Archival Report

Biological Psychiatry

Left Prefrontal High-Frequency Repetitive Transcranial Magnetic Stimulation for the Treatment of Schizophrenia with Predominant Negative Symptoms: A Sham-Controlled, Randomized Multicenter Trial

Thomas Wobrock, Birgit Guse, Joachim Cordes, Wolfgang Wölwer, Georg Winterer, Wolfgang Gaebel, Berthold Langguth, Michael Landgrebe, Peter Eichhammer, Elmar Frank, Göran Hajak, Christian Ohmann, Pablo E. Verde, Marcella Rietschel, Raees Ahmed, William G. Honer, Berend Malchow, Thomas Schneider-Axmann, Peter Falkai, and Alkomiet Hasan

ABSTRACT

BACKGROUND: Investigators are urgently searching for options to treat negative symptoms in schizophrenia because these symptoms are disabling and do not respond adequately to antipsychotic or psychosocial treatment. Meta-analyses based on small proof-of-principle trials suggest efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of negative symptoms and call for adequately powered multicenter trials. This study evaluated the efficacy of 10-Hz rTMS applied to the left dorsolateral prefrontal cortex for the treatment of predominant negative symptoms in schizophrenia.

METHODS: A multicenter randomized, sham-controlled, rater-blinded and patient-blinded trial was conducted from 2007–2011. Investigators randomly assigned 175 patients with schizophrenia with predominant negative symptoms and a high-degree of illness severity into two treatment groups. After a 2-week pretreatment phase, 76 patients were treated with 10-Hz rTMS applied 5 days per week for 3 weeks to the left dorsolateral prefrontal cortex (added to the ongoing treatment), and 81 patients were subjected to sham rTMS applied similarly.

RESULTS: There was no statistically significant difference in improvement in negative symptoms between the two groups at day 21 ($p = .53$, effect size = .09) or subsequently through day 105. Also, symptoms of depression and cognitive function showed no differences in change between groups. There was a small, but statistically significant, improvement in positive symptoms in the active rTMS group ($p = .047$, effect size = .30), limited to day 21.

CONCLUSIONS: Application of active 10-Hz rTMS to the left dorsolateral prefrontal cortex was well tolerated but was not superior compared with sham rTMS in improving negative symptoms; this is in contrast to findings from three meta-analyses.

Keywords: Brain stimulation, Evidence-based psychiatry, Negative symptoms, Randomized controlled trial, Repetitive transcranial magnetic stimulation, Schizophrenia

http://dx.doi.org/10.1016/j.biopsych.2014.10.009

Schizophrenia is the most debilitating psychiatric disorder and is associated with a significant disease-related burden leading to tremendous direct and indirect treatment costs (1,2). Among the complex symptoms of schizophrenia, negative symptoms such as amotivation and affective flattening remain some of the most vexing challenges for effective treatment and improvement in outcome (3–5). These symptoms are highly prevalent, are very stable over time, are associated with cognitive impairment, and predict poor functional outcome and quality of life (3–5). For many patients, negative symptoms persist in the face of effective antipsychotic drug treatment of positive symptoms such as hallucinations and delusions, and adjunctive medications or psychosocial interventions have limited benefit (6).

Repetitive transcranial magnetic stimulation (rTMS) is a neuromodulatory noninvasive brain stimulation technique using repetitive application of magnetic pulses through the scalp leading to an excitability shift up in the stimulated cortical areas that can last several hours (7). Pharmacologic challenges in healthy subjects and repetitive measures of motor cortical excitability indicate that the brain activity changes after rTMS are related to molecular processes of plasticity (7). Certain rTMS devices with specific protocols have been approved by the U.S. Food and Drug

ISSN: 0006-3223

Administration for patients with depression with poor or incomplete response to pharmacotherapy (8). Positron emission tomography studies indicate that rTMS increases brain activity and cerebral blood flow both at the site of cortical stimulation and in interconnected sites and that these effects outlast the duration of stimulation (9–12). High-frequency rTMS applied to the dorsolateral prefrontal cortex (DLPFC) can modulate extrastriatal and mesostriatal dopaminergic pathways that may contribute to negative symptoms (13,14), suggesting rTMS may be a promising therapeutic option for negative symptoms of schizophrenia. This possibility is particularly important because reduced left DLPFC activation (15) and reduced prefrontal white matter volumes (16) have been linked to negative symptoms of schizophrenia and facilitatory and inhibitory DLPFC projections are critically involved in the modulation of dopaminergic networks (17,18). However, physiologic studies indicate disrupted plasticity in schizophrenia, which may reduce the efficacy of noninvasive brain stimulation (19–21).

