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Interest of targeting either cortical area Brodmann 9 or 46 in rTMS treatment for depression: A preliminary randomized study

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HIGHLIGHTS

- Both BA 9 and BA 46 appear to be effective cortical targets to treat depression with rTMS.
- Neither of these two cortical areas seems to be a more appropriate stimulation target to treat depression.
- There is no obvious interest in changing from one of these targets to the other when the first is ineffective.

ABSTRACT

Objective: To assess the interest of specifically targeting Brodmann Areas (BA) 9 or 46 for rTMS treatment of depression.
Methods: Patients with Treatment-Resistant Depression were randomly assigned to two treatment groups to receive either rTMS on BA 9 or on BA 46. Each patient underwent 10 sessions of 1 Hz-rTMS for 2 weeks. The Hamilton and Montgomery–Asberg Depression Rating Scales (HDRS, MADRS) were used under blind conditions to assess the therapeutic response (50% improvement). A Wilcoxon signed-rank test was used to compare the depression rating scales scores obtained before and after the 10 rTMS sessions for each of the two groups. The therapeutic results in the two groups were compared using the Mann–Whitney–Wilcoxon test. We also reported the effect sizes using Hedges's *g*.
Results: Fifteen patients were included. Stimulation of both BA 9 ($n = 7$) and BA 46 ($n = 8$) led to similar therapeutic responses in the two groups (with moderate effect size), such as the mean decrease in HDRS (BA 9: $p = 0.015$; BA 46: $p = 0.010$) and MADRS (BA 9: $p = 0.042$; BA 46: $p = 0.038$) scores.
Conclusion: Our results do not come out in favor of one or the other BA.
Significance: Stimulation of BA 9 and BA 46 appears to be equally effective in the treatment of depression.

1. Introduction

Since Barker et al. proposed the therapeutic use of magnetic fields in 1985 (Barker et al., 1985), repetitive Transcranial Magnetic Stimulation (rTMS) has generated enormous interest in various medical fields. This neurostimulation technique utilizes rapidly changing magnetic field pulses via a metallic coil placed against the patient's cranium to induce electric currents in the underlying cortical tissue (Fox et al., 2012). The stimulators and coils currently in production, which develop about 1.5–2.0 Tesla (T) at the face of the coil, induce a sufficiently strong electric field to depolarize neurons (Rossi and Hallett, 2009). When TMS pulses are applied repetitively, they can thus modulate cortical excitability (Rossi

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and Hallett, 2009). This innovative, non-invasive therapy, which is known to be safe (O'Reardon et al., 2007), has been investigated for the treatment of several psychiatric disorders. Several controlled studies have been conducted to evaluate the efficacy of rTMS on Treatment-Resistant Depression (TRD). The choice of site for stimulation is based on imaging findings that implicate this region in the pathophysiology of depression and in antidepressant effects (O'Reardon et al., 2007). Most of the trials, including a large international multi-center trial, found that active rTMS treatment was more effective than sham stimulation in the treatment of depression (O'Reardon et al., 2007; Fitzgerald et al., 2009).

However, despite this evidence about the improvements achieved with rTMS for the treatment of major depression, concerns about the efficacy continue to be expressed, as many studies have reported limited effect sizes or response rates (Fitzgerald et al., 2009; Loo and Mitchell, 2005). According to Lam's meta-analysis, which included 24 studies ($n = 1092$ patients), pooled response and remission rates were 24% and 17% for active rTMS, and 9% and 5% for sham, respectively (Lam et al., 2008).

The limited response rates of rTMS on depressive disorders can be explained by the fact that rTMS studies often focus on depressive patients who have failed to respond to several antidepression medications, i.e. suffering from resistant depression (George et al., 2010). We may also suggest, however, that the limited response rate is consecutive to an inadequate stimulation parameter, such as the poor definition of the cortical target. Indeed, the vast majority of clinical trials in depression positioned the TMS coil on the scalp 5 cm anterior to the optimal site to elicit a motor twitch in the distal hand muscle (Rossi and Hallett, 2009). This "5 cm method" is presumed to target the dorsolateral prefrontal cortex (DLPFC), the target used to treat depression with rTMS. However, in some cases, the "5 cm method" may fail to reach the DLPFC, and may lead to stimulation of the premotor cortex, which is probably a poor region for stimulation (Johnson et al., 2013). Some studies using a neuronavigation system, which allows the coil to be positioned on the scalp to stimulate a brain site identified on an MRI scan for individual subjects, have also confirmed that the "5 cm method" to target the DLPFC does not provide reliable positioning (Herwig et al., 2001). Further studies using a neuronavigation system showed that placing the coil 2–3 cm anterior to the motor-twitch site to target the DLFPC was associated with improved response rates in rTMS (Fitzgerald et al., 2009; Herbsman et al., 2009). Without any doubt, optimized positioning of the stimulations will play a role in a patient's response to TMS therapy (Johnson et al., 2013).

