Behavioural Brain Research 237 (2013) 300–307

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

The effect of long-term high frequency repetitive transcranial magnetic stimulation on working memory in schizophrenia and healthy controls—A randomized placebo-controlled, double-blind fMRI study

Birgit Guse[a,b,*], Peter Falkai[a], Oliver Gruber[a], Heather Whalley[c], Lydia Gibson[d], Alkomiet Hasan[a], Katrin Obst[e], Peter Dechent[f], Andrew McIntosh[c], Boris Suchan[b], Thomas Wobrock[a]

[a] University Medical Centre, Department of Psychiatry and Psychotherapy, Georg August University Göttingen, von-Siebold-Str. 5, D-37075 Göttingen, Germany
[b] Institute of Cognitive Neuroscience, Department of Neuropsychology, Ruhr University Bochum, Universitätsstr. 150, D-44780 Bochum, Germany
[c] Division of Psychiatry, Royal Edinburgh Hospital, University of Edinburgh, Kennedy Tower, Morningside, Edinburgh EH10 5HF, UK
[d] Institute of Psychology, Department of Experimental Psychology, Georg-August-University Göttingen, Goßlerstraße 14, D-37073 Göttingen, Germany
[e] Institute of Psychology, Department of Social Psychology, University Jena, Humboldtstr. 26, D-07743 Jena, Germany
[f] MR-Research in Neurology and Psychiatry, University Medical Center Göttingen, Robert-Koch-Str. 40, D-37075 Göttingen, Germany

HIGHLIGHTS

- 3-week HF rTMS does not alter brain activation during working memory.
- Schizophrenia patients do not significantly differ from controls after treatment.
- Long-term HF rTMS does not change cognitive performance.
- Active rTMS is not superior to placebo rTMS.

ARTICLE INFO

Article history:
Received 31 May 2012
Received in revised form 29 August 2012
Accepted 17 September 2012
Available online 27 September 2012

Keywords:
rTMS
fMRI
Middle frontal gyrus
Schizophrenia
Healthy controls
Long term effect
Working memory
Cognition

ABSTRACT

In schizophrenia patients negative symptoms and cognitive impairment often persist despite treatment with second generation antipsychotics leading to reduced quality of life and psychosocial functioning. One core cognitive deficit is impaired working memory (WM) suggesting malfunctioning of the dorsolateral prefrontal cortex. High frequency repetitive transcranial magnetic stimulation (rTMS) has been used to transiently facilitate or consolidate neuronal processes. Pilot studies using rTMS have demonstrated improvement of psychopathology in other psychiatric disorders, but a systematic investigation of working memory effects outlasting the stimulation procedure has not been performed so far. The aim of our study was to explore the effect of a 3-week high frequency active or sham 10 Hz rTMS on cognition, specifically on working memory, in schizophrenia patients ($n = 25$) in addition to antipsychotic therapy and in healthy controls ($n = 22$). We used functional magnetic resonance imaging (fMRI) to compare activation patterns during verbal WM (letter 2-back task) before and after 3-weeks treatment with rTMS. Additionally, other cognitive tasks were conducted. 10 Hz rTMS was applied over the left posterior middle frontal gyrus (EEG electrode location F3) with an intensity of 110% of the individual resting motor threshold (RMT) over a total of 15 sessions. Participants recruited the common fronto- parietal and subcortical WM network. Multiple regression analyses revealed no significant activation differences over time in any contrast or sample. According to the ANOVAs for repeated measures performance remained without alterations in all groups. This is the first fMRI study that has systematically investigated this topic within a randomized, placebo-controlled, double-blind design, contrasting the effects in schizophrenia patients and healthy controls.

1. Introduction

Schizophrenia is a major mental illness characterized by positive symptoms (e.g. delusions, hallucinations), negative symptoms (e.g. apathy, blunted affect, emotional/social withdrawal) and cognitive dysfunction. Research from the last twenty years indicates

* Corresponding author at: University Medical Centre, Department of Psychiatry and Psychotherapy, Georg-August-University Göttingen, Von-Siebold-Straße 5, D-37075 Göttingen, Germany. Tel.: +49 0 551 39 10114; fax: +49 0 551 39 9337.
E-mail address: bguse@gwdg.de (B. Guse).

0166-4328/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2012.09.034

that these impairments in cognition are one of the main predictors for poor social and functional outcome and a main reason for disability in schizophrenia patients [16,18,24]. Cognitive impairment in schizophrenia generally includes the domains of attention and concentration, psychomotor speed, learning and memory as well as executive functions [30,32]. One of the core cognitive deficits is working memory (WM) as part of a disturbed central executive system [6,53]. Working memory implies the short term retention of information that is no longer accessible in the environment and the manipulation of this information for guiding behavior [9]. Over the past few decades, studies have provided a substantial body of evidence supporting a critical role for bilateral prefrontal, anterior cingulate and parietal regions in mediating WM performance (e.g. [50]; for review [54]). The middle frontal gyrus (Brodmann area (BA) 9/46) is known to be mainly activated during the manipulation and executive monitoring of incoming stimuli (e.g. [55]), whereas the inferior frontal gyrus (BA 44) and parts of the superior frontal gyrus (premotor and supplementary motor area, BA 6) as well as parietal association cortices are most sensitive for maintenance processes (e.g. [38]).

