Brain Stimulation xxx (2018) 1–5

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Predictive value of dorso-lateral prefrontal connectivity for rTMS response in treatment-resistant depression: A brain perfusion SPECT study

Raphaëlle Richieri [a, b, c, *], Antoine Verger [d, e, f], Laurent Boyer [b, g], Mohamed Boucekine [b], Anthony David [c], Christophe Lançon [a, b], Michel Cermolacce [a], Eric Guedj [d, h, i]

[a] Department of Psychiatry, La Conception University Hospital, 13005 Marseille, France
[b] Aix-Marseille Univ, EA 3279 - Self-perceived Health Assessment Research Unit, 13005 Marseille, France
[c] Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[d] Service Central de Biophysique et Médecine Nucléaire, Hôpital de la Timone, APHM, 13005 Marseille, France
[e] Department of Nuclear Medicine & Nancyclotep Imaging Platform, 54000 Nancy, France
[f] IADI, INSERM U947, 54000 Nancy, France
[g] Department of Public Health, Assistance Publique - Hôpitaux de Marseille, Marseille, France
[h] Aix-Marseille University, INT, CNRS UMR 7289, 13005 Marseille, France
[i] Aix-Marseille University, CERIMED, 13005 Marseille, France

ARTICLE INFO

Article history:
Received 15 October 2017
Received in revised form
19 March 2018
Accepted 14 May 2018
Available online xxx

Keywords:
Connectivity
SPECT
Repetitive transcranial magnetic stimulation
Treatment resistant depression
Predictive value

ABSTRACT

Background: Previous clinical trials have suggested that repetitive transcranial magnetic stimulation (rTMS) has a significant antidepressant effect in patients with treatment resistant depression (TRD). However, results remain heterogeneous with many patients without effective response.
Objective: The aim of this SPECT study was to determine before treatment the predictive value of the connectivity of the stimulated area on further rTMS response in patients with TRD.
Methods: Fifty-eight TRD patients performed a brain perfusion SPECT before high frequency rTMS of the left dorsolateral prefrontal cortex (DLPFC). A voxel based-analysis was achieved to compare connectivity of the left DLPFC in responders and non-responders using inter-regional correlations ($p < 0.005$, corrected for cluster volume). A multiple logistic regression model was thereafter used with the goal of establishing a predictive score.
Results: Before rTMS, responders exhibited increased SPECT connectivity between the left DLPFC and the right cerebellum in comparison to non-responders, independently of age, gender, severity of depression, and severity of treatment resistance. The area under the curve for the combination of these two SPECT clusters to predict rTMS response was 0.756 ($p < 0.005$).
Conclusions: SPECT connectivity of the left DLPFC predicts rTMS response before treatment.

1. Introduction

Approximately two-thirds of patients receiving initial antidepressant therapy do not achieve remission, and 20% have persistent resistance to conventional pharmacological treatments [1]. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and well-tolerated method that may be an effective alternative therapeutic approach. Although previous clinical trials have suggested that rTMS has a significant antidepressant effect, results remain heterogeneous with many patients showing no response [2]. Regarding the medical cost of rTMS, which is time-consuming for both the physician and the patient, the identification of biomarkers of predictive response to rTMS seems necessary to optimize its effectiveness [3].

Using 99mTc-Ethyl-Cysteinate-Dimer (ECD) single photon emission computed tomography (SPECT), we previously reported that patients with Treatment-Resistant Depression (TRD) showed significant frontal and temporal hypoperfusion, with a left-side predominance [4,5]. Moreover, prior to treatment, non-responder

* Corresponding author. Pôle Psychiatrie, Addictologie et Pédopsychiatrie, Hôpital Sainte Marguerite, 270 Avenue Sainte Marguerite, 13009 Marseille, France.
E-mail address: raphaellemarie.richieri@ap-hm.fr (R. Richieri).

https://doi.org/10.1016/j.brs.2018.05.010
1935-861X/

patients showed greater hypoperfusion in the left medial and bilateral superior frontal cortices, in the left uncus/para-hippocampal cortex, and in the right thalamus after rTMS of the dorso-lateral prefrontal cortex (DLPFC). These results suggest potential predictive value of 99mTc-ECD SPECT imaging involving remote regions from the stimulated area [4–6].

On the other hand, the study of connectivity in SPECT is gaining interest in depression and neurologic disorders [5,7–10]. Seed correlations or interregional correlation analysis (IRCA) is one of the main approaches proposed to study SPECT connectivity [10,11]. This approach involves picking a reference location and quantifying the correlation with perfusion for every other brain area, as previously described [5,8]. SPECT connectivity has been shown to be disturbed in TRD patients, who show higher connectivity between left frontal and left cerebellar regions in comparison to healthy subjects [5]. Indeed, in addition to its role in motor coordination, the cerebellum may play an important role in cognitive processing and emotional control by modulating limbic regions [12]. Interestingly, also by using SPECT connectivity, we have recently reported that the clinical effects of rTMS were related to changes in connectivity between the stimulated area and remote medial temporal limbic areas [8], explaining perfusion changes within the left perirhinal cortex found after treatment [6].

