Parieto-temporal alpha EEG band power at baseline as a predictor of antidepressant treatment response with repetitive Transcranial Magnetic Stimulation: A preliminary study

Article in Journal of Affective Disorders · March 2012

CITATIONS
22

READS
129

6 authors, including:

Jean-Arthur Micoulaud Franchi
Centre Hospitalier Universitaire de Bordeaux
227 PUBLICATIONS 863 CITATIONS

Michel Cermolacce
Assistance Publique Hôpitaux de Marseille
126 PUBLICATIONS 612 CITATIONS

Raphaëlle Richieri
Assistance Publique Hôpitaux de Marseille
120 PUBLICATIONS 878 CITATIONS

Anderson Loundou
Aix-Marseille Université
256 PUBLICATIONS 4,588 CITATIONS

Some of the authors of this publication are also working on these related projects:

French Housing First Programme View project

Psy-Coh SZ View project
Parieto-temporal alpha EEG band power at baseline as a predictor of antidepressant treatment response with repetitive Transcranial Magnetic Stimulation: A preliminary study

Jean-Arthur Micoulaud-Franchi\textsuperscript{a,b,*}, Raphaëlle Richier\textsuperscript{a,d}, Michel Cermolacce\textsuperscript{a,b}, Anderson Loundou\textsuperscript{c}, Christophe Lancon\textsuperscript{a,d}, Jean Vion-Dury\textsuperscript{a,b,e}

\textsuperscript{a} Pôle de Psychiatrie “Solaris”, Centre Hospitalier Universitaire de Sainte-Marguerite, 270 Bd de Sainte-Marguerite, 13009 Marseille, France
\textsuperscript{b} Institut de Neurosciences Cognitives de la Méditerranée, INCM-CNRS UMR 6193, 31 Chemin Joseph Aiguier 13402 Marseille cedex 20, France
\textsuperscript{c} Unité d’Aide Méthodologique à la Recherche clinique, DRRC/AP-HM, Laboratoire de Santé Publique, Faculté de Médecine, 27 bd Jean Moulin, 13385 Marseille cedex 05, France
\textsuperscript{d} Laboratoire de santé publique évaluation des systèmes de soins et santé perçue, Université de la Méditerranée, EA 3279, Faculté de Médecine, 27 bd Jean Moulin, 13385 Marseille cedex 05, France
\textsuperscript{e} Unité de Neurophysiologie et Psychophysiology, Pôle de Psychiatrie Universitaire, CHU Sainte-Marguerite, 270 Bd Sainte-Marguerite, 13009 Marseille, France

\textbf{Article Info}

\textbf{Article history:}
Received 31 October 2011
Received in revised form 19 December 2011
Accepted 20 December 2011
Available online xxxx

\textbf{Keywords:}
Depression
Repetitive transcranial magnetic stimulation
Alpha band power
Biomarkers

\textbf{Abstract}

\textbf{Background:} The aim of this preliminary study was to determine the predictive value of absolute alpha band power measured during the rest EEG eyes closed task for responses to 20 sessions of high frequency repetitive transcranial stimulation (rTMS) in the left dorsolateral prefrontal cortex in patients with pharmacoresistant major depressive episode.

\textbf{Methods:} 13 major depressive disorders (8 males) and 8 bipolar disorders (6 males) were included (mean age 58 years). Spearman correlations between pretreatment alpha band power in height regions of analysis and absolute improvement in Beck Depression Inventory Short Form (ΔBDI-SF) were analyzed. The predictive value of alpha band power for classifying patients as responders and non-responders to rTMS was determined using Receiver Operating Characteristic (ROC) curve.

\textbf{Results:} Spearman correlation analysis revealed that ΔBDI-SF correlated significantly and negatively with alpha band power on the right ($r = -0.673$, $p = 0.001$) and left parieto-temporal regions ($r = -0.638$, $p = 0.002$). The area under the ROC curve for the right parieto-temporal was .815, $p = 0.0037$. The cut-off point that maximized both sensitivity and specificity was 1.49 $\mu$V. Sensitivity, specificity, positive and negative predictive values were 100, 66, 80, 100\% respectively.

