Brain Stimulation 8 (2015) 1162–1167

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Cortical Anatomical Variations and Efficacy of rTMS in the Treatment of Auditory Hallucinations

Clément Nathou [a,b,c], Grégory Simon [d,e], Sonia Dollfus [a,b,c,*], Olivier Etard [b,f]

[a] CHU de Caen, Department of Psychiatry, Centre Esquirol, Caen F-14000, France
[b] Unicaen, UFR of Medicine, Caen F-14000, France
[c] Unicaen, UMR 6301, Centre Cyceron, Caen F-14000, France
[d] Unicaen, LaPsyDÉ, Caen F-14000, France
[e] CNRS, UMR 8240 LaPsyDÉ, Paris F-75005, France
[f] CHU de Caen Laboratory of Neurological Functional Exploratory, Caen F-14000, France

ARTICLE INFO

Article history:
Received 21 December 2014
Received in revised form
23 April 2015
Accepted 7 June 2015
Available online 25 June 2015

Keywords:
TMS
Auditory hallucinations
Schizophrenia
Scalp-to-cortex distance

ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) shows high inter-subject variability in its efficacy for treating resistant auditory verbal hallucinations in schizophrenia. Currently, the response of an individual patient to rTMS treatment cannot be predicted. It is possible that cortical anatomical characteristics could affect the therapeutic response.
Objective: We hypothesized that rTMS efficacy is related to anatomical variations underlying the stimulation target in the left temporal cortex. We investigated two regions of interest (ROIs) that have been implicated in rTMS: the left temporal cortex, where the stimulation is delivered, and the primary hand motor cortex, where the stimulation strength is determined by the resting motor threshold (rMT).
Methods: Fifteen patients with schizophrenia (DSM IV) underwent rTMS and magnetic resonance imaging. The scalp-to-cortex distance (SCD) and the grey matter density (GMD) were measured in both ROIs. Linear regression models were used to investigate the relationships between these measures and the clinical efficacy of rTMS.
Results: Treatment efficacy was highly predicted by the temporal SCD and the GMD in the temporal and primary hand motor cortex regions. In contrast, the rMT was not predicted by the primary hand motor cortex SCD or GMD.
Conclusion: These results suggest that rTMS treatment efficacy could be related to the depth of the temporal target. The data raise the question of whether rMT is the best measure for assessing the stimulation intensity in treating patients with schizophrenia.

Background

Repetitive transcranial magnetic stimulation (rTMS) treatment can decrease auditory hallucinations in individuals with resistant auditory verbal hallucinations (AVH) [1]. However, even though several meta-analyses concluded that rTMS treatment is efficacious for this indication [2–4] the results of several recent studies [5–7] have tempered the optimism of the earliest studies. Specifically, the efficacy of rTMS shows high inter-individual variability (see Ref. [8] for review), and there is a large placebo effect, particularly with the active coil positioned at 45° [9]. Moreover, the response time is also variable, with only half of patients responding 8 weeks after treatment [10]. A meta-analysis by Slotema et al. [11] found a low but significant effect size for rTMS applied to the left temporoparietal area at low frequency, and the authors noted that there is declining interest in using rTMS. In view of this finding, other stimulation paradigms, such as high-frequency stimulation [5] or continuous theta-burst stimulation [12] are of great interest. Importantly, no factor has been identified that predicts the response of patients with AVH to rTMS. However, it seems possible that some cortical anatomical characteristics of the stimulation target could affect the therapeutic response to rTMS.

In the treatment of AVH, the cortical target of rTMS is usually the left temporoparietal junction [13–15], which is where anatomical

Conflicts of interest: None.

* Corresponding author. UMR 6301 - CNRS - CEA – UCBN, GIP Cyceron, Boulevard Henri Becquerel, BP 5229 - 14074 Caen Cedex 5, France. Tel.: +33 231065018.
E-mail address: dollfus-s@chu-caen.fr (S. Dollfus).

http://dx.doi.org/10.1016/j.brs.2015.06.002
1935-861X/

alterations have been reported in patients with schizophrenia [16–18]. Moreover, AVH severity correlates with a decrease in the grey matter volume of the left temporal superior gyrus [19–24]. These cortical alterations may explain the decreased response to rTMS in some patients. Indeed, focal cortical temporal atrophy could be responsible for an increase in the distance between the rTMS stimulation coil applied to the scalp and the therapeutic target (i.e. the scalp-to-cortex distance; SCD), and/or for modifications in cortical excitability that could lead physicians to underestimate the power of stimulation required to treat the patient. This phenomenon is not currently taken into account in the classical procedure used for rTMS. Moreover, the rTMS intensity is determined using the resting motor threshold (rMT). rMT is a clinical variable measured in the motor cortex. It is considered to reflect overall brain excitability in healthy subjects because of its intra-individual stability [25,26] and because of its significant diurnal [27] and inter-individual variations [28–30]. Cortical atrophy leads to modifications in excitability [31], and such modifications are found mainly in regions such as the left temporal region in patients with schizophrenia [19]. rMT may also depend on microstructural properties of the white matter beneath primary motor cortex of the hand [32]. This calls into question the relevance of the rMT without adjustment for SCD as a reliable way to assess the rTMS intensity. To our knowledge, no study has investigated whether the cortical anatomical characteristics in patients with schizophrenia affect the efficacy of rTMS treatment.

