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Baseline Brain Metabolism in Resistant Depression and Response to Transcranial Magnetic Stimulation

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Neuroimaging studies of patients with treatment-resistant depression (TRD) have reported abnormalities in the frontal and temporal regions. We sought to determine whether metabolism in these regions might be related to response to repetitive transcranial magnetic stimulation (TMS) in patients with TRD. Magnetic resonance images and baseline resting-state cerebral glucose uptake index (gluMI) obtained using ^{18}F-fluorodeoxyglucose positron emission tomography were analyzed in TRD patients who had participated in a double-blind, randomized, sham-controlled trial of prefrontal 10 Hz TMS. Among the patients randomized to active TMS, 17 responders, defined as having 50% depression score decrease, and 14 nonresponders were investigated for prestimulation glucose metabolism and compared with 39 healthy subjects using a voxel-based analysis. In nonresponders relative to responders, gluMI was lower in left lateral orbitofrontal cortex (OFC), and higher in left amygdala and uncinate fasciculus. OFC and amygdala gluMI negatively correlated in nonresponders, positively correlated in responders, and did not correlate in healthy subjects. Relative to healthy subjects, both responders and nonresponders displayed lower gluMI in right dorsolateral prefrontal (DLPFC), right anterior cingulate (ACC), and left ventrolateral prefrontal cortices. Additionally, nonresponders had lower gluMI in left DLPFC, ACC, left and right insula, and higher gluMI in left amygdala and uncus. Hypometabolisms were partly explained by gray matter reductions, whereas hypermetabolisms were unrelated to structural changes. The findings suggest that different patterns of frontal–temporal–limbic abnormalities may distinguish responders and nonresponders to prefrontal magnetic stimulation. Both preserved OFC volume and amygdala metabolism might precondition response to TMS.

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INTRODUCTION

Treatment-resistant depression (TRD) occurs in 20 to 30% of depressed patients and leads to severe disability (Greden, 2001). Neuroimaging studies focused on TRD patients are rare, and have reported decreased blood flow or glucose metabolism in prefrontal regions such as the anterior cingulate cortex (ACC) (Mayberg *et al*, 1994, 1997b; Drevets *et al*, 1997; Ketter *et al*, 2001; Konarski *et al*, 2007), and in anterior temporal cortices (Mayberg *et al*, 1994). Differential frontal–temporal changes have been reported in medication responder and nonresponder subgroups of depressed patients. Responders to antidepressants were found to have lower pretreatment glucose metabolism in both left amygdala region and temporal cortex, and in bilateral frontal cortices (Little *et al*, 2005). In line with these findings, higher resting-state hippocampus–amygdala blood flow was found in a group of TRD compared with nonresistant patients and healthy controls (Hornig *et al*, 1997). Cortical–limbic balance involving orbitofrontal cortex (OFC), ACC, hippocampus, and dorsolateral prefrontal cortex (DLPFC) might differentiate responders from nonresponders to antidepressant medications (Seminowicz *et al*, 2004).

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Repetitive transcranial magnetic stimulation (TMS) has been proposed as a potential treatment for TRD (George *et al*, 1995; Pascual-Leone *et al*, 1996) that can easily be applied in clinical settings and is well tolerated. This procedure aims at stimulating the left DLPFC in order to increase brain metabolism in prefrontal areas using high stimulation frequencies (>5 Hz). However, although a number of studies have now demonstrated the clinical effectiveness of TMS in TRD patients (Lam *et al*, 2008), the effects remain variable and factors predictive of response remain poorly understood (Loo and Mitchell, 2005; Herrmann and Ebmeier, 2006; Lisanby *et al*, 2009). As this therapy is time consuming and costly, it is necessary to determine whether brain factors could influence or predict outcome. High-frequency TMS of prefrontal regions, as used to treat depression, has been shown to modulate ACC and caudate nucleus activity in healthy subjects (Barrett *et al*, 2004). In addition, blood flow decreases in OFC and ACC have been reported after treatment with high-frequency TMS (Nadeau *et al*, 2002) in *responders* to TMS. So far, however, it is not clear whether prestimulation functional anatomy could influence TMS efficacy and predict response.

We *a priori* hypothesized that TRD patients who were *nonresponders* to TMS would have specific alterations in those frontal–temporal–limbic regions involved in TRD and in TMS effects, and also in the uncinate fasciculus, a frontal–temporal fiber tract that we have reported to be altered in patients with affective disorders (Houenou *et al*, 2007). We used [^{18}F]-fluorodeoxyglucose positron emission tomography ([^{18}F]-FDG-PET) to determine whether resting functional brain characteristics at baseline could differentiate responders from nonresponders to 10 Hz TMS in a group of TRD patients. Additionally, we searched for a potential influence of structural anatomy on metabolism, and for functional correlations within the regions involved in response to TMS.

SUBJECTS AND METHODS

The investigation was performed in accordance with the Declaration of Helsinki. The study was approved by the ethics committee Ile-de-France 6, Paris. Written informed consent was obtained from all subjects after full description of the study.