\textbf{Limitations:} The population was small and lacked homogeneity concerning affective disorders (unipolar and bipolar disorder). The use of a self-rating subjective scale (BDI-SF) to measure the severity of depression could be criticized.

\textbf{Conclusions:} Pretreatment alpha band power on parieto-temporal regions could be a predictor for response to rTMS in patients with homogenous demographic/clinical features. The association between electrical activity and the perfusion under each electrode need to be examined.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Objective neurophysiological markers could lead to use repetitive transcranial magnetic stimulation (rTMS) in an optimal way to enhance antidepressant responses. At this aim, most of studies have used neuroimaging analyses by single photon emission computed tomography (SPECT) (Richieri et al., 2011) and positron emission tomography (PET)
2. Methods

2.1. Participants

Twenty-one right-handed patients who met Diagnostic and Statistical Manual of Mental Disorder 4th ed. (DSM-IV) criteria for Major Depressive Episode participated in the study. Major Depressive Disorder and Bipolar Disorder according to the DSM-IV criteria were included (American Psychiatric Association, 2000). Inclusion criteria were: non-responders to rTMS. Demographic and clinical predictive factors were controlled.

2.2. rTMS treatment

rTMS was performed using a Medtronic MagPro X100 stimulator and a figure eight-shaped water-cooled coil (Medtronic Inc., Minneapolis, Minnesota, USA). At the first rTMS session, the motor threshold was defined as the minimum intensity leading to the most prominent abdication of the right abductor pollicis brevis muscle after stimulation of the left motor cortex. This movement was determined by an electromyogram recording. During the treatment, the coil was positioned 5 cm anterior and in a parasagittal line from the motor cortex. So, rTMS was delivered to the left DLPFC at a frequency of 10 Hz at 120% left motor threshold. Each session consisted of five-second trials with a 25-second inter-trial interval (total of 2,000 pulses per session). Twenty treatment sessions were administered within a 4-week period.

2.3. EEG recording

A conventional EEG was performed during the week before the first rTMS in all subjects under the same conditions. EEG was recorded on an EB-Neuro Galileo system (Fiorenza, Italy) using 26 cup electrodes located according to the international 10–20 system: Fp1/p2, F7/8, F3/4, Fz, FC3/4, FCz, C3/4, T3/4, Cz, CP3/4, CPz, P3/4, T5/6, Pz, O1/2, and Oz. The reference electrode was positioned on the nose, and the ground was on an Fpz electrode. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the center of the left eyebrow and 1.5 cm below the center of the left bottom eyelid. Electrode impedance was maintained below 5 kΩ. Data were digitalized continuously at 1024 Hz, with a 12-bit resolution. A low pass filter was set at 100 Hz prior to the digitalization.

2.4. EEG data analysis

On 5 minute resting state with eyes closed, Fast Fourier Transformation was performed on the dedicated EB-Neuro software from epochs visually screened to remove eye movement or muscle artifacts and other recording artifacts. The resulting power spectra were then averaged for each electrode position over the alpha band (8–13 Hz). Data were averaged on 8 regions of analysis to examine anterior vs. posterior and left vs. right possible differences: medial frontal (F3 and F4), centro-temporal (C3, T3 and C4, T4), parieto-temporal (P3, T5 and P4, T6), and occipital (O1 and O2).

