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Preliminary communication

Resting electroencephalographic correlates of the clinical response to repetitive transcranial magnetic stimulation: A preliminary comparison between unipolar and bipolar depression

Agata Woźniak-Kwaśniewska [1,a], David Szekely [2,a,b], Sylvain Harquel [c,d], Thierry Bougerol [b], Olivier David [a,*]

[a] EA 4617 Fonctions Cérébrales et Neuromodulation, Grenoble Institut des Neurosciences, Université Joseph Fourier, Grenoble, France
[b] Clinique Universitaire de Psychiatrie, Pôle Psychiatrie Neurologie, Centre Hospitalier Universitaire, Grenoble, France
[c] UMR 5105 UPMF CNRS, Laboratoire Psychologie Neurocognition, Saint Martin d'Hères, France
[d] UMS IRMaGe, Grenoble, France

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ABSTRACT

Background: Major depressive disorder (MDD) and bipolar disorder (BP) are two different types of mood disorders, sometimes difficult to distinguish from their depressive symptoms, and for which repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) has been proposed to treat refractory patients. Here we studied whether the electroencephalogram (EEG) at rest could be used to predict the therapeutic response to left DLPFC 10 Hz rTMS, and to which extent BP and MDD patients show similar correlation between the clinical response and the cortical networks at rest.
Methods: Eight MDD (6 females) and 10 BP patients (6 females) were included. The rTMS therapy consisted of 10 to 20 neuronavigated sessions, with 2000 pulses continuously applied at 120% motor threshold for each session. RTMS sessions at the beginning, middle and end of the therapy were performed while recording EEG signals. EEG spectral power was partitioned using the common physiological frequency bands and was statistically analysed at the scalp level and after cortical source reconstruction.
Results: We found significantly higher power in theta and beta bands in BP patients than in MDD patients, mainly localised in the prefrontal cortex. In addition, responders showed higher power in delta and theta bands in parietal regions and weaker frontal alpha power, when compared to non-responders.
Discussion: These preliminary findings on a small cohort suggest that pre-treatment EEG oscillatory patterns may have some predictive value regarding rTMS therapy, both for MDD and BP disorders.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) of dorsolateral prefrontal cortex (DLPFC) has been shown to be an effective therapeutic treatment for major depressive disorder (MDD) (Carpenter et al., 2012; Fitzgerald et al., 2006; George et al., 2000, 1995; Pascual-Leone et al., 1996). Studies on rTMS in bipolar depression (BP) are less numerous (Dell'Osso et al., 2009; Dolberg et al., 2002; Tamas et al., 2007). Neurobiological mechanisms underlying the therapeutic response to rTMS are supposed to involve brain areas remote from the targeted site, thereby altering oscillatory activity, plasticity and connectivity of neural networks at a large scale. In particular, it is likely that the limbic-cortical network, composed of cortical (dorsolateral, medial and ventral prefrontal cortices) and limbic (hippocampus and amygdala) structures (Li et al., 2010), is modulated by rTMS of DLPFC.

EEG brought important neurophysiological information about depression and various studies have found that typically 20–40% of depressed patients have EEG abnormalities, with several characteristics and controversial patterns (Coburn et al., 2006). Moreover, up to 80% of psychiatric patients present various EEG abnormalities on

Abbreviations: ANOVA, analysis of variance; BP, bipolar disorder; CGI, Clinical Global Impression; BDI, Beck Depression Inventory; DLPFC, dorso-lateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder 4th edition; EEG, electroencephalography; FFT, fast Fourier transform; ICA, independent component analysis; MADRS, Montgomery Asberg Depression Rate Scale; MDD, major depressive disorder; MRI, magnetic resonance imaging; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; YMRS, Young Mania Rating Scale

* Corresponding author. Tel.: +33 4 56 52 05 86; fax: +33 4 56 52 05 98.
E-mail address: Olivier.David@inserm.fr (O. David).
[1] Present address: Universität zu Lübeck, Institute of Physiology, Ratzeburger Allee 160, D-23562 Luebeck.
[2] Present address: Clinique de Psychiatrie, Centre Hospitalier Princesse Grace, 1 avenue Pasteur, BP 489 MC 98012 Cedex, Principauté de Monaco.

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contrary to only 10% of healthy subjects (Begić et al., 2011; Coburn et al., 2006). Increased frontal EEG asymmetry, as measured by relatively higher left than right alpha band activity, has been proposed to characterise depressed individuals (Allen et al., 2004; Debener et al., 2000; Vuga et al., 2006) and to be a state-marker of depression (Carpenter et al., 2012; Debener et al., 2000; Fitzgerald et al., 2006; George et al., 2000, 1995; Pascual-Leone et al., 1996). In addition, many studies have shown the association of theta alterations with treatment response to antidepressants, although these findings are inconsistent across studies (Dell'Osso et al., 2009; Dolberg et al., 2002; Heikman et al., 2001; Iosifescu et al., 2009; Knott et al., 2001, 1996; Tamas et al., 2007). In general, the modulations in frontal theta band have been interpreted as reflecting altered activity in the anterior cingulate cortex implicated in emotional regulations (Iosifescu, 2011; Li et al., 2010).