Participants

Pretrial PET and magnetic resonance imaging (MRI) data from the 34 patients who were initially randomized to an active arm in a double-blind, sham-controlled trial of 10 Hz TMS including 48 patients (Paillère Martinot *et al*, 2009) were considered for the present imaging study. The patients had a DSM-IV-TR diagnosis of Major Depressive Disorder established by clinical interview using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan *et al*, 1998), with criteria for treatment resistance to at least two trials of antidepressants of different classes given at adequate doses (>150 mg/day in an equivalent dose of imipramine) and duration (at least 4 weeks for each drug). Exclusion criteria included age >65 years, pregnancy, alcohol or substance dependence in the past 6 months, electroconvulsive therapy (ECT) treatment in the past 6 months, any present medical condition, history of epileptic seizures, history of neurological disorders or substantial brain damage, and contraindication to magnetic fields. On examination of the patient medical charts, three patients were excluded; past early-onset alcoholism in 2 patients and a possible diagnosis of fibromyalgia in one patient. Indeed, alcoholism with onset in adolescence might have modified brain structure (Chanraud *et al*, 2007), and fibromyalgia has been reported to alter brain activity in frontocingulate areas (Burgmer *et al*, 2009).

Thus, data from 31 patients were analyzed in the present study (mean (SD) age = 47.7 (7.3); range: 30.5–59.5, 20 women). They had on average 7.4 (4.4) years of education after primary school, and were not paid for their participation.

A total of 39 paid healthy comparison subjects with no personal or family history of psychiatric or neurologic disorder, as assessed by a medical examination, were recruited by word of mouth from community volunteers during the same time period (age: mean (SD) = 45.2 (11.8); range: 25–62, 25 women; years of education after primary school: mean (SD) = 9.10 (4.8)). Patients and healthy subjects did not differ in age ($t = 0.99$, df = 68, $p = 0.32$), gender (χ^2 test = 0.000, $p = 0.98$), years of education ($t = 1.53$, df = 67, $p = 0.13$), or Annett's (1970) laterality score (patients: mean (SD) = 85.7 (49.3), healthy subjects: 89.4 (26.5), $t = 0.40$, df = 67, $p = 0.69$).

TMS Protocol

Design. The stimulation procedure and determination of PET-derived targets for TMS have been described elsewhere (Paillère Martinot *et al*, 2009). Briefly, after scanning, the patients were randomized to treatment with PET-guided, active-standard or sham-standard TMS, and subsequently underwent 10 sessions of 10 Hz TMS delivered at 90% motor threshold with 1600 pulses/session, using a Magstim super-rapid device with active and sham air-cooled figure-of-eight coils (Magstim, Withland, Dyfed, UK). Guided TMS was on a prefrontal target determined with FDG-PET. Standard stimulation was as usual left prefrontal, 5 cm anterior to the hot spot of the hand motor cortical region. Patients and raters were blind to TMS modality.

Treatment allocation. The 31 patients in this imaging study had been randomly allocated to standard TMS ($n = 9$ in responder group, $n = 6$ in nonresponder group) or to PET-guided TMS ($n = 8$ in responders, $n = 8$ in nonresponders; Table 1). No difference in allocation was found across groups ($\chi^2 = 0.31$, df = 1, $p = 0.56$). No patient randomized to sham TMS was analyzed in the present study, as response to sham TMS might be related to different mechanisms than response to active treatment, and as there were only 3 responders out of 14 sham-treated patients in that group.

Clinical Assessment

Baseline assessment was performed on the day before scanning using the Montgomery–Åsberg Depression Rating

Table 1 Demographic, Clinical, and Stimulation Characteristics of Responders and Nonresponders to rTMS