2.5. Statistical analysis

Spearman's rank order correlation was used to examine the relationship between alpha band power at baseline in each region of analysis and ΔBDI-SF. Bonferroni correction was applied for multiple testing.
A predictive score that would classify patients into the responders versus non-responders groups was calculated using the region of analysis where the alpha band power correlated most significantly to ΔBDI-SF. Receiver operating characteristic curve (ROC) was calculated and the area under the curve (AUC) was measured for the selected variable. Sensitivity, specificity, and positive/negative predictive values, as well as their confidence intervals, were computed. A cut-off point was obtained by selecting the point on the ROC curve that maximized both sensitivity and specificity. The chosen cut-off point classified the highest number of individuals correctly and, thus, the lowest number incorrectly (maximizing both sensitivity and specificity) (Richieri et al., 2011).

BDI-SF, CGI and STAI-YA at baseline, age, illness duration, episode duration, number of bipolar disorder, and types of medications, were compared between responders and non-responders using Mann Whitney U test for continuous variable and chi-square tests for categorical variable (Table 1).

3. Results

Twelve patients (57%) were responders to rTMS, and nine were non-responders (43%). No statistically significant differences in demographic and clinical characteristics were observed (p > .05) between responder and non-responders (Table 1). All patients were medicated. Patients were treated with antidepressant monotherapy (n = 10), combination of antidepressants (n = 2) or combination of antidepressant and mood stabilizer (n = 9). Among them, four patients were treated with anticonvulsants. Treatment was not significantly different between responder and non-responders (p = .424).

Spearman correlation analysis revealed that ΔBDI-SF correlated significantly and negatively with alpha band power on the right (r = −.673, p = .001, Fig. 1) and left parietotemporal regions (r = −.638, p = .002). Correlations were not significant in other regions of analysis. Supplementary analyses did not found significant correlation between other standard EEG band power (delta 1.5–3.5, theta 4–7 Hz and beta 14–20 Hz) and ΔBDI-SF.

The ROC AUC for the right parietotemporal was .815 [.587; .948], p = .0037. The cut-off point that maximized both sensitivity and specificity was 1.49 μV. This point is reported in Fig. 1. Sensitivity, specificity, positive and negative predictive values were 100% [73; 100.0], 66% [66; 92.5], 80% [51.4; 94.7], and 100% [51.7; 100.0], respectively.

4. Discussion

Parieto-temporal alpha band power at baseline might be an important predictor of antidepressant response following 4 weeks of left DLPFC 10 Hz rTMS as add-on treatment in pharmacoresistant depression. In agreement with Price et al., we found a negative correlation between alpha band

![Fig. 1. Scatterplot between absolute improvement in BDI-SF (ΔBDI-SF) after treatment with rTMS and rTMS pretreatment absolute alpha band power (in μV) measured on right parietotemporal region during the rest EEG eyes closed task. The higher the alpha band power value at baseline in parietotemporal cortical areas before rTMS treatment, the lower the antidepressant response to the rTMS course was. The gray vertical line is the cut-off point (1.49 μV) calculated on the receiver operating characteristic curve to maximize both sensitivity and specificity. Note that similar result was obtained with alpha band power in left parietotemporal region.](image)

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of responders and non-responders (n = 21) presented as mean values m (S.D.) or as number of patients (n) with percentage (%). Mann Whitney U test for continuous variable and chi-square tests for categorical variable were used.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (n = 12)</td>
<td>Non responders (n = 9)</td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years old), m (S.D.)</td>
<td>56.75 (12.29)</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>9 (75)</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder, n (%)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Bipolar disorder, n (%)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Illness duration (years), m (S.D.)</td>
<td>18.41 (12.03)</td>
</tr>
<tr>
<td>Episode duration (months), m (S.D.)</td>
<td>13.08 (11.62)</td>
</tr>
<tr>
<td>BDI-SF score at baseline, m (S.D.)</td>
<td>21.41 (4.91)</td>
</tr>
<tr>
<td>STAI Y-A score at baseline, m (S.D.)</td>
<td>68 (5.2)</td>
</tr>
<tr>
<td>CGI score at baseline, m (S.D.)</td>
<td>5.3 (0.5)</td>
</tr>
</tbody>
</table>

BDI-SF: Beck Depression Inventory Short Form.
STAI-YA: State Trait Anxiety Inventory for Adults.
CGI: Clinical Global Impression-Severity.

power before rTMS and BDI-SF amelioration (Price et al., 2008). Contrary to previous studies, we did not find any difference in demographic or clinical features between responders and non-responders (Fregni et al., 2006). One explanation could be the relative pharmacoresistant homogeneity of our sample because we only recruited patients who had failed at least two medication trials and who would therefore have all been classified into a poor outcome group.