In the current study, we hypothesize that differences in SPECT connectivity of the left DLPFC before rTMS may be related to later clinical response in patients with TRD.

2. Materials and methods

2.1. Subjects

This retrospective study, conducted in a public psychiatric university hospital, involved 58 right-handed TRD patients, treated with high-frequency (HF) rTMS, as described previously [8]. All participants met DSM-IV TR criteria for major depressive disorder (unipolar or bipolar depression) without psychotic features, and gave informed consent. TRD was defined as a non-response to at least two different classes of antidepressant medications for the current episode at the time of enrolment. All patients had maintained stable doses of antidepressant and/or mood stabilizer medications for at least 2 weeks before treatment and until completing the course of rTMS. Finally, a group of 55 healthy subjects was extracted from a local normal 99mTc-ECD SPECT database constituting a control population approved by our local ethics committee (Clinical Trials Ref: NCT00484523), with similar age and gender as those of the patients group ($p > 0.15$, 49.8 ± 16.6 years old, 32 women), to compare results of connectivity analysis with patients.

2.2. Data collection

The following data were recorded: demographic characteristics: gender and age; clinical characteristics: duration of illness, episode duration, depression severity using the 21-item Beck Depression Inventory (BDI-II) [13], and anxiety severity using the State Trait Anxiety Inventory (STAI-YA) [14]. The overall level of depression varies from minimal (score of 10) to severe (score > 29) depression. All patients were assessed twice with the BDI-II and STAI-YA: before rTMS, and after 20 rTMS sessions. RTMS response was defined as at least 50% reduction in the baseline BDI-II score. Level of treatment-resistant severity was assessed with the Maudsley Staging Method (MSM) which is a point-based staging method that measures level of treatment-resistant severity of the index episode by incorporating 3 factors: treatment, severity of illness, and duration of episode [15]. The overall level of treatment resistance varies from minimal (score of 3) to severe (score of 15) resistance.

2.3. RTMS treatment

Magnetic stimulation was performed using a Medtronic MagPro ×100 stimulator and a figure eight-shaped water-cooled coil (Medtronic Inc., Minnesota). Twenty sessions of rTMS were delivered daily but not including weekends, to the left DLPFC, situated 6 cm anterior to the motor "hotspot" for the contralateral hand muscles, with a frequency of 10 Hz with a 25-s inter-train interval (2000 pulses/day) at 120% of the resting motor threshold.

2.4. SPECT protocol

Brain perfusion SPECT was performed after injection of 740 MBq of 99mTc-ECD in all patients and healthy subjects, with the same camera and under the same conditions, during the week before rTMS in patients as previously reported [8].

A voxel-by-voxel group study design was employed using SPM8 (Wellcome Department of Cognitive Neurology, University College, London), running on Matlab (MathworksInc, Sherborn, MA), with normalization by proportional scaling. Based on the hypothesis that baseline connectivity of the stimulated area could explain further clinical response to the rTMS, we then studied SPECT connectivity of the left DLPFC. For this purpose, normalized perfusion values of the left BA46 volume-of-interest of PickAtlas® (ANSIR Laboratory, Department of Radiologic Sciences WFU School of Medicine, USA) used for the analysis of the left DLPFC and illustrated in Fig. 1A, were individually extracted using Marsbar® (Marseille, France) software. Then a full factorial model of analysis was used with normalized perfusion of the left BA46 values as an interaction covariate to study inter-regional correlation, between responders and non-responders, with age, gender, depression severity (BDI) and therapeutic resistance (MSM) scores as covariates. The SPM (T) maps were obtained at a height threshold of $p < 0.005$ for the voxel, with clusters including at least 102 voxels (the expected threshold provided by SPM after simulation) to correct for volume, to avoid type II errors as recommended [16]. The normalized values of significant clusters from the full-factorial analysis were finally extracted using Marsbar® (Marseille, France) software, and used to calculate correlation coefficients with left DLPFC normalized values in responders, non-responders and healthy subjects. MNI coordinates were used to identify brain structures.

2.5. Statistical analysis

Quantitative variables are expressed as means ± standard deviations, and categorical variables as percentages. For patient's characteristics, t-tests were done for mean comparisons for quantitative variables while Chi-2 tests were done for categorical variables. Statistical parameters for SPM comparison between responders and non-responders at baseline are detailed above. Spearman coefficients were used to calculate correlations between normalized values of significant clusters from the full-factorial analysis with clinical scores and left DLPFC normalized values in responders, non-responders and healthy subjects. Then, multiple logistic regression models including the normalized values of left DLPFC and of significant clusters from the SPM analysis, and their interaction, were used with the goal of establishing a predictive score to classify patients in the responder vs non-responder groups. For this purpose, we split the data into two samples: a training sample including 2/3 of the data and a test sample including the remaining 1/3. Multiple logistic regression was performed to predict response to treatment using the training dataset. Predictive

Please cite this article in press as: Richieri R, et al., Predictive value of dorso-lateral prefrontal connectivity for rTMS response in treatment-resistant depression: A brain perfusion SPECT study, Brain Stimulation (2018), https://doi.org/10.1016/j.brs.2018.05.010