Brain Stimulation 7 (2014) 559–563

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Repetitive Transcranial Magnetic Stimulation (rTMS) Improves Facial Affect Recognition in Schizophrenia

Wolfgang Wölwer [a,*], Agnes Lowe [a], Jürgen Brinkmeyer [a], Marcus Streit [a,1], Mareke Habakuck [a], Marcus W. Agelink [b], Arian Mobascher [c], Wolfgang Gaebel [a], Joachim Cordes [a]

[a] Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich Heine University Düsseldorf, Bergische Landstrasse 2, 40629 Düsseldorf, Germany
[b] Department of Psychiatry, Psychotherapy and Preventive Medicine, Ruhr-University Bochum, Alexandrinenstr. 1-3, 44791 Bochum, Germany
[c] Department of Psychiatry and Psychotherapy, Johannes Gutenberg-University Mainz, Untere Zahlbacher Str. 8, 55131 Mainz, Germany

ARTICLE INFO

Article history:
Received 15 January 2014
Received in revised form
17 April 2014
Accepted 30 April 2014
Available online 22 May 2014

Keywords:
Schizophrenia
Facial affect recognition
Repetitive transcranial magnetic stimulation (rTMS)

ABSTRACT

Objective: Facial affect recognition, a basic building block of social cognition, is often impaired in schizophrenia. Poor facial affect recognition is closely related to poor functional outcome; however, neither social cognitive impairments nor functional outcome are sufficiently improved by antipsychotic drug treatment alone. Adjunctive repetitive transcranial magnetic stimulation (rTMS) has been shown to enhance cognitive functioning in both healthy individuals and in people with neuropsychiatric disorders and to ameliorate clinical symptoms in psychiatric disorders, but its effects on social cognitive impairments in schizophrenia have not yet been studied. Therefore, we evaluated the effects of sham-controlled rTMS on facial affect recognition in patients with chronic schizophrenia.
Method: Inpatients ($N = 36$) on stable antipsychotic treatment were randomly assigned to double-blind high-frequency (10 Hz) rTMS or sham stimulation for a total of ten sessions over two weeks. In the verum group, each session consisted of 10 000 stimuli (20 trains of 5 s) applied over the left dorsolateral prefrontal cortex at 110% of motor threshold. Facial affect recognition was assessed before (T0) and after (T1) the ten sessions.
Results: Facial affect recognition improved significantly more after rTMS (accuracy change: mean = 8.9%, SD = 6.0%) than after sham stimulation (mean = 1.6%, SD = 3.5; Cohen's $d = 1.45$). There was no correlation with clinical improvement.
Conclusion: Our results indicate that prefrontal 10 Hz rTMS stimulation may help to ameliorate impaired facial affect recognition in schizophrenia.

Introduction

Impairments in social cognition, in particular facial affect recognition, are well established in schizophrenia and have received growing attention in recent years [1,2]. One of the main reasons for this interest is their robust association with poor functional outcome [3]. Because schizophrenia patients often report poor functional abilities to be one of the most disturbing consequences of their disorder, improvement of functional outcomes has become an important treatment target [4]. Amelioration of social cognitive impairments is thought to be a promising means to achieve this aim. Neither typical nor atypical antipsychotic medication significantly improves deficits in facial affect recognition [5,6]. However, adjuvant cognitive remediation focusing on social cognition in general or on facial affect recognition in particular has shown promising results [7]: According to a recent meta-analysis, social cognitive training programs have moderate-to-large effects on both social cognitive performance (in particular facial affect recognition) and observer-rated community and institutional function [8]. Other add-on treatments, like innovative brain stimulation methods, have not yet been investigated with regard to their effects on social cognitive impairments in schizophrenia.

Clinical trial registration information: ClinicalTrial.gov Identifier: NCT00169689.
Role of the funding source: The study was self-financed by means of the department. The technical support by Medtronic had no impact on study design, data collection, analysis, or interpretation, writing of the report, or the decision to submit the paper for publication.
Conflicts of interest: The authors declare that they have no conflicts of interest in relation to the subject of this study.
* Corresponding author. Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine-University Düsseldorf, LVR-Klinikum Düsseldorf, Bergische Landstrasse 2, 40629 Düsseldorf, Germany. Tel.: +49 211 9222002; fax: +49 211 9222020.
E-mail address: woelwer@uni-duesseldorf.de (W. Wölwer).
[1] Deceased.

1935-861X/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2014.04.011

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, safe, well-tolerated therapeutic tool that has fewer side effects than antipsychotic medication [9]. It is becoming increasingly important in the treatment of psychiatric disorders [10,11], in particular (treatment-resistant) depression [12–14]. In schizophrenia, evidence suggests that low-frequency (about 1 Hz) rTMS attenuates auditory hallucinations and that high-frequency (about 10 Hz) rTMS may have positive effects on negative symptoms [15–18]. The evidence concerning the putative effects of rTMS on cognition is inconsistent, but a growing body of evidence shows that high-frequency rTMS enhances cognitive performance in healthy individuals [19] and in people with neuropsychiatric disorders [20,21]. A systematic review found that effects are greater in patients than in healthy volunteers [22]. Previous research was primarily concerned with basic cognitive functions, particularly attention, memory, and executive functions like decision-making and reasoning [19,21]. The few studies in healthy volunteers that investigated rTMS effects on social cognition or processing of emotional information, in particular facial affect, suggest that these processes can be enhanced [23] or disturbed [23–26], depending on the stimulation characteristics (frequency, duration, location of stimulation). Thus, rTMS with appropriate stimulation characteristics might be a promising method to alleviate impairments in social cognition in schizophrenia patients.

