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CHANGES IN DORSOLATERAL PREFRONTAL CONNECTIVITY AFTER rTMS IN TREATMENT-RESISTANT DEPRESSION: A BRAIN PERFUSION SPECT STUDY

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Abstract

1
2 Purpose: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and safe
3
4 alternative to electroconvulsive therapy for Treatment-Resistant Depression (TRD). After
5
6 rTMS, changes in brain SPECT perfusion have been remotely identified within medial temporal
7
8 limbic areas, while no local effects have been found within the left dorsolateral prefrontal cortex
9
10 (DLPFC) - i.e. under the coil. Functional changes in connectivity may underlie these remote
11
12 effects. Interestingly, functional connectivity has been recently investigated using perfusion
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14 SPECT, and abnormalities identified in TRD patients. The aim of the present study is to
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16 evaluate perfusion and connectivity SPECT changes in TRD patients after rTMS of the left
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18 DLPFC. We hypothesize that changes in DLPFC networks may explain remote hypoperfusions
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20 found after rTMS.
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26 Methods: Fifty-eight TRD patients performed a brain SPECT before and after high frequency
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28 rTMS of the left DLPFC. Whole-brain voxel-based changes in perfusion were evaluated with
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30 SPM8, and inter-regional correlation analysis performed to study left DLPFC functional
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32 connectivity ($p < 0.005$, corrected for cluster volume).
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36 Results: After rTMS, patients were significantly improved on Beck Depression Inventory score
37
38 ($p < 0.0001$). Considering a 50% reduction threshold, 27 patients were identified as responders
39
40 (47%). After rTMS, perfusion changes were not found locally within the left DLPFC, but
41
42 remotely within the bilateral temporal lobes, including limbic areas. Inter-regional correlation
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44 SPECT analysis brings out a decrease of connectivity between the left DLPFC and both the
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46 cingulate/medial frontal cortex and bilateral medial temporal limbic areas, in relation with the
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48 clinical response.
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53 Conclusions: rTMS of DLPFC in TRD patients leads to remote temporal hypoperfusions in
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55 relation with changes in functional connectivity between the DLPFC and the Default Mode
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57 Network, especially including medial temporal limbic areas.
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Key-words: Repetitive transcranial magnetic stimulation (rTMS), treatment resistant depression, Single-photon emission computed tomography (SPECT), SPM, Connectivity.

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1. Introduction

In developed countries, major depression is the most prevalent lifetime psychiatric disorder, with up to 30% of patients failing to respond to pharmacological medications [1]. In this context of Treatment-Resistant Depression (TRD), repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and safe alternative to electroconvulsive therapy [2,3].

Functional brain substrate associated with the antidepressant effect of rTMS remains however misunderstood. Previous studies have identified functional changes in remote limbic areas, but no local effects - i.e. under the coil [3,4]. In details, Paillère-Martinot and al. reported that rTMS of the left dorsolateral prefrontal cortex (DLPFC) in TRD patients was not associated with a local decrease of PET metabolism, even after MRI guidance [3]. We moreover showed a reduction of SPECT perfusion in deep areas, particularly in medial temporal limbic areas [4], which is known to play an important role in mood regulation. These remote brain SPECT abnormalities have been therefore proposed as biomarkers of the predictive response and follow-up of TRD patients treated by rTMS [4,5].

rTMS may induce functional changes in connectivity, and thus underlie these remote hypoperfusions, and consequently explain the brain substrate of the antidepressant effect. Interestingly, functional connectivity has been recently investigated using inter-regional correlation analysis of SPECT perfusion [6], and abnormalities identified in TRD patients [2].

The aim of the present study is to evaluate perfusion and connectivity SPECT changes in TRD patients after rTMS of the left DLPFC. We hypothesize that changes in DLPFC networks may explain remote hypoperfusions found after rTMS.

2. Materials and Methods

2.1. Subjects

This study, conducted in a public psychiatric teaching hospital, involved a retrospective review of all right-handed TRD patients treated with rTMS of the left DLPFC from January 1, 2013, to December 31, 2013, and followed by brain SPECT [7]. This population of 58 patients constitutes an extension of our previous SPECT report of 33 patients [4]. This gain in statistical power is better suited to study SPECT connectivity using inter-regional correlation analysis. In details, all patients met DSM-IV criteria for major depressive disorder (unipolar or bipolar depression), and signed informed consent; they were included on non-response criteria to pharmacological treatment using a minimum of two distinctly different classes of antidepressant medications for episodes occurring at the time of enrolment or earlier.

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). Twenty sessions of rTMS were delivered daily to the left DLPFC, situated 6 cm anterior to the motor “hotspot” for the contralateral hand muscles, with a frequency of 10Hz with a 25-second inter-train interval (2,000 pulses/day) at 120% of the resting motor threshold, as already described [5].

RTMS response was defined as at least 50% reduction in the baseline Beck Depression Inventory (BDI-II score) [5].