Variable	Responders ($n = 17$)	Nonresponders ($n = 14$)	*P*-value[a]
Gender (M/F), *n*	6/11	5/9	0.98
Age, years, mean (SD)	48.7 (6.2)	46.4 (8.6)	0.40
Education, years[b], mean (SD)	7.1 (4.6)	7.8 (4.3)	0.69
Annett scale laterality score, mean (SD)	75.9 (64.5)	98.5 (3.2)	0.22
Age at onset, years mean (SD)	30.1 (10.9)	26.1 (8.2)	0.27
Duration of illness, years, mean (SD)	18.2 (10.9)	20.1 (6.6)	0.58
Duration of episode, years, mean (SD)	3.6 (2.7)	2.1 (1.7)	0.10
Family depression, *n* (%)	9 (53)	5 (36)	0.34
Bipolar resistant depression, *n* (%)	6 (35)	5 (36)	0.98
Number of depressive episodes, mean (SD)	3.3 (1.6)	4.07 (2.09)	0.30
Number of manic episodes, mean (SD)	0.6 (1.2)	0.4 (0.8)	0.44
Comorbid Anxiety Disorder, *n* (%)	3 (18)	4 (29)	0.47
Tyrer anxiety scale score, mean (SD)	20.2 (1.8)	20.7 (2.1)	0.87
Left-guided/right-guided/left standard rTMS, *n*	6/2/9	3/5/6	0.26
18-FDG dose, Mbq, mean (SD)	154.1 (7.6)	157.3 (10.8)	0.36
MADRS scores, mean (SD)			
Baseline	32.1 (7.7)	35.1 (6.3)	0.26
End point	8.9 (4.0)	27.6 (9.0)	<0.001
% Improvement	71.0 (12.8)	21.5 (20.2)	<0.001
HDRS scores, mean (SD)			
Baseline	25.2 (4.5)	26.7 (5.7)	0.41
End point	9.0 (3.3)	21.6 (6.8)	<0.001
% Improvement	63.7 (12.2)	19.0 (16.1)	<0.001
Ongoing medications, n *(%)*			
Antidepressants	8 (47)	6 (43)	0.81
Mood stabilizers	5 (29)	6 (43)	0.48
Antipsychotics	7 (41)	7 (50)	0.37
Benzodiazepines	7 (41)	8 (57)	0.28
Past medications, n *(%)*			
Antidepressants	17 (100)	14 (100)	>0.99
Mood stabilizers	9 (53)	9 (64)	0.72
Antipsychotics	8 (47)	10 (71)	0.27
Benzodiazepines	11 (65)	11 (78)	0.46
ECT	6 (35)	7 (50)	0.92

Abbreviations: ECT, electroconvulsive therapy; 18-FDG, 18-fluorodeoxyglucose; HDRS, Hamilton depression rating scale, 21 items; MADRS, Montgomery & Äsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation.
[a]The χ^2 tests, Fisher's exact tests, and *t*-tests were used when appropriate. All statistics were two tailed.
[b]Years of education after primary school.

Scale (MADRS) (Montgomery and Asberg, 1979), the 21-item Hamilton Depression Rating Scale (Ham-D) (Hamilton, 1960), and the Tyrer anxiety scale (Tyrer *et al*, 1984).

Response to TMS, defined as at least 50% decrease from baseline MADRS score, as in another TMS study of depressed patients (O'Reardon *et al*, 2007), was assessed using the last clinical assessment performed just after the final TMS session. Among the actively treated patients, 17 were responders and 14 were nonresponders to TMS.

Treatments

Previous medication was titrated down to a minimal dose that did not lead to significant clinical worsening for at least 2 weeks before scanning. In all, 5 responders and 4 nonresponders had a stage II resistance (failure to at least two adequate trials of antidepressants) according to Thase and Rush criteria (Thase and Rush, 1997), 9 responders and 5 nonresponders a stage III (stage II and failure to tricyclics), 2 responders and 5 nonresponders a stage IV (stage III and failure to monoamine oxidase inhibitors (MAOIs)), and one patient had a stage V resistance (stage IV and ECT resistance) in the responder to TMS group (Supplementary Table S1).

Comorbidities

A total of 7 patients met criteria for a comorbid diagnosis of anxiety disorder (panic disorder with or without agoraphobia, or generalized anxiety disorder); 11 patients had resistant depression in the course of bipolar disorder. Among the latter patients, three had a bipolar II type disorder, all of which were in the nonresponder group. These comorbid diagnoses were equally distributed in both groups (Table 1).

Scanning Protocols

All participants were investigated at rest. They were instructed to lie and relax in the PET camera with eyes closed, in a quiet room with low dimmed light. Head movement was restricted with an individually molded thermoplastic mask.

[^{18}F]-FDG-PET 3D images were obtained following a transmission scan for attenuation correction from a Siemens ECAT EXACT HR+ tomograph that collects 63 simultaneous slices (intrinsic in-plane resolution: 4.3 mm; voxel size: $2.42 \times 2.42 \times 2.43\,mm^3$). A summed image corresponding to the attenuation- and decay-corrected uptake of the [^{18}F]-FDG, expressed in activity concentration (Bq/ml), was obtained from two 3D time frames (10 min each) collected 30–50 min after intravenous injection of the radioligand. The mean (SD) injected ^{18}F-fluorodeoxyglucose radioactivity was 155.6 (9.25) MBq in the patients (see Table 1 for doses in groups), and 155.78 (19.65) MBq in healthy subjects ($t = 0.04$, $df = 67$, $p = 0.96$).

The 3D structural MRIs were acquired on a 1.5 Tesla GE Signa scanner (General Electrics Medical Systems, Milwaukee, WI) using a T1-weighted spoiled gradient-recalled sequence (124 contiguous slices; field of view 24 cm; 256×256 matrix; voxel size: $0.94 \times 0.94 \times 1.3\,mm^3$).

Each of the [^{18}F]-FDG-PET and T1-weighted images were visually inspected for artifacts.