Impaired facial affect recognition in schizophrenia is probably related to a dysfunctional interaction between prefrontal and temporal cortex areas [27,28]. Prefrontal cortex areas are an important part of the neural network that processes emotional stimuli [29]. Studies of transcranial stimulation over the prefrontal cortex by either rTMS or direct current stimulation (tDCS) found lateralized changes in behavioral reactions to stimuli with emotional valence [30], an improvement in cognitive theory of mind tasks, a subcomponent of social cognition [31], and improved emotional face identification [32].

Against this background, in the present study we assessed in schizophrenia inpatients the effects on facial affect recognition of add-on treatment with high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC). We hypothesized that rTMS would improve cognitive performance more than sham rTMS.

Methods

Design and participants

The study was part of a comprehensive study on the clinical efficacy of rTMS in schizophrenia, which is described in more detail elsewhere [33,34]. The study followed a randomized, double-blind control group design. Assessments were performed before (T0) and after (T1) two weeks of daily (Monday–Friday) rTMS or sham control treatment as an add-on to stable antipsychotic drug treatment. Patients were allocated by block-wise randomization in a ratio of 4:3 to the verum rTMS or sham stimulation group.

Participants comprised $n = 35$ right-handed inpatients with a diagnosis of schizophrenia according to DSM-IV [35] and a history of at least three acute episodes. Exclusion criteria were alcohol or substance dependence in the last two years; neurological disorders; cardiac pacemaker; and a history of brain trauma, seizures, or neurosurgery. All patients had received stable antipsychotic medication for at least two weeks before the study, and the same medication was continued throughout the study. Additional treatment with lorazepam (1 mg per day) was allowed during the study. All patients provided written informed consent. The study was approved by the ethics committee of the Heinrich Heine University Duesseldorf, Germany.

After giving written informed consent, three patients refused to participate in the study and dropped out before the first rTMS stimulation. The remaining 32 patients (verum rTMS: $n = 18$, sham stimulation: $n = 14$) completed the study. The verum group consisted of 4 female and 14 male patients, and the sham group of 3 female and 11 male patients. Patients in the verum group had a mean age of 34.3 years (range 22–59 years) and a mean duration of illness of 5.7 years (SD = 5.2); patients in the sham group had a mean age of 34.4 years (range 19–51 years) and a mean duration of illness of 5.6 years (SD = 8.7). The antipsychotic and mood stabilizing drug profile for the verum and sham groups (18/14) was as follows: amisulpride 2/2, aripiprazole 2/2, clozapine 3/2, flupentixol 1/0, fluphenazine 1/0, haloperidol 0/1, lithium 1/0, olanzapine 4/6, perazine 1/0, pipamperone 3/1, quetiapine 1/1, risperidone 4/5, valproate 1/1 and ziprasidone 1/0. The chlorpromazine equivalent dose was significantly lower in the verum (466 ± 249 mg CPZ) than in the sham group (804 ± 366 mg CPZ, $P = 0.007$), but there was no association between chlorpromazine equivalent dose and cognitive performance. Demographic and clinical characteristics, psychopathology and neurocognitive performance at baseline did not differ significantly between the groups (Table 1).

rTMS stimulation

rTMS was applied with a MagPro X100 stimulation system and a figure-eight coil (MC-P-B70; diameter 100 mm) that can deliver magnetic pulses up to 100 Hz within a magnetic field of up to 4.1 T. Stimulation intensity was 110% of the motor threshold, which had been assessed at the beginning of the first session in both groups. Sham stimulation was performed with a sham coil system (MC-P-B70) without a magnetic field. The sham procedure elicited no tactile sensation at the site of stimulation and induced no significant cortical stimulation. Each coil was placed over the left DLPFC, located 5 cm anterior to and in a parasagittal plane with the point of the maximum stimulation of the abductor pollicis brevis muscle. Participants received a total of ten sessions of stimulation. Sessions were applied daily, except at the weekend, between 1.00 p.m. and 3.00 p.m. for two weeks. Each daily session entailed 10 Hz stimulation, consisting of 20 trains of 5 s duration with an inter-train interval of 55 s, resulting in a total of 1000 electromagnetic stimuli.

Table 1
Baseline clinical and neurocognitive characteristics of the sample.

	Possible range	Verum rTMS $n = 18$	Sham stimulation $n = 14$	Group comparison[a]
		Mean [SD]	Mean [SD]	
Clinical characteristics (baseline)[b,c]				
CGI-S	1–7	4.8 [0.7]	4.6 [0.7]	n.s.
PANSS general	16–112	40.9 [8.6]	40.3 [12]	n.s.
PANSS negative	7–49	23.7 [6.8]	26.8 [9.0]	n.s.
PANSS positive	7–49	14.4 [4.4]	14.4 [4.6]	n.s.
GAF	1–100	55.7 [11.4]	55.4 [11.5]	n.s.
Neurocognitive performance (baseline)[b]				
MWT	71–145	101.2 [13.9]	101.8 [16.2]	n.s.
D2	70–130	102.9 [21.3]	92.2 [13.5]	n.s.
TMT-A	max. 180 s	35.9 [30.8]	48.9 [61.7]	n.s.
TMT-B	max. 300 s	86.6 [38.5]	75.2 [33.7]	n.s.
WCST categories	0–6	3.5 [2.4]	3.3 [2.1]	n.s.

CGI-S: Clinical Global Impression Scale – severity index, PANSS: Positive and Negative Syndrome Scale, GAF: Global Assessment of Functioning Scale, MWT: "Mehrfachwahl-Wortschatztest", D2: D2 attention test, TMT-A,-B: Trail Making Test versions A and B, WCST: Wisconsin Card Sorting Test.

[a] Independent *t* test.

[b] Adapted from Ref. [33].

[c] Adapted from Ref. [34].