature of treatment performed the ratings.

Brain SPECT

SPECT imaging was performed 1–2 days before the beginning of the rTMS series and 1–2 days after its termination. All subjects received an intravenous injection of 650 MBq of technetium-99 bicisate (ECD; DuPont Pharma) and were in a quiet, dimmed room in a supine position with eyes closed and ears unplugged. SPECT images were obtained with a triple-headed camera (Siemens, Germany) equipped with low-energy ultra-high resolution parallel-hole collimators. SPECT acquisition was initiated about 60 min after tracer injection. Continuous transaxial tomograms were reconstructed using filtered backprojection with a Butterworth filter (Nyquist, 0.4, Ortho 2, cut-off).

Analyis of cerebral SPECT imaging was performed by using Statistical Parametric Mapping (SPM 99, The Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London) implemented in MATLAB 6.0 (The Mathworks Inc., Natick, MA, USA), offering the possibility of searching for differences without focusing on a predefined cortical area. This procedure is in contrast to hypothesis-driven approaches, which predefine anatomical regions of interest and compare those with

reference regions (e.g. the cerebellum). Spatial preprocessing of each scan from each subject was performed, including realignment to a standard SPECT template available in SPM 99: co-registration, normalization, smoothing (Gaussian filter, 10 mm FWHM) and proportional scaling to a grand mean of 50. The SPM analysis was carried out with a design model of two conditions (one scan/condition).

Statistics

Student's t test and χ^2 tests were used to compare the demographic and clinical characteristics of the two groups. With regard to the clinical ratings, the overall effect of treatment over time in the two groups was compared by using a set of repeated measures analysis of variance (ANOVA) with treatment as the between-group factor and time as the within-subject factor. With regard to SPECT imaging, in both the placebo and the active group paired t tests were performed on mean voxel values with the omnibus null hypothesis that there are no effects of interest in any brain region. Corrections for multiple comparisons were made ($p \leqslant 0{\cdot}05$).

RESULTS

Twenty patients completed the treatment protocol. In the active group, patients usually noticed no adverse effects except for slight discomfort at the site of stimulation. Three patients in this group reported transitory mild headache. No exacerbation of psychotic symptoms was found. The treatment groups did not differ with respect to the duration of the various medications. In particular, in both treatment groups the duration of atypical antipsychotics did not differ ($t = -0{\cdot}343$; $p = 0{\cdot}863$). Furthermore, the time interval between the last medication change and TMS initiation was not statistically significant between the treatment groups ($t = 1{\cdot}066$; $p = 0{\cdot}303$).

With regard to the clinical ratings, both groups showed improvement over time on the various ratings. However, the active group demonstrated greater treatment effects relative to the sham-treated group (Fig. 1). In particular, the set of repeated measures ANOVA revealed a significant treatment × time interaction for PANSS Negative (Wilk's lambda $F = 11{\cdot}524$; $p = 0{\cdot}03$), which indicated a superior degree of improvement in the active group relative to the sham group. PANSS General Psychopathology did not approach significance, but showed a greater trend for improvement in the active group as compared with the sham group (Wilk's lambda $F = 3{\cdot}126$; $p = 0{\cdot}094$). In contrast, PANSS Positive demonstrated a non-significant trend for worsening following active relative to sham stimulation (Wilk's lambda $F = 4{\cdot}036$; $p = 0{\cdot}06$). In analogy to the PANSS ratings, both the MADRS and the CDSS showed improvement which was more obvious in the active group compared with the sham group, but did