The higher the alpha band power value at baseline in parieto-temporal cortical areas before rTMS treatment, the lower the antidepressant response to the rTMS course was. Some data suggest that alpha activity negatively correlates with cerebral activity (Cook et al., 1998). Thus our results are compatible with neuroimaging studies demonstrating that hypo-perfusion on centro-temporal and parieto-temporal cortical areas are associated with poorer outcomes (Mottaghy et al., 2002; Richieri et al., 2011). The association between electrical activity and the perfusion under each electrode measured in our previous study is currently under evaluation (Richieri et al., 2011).

The ROC analysis demonstrates that baseline alpha band power on the right parieto-temporal region was a good predictor for classifying depressive patients in responders and non-responders to rTMS. When compared to PET scan or SPECT, EEG based measurement might afford an easy and convenient method to measure cut-off values and to identify patient populations most likely to benefit from rTMS compared to other treatments. Interestingly, previous studies have explored the predictive value of alpha band power at baseline for antidepressant pharmacological treatment outcome (Bruder et al., 2008; Knott et al., 1996; Ulrich et al., 1984). In contrast to our results, Bruder et al. (2008) showed a positive relationship between occipital region alpha band power and outcome to selective serotonin reuptake inhibitor antidepressant (Bruder et al., 2008). Similar results were shown with tricyclic (Knott et al., 1996; Ulrich et al., 1986). These opposite results between pharmacological and rTMS treatments suggest that two different neurophysiological mechanisms underlie the antidepressant action of drugs and magnetic stimulation. Moreover, these opposite results open a way to maximize the antidepressant responses of rTMS by introducing a possible subgroup selection therapeutic strategy. Nevertheless, future trials with prospective design are required to confirm these results.

Several limitations should be considered in our study. The first one is that our population was small and lacked homogeneity concerning affective disorders (unipolar and bipolar disorder). These two groups of patients were however not different regarding alpha band power, demographic and clinical characteristics. The second limitation is related to open-label trial features, in which enrolled participants receive pharmacologic treatment and benefit from rTMS as an add-on therapy. As participants were medication resistant and as antidepressants may increase alpha band power (Itil et al., 1983), it is possible that alpha band power would be different compared to non-pharmacoresistant depressive major episode (Hegerl et al., 2011; Pollock and Schneider, 1990) and it is not certain to what extent our results are representative of depressed patients in general. Third, the use of a self-rating subjective scale (BDI) to measure the severity of depression could be criticized (Richieri et al., 2011; Seemuller et al., 2011). However, several studies have supported a satisfactory convergent validity between the BDI and the Hamilton Depression Rating Scale (HDRS) or the Montgomery-Asberg Depression Rating Scale (MADRS) (Bouvard et al., 1992; Collet and Cottraux, 1986).

A follow-up study with a larger and more controlled cohort of patients is warranted. Despite these limitations, our preliminary study has highlighted the fact that EEG-neuropsychological markers should easily and informatively be used in clinical practice as objective predictors to rTMS treatment in depression.

Role of the funding source
This work was supported by INSERM (Centre d’Investigation Clinique, CIC, Hôpital de la Conception, Marseille), and AP-HP (PHRC 2007/09).

Conflict of interest
The authors report no conflicts of interest.

Acknowledgments
We thank Dr. Aileen McGonigal for help with the English-language editing.

References


