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Equivalent brain SPECT perfusion changes underlying therapeutic efficiency in pharmacoresistant depression using either high-frequency left or low-frequency right prefrontal rTMS

Raphaëlle Richieri [a,b,*], Laurent Boyer [b], Romain Padovani [a,b], Marc Adida [a], Cécile Colavolpe [c,d], Olivier Mundler [c,d], Christophe Lançon [a,b], Eric Guedj [c,d,e]

[a] Hôpital Sainte Marguerite, Pôle de Psychiatrie Universitaire, 13009 Marseille, France
[b] Université d'Aix-Marseille, EA 3279, Unité de Recherche Santé Perçue, 13005 Marseille, France
[c] Service Central de Biophysique et Médecine Nucléaire, Hôpital La Timone, 13005 Marseille, France
[d] CERIMED, Aix-Marseille Université, 27, boulevard Jean Moulin, 13385 Marseille cedex 05, France
[e] INT, CNRS UMR 7289, Aix-Marseille Université, 27, boulevard Jean-Moulin, 13385 Marseille cedex 05, France

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ABSTRACT

Background: Functional neuroimaging studies have suggested similar mechanisms underlying antidepressant effects of distinct therapeutics.
Objective: This study aimed to determine and compare functional brain patterns underlying the antidepressant response of 2 distinct protocols of repetitive transcranial magnetic stimulation (rTMS).
Methods: 99mTc-ECD SPECT was performed before and after rTMS of dorsolateral prefrontal cortex in 61 drug-resistant right-handed patients with major depression, using high frequency (10 Hz) left-side stimulation in 33 patients, and low frequency (1 Hz) right-side stimulation in 28 patients. Efficiency of rTMS response was defined as at least 50% reduction of the baseline Beck Depression Inventory score. We compared the whole-brain voxel-based brain SPECT changes in perfusion after rTMS, between responders and non-responders in the whole sample ($p<0.005$, uncorrected), and separately in the subgroup of patients with left- and right-stimulation.
Results: Before rTMS, the left- and right-prefrontal stimulation groups did not differ from clinical data and brain SPECT perfusion. rTMS efficiency (evaluated on % of responders) was statistically equivalent in the two groups of patients. In the whole-group of responder patients, a perfusion decrease was found after rTMS, in comparison to non-responders, within the left perirhinal cortex (BA35, BA36). This result was secondarily confirmed separately in the two subgroups, i.e. after either left stimulation ($p=0.017$) or right stimulation ($p<0.001$), without significant perfusion differences between these two subgroups.
Conclusions: These data show that distinct successful rTMS protocols induce equivalent brain functional changes associated to antidepressive efficiency, consisting to a remote brain limbic activity decrease within the left perirhinal cortex. However, these results will have to be confirmed in a double-blind randomized trial using a sham control group.

1. Introduction

Prefrontal repetitive transcranial magnetic stimulation (rTMS) is a non-invasive well-tolerated alternative technique to pharmacological treatment or electroconvulsivotherapy (ECT) proposed in major depressive episodes (George and Post, 2011; Rumi et al., 2005) both in unipolar (Lam et al., 2008; Richieri et al., 2010; Schutter, 2010; Slotema et al., 2010) and in bipolar patients (Dell'Osso et al., 2009; Richieri et al., 2010; Tamas et al., 2007). Meta-analyses have highlighted a threshold of 50% decrease in symptom severity, in up to 76% of patients, using rTMS protocols based on high-frequency left stimulation or low-frequency right stimulation of the dorsolateral prefrontal cortex (DLPFC) (Gross et al., 2007; Schutter, 2010; Slotema et al., 2010). Accordingly, the U.S. Food and Drug Administration has recently approved rTMS for patients who have not responded to antidepressant medication. The mechanisms of action of prefrontal rTMS as an antidepressant are, however, still not fully elucidated.

Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; DLPFC, Dorsolateral Prefrontal Cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; ECT, Electroconvulsivotherapy; rCBF, regional Cerebral Blood Flow; rTMS, repetitive Transcranial Magnetic Stimulation; STAI, State Trait Anxiety Inventory; 99mTc-ECD SPECT, 99m Tc-Ethyl Cysteinate Dimer Single-Photon Emission Computed Tomography.

* Corresponding author at: Hôpital Sainte Marguerite, Pôle Psychiatrie Universitaire, 270, Boulevard Sainte Marguerite, 13274 Marseille Cedex 9, France. Tel.: +33 4 91 74 46 01; fax: +33 4 91 74 62 16.
E-mail address: raphaellemarie.richieri@ap-hm.fr (R. Richieri).

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Based on the report of a left prefrontal hypometabolism in depressive patients, George et al. (1995) first proposed to stimulate the left DLPFC with high-frequency (>5 Hz). Later, in accordance with the interhemispheric functional asymmetry described in neuroimaging studies (Maeda et al., 2000; Mottaghy et al., 2002; Rotenberg, 2004), rTMS protocols were developed using low-frequency stimulation (≤1 Hz) of the right DLPFC (Januel et al., 2006). The choice of distinct frequency comes from electrophysiological data of the motor cortex, showing that high-frequencies may have an excitatory effect while low-frequencies tend to suppress cortical excitability (Chen et al., 1997; Pascual-Leone et al., 1994). Interestingly, the efficiency of low-frequency rTMS stimulation of the right DLPFC and of high-frequency rTMS stimulation of the left DLPFC seems to be similar in depressed patients (Fitzgerald et al., 2009; Hoppner et al., 2003; Isenberg et al., 2005). Nevertheless, the comparative neural effects of high-frequency left stimulation and low-frequency right stimulation have not been studied in depressed patients. Based on the report of frontal functional asymmetry in depressed patients at the expense of the left hemisphere, and based on the known brain effects of low-frequency vs. high-frequency stimulation (inhibition vs. excitation), we hypothesize that low-frequency rTMS of the right DLPFC and high-frequency rTMS of the left DLPFC generate similar functional changes when rTMS is efficient.

Moreover, functional changes specifically associated to the antidepressive response remain unclear after either left or right rTMS. Indeed, most neuroimaging studies compared global functional changes after rTMS, and not those specifically related to the antidepressive efficiency, revealing discrepant complex patterns of local and remote changes (Catafau et al., 2001; Conca et al., 2002; Kito et al., 2008a; Loo et al., 2003; Mottaghy et al., 2002; Nahas et al., 2001; Peschina et al., 2001; Speer et al., 2000; Zheng, 2000).

On the other hand, functional neuroimaging studies have suggested similar mechanisms that underlie the antidepressant effects of distinct therapeutics. Antidepressant effects of somatic therapies such as drugs (Drevets et al., 2002a; Kennedy et al., 2001; Mayberg et al., 2000; Smith et al., 2002), vagal nerve stimulation (Henry et al., 1998), or deep brain stimulation (Lozano et al., 2008) all seem related to the reduction of limbic activity, which plays a key role in emotional and mood regulations. Changes in prefrontal activity are also described, but with some discrepancies after treatment (i.e. increased or decreased activity), and not related to antidepressive efficiency (Fitzgerald et al., 2006). These findings are consistent with the model of a dysregulated fronto-limbic network, whose normalization could underlie therapeutic efficiency (Mayberg, 2003; Rigucci et al., 2010). Likewise, antidepressant effects of rTMS should also consist in a decreased activity of limbic structures, whatever the protocol of stimulation used.

99mTc-ethyl cysteinate dimer single-photon emission computed tomography (99mTc-ECD SPECT) is a valuable tool to investigate regional cerebral blood flow (rCBF) in a range of psychiatric disorders, including depression (Richieri et al., 2011; Rigucci et al., 2010). Our study aimed to determine and compare the whole-brain voxel-based specific antidepressive rCBF effects of left-high and right-low frequency prefrontal rTMS in patients with pharmacoresistant depression.