Image Processing

All of the [^{18}F]-FDG-PET and structural images were processed with Statistical Parametric Mapping software package (SPM5, Wellcome Department of Cognitive Neurology, University College, London, UK; http://www.fil.ion.ucl.ac.uk/spm), implemented on Matlab (The Mathworks, Natik, MA; http://www.mathworks.com).

Structural preprocessing. To take into account a possible effect of structure on [^{18}F]-FDG images, voxel-based morphometry (VBM) was performed using the unified segmentation implemented in SPM5 (Ashburner and Friston, 2005). T1-weighted images were spatially normalized, segmented into gray and white matter, and modulated before being smoothed with a 10-mm full-width half-maximum (FWHM) isotropic Gaussian kernel.

[^{18}F]-FDG-PET preprocessing. For the healthy subject group, each [^{18}F]-FDG image was coregistered to its corresponding T1-weighted image using a rigid-body model. Transformation matrices obtained during the spatial normalization of the T1-weighted images to the MNI template were then applied to the resulting [^{18}F]-FDG images. The mean image of these [^{18}F]-FDG images was computed, providing a [^{18}F]-FDG template that was then smoothed with an 8-mm FWHM isotropic Gaussian kernel. Finally, the [^{18}F]-FDG images of all subjects were spatially normalized to this template and smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Statistical Analysis

Demographic and clinical data. Analyses were performed using JMP 8 software from SAS (SAS Institute, SAS Campus Drive, Cary, NC). Unpaired *t*-tests and χ^2 tests were used for comparing continuous and categorical variables, respectively, in between-group comparisons. Statistical significance was defined as $p<0.05$, two tailed.

Image analysis. Voxel-wise comparisons were performed using SPM5 within the framework of the general linear model (GLM). All results were obtained within the mask of the hypothesized regions of interest, drawn using Wake Forest University (WFU) PickAtlas (Maldjian *et al*, 2003), including inferior frontal, middle frontal, superior frontal, medial frontal, and orbital gyri, ACC, inferior temporal and parahippocampal gyri, insula, amygdala, caudate, and 'extra-nuclear' fiber tracts. Brain locations were reported as *x*, *y*, and *z* coordinates in Montreal Neurologic Institute (MNI) space and WFU PickAtlas was used to convert MNI coordinates into Talairach coordinates. The Talairach and Tournoux atlas (Talairach and Tournoux, 1988) was used to identify brain regions and approximate Brodmann areas (BA).

MRI image analysis. Group comparisons of structural images were performed on gray matter and white matter tissues using an analysis of covariance (ANCOVA) with group (nonresponders, responders, and healthy subjects) as between-subject factor and age, gender, and total intracranial volume as confounding covariates. An F-test was used to compare the three groups. Significance threshold was set at $p<0.05$, false discovery rate (FDR) corrected for multiple comparisons.

PET image analysis. The [^{18}F]-FDG 3D images were entered into the GLM within SPM5; in order to control for global glucose uptake effects, we used proportional scaling global normalization, yielding an index of regional- relative to global- glucose uptake (gluMI). Baseline gluMI values were compared between responder, nonresponder patients, and healthy subjects using an ANCOVA, with group as between-subject factor and age and gender as confounding covariates. An F-test was used to compare the three groups. Significance threshold was set at $p<0.05$, FDR corrected for multiple comparisons. Thereafter, *post hoc* *t*-tests were performed within the regions where the F-test was significant. The 'healthy group *versus* responders', 'healthy group *versus* nonresponders', and the 'responders *versus* nonresponders' contrasts were examined. Significance was set at $p<0.001$, uncorrected. Cluster significance thresholds (extent threshold) were set at 10 contiguous voxels (voxel size $=8\,mm^3$) to reduce type I errors introduced by potential noise.

PET-MRI analysis. Relations between gluMI and structure were assessed using the biological parametric mapping (BPM) toolbox (Casanova *et al*, 2007). BPM combines information from different imaging modalities on a voxel-wise basis using the GLM. Imaging variables are integrated on a voxel-wise basis, and hence each voxel has a unique regression design that includes the value of each imaging modality for that voxel. Group comparisons of regional cerebral gluMI after accounting for volumetric changes were performed using an ANCOVA with group as between-subject factor, age and gender as basic confounding covariates, and structural images as voxel-dependent confounding covariate. The *t*-tests were performed within the same regions where the F-test of the PET analysis was significant. The 'healthy group *versus* responders', 'healthy group *versus* nonresponders', and the 'responders *versus* nonresponders' contrasts were examined. Significance was set at $p<0.001$, uncorrected. Cluster significance thresholds (extent threshold) were set at 10 contiguous voxels (voxel size $=8\,mm^3$).

Correlation analyses. In order to explore the relationships between gluMI in different regions (PET regional correlations) or between gluMI and clinical scores (PET-clinical symptoms correlations), individual gluMI values at significant peak voxels were extracted from the SPM F-map. Correlation analyses were performed with JMP 8. All correlations were examined using ANCOVAs with group as between-subject factor.