The high precision achieved with a neuronavigation system, however, raises new questions concerning the optimal cortical target to treat depressive disorders. Indeed, the DLPFC is a large cortical region that comprises different areas to target, in particular two different cyto-architectural sub-regions, Brodmann Areas 9 and 46 (BA 9 and BA 46). These two areas have been considered putative targets in the treatment of depression with repetitive TMS (rTMS), and it has been found that accurate targeting of these cortical regions increases the efficacy of this treatment (Herbsman et al., 2009; Fitzgerald et al., 2009).

To our knowledge, no studies have compared the effects of rTMS of BA 9 with those of BA 46. In the absence of any consensus about which sites to target, studies using neuronavigation positioned the coil so that the magnetic field produced stimulation throughout parts of both areas 9 and 46 (Fitzgerald et al., 2009). But, as observed with other BA (i.e. the primary motor cortex), it is possible that since BA 9 and 46 do not have the same types of cells, their involvement in mood disorders may differ, and they may therefore respond differently to rTMS treatment. Given the above, we may imagine that only one of the two cortical targets could be an effective target to treat depression. This might explain why previous studies that did not use a neuronavigation system or a targeting process to target the two cortical sub-regions showed moderate response rates, since they sometimes stimulated the effective cortical target and sometimes the other one.

We hypothesized that only one of these two cortical targets could be effective in reducing the symptoms of depression. We therefore verified the efficacy of rTMS applied to the two cortical targets in depressive patients in order to answer the following questions:

1. Are both BA 9 and BA 46 potential targets for the treatment of depression with rTMS?
2. Is one of these two cortical targets more appropriate to treat depression?
3. Is there any interest in changing from one of these targets to the other when the first is ineffective?

We therefore conducted a study in which patients suffering from depression were randomly assigned to receive rTMS targeted on BA 9 and BA 46. The efficacy these two stimulation parameters were assessed with a common depression rating scale. We did not use sham stimulations as a control since many publications including double-blind randomized sham-controlled studies and meta-analyses support the antidepressant efficacy of the technique (Dell'osso et al., 2011).

2. Methods

2.1. Participants

Male and female in-patients and outpatients, older than 18 and suffering from Treatment-Resistant Depression (TRD) were enrolled in the study. The study was conducted at our center with active enrollment during a period of 12 months extending from February 2010 to February 2011.

The depressive disorder was defined as Major Depressive Disorder in accordance with DSM-IV criteria (APA, 2000). The resistance criteria were defined as in previous rTMS' studies by the lack of response to adequate treatment (6 weeks) with more than two classes of antidepressants during the current episode of depression (Fitzgerald et al., 2009, 2003), which corresponds to step 2 of the Thase and Rush classification scheme of TRD (Thase and Rush, 1995).

To qualify for enrollment, patients were required to have a total score of $\geqslant 22$ on the 21-item Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1960). After this screening assessment, patients had to be able to go without their psychiatric medications (withdrawal for at least 1 week followed by 1 week of psychotropic washout before starting rTMS treatment). Moreover, a patient was considered eligible for the study if the HDRS score did not improve by more than 25% between the screening assessment and the assessment conducted just before starting the first rTMS session (baseline).

Patients were excluded from the study if they had a clinical diagnosis of bipolar I or II disorder, a history of current substance abuse (except nicotine), and a history of seizures or other neurological conditions. Additional exclusion criteria were clinically significant comorbid disease such as liver, kidney or heart failure, and a pacemaker. Female patients were excluded if they were pregnant or lactating.

2.2. Study design

The study had three phases (Fig. 1):

The first phase was a lead-in phase, in which all psychotropic drugs were progressively stopped in order to have a 1-week