The main interest of EEG recordings in a clinical setting for depression is to try to predict the response to therapy. In this context, inter-hemispheric asymmetry of occipital alpha and prefrontal theta bands have been reported as a valuable pretreatment EEG features to differentiate responders from non-responders (Bruder et al., 2008; Carpenter et al., 2012; Fitzgerald et al., 2006; George et al., 2000, 1995; Iosifescu et al., 2009; Pascual-Leone et al., 1996). Alpha asymmetry at baseline was also identified as a possible discriminator: responders showed greater alpha power over right than over left hemisphere, whereas non-responders tended to show the opposite pattern (Bruder et al., 2008, 2001; Dell'Osso et al., 2009; Dolberg et al., 2002; Knott et al., 1996; Tamas et al., 2007; Tenke et al., 2011; Ulrich et al., 1984). However, only one study was published so far on the predictive value of EEG to 10 Hz rTMS therapy for depression (Li et al., 2010; Micoulaud-Franchi et al., 2012). These authors reported a negative correlation of the variation in the clinical response, between the baseline and the end of 10 Hz rTMS therapy, with alpha band power in left and right parietal-temporal regions.

Here, we aimed to further assess how EEG at rest could be used to predict the therapeutic response to left DLPFC rTMS at 10 Hz in BP and MDD patients. We also wanted to evaluate whether BP and MDD patients show similar correlation between the clinical response and the resting state cortical networks.

2. Methods

2.1. Participants

This study was approved by the ethical committee of Grenoble University Hospital (ID RCB: 2011-A00114-37) and all participants gave a written informed consent. Twenty right-handed patients were recruited from the Psychiatry Department of Grenoble University Hospital after an interview with the psychiatrist (D.S.) in charge of their rTMS therapy. Data could be used in 18 out of the 20 patients. All those patients met criteria for major depressive episode (8 MDD patients; 6 females; age range 44–64, mean 52.1 ± 7.8) or bipolar depressive episode (10 BP patients, 6 females, age range 32–69, mean 48.7 ± 12:6) according to the Diagnostic and Statistical Manual of Mental Disorder 4th ed. (DSM-IV). Inclusion criteria for MDD included non-response to pharmacological treatment of depression level of resistance 3 on Thase and Rush criteria (Coburn et al., 2006; Thase and Rush, 1997) using a minimum of two distinctly different classes of antidepressant medications for actual depressive episode (appropriate doses and duration) occurring at the time of enrolment or earlier. Bipolar patients who met mixed characteristic (according to DSM-IV) were not included in the study. For all patients, exclusion criteria included age under 18 years, drug abuse, current comorbid major mental disorders assessed by clinical examination in axe II (DSM IV-TR), neurological illness or convulsive disorders, and previous treatment with electroconvulsivotherapy.

Pre-treatment with an antidepressant and/or mood stabiliser medication of MDD patients has been unmodified for at least four weeks prior to the entry in the study, and remained unchanged throughout the course of the study. For BP patients, mood stabiliser medication has been optimised according to recent recommendation (Begić et al., 2011; Coburn et al., 2006; Frances et al., 1998), then maintained at an unmodified dosage for at least two weeks prior to the entry in the study, and remained unchanged throughout the course of the study. No benzodiazepines were administered two weeks before and during rTMS treatment. Only cyanemazine and hydroxyzine were tolerated during the study.

Clinical evaluation was performed using the Montgomery Asberg Depression Rate Scale (MADRS) (Allen et al., 2004; Debener et al., 2000; Montgomery and Asberg, 1979; Vuga et al., 2006), 13-item Beck Depression Inventory (BDI-Short Form) (Beck et al., 1996; Debener et al., 2000) and Clinical Global Impression (CGI). On average, MADRS at inclusion was 24.6 ± 9.3 for MDD patients and 23.6 ± 3.2 for BP patients. Duration of illness was 10.3 ± 6.4 years for MDD patients and 18.9 ± 10.9 years for BP patients. For BP patients, maniac or mixed symptoms were evaluated on clinical examination using the Young Mania Rating Scale (YMRS) (Heikman et al., 2001; Iosifescu et al., 2009; Knott et al., 2001, 1996; Young et al., 1978). All patients were assessed at inclusion, before the first EEG recording and after each of the 5 rTMS sessions by the same senior psychiatrist (D.S.). The response to rTMS treatment was defined as at least 50% reduction of the baseline MADRS scores. Patients were qualified as responders when MADRS score was less than 10. If YMRS was more than 15, at inclusion or during the course of rTMS treatment, patients were excluded from the trial.

2.2. rTMS sessions

At the first rTMS session, resting motor threshold (RMT) of the right thumb abductor was determined by measuring electromyographic responses (MEP Monitor, Tonika Elektronic A/S, Denmark) to single TMS pulses to the left motor cortex. The motor threshold was defined as the minimum stimulation intensity capable to induce at least 5 motor evoked potentials of at least 50 μV peak-to-peak amplitude in 10 single TMS stimulations (Iosifescu, 2011; Pascual-Leone et al., 1996). During rTMS treatment, the stimulation was guided by a neuronavigation system (Premium Edition, Localite GmbH, Germany) to precisely define the neuroanatomical target of TMS on the patient MRI. The TMS coil was then positioned over the left DLPFC target point, defined as the intersection between Brodmann areas 9 and 46 along the middle frontal gyrus. Active rTMS was performed using a MagPro × 100 TMS stimulator (Tonica Elektronik A/S, Denmark) with butterfly MCF-B65-cooled coil (Tonica Elektronik A/S, Denmark). The coil was placed tangentially to the scalp to produce the highest level of the stimulation on the cortical region parallel to the coil (Chen et al., 2003). The handle was placed backward and laterally, approximately at 45° from the midline perpendicular to the central sulcus. According to the standard procedure for depression treatment at Grenoble University Hospital, the left DLPFC was stimulated at a frequency of 10 Hz in 5-s trains at 120% of the estimated RMT. Forty trains were given in each session (2000 pulses per session) with a 25-s inter train interval. A maximum of twenty sessions were administrated within a 4-week period.

2.3. EEG acquisition

Patients were seated in a reclining armchair with neck and back supported with a pillow, arms relaxed and eyes closed. EEG