These results are in line with functional and cytoarchitectural studies pointing to a tightly knit and specific network of frontal-mediated working memory functions (for review [35,40,56]). The prefrontal cortex, especially the dorsolateral prefrontal cortex (DLPFC, BA 9/46), has an important role in working memory and is, above all, well located for transcranial magnetic stimulation (TMS) [27]. In this context, Mull and Seyal [33] investigated whether transient functional disruption of the dorsolateral prefrontal cortex (DLPFC) with TMS would impair performance in a verbal WM task. Participants were presented sequences of letters and asked to decide if the letter just displayed was the same as the letter presented three trials back (n-back task). The study revealed an effect on task accuracy when TMS was applied to the left DLPFC between letter presentations. Thus, as inhibitory repetitive TMS (rTMS) induces virtual lesion in the prefrontal cortex interfering with cognitive performance, facilitatory stimulation has been discussed to have the potential to improve cognitive performance and memory functions [41]. The application of transcranial magnetic stimulation is one possibility to modulate activity states and to interfere with the function of certain brain areas. Physiological studies of the primary motor cortex conducted in healthy subjects indicate that, dependent on the frequency and pattern of the stimulation protocol, repetitive TMS can induce a long-lasting enhancement or reduction of cortical excitability (for review see [20,61]). In general, low frequency (<1 Hz) rTMS reduces and high frequency rTMS (>5 Hz) enhances cortical excitability, but the recently introduced theta-burst protocol (TBS, a modified repetitive TMS protocol) applied at very high-frequencies (50 Hz) does not follow this frequency-rule [44]. Dependent on whether the TBS is applied in an intermittent or continuous pattern, the effects are facilitatory or inhibitory. In addition to that, we also know from recently published studies that the effects of TBS and rTMS are dependent on many different factors, like history of synaptic plasticity, the interneuron networks recruited by the TMS pulse, current activity of the membrane potential, and pharmacological modulation [44,21,22]. All these factors contribute to the high interindividual variability of physiological and behavioral responses following TBS and rTMS.

However, there is emerging evidence that some established repetitive TMS protocols have the capacity to induce plasticity shifts of the stimulated and interconnected brain areas and, therefore, to modulate behavioral and cognitive functions (for review see [41,61,44,48]).

Based on these physiological findings, repetitive TMS has been successfully used to improve motor performance and motor learning [4,11,37,41]. Beyond the influence on the motor system there is growing evidence showing transient neuronal facilitation and cognitive process enhancement due to rTMS in healthy subjects. Evers et al. [12] studied visually evoked event-related potentials (ERP) and mean choice reaction time measured before and after 20 Hz rTMS (compared to sham and 1 Hz single TMS) applied to the left and right prefrontal cortex in healthy subjects. Results revealed a significant decrease of P3 latencies and reaction time due to 20 Hz rTMS of the left but not right PFC. In a combined study using TMS and near-infrared spectroscopy, Yamanaka et al. [60] administered 5 Hz or sham TMS to the left or right parietal cortex of healthy subjects during the delay period of a spatial WM task (control task: visuospatial attention task). Reaction times improved in the spatial WM task only after active stimulation of the right parietal cortex. This effect was attended by significantly increased frontal oxygenated hemoglobin (oxy-Hb) levels during the WM task and reduced levels during the control task reflecting a selectively facilitating effect on spatial WM. Klimesch et al. [29] could show that rTMS at individual upper alpha frequency (IAF + 1 Hz) delivered to the mesial frontal (Fz) and right parietal (P6) cortex can enhance the performance in a mental rotation task.

However, most studies raise limitations concerning the focus on direct cognitive effects of single sessions. Repeated session designs applying daily rTMS to test gradual or cumulative alterations in after-effects should be proven for therapeutic purposes. Until now, some circumscribed outlasting or consolidation effects of rTMS and other non-invasive brain stimulation techniques have been described in the human motor system indicating long-lasting behavioral effects (e.g. [41,42,61], see above). The transfer of these motor-system findings to prefrontal regions and the increase of stimulation sessions is essential for treatment application in neuropsychiatric diseases associated with working memory and other cognitive deficits.

We have recently reviewed the effects of high-frequency repetitive TMS (>1 Hz) on cognitive functions and revealed that stimulation protocols using frequencies between 10 Hz and 20 Hz and 80–110% of the individual resting motor threshold are most likely to result in an improvement of cognitive functions. Furthermore, our review indicates that improvements depend on the repetition rate of rTMS sessions and that patients with neuropsychiatric disorders do show usually greater improvements than healthy controls [19]. In schizophrenia patients, facilitatory rTMS applied to the frontal lobe has been discussed to be effective in the treatment of negative symptoms (Meta-Analysis and review [10]). Within some of these studies targeting negative symptoms via frontal repetitive TMS, cognitive effects of the stimulation were additionally investigated, whereas only one of five randomized controlled trials showed a beneficial effect in schizophrenia patients [8].

To explore the neurobiology underlying non-invasive brain stimulation related functional changes in the frontal lobe, placebo-controlled, randomized and double-blind studies using techniques of experimental neurophysiology and functional brain imaging are necessary.

In particular, multimodal studies contrasting effects on the diseased versus healthy brain are needed to get a better understanding of process in the frontal cortex. Therefore, the aim of our combined long-term rTMS and fMRI study was to investigate whether long-term rTMS is a promising tool to modulate working memory in healthy subjects and in schizophrenia patients that outlasts the stimulation procedure. In this context, we were interested in functional cerebral alterations of the frontal lobe evaluated by fMRI as well as behavioral performance effects due to rTMS treatment.