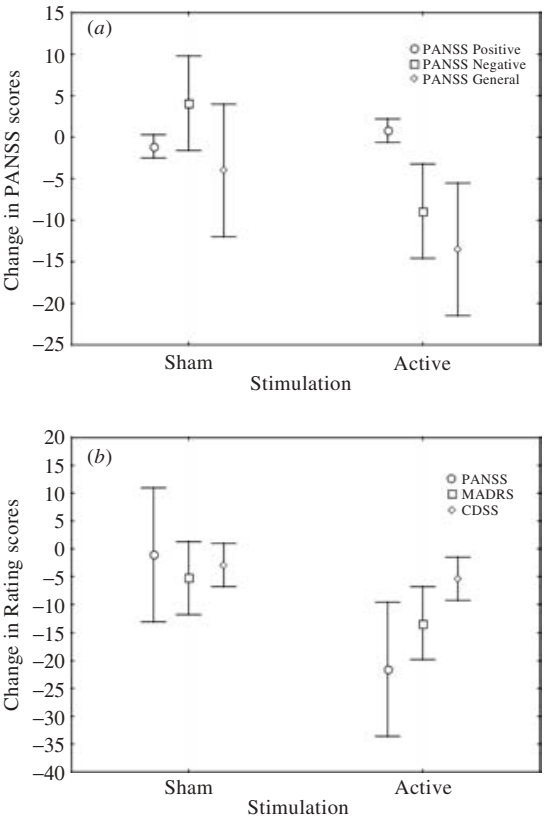

FIG. 1. Change of clinical rating scores following active and sham stimulation. Therapeutic improvement is indicated by a decrease of values. (*a*) Positive and Negative Symptoms Scale (PANSS) subscales in the sham and actively stimulated groups. Note that PANSS Negative was significantly decreased in the active group compared with the sham group. (*b*) PANSS, Montgomery–Asberg Depression Rating Scale (MADRS) and Calgary Depression Scale for Schizophrenics (CDSS) scales in the sham and actively treated groups. Note that MADRS and CDSS showed a similar trend for improvement as the PANSS without, however, reaching statistical significance.

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not reach statistical significance (MADRS: Wilk's lambda $F=3{\cdot}446$; $p=0{\cdot}08$; CDSS: Wilk's lambda $F=0{\cdot}911$; $p=0{\cdot}35$). When looking at a multivariate regression model that included CDSS as a predictor for PANSS Negative we could not find a significant effect. In addition to the simple between-groups analysis, we evaluated more elaborate statistical models including covariates such as age, sex and duration of illness for all of these ratings (PANSS, MADRS and CDSS). However, we could not find a change of effect or significance.

Analysing the SPECT data, no significant effect or any trend to significance on the rCBF in any cerebral region could be noted over time following active or sham stimulation.

DISCUSSION

The results of this study point to two intriguing aspects when treating schizophrenia with rTMS. First, treatment efficacy of high-frequency rTMS in schizophrenia is not due to a selective improvement of depressive symptoms, as has been shown in treating PTSD (Rosenberg *et al.* 2002), but has specific beneficial effects preferentially on negative symptoms. Secondly, our SPECT data do not support the hypothesis that rTMS effects in schizophrenia result from frontal cortex activation or from alteration of activity in the anterior cingulate cortex. In particular, this brain structure seems to play a pivotal role in mediating antidepressant rTMS effects in affective disorders (Teneback *et al.* 1999; Zheng, 2000). Disentangling negative from depressive symptoms by using the CDSS, we could support most recent findings, demonstrating reduction of negative symptoms following high-frequency rTMS (Cohen *et al.* 1999; Nahas *et al.* 2000; Rollnik *et al.* 2000; Hoffman & Boutros, 2001; Yu *et al.* 2002). Moreover, our SPECT data could confirm previous results of an uncontrolled study, using TC-HMPAO (technetium 99m hexamethylpropyleneamine oxime labelled) SPECT in evaluating effects of high-frequency rTMS in six schizophrenic patients. Despite improvement of negative symptoms, this study failed to demonstrate change of frontal cortex activity after rTMS (Cohen *et al.* 1999).