Three meta-analyses of relatively small, heterogeneous single-center trials (with a maximum of 18 patients per treatment group; main target region was left DLPFC) of rTMS for negative symptoms suggest an effect size of .27–.53 compared with sham rTMS (18,22–24). Although there is still no evidence from multicenter randomized controlled trials, the application of rTMS for the treatment of negative symptoms of schizophrenia is a complementary treatment option discussed in the field. Our goal was to determine whether active 10-Hz rTMS would be superior to sham rTMS for the treatment of negative symptoms in patients with schizophrenia in the first large and adequately powered, multicenter, randomized controlled clinical trial.

METHODS AND MATERIALS

Written informed consent was obtained from all subjects after complete description of the study. The local ethics committees approved the protocol, which was conducted in accordance with the Declaration of Helsinki.

Subjects

We enrolled 197 inpatients and outpatients from three German university hospital centers (Goettingen, Duesseldorf, Regensburg) for this multicenter randomized, sham-controlled, rater-blinded and patient-blinded clinical trial. The inclusion criteria were International Classification of Diseases, Tenth Revision, diagnosis of schizophrenia (25) (F20.xx, confirmed by the Mini-International Neuropsychiatric Interview Plus interview (26)), age 18–60 years, and an illness duration of at least 1 year. A predominantly negative symptom syndrome was confirmed by a Positive and Negative Syndrome Scale (PANSS) (27) negative subscore >20 points, one of items N1–N7 scoring ≥4, and no reduction of ≥10% in PANSS negative subscore in the 2 weeks before intervention. Antipsychotic medication had to be stable for 2 weeks before study inclusion. The exclusion criteria were clinically relevant psychiatric comorbidity (including current misuse of or dependence on illegal drugs or alcohol), concomitant treatment with anticonvulsant drugs or benzodiazepines (lorazepam >2 mg/day, diazepam >10 mg/day), history of epileptic seizures or epileptic activity on baseline electroencephalography (EEG), previous treatment with rTMS, a contraindication for rTMS, verbal IQ <85, clinically relevant unstable medical conditions, involuntary hospitalization, or pregnancy (28).

Intervention

From 2007–2011, patients with schizophrenia entered a pretreatment assessment 12–16 days before the baseline visit at day 0. Patients meeting the exclusion criteria in this pretreatment period were withdrawn from the study. Eligible patients entered a 3-week, rater-blinded and patient-blinded, parallel-group rTMS intervention (active rTMS vs. sham rTMS added to ongoing treatment) period completed by day 21, followed by a 12-week extension phase (assessments at days 28, 45, and 105; no further rTMS treatment) (Figure 1). Patients randomly assigned to the active condition received 10-Hz rTMS applied to the left DLPFC (EEG International 10-20 system, F3-electrode, five treatment sessions per week during the 3-week treatment period) with an intensity of 110% of the individual resting motor threshold (29) and 1000 stimuli (20 trains with 50 stimuli per train, 30-sec intertrain interval) per session (30). Patients randomly assigned to the sham intervention were treated identically, but the magnetic coil was tilted over one wing at an angle of 45 degrees leading to similar skin sensations with significantly reduced biological activity compared with active stimulation (31) (see Figure S1 in Supplement 1 for an example of coil orientation). The F3-position is assumed to correspond to Brodmann areas 8, 9, or 46 on the media frontal gyrus (32–34). All participating sites used the same stimulators (MagPro X100; Medtronic A/S, Copenhagen, Denmark) and passively cooled MCF-B65 figure-of-eight coils (Medtronic A/S).

Study monitoring for safety and Good Clinical Practice aspects was performed by the Coordination Centre for Clinical Trials Duesseldorf (http://www.uniklinik-duesseldorf.de/kks). The trial has been registered at http://www.clinicaltrials.gov (NCT00783120), and the trial protocol has been published (30). The randomization procedure is described in Supplement 1.

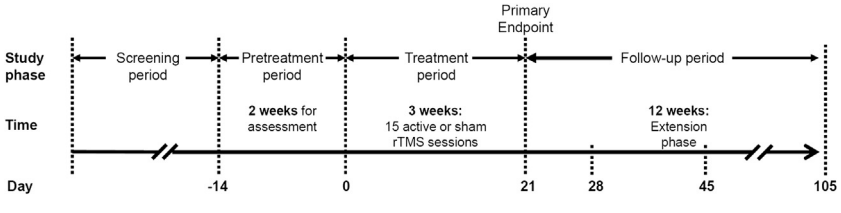

Figure 1. Trial study plan. After a screening period, patients with schizophrenia entered a pretreatment assessment 12–16 days before the baseline visit at day 0. Patients meeting the exclusion criteria in this pretreatment period were withdrawn from the study. Eligible patients entered a 3-week, patient-blinded and rater-blinded, parallel-group repetitive transcranial magnetic stimulation intervention (active vs. sham repetitive transcranial magnetic stimulation) period followed by a 12-week extension phase (extension-phase visits at days 28, 45, and 105; no treatment in either group). rTMS, repetitive transcranial magnetic stimulation.