As our aim was to examine intergroup differences, we report herein the interaction effects between groups and correlations. Significance was set at $p<0.05$ Bonferroni corrected, for all ANCOVAs. The *post hoc* correlations were performed in each group using Pearson's *r* test, when an interaction effect was significant.

RESULTS

Demographic, Clinical, and Treatment Characteristics of the Patients

Responders to TMS did not differ from nonresponders with regard to clinical symptoms at baseline, disease history, comorbidities, family history of depression, TMS parameters, and type of ongoing and past treatments including antidepressants, mood stabilizers, antipsychotics, benzodiazepines, or ECT prescriptions. No difference was found between subgroups regarding the resistance stage ($\chi^2 = 1.48$, df = 2, $p = 0.48$; Table 1 and Supplementary Table S1).

Additionally, bipolar (BP) and unipolar (UP) TRD patients did not differ regarding age (BP: mean age (SD) = 47 (5.9), UP: mean age (SD) = 47.8 (8.1), Student's *t*-test score = 0.27, df = 29, $p = 0.79$), gender (BP: 6 women, 5 men, UP: 14 women, 6 men, $\chi^2 = 0.73$, df = 1, $p = 0.39$), age at onset (BP: 26.3 (7.7), UP: 29.3 (10.8), *t*-score = 0.82, df = 28, $p = 0.42$), duration of illness (BP: 20.7 (7.3) years, UP: 18.2 (10.0) years, *t*-score = 0.73, df = 28, $p = 0.47$), duration of depressive episode (BP: 3.4 (3.3) years, UP: 2.7(1.8) years, *t*-score = 0.77, df = 28, $p = 0.44$), number of depressive episodes (BP: 4.2 (1.9), UP: 3.4 (1.8), *t*-score = 1.07, df = 27, $p = 0.29$), or family history (BP: yes = 4, UP: yes = 10, $\chi^2 = 0.54$, df = 1, $p = 0.46$). UP and BP did not differ in depression scores improvement rate (BP: 55.6% (9.0%), UP: 44.8% (6.7%), *t*-score = 0.96, df = 29, $p = 0.34$).

PET Findings

There was a main effect of group on the [^{18}F]-FDG-PET images before accounting for structural differences, as evidenced by the results of the F-test, which revealed a pattern of several regions (Table 2). The *post hoc t*-tests performed in those regions showed that both responders and nonresponders to TMS had, in comparison with healthy subjects, lower prefrontal gluMI in right ACC, right DLPFC, and left ventrolateral prefrontal cortex (VLPFC). Additionally, nonresponders had lower gluMI in *left* ACC, *left* DLPFC, right and left anterior insula, and left OFC. They also displayed *higher* gluMI in left inferior temporal–limbic regions including uncus, left amygdala, and left uncinate fasciculus. No significantly higher gluMI values were found in responders in comparison with healthy subjects. In nonresponders relative to responders, gluMI was higher in the left amygdala, uncinate fasciculus, and anterior commissure, and lower in the left OFC (Table 2 and Figure 1).

MRI Corrected PET Findings

When accounting for volume differences, regions that survived the volume correction included right ACC, right and left insula, left DLPFC, left uncus at BA20, and left amygdala (Table 2). Volume fully accounted for lower gluMI in the left OFC, left VLPFC (BA9/47), left ACC, and

Table 2 Differences in Regional Cerebral Glucose Metabolism Index between 17 Responders and 14 Nonresponders to rTMS Compared with 39 Healthy Subjects

Brain region	Main effect of group[a]						Group comparison, *t*-value[b]					Volume corr.[c], *t*-value[b]			
	BA	Cluster size[d,e]	*x, y, z* MNI coordinates[f]			F-test[a]	R < HS	NR < HS	NR > HS	R > NR	R < NR	R < HS	NR < HS	NR > HS	R < NR
Right MFG	9	317	34	12	38	11.42	3.55	4.14	—	—	—	—	—	—	—
Right insula	45	191	36	22	12	9.75	—	3.97	—	—	—	—	3.25	—	—
Right ACC	32	850	12	34	22	13.67	3.37	4.85	—	—	—	3.56	4.22	—	—
Left ACC	32	—	−2	38	28	9.03	—	4.07	—	—	—	—	—	—	—
Left MFG	9	26	−40	28	42	7.86	—	3.93	—	—	—	—	3.53	—	—
Left IFG	9	630	−40	8	38	9.86	3.49	3.84	—	—	—	3.32	—	—	—
Left IFG	47	—	−48	14	24	9.60	4.10	3.46	—	—	—	3.57	—	—	—
Left MFG	46	—	−44	26	26	9.52	—	4.18	—	—	—	3.32	3.43	—	—
Left MFG (orbital)	10	43	−32	50	−4	8.17	—	3.94	—	3.79	—	—	—	—	—
Left insula	45	60	−32	26	8	8.28	—	3.80	—	—	—	3.77	3.22	—	—
Left amygdala	—	439	−24	−2	−28	13.10	—	—	4.84	—	4.60	—	—	4.79	4.57
Left ITG (uncus)	20	—	−32	−10	−38	8.82	—	—	4.20	—	—	—	—	4.33	—
Left UF	—	93	−32	4	−10	8.41	—	—	3.60	—	3.87	—	—	3.51	3.80
Left AC	—	—	−32	−8	−10	9.05	—	—	—	—	4.23	—	—	—	4.08