2.4. SPECT protocol

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2 Brain SPECT was performed in all patients, with the same camera, and under the same
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4 conditions [5], during the week before and a week after the end of rTMS. The subjects
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6 received an injection of 740 MBq of ^{99m}Tc-ECD, and were placed at rest for one hour, in
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8 quiet surroundings with their eyes closed. SPECT image acquisition was performed using a
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10 double-headed rotating gamma camera (ECAM, Siemens) equipped with a fan beam
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12 collimator. Thirty-two 40-second projections per subject were collected in 128x128 matrix.
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14 Tomographic 3D reconstruction was performed using a filtered back projection algorithm.
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21 A voxel-by-voxel group study was then achieved using SPM8 (Wellcome Department of
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23 Cognitive Neurology, University College, London), running on Matlab (MathworksInc,
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25 Sherborn, MA). Standard quantitative paired t-test analysis was performed before/after rTMS,
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27 with type of major depressive disorder (unipolar or bipolar depression) and age of patients as
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29 nuisance variables. The SPM (T) maps were obtained at a height threshold of $p < 0.005$ for the
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31 voxel, with clusters including at least 57 voxels to correct for the volume (more than the
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33 expected volume). A small volume correction was also used to specifically search for the left
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35 medial temporal cluster reported in our initial work [4], using the same volume sphere
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37 previously found (600 mm³). For connectivity analysis of the left DLPFC, normalized
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39 perfusion of the left BA46 volume-of-interest of PickAtlas
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41 (<http://fmri.wfubmc.edu/software/pickatlas>) was used as an interaction covariate to study
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43 inter-regional correlation, as previously described [2,6]. The normalized values extracted from
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45 the first paired t-test analysis were used to calculate correlations coefficients between the
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47 different areas. MNI coordinates were converted into Talairach coordinates, and brain
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49 structures identified using the Talairach Daemon database
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51 (<http://ric.uthscsa.edu/projects/talairachdaemon.html>).
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3. Results

3.1. Patient characteristics

The 58 included patients (53.8 years \pm 14.0; 37 women) had depression with initial high severity (BDI-II=30.6 \pm 9.3), and pharmaco-resistance (number of previous antidepressant treatments used for the current episode: 4.1 \pm 1.7). The disease duration was of 16.7 years \pm 11.7; and the episode duration of 17.6 months \pm 56.8. Forty-four patients had a unipolar depression, and 14 a bipolar depression (no significant differences between the two groups for all these clinical characteristics). These characteristics are reported in Table 1, with also previous medications.

After rTMS, patients were significantly improved with persistent depression of mild severity (BDI-II=20.8 \pm 12.6; $p < 0.0001$, paired t-test). Considering a 50% reduction threshold in the baseline BDI scores to define clinical response [5], 27 patients were identified as responders (47%).

3.2. Changes in SPECT perfusion after rTMS

Decrease in perfusion was found after rTMS in the left lateral temporal (BA21; $k=67$, T-score=3.6) and the right medial temporal (BA36; $k=64$, T-score=3.2) lobes ($p < 0.005$, corrected for cluster volume; Figure 1). No perfusion change was identified within the left DLPFC.

3.3. Changes in connectivity after rTMS

As showed in Figure 2, a decrease of connectivity was noticed after rTMS between on the one hand the left DLPFC, and on the other hand: the right medial prefrontal cortex (BA9 and BA10; $k=277$, T-score=4.1), the anterior cingulate (BA32; $k=181$, T-score=3.3) and

1 posterior cingulate (BA29 and BA30; k=139, T-score=3.3) cortices, the right uncus and para-
2 hippocampal area (BA20, BA28, BA34 and BA36; k=701, T-score=4.7) ($p < 0.005$, corrected
3 for cluster volume). After small correction volume, a significant decrease of connectivity was
4 also identified between the left DLPFC and the left medial temporal lobe within the uncus
5 (BA20; k=109, T-score=3.5). In details, losses of correlation were found after rTMS between
6 the left DLPFC and all these areas ($p > 0.05$), except for either left or right uncus with
7 significant anti-correlations with the left DLPFC after rTMS (respective correlation
8 coefficients of -0.42 and -0.30; $p < 0.05$).

9 ANOVA showed significant effect of response vs. non-response status on all clusters
10 identified in the connectivity analysis (left DLPFC, $p = 0.0077$; cingulate cluster, $p = 0.0010$;
11 right medial temporal lobe, $p = 0.0154$), except for the left medial temporal lobe (only a trend,
12 with $p = 0.054$).

13 **4. Discussion**

14 RTMS effects have been previously reported using various neuroimaging modalities [3-5].
15 Nevertheless, rTMS is supposed to modulate brain connectivity, and very few neuroimaging
16 studies specifically investigated this issue. To the best of our knowledge, this rTMS report is
17 the first studying brain connectivity using SPECT, while perfusion SPECT has been
18 previously identified as a potential biomarker in this indication [4-5].

19 In details, we studied brain functional effects of rTMS over the left DLPFC in 58 TRD
20 patients, using a whole-brain voxel-based SPECT analysis of both perfusion and left DLPFC
21 connectivity. As expected [3,4], no local changes in DLPFC occurred under the coil. Remote
22 effects were identified, with decreased SPECT perfusion of bilateral temporal lobes, including

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limbic areas. Interestingly, we showed that these remote hypoperfusions are associated with changes in functional connectivity between on the one hand the left DLPFC (i.e. the coil target), and on the other hand: the medial prefrontal cortex, the cingulate cortex, and the medial temporal limbic areas. In this line, functional changes in connectivity induced by rTMS may underlie the remote found hypoperfusions, and consequently explain the brain substrate of the antidepressant effect, considering the involvement of these brain regions in mood regulation, and relationships here found with the clinical response.