Accordingly, we hypothesized that rTMS efficacy could be related to anatomical variations underlying the stimulation target applied to the left temporal cortex. We investigated two regions of interest that have been implicated in rTMS: the left temporal cortex, where the stimulation is delivered, and the left primary hand motor cortex (PHMC), where the stimulation strength is assayed.

Methods

Subjects

We collected existing data from participants of two therapeutic studies: one open study [33] and one ongoing controlled trial (ClinicalTrials.gov: NCT01022489) that both used the same high-frequency (20 Hz) protocol. We included 15 consecutive rTMS-naïve patients (age (mean ± SD): 36.4 ± 10.7; 8 women) with schizophrenia and with the same MRI acquisition data in whom high frequency (20 Hz) active rTMS treatment over the left temporal lobe was used to reduce auditory hallucinations. All patients provided informed written consent in accordance with the Declaration of Helsinki. The local ethics committee (Comité de Protection des Personnes Nord-Ouest, France) approved the experimental protocol used for recruiting the participants.

Treatment protocol and motor threshold measurements

The rTMS treatment protocol comprised 4 stimulation sessions on 4 consecutive half-days (a total of 2 days of treatment). Each stimulation session consisted of 13 trains of 10-s duration, with 200 pulses for each train (20 Hz frequency). The intertrain interval was 50 s for a total of 2600 pulses. The treatment protocol was delivered at 80% of the intensity of the individually determined rMT, which was defined as the minimum intensity of stimulation that induced a motor evoked potential with at least 50 μV amplitude responses [29] in exactly half of the trials [34]. Since the rMT was measured before each stimulation session using electromyography on the first dorsal interosseus muscle, we calculated an 'average rMT' using the four measurements for each of the 15 patients in order to overcome the intra-individual diurnal variations of this variable.

Clinical evaluation

Before the first stimulation session, we evaluated the clinical status of patients using the Auditory Hallucination Rating Scale (AHRS) [35]. This questionnaire assesses the frequency of hallucinations, how real they seem to the patient, the intensity of the dominant voice, the number of voices, the content of the predominant voice, the influence of the hallucinations on patient behavior, and the importance of the anxiety they generate. The maximum score is 41. A second evaluation was performed 2 weeks after the treatment, which is the mean delay time until the maximal effect of rTMS can be evaluated [33]. We calculated the ratio of the AHRS scores, Δ-AHRS, in each patient using the pre- (D1) and post-treatment (D14) assessments and the formula (D14 − D1)/D1. The ratio was considered to reflect treatment efficacy.

Anatomical brain measures

All subjects underwent anatomical magnetic resonance imaging (MRI) acquisition before rTMS treatment. MRI was performed on a 3 Tesla MR Scanner (Achieva 3.0 Tesla Quasar Dual, Philips Healthcare, the Netherlands). We acquired three-dimensional T1-weighted spoiled gradient images (field of view (FOV) = 256 mm, slice thickness = 1 mm isotropic, 128 slices, matrix size = 192 × 192 voxels).

Using anatomical brain images in native space, we calculated several anatomical indices. A general index was the total intracranial volume (TIV), which was estimated for each subject using SPM8 software and which corresponds to the sum of the volumes of the cerebrospinal fluid, grey matter, and white matter. In addition, a region of interest (ROI) was determined from individual MR images that allowed us to compute the scalp to cortex distance (SCD) and the grey matter density (GMD) underlying the stimulation region. The temporal ROI was a sphere with a 5-mm radius that was centered on a point determined according to the criteria of the large rTMS trial (ClinicalTrials.gov: NCT01022489). Briefly, using MRIcroN software, we identified the orthogonal projection point on the left superior temporal sulcus of the verticalization of the left Sylvian sulcus (Fig. 1A) which corresponded to the target use in our controlled trial. We chose this particular point because of its proximity to the target previously used in our open trial [33] and also because of its proximity to the Heschl gyrus and the temporoparietal junction and its congruence with the semantic network implied in AVH [36–39]. The second ROI, the PHMC ROI, was a sphere with a 5-mm radius that was centered on a point determined according to the procedure described by Yousry et al. [40]. The left primary hand motor cortex is located in the left precentral gyrus, which appears as an inverted omega in the axial plane and as a posteriorly directed hook in the sagittal plane. We considered the center of this area in both planes (Fig. 1B). Using MRIcroN software, in each subject we measured the distances between the scalp and the center of the temporal ROI (SCD_T), and between the scalp and the center of the PHMC ROI (SCD_{PHMC}). The software allowed us to create a spherical 3D volume with its origin on the ROI center and to vary the radius of this newly created object. We considered the shortest radius of the spherical volume that crossed outside the head model to be the SCD.

Finally, using SPM8 software, a specific template comprising the patients' T1 images was created. This template was used to segment grey and white matter as well as cerebrospinal fluid. Next, GMD was extracted for each subject from the native grey matter images using