We hypothesized that the functional effects of high frequency left- and low frequency right-rTMS applied over the DLPFC are similar, for a same level of antidepressive response, and that they consist of decreased limbic activity, as previously reported for other types of treatment (Drevets et al., 2002a; Henry et al., 1998; Kennedy et al., 2001; Lozano et al., 2008; Mayberg et al., 2000; Smith et al., 2002).

2. Materials and methods

2.1. Subjects

This study conducted in a public psychiatric teaching hospital in Marseilles involved a retrospective review of all right-handed patients with pharmacoresistant depression treated with DLPFC rTMS from January 1, 2010, to August 30, 2010 for left high-frequency stimulation, and from September 1, 2010 to December 31, 2010 for right low-frequency stimulation.

All patients (N = 61) met DSM-IV criteria for major depressive disorder (unipolar or bipolar depression) (APA, 1994). Inclusion criteria also included non-response to pharmacological treatment of depression using a minimum of two distinctly different classes of antidepressant medications for episodes occurring at the time of enrolment or earlier (Thase and Rush, 1997), and written informed consent. Exclusion criteria were based on the following criteria: age under 18 years, neurological disorders or convulsive disorders, and previous rTMS or ECT treatments. Pre-treatment with an antidepressant and/or mood stabilizer medication had to have been stable for at least 2 weeks prior to entry in the study and to have remained unchanged throughout the course of the study. No benzodiazepines were administrated during rTMS treatment.

2.2. rTMS treatment

Magnetic stimulation was performed using a Medtronic MagPro X100 stimulator and a figure eight-shaped water-cooled coil (Medtronic Inc., Minnesota). At the first rTMS session, each subject underwent a determination of his or her motor threshold. The motor threshold was defined as the minimum intensity that produced the most prominent abduction of the right abductor pollicis brevis muscle after stimulation of the left motor cortex and of the left abductor pollicis brevis muscle after stimulation of the right motor cortex, holding the coil with the handle pointing from 45° dorsally to laterally. The coil was positioned 5 cm anteriorly and in a parasagittal plane from the location that maximized movement in the right or left abductor pollicis brevis as determined by an electromyogram. Because most studies first showed antidepressant efficacy with high-frequency stimulation over the left DLPFC, we initially chose this protocol. From September 1, 2010, our clinical group changed the lateralization because low-frequency rTMS presents potential advantages over high-frequency. Indeed, low-frequency rTMS may be safer and better tolerated because of the shorter duration of daily session and lower risk of seizure induction (Eche et al., 2012; Rossi et al., 2009). rTMS was delivered to the left DLPFC at a frequency of 10 Hz at 120% of right motor threshold. Each session consisted of five-second trains with a 25-second inter-train interval (2000 pulses per day). rTMS was delivered to the right DLPFC at a frequency of 1 Hz at 120% of left motor threshold. In line with previous studies (Schutter, 2010), session consisted of 60-second trains with a 30-second inter-train interval (360 pulses per day). Twenty treatment sessions were administered in a 4-week period (five sessions per week).

2.3. Data collection

The following data were recorded: (1) demographic characteristics: gender and age; and (2) clinical characteristics: duration of illness, episode duration, depression severity using the 13-item Beck Depression Inventory (BDI short-form) and Clinical Global Impression (CGI), and anxiety severity using the State Trait Anxiety Inventory (STAI) (Spielberger et al., 1985). All patients were assessed twice with the BDI, CGI, and STAI: before rTMS (t0, i.e. baseline), and after 20 rTMS sessions (t1). RTMS response was defined as at least 50% reduction in the baseline BDI score (Holtzheimer et al., 2001). The cutoffs used are as follows: 0–3: no depression; 4–7: minimal depression; 8–15: mild to moderate depression; and 16–39: severe depression (Beck et al., 1988).

2.4. SPECT protocol

Brain SPECT was performed in all patients, with the same camera, and under the same conditions (Richieri et al., 2011). In patients, this exam was performed during the week before rTMS, and a second SPECT scan was obtained during the week after the end of the rTMS