Medial prefrontal cortex, cingulate cortex and medial temporal limbic areas are key components of the Default Mode Network (DMN), which is involved in rumination, self-referential processing, and episodic memory retrieval. In absence of effective treatment, connectivity of this network is supposed to be increased in depression state [8]. Our results suggest a disruption of the link between the DLPFC and the DMN, corresponding to a loss of connectivity after rTMS. In this line, using fMRI, with therefore findings more difficult to directly extrapolate to brain SPECT hypoperfusions, the only two connectivity studies of the DLPFC previously reported after rTMS in TRD patients, strengthen this hypothesis with concordant results: a reduction of DLPFC-DMN hyper-connectivity [9] found in 17 patients, and a loss of connectivity between the DLPFC and the caudate found in 24 patients [10]. Caudate nucleus is particularly known to be involved in motivation, and indeed receives strong innervation from the prefrontal cortex which is a part of the DMN [10]. Interestingly, previous studies also found reduction of DMN hyper-connectivity after treatment by antidepressant drug [11,12], suggesting thus common antidepressant effect on brain connectivity independently of the therapeutic option (drug vs. rTMS). In this line, clusters identified in our connectivity analysis were statistically associated with clinical response.

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Beside these losses of correlation, interpreted as losses of connectivity, we also found after rTMS anti-correlations between the left DLPFC and bilateral uncus, which are also part of both the DMN and the limbic system. These structures are known to be closely associated with frontal areas, through a network playing a central role in emotional regulation, specifically in depression [5]. Anti-correlated networks have been previously also considered as functional disconnections [8,9], and could be a feature of rTMS changes.

Our study has nevertheless several limitations. Interpretation of these data should be performed in the context of the study design, namely, a retrospective study who suffers from the absence of randomization, placebo controls and blinding of response-rates. Further connectivity studies will be needed to investigate relationship with depression severity and long-term outcome.

On the whole, rTMS of DLPFC in TRD patients is not associated with local changes in DLPFC perfusion, but leads to remote temporal hypoperfusions in relation with changes in functional connectivity between the DLPFC and the Default Mode Network, especially including medial temporal limbic areas, which could consequently explain the brain substrate of the antidepressant effect through the involvement of this network and these areas in the mood regulation.

Compliance with Ethical Standards

1
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3
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6
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8

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10 Conflict of Interest: The authors declare that they have no conflict of interest.
11

12 Ethical approval: All procedures performed in studies involving human participants were in
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14 accordance with the ethical standards of the institutional and/or national research committee
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16 and with the 1964 Helsinki declaration and its later amendments or comparable ethical
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18 standards.
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21 Informed consent: Informed consent was obtained from all individual participants included in
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24 the study.
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Table 1. Clinical characteristics of patients.

	M	SD ¹
Age	53.8	14.0
Gender N, (%) ²		
Female	37	(63.8)
Male	21	(36.2)
Type of depression		
Bipolar, N (%)	14	(24.1)
Unipolar, N (%)	44	(75.9)
Duration of illness (years)	16.7	11.7
Duration of depressive episode (months)	17.6	56.8
Number of episodes' lifetime N (%)		
1	14	(24.1)
2	9	(15.5)
3	12	(20.7)
4	3	(5.2)
5 and more	20	(34.5)
Failed antidepressant trials current episode	4.1	(1.7)
Concomitant medication, N (%)	52	(89.7)
Antidepressant	52	(89.7)
Lithium	1	(1.7)
Atypical antipsychotic	7	(12.1)
BDI score	30.6	9.3
STAI-A score	63.2	10.9
MSM score	7.3	2.0

¹ Mean (Standard Deviation)

² Effective (Percentage)

BDI: Beck Depression Inventory short form; STAI – A: State Anxiety Inventory – State; MSM: Maudsley Staging Method

Figure legends

Figure 1. Anatomical localization of areas of decreased perfusion after rTMS ($p < 0.005$, $k > 57$) projected onto sections of a normal MRI set spatially normalized and smoothed into the standard SPM8 template. After rTMS, patients showed a decreased SPECT perfusion in left lateral temporal (BA21) and right medial temporal lobes (BA36).

Figure 2. Anatomical localization of areas of decreased SPECT functional connectivity with the left DLPFC after rTMS ($p < 0.005$, $k > 57$), projected onto sections of a normal MRI set spatially normalized and smoothed into the standard SPM8 template. After rTMS, patients showed a decreased functional connectivity between the left DLPFC on the one hand, and the right prefrontal mesial cortex (BA9 and BA10), the anterior cingulate (BA32) and posterior cingulate (BA29 and BA30) cortices (A), and the bilateral medial temporal lobe (BA20, BA28, BA34 and BA36) (B) on the other hand.