Recent findings concerning biological effects of high-frequency rTMS may provide a unifying framework which offers an interesting interpretation of these clinical and neuroimaging data. In particular, current studies provide evidence that high-frequency rTMS of frontal brain regions modulates the dynamic release patterns of dopamine in both the mesolimbic and mesostriatal systems. In this context, concentration of dopamine was selectively elevated in the dorsal striatum and the shell of the nucleus accumbens after rTMS of the rat brain (Keck *et al.* 2002). Moreover, high-frequency rTMS of the human prefrontal cortex induced biological effects comparable to those demonstrated in animals. Using [^{11}C]raclopride and positron emission tomography (PET), a significant rTMS-induced increase in dopamine release could be demonstrated in the caudate nucleus of treated probands (Strafella *et al.* 2001). For this reason, rTMS-mediated activation of the dopaminergic mesolimbic and mesostriatal system may underlie improvement of negative and depressive symptoms. With regard to our study, the significant reduction of negative symptoms together with a similar trend for improvement of depressed mood may reflect correction of dysfunctional dopaminergic neurotransmission which is thought to be associated with negative symptoms (Heimer *et al.* 1997) as well as with depressive symptoms (Bowden *et al.* 1997). Increase in dopaminergic neurotransmission may additionally explain why high-frequency rTMS is able to induce psychotic symptoms (Zwanzger *et al.* 2002) and why high-frequency stimulation is considered not to be effective in treating delusional symptoms of depression (Grunhaus *et al.* 2000). Consistent with this view, the PANSS positive subscale showed a trend towards worsening in our schizophrenic patients treated with active stimulation as compared with sham stimulation. Since our study was designed to replicate and to accurately assess the form of improvement in schizophrenic patients as previously shown by Rollnik *et al.* (2000), a power assumption based on this former study enabled us to use a small sample size. With a larger sample size the trend for worsening of positive symtoms might have been significant. This clinical fact may decisively limit the use of this application in schizophrenic patients and should be investigated in a further study which exclusively addresses this issue.

In the light of these biological findings, high-frequency rTMS-induced changes of cortical activity should occur in ventro- and dorsostriatal

areas of the brain. Due to the poorer spatial resolution of SPECT in comparison with PET, changes of activity in these brain areas are difficult to detect and may explain why our study and that of Cohen *et al*. (1999) failed to demonstrate neurobiological effects of rTMS when using SPECT imaging. Considering the general approach of our method comparing the rCBF-baseline status in a pre- and post-therapy setting, it might be that functional neuroimaging using activation paradigms arising from cognitive tasks (fMRI (magnetic resonance imaging) or O-15 PET) is more sensitive for detecting changes than rCBF-SPECT.

In contrast to our SPECT data obtained from schizophrenic patients, high-frequency rTMS treatment of affective disorders has been shown to modulate activity in the anterior cingulate cortex (Teneback *et al*. 1999; Zheng, 2000). This lack of rTMS effects on anterior cingulate activity in schizophrenia may reflect abnormal functional neuroanatomy of this brain structure in schizophrenic patients (Woodruff *et al*. 1997; Fletcher *et al*. 1999). Additionally, this fact may explain why rTMS treatment of our schizophrenic patients reduced depressive symptoms less efficiently than negative symptoms.

In summary, our study gives further support to the hypothesis that high-frequency rTMS may be of particular benefit in patients with a low level of subcortical dopamine function as reflected by depressive and negative symptoms (Strafella *et al*. 2001; Keck *et al*. 2002). Despite these encouraging results, correct interpretation of our data should consider several confounding factors. First, optimal blinding conditions in TMS studies are currently not available (Siebner *et al*. 2003). Using a sham-coil system, we could exclude any effective stimulation of the brain which appears under other sham conditions, such as angling the 'active' coil off the head (Lisanby *et al*. 2001). However, stimulation with a sham coil does not generate somatic sensations as known by active rTMS application. The absence of tactile sensations may have influenced the patients' expectations. Based on this fact, we tried to reduce this possible bias by choosing a parallel design, in contrast to a crossover design, which allows direct comparison of both treatment conditions (active versus sham stimulation) in the same patient. Secondly, stable antipsychotic medication for at least two weeks prior to rTMS treatment may be too short a time for attributing clinical changes exclusively to the TMS intervention. However, the treatment groups did not differ with respect to the duration and change of medication prior to the rTMS intervention, suggesting that rTMS may play a pivotal part in improving negative and depressive symptoms in schizophrenic patients.

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DECLARATION OF INTEREST

None.

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