Abbreviations: AC, anterior commissure; ACC, anterior cingulate cortex; BA, Brodmann area; ellipses, no cluster retrieved by comparison, or not applicable; HS, healthy subject; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; NR, nonresponder; R, responder; UF, uncinate fasciculus.
[a]Statistics at voxel level (F-test, df = 2, 65), corresponding to a minimum corrected threshold of $p < .05$ false discovery rate (FDR) corrected, with height threshold F = 6.97, and extent threshold $k = 10$ voxels.
[b]The *post hoc* test, height threshold was set at $p < 0.001$, uncorrected, and extent threshold was set at 10 voxels.
[c]Volume corr., volume corrected analysis of PET images with T1 anatomic images as voxel-dependent confounding covariate.
[d]Empty cells indicate that the region is included in the same cluster as the region immediately above.
[e]Cluster size is expressed in number of voxels, with voxel size = 8 mm^3.
[f]Montreal Neurological Institute, in millimeters, for significant peak voxels.

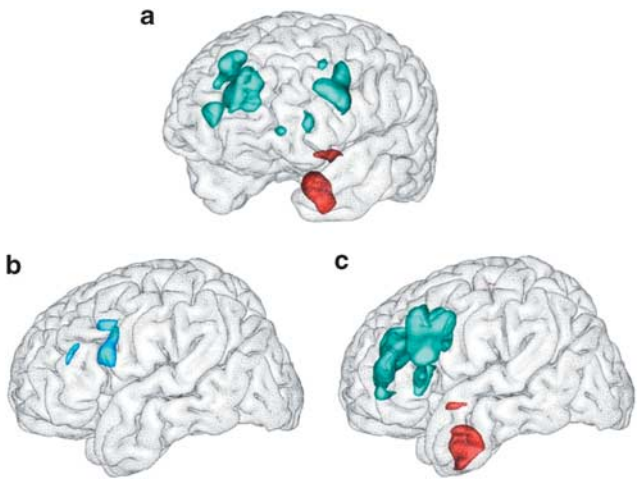

Figure 1 (Top, left frontal view) Main comparison (F-test) between responders, nonresponders, and healthy subjects. Height threshold: $p<0.05$, false discovery rate corrected; extent threshold: 10 voxels (a). (Bottom, lateral views) The *t*-maps of baseline regional cerebral glucose metabolism index (gluMI) in 17 responders to rTMS (b, left) and in 14 nonresponders (c, right) compared with 39 healthy subjects, respectively (height threshold: $p<0.001$; extent threshold: 10 voxels); red color indicates higher gluMI, and blue indicates lower gluMI. Statistical maps are projected on a normalized brain mesh.

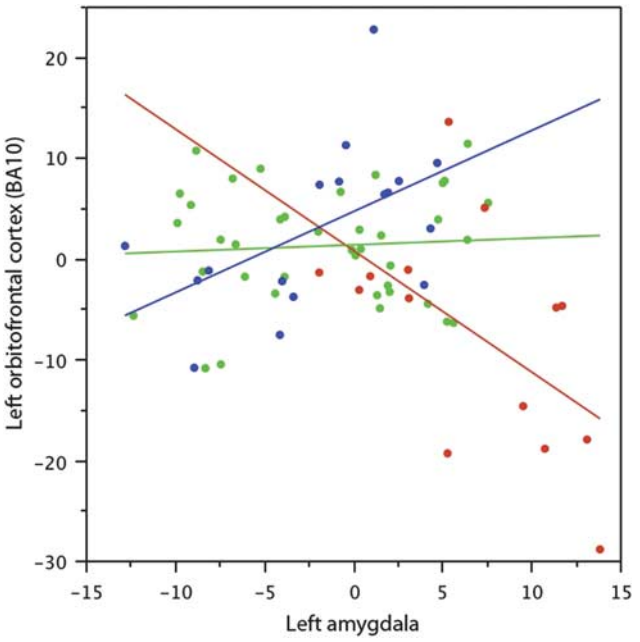

Figure 2 Regional correlations between regional cerebral glucose metabolism index in left frontal BA10 at MNI coordinates ($x=-32$, $y=50$, $z=-4$) and in left amygdala ($x=-24$, $y=-2$, $z=-28$). Interaction: $F=8.20$, $df=2$, $p<0.001$. Red indicates negative correlation in nonresponders, Pearson's $r=-0.55$, $p=0.042$. Blue indicates positive correlation in responders, Pearson's $r=0.52$, $p=0.031$. Green indicates no correlation in healthy subjects, Pearson's $r=0.07$, $p=0.68$.

right DLPFC. Higher gluMI was not related to white matter volume in uncinate fasciculus or in anterior commissure.

MRI Findings

Voxel-based comparison of the GM maps revealed no main effect of group at the $p<0.05$, FDR corrected for multiple comparisons. However, at a more permissive threshold, GM volume reductions were observed in some regions where gluMI was low, including the left OFC (BA10, $t=3.52$, $p<.001$ unc, $k=36$ voxels) in nonresponders relative to responders and relative to healthy subjects ($t=2.87$, $p<.002$, $k=312$ voxels), and in the left ACC (BA 32, $t=3.40$, $p<.001$ unc, $k=46$) in nonresponders relative to healthy subjects. No regional difference was found in white matter maps between responders, nonresponders, and healthy subjects.

FDG-PET Regional Correlations

Responders, nonresponders, and healthy subjects significantly differed in several PET regional correlations.

Interactions (F-tests). Significant interactions (gluMI × group) were found between left OFC and several regions in which metabolic level was independent of structure. Regions included left amygdala ($F=8.20$, $df=2$), left DLPFC at BA9 ($F=11.79$, $df=2$), left VLPFC at BA9 ($F=14.34$, $df=2$), right ACC ($F=8.18$, $df=2$), and left uncus (BA20) ($F=8.31$, $df=2$).

Post hoc *tests.* In the nonresponders, left amygdala gluMI was negatively correlated with gluMI in the left OFC, whereas a positive correlation in the responders and no correlation in the healthy subjects was observed (Figure 2 and Table 3). A negative correlation was also found in nonresponders between gluMI in left uncus and left OFC, but no correlation was found in responders or in healthy subjects. Positive correlations were observed in nonresponders, but not in other groups, between OFC and (1) prefrontal regions including left DLPFC at BA9; (2) left VLPFC at BA9; and (3) right ACC.

Table 3 Regional Correlations of Glucose Metabolism with Orbitofrontal Cortex across Groups

	Healthy subjects ($n=39$)	Responders ($n=17$)	Nonresponders ($n=14$)
Right ACC (BA32)	$r=0.31$; $p=0.06$	$r=-0.19$; $p=0.47$	**$r=0.77$; $p=0.001$**
Left MFG (BA9)	$r=0.19$; $p=0.25$	$r=-0.20$; $p=0.45$	**$r=0.92$; $p<0.001$**
Left IFG (BA9)	$r=0.04$; $p=0.25$	$r=0.02$; $p=0.45$	**$r=0.92$; $p<0.0001$**
Left uncus (BA20)	$r=0.02$; $p=0.92$	$r=0.14$; $p=0.58$	**$r=-0.70$; $p=0.005$**
Left amygdala	$r=0.07$; $p=0.68$	**$r=0.52$; $p=0.03$**	**$r=-0.55$; $p=0.04$**

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; *p*, probability value; *r*, Pearson's correlation coefficient.
Significant correlations are indicated in bold.

Clinical Correlations

No significant interaction (gluMI × group) was found between gluMI and baseline scores of depression, anxiety

scores, or between gluMI and change in depression scores after TMS.

DISCUSSION

Pretreatment brain glucose metabolism at rest and regional volumes were investigated in patients with resistant depression to assess whether these characteristics could differentiate responders and nonresponders to prefrontal TMS. Nonresponders had a pattern of widespread low prefrontal metabolism associated with high temporal–limbic resting-state metabolism. Low metabolism was related to variations in GM volume in several regions, notably in left OFC and ACC, where lower GM volume was observed in nonresponders. Uniquely, different correlations between left amygdala and left OFC metabolism distinguished the nonresponders, responders, and healthy subject groups.

Functional Correlates of Response to TMS

Few studies have examined brain correlates of antidepressant response to high-frequency TMS and most of those studies have used single-photon emission computerized tomography (SPECT) in smaller groups of patients, pooling both medication-resistant and nonresistant depressed patients, with response defined as a 30% decrease in depression scores (50% in the present study). *Responders* to TMS have been found to have higher blood flow in inferior frontal lobe before stimulation (Teneback *et al*, 1999), or lower blood flow in amygdala (Nadeau *et al*, 2002) than nonresponders, consistent with our results. Improvement in depression scores with TMS has also been found to positively correlate with blood flow in the anterior cingulate (Langguth *et al*, 2007) and in the right peri-insular region (Mottaghy *et al*, 2002).

Consistent with other studies of TRD patients (Videbech, 2000; Konarski *et al*, 2007), the present findings point to a pattern of decreased prefrontal glucose metabolism, particularly in regions involved in TMS response, including the insula, the ACC, and the OFC. In *nonresponders* to TMS relative to responders, low glucose metabolism was observed in these regions, and related to lower GM volumes in the left ACC and in the rostral part of the left OFC. In line with this finding, hypometabolism in OFC has been hypothesized to be related to GM reduction in more severely ill patients such as the nonresponders to TMS in our study (Drevets, 1999), whereas normal glucose metabolism in OFC has been reported in medication-resistant depressives with no GM reduction (Drevets, 2000; Drevets *et al*, 2002). Thus, the present results support that OFC gray matter volume reduction might precondition a negative response to prefrontal TMS.

A functional pattern of prefrontal hypometabolism associated with temporal–limbic hypermetabolism has previously been reported in various groups of depressed patients regardless of resistance to treatment (Konarski *et al* 2007; Brooks *et al*, 2009; Savitz and Drevets, 2009). In the present study, a functional amygdala hypermetabolism was only observed in the TRD nonresponders to TMS, regardless of GM volume. Thus, the present findings raise the hypothesis that high metabolic levels of the temporal–limbic regions, particularly the amygdala, might precondition nonresponse to prefrontal TMS.

Frontal–Limbic Correlations in Resistant Depressives

Distinct correlations were found between OFC and the *amygdala* in nonresponders, responders, and healthy subjects, indicating different frontal–limbic relations depending on the group. The OFC is involved in coding of the identity of the sensory stimuli and their rewarding properties (Schultz *et al*, 1998), and is connected with the lateral nuclei of the amygdala, whose activity appears closely related to the context and level of aversiveness of the stimuli (Zald, 2003). Through inhibitory projections to the amygdala, the lateral OFC is consequently involved in controlling information processing, particularly representation of rewards and punishments, and regulates behavior expression and emotional responses (Hooker and Knight, 2006). Thus, GM reductions in this region may disturb interactions between orbital cortex and projections to the amygdala, and to other connected regions such as the cingulate cortex or the striatum. Our findings are consistent with a frontal–limbic dysregulation in the subgroup of *nonresponders*, leading to decreased frontal cortical regulation of temporal–limbic activation in response to negative stimuli, as has previously been hypothesized in TRD (Mayberg, 1997a). In these patients, and as prefrontal TMS seems to modulate OFC activity (Nadeau *et al*, 2002), GM reduction of the OFC might partly account for the observed specific resistance to TMS. Such resistance to TMS in these patients may additionally be related to altered white matter tracts in the ventral frontal–temporal–limbic network. Indeed, higher glucose metabolism was detected in left uncinate fasciculus and anterior commissure in *nonresponders*, independently of white matter volumes. As pointed out by Buchbaum *et al* (2007), the increased metabolism might reflect increased energy need due to defects in white matter that, in turn, may lead to inefficiency in brain circuitry. The uncinate fasciculus is a bidirectional pathway that links the anterior temporal lobe and amygdala with the medial and orbital prefrontal cortices, and the anterior commissure is a fiber bundle that connects the inferior temporal with sites including the amygdala and OFC (Schmahmann and Pandya, 2006). Thus, it can be speculated that because of changes in the OFC/VLPFC, and connecting white matter tracts such as the uncinate fasciculus, TMS would fail to modulate the prefrontal cortex and temporal–limbic structure activity through the ventral-limbic pathway.

Limitations

First, although there is no larger FDG-PET study associated with a controlled TMS trial, the short treatment duration might be seen as a limitation. Indeed, TMS has been found to be more effective with longer treatment durations (O'reardon *et al*, 2007). Thus, some nonresponder patients in this study would perhaps have been responders had they been treated over a longer period of time. However, despite the small number of subjects and short treatment duration, the results of the clinical trial (Paillère Martinot *et al*, 2009) showed that the chosen protocol accelerated the effect of

TMS, with a strong effect size (Cohen's $d = 0.78$; Cohen, 1988) over sham stimulation, probably accounting for the high response rate in the study.

A second limitation relates to previous medication. It was not possible to withdraw all treatments in these difficult patients, and it was not possible to assess all the dosages prescribed along their illness as they had very long illness durations. However, antidepressant and mood stabilizers were prescribed in usual standard dosages in all the patients. Effects of medication on FDG measures have been studied in a few studies, with inconsistent results. Apparently, brain metabolic responses to antidepressants vary according to the underlying pathophysiology of the patient and the degree of symptomatic improvement (Saxena *et al*, 2002), and chronic antidepressant drug treatment might reduce metabolism in the amygdala and ventral ACC in depressed subjects showing a positive treatment response only (Drevets *et al*, 2002). Here, the patients were all similarly resistant to medication according to Thase and Rush criteria, and the number of patients on antidepressants and duration of illness or episode were comparable across groups. Also, the number of patients on antipsychotics and the dosages were very small and similar in both patient groups, as was the number of patients on mood stabilizers; thus, it is unlikely that their effect would have confounded the metabolic findings. Finally, most patients were on low doses of benzodiazepines, which have been reported to induce decreases in glucose metabolic rates in regions such as the basal ganglia, thalamus, or visual cortex (Martinot, 1992). These effects might have blurred some differences with the comparison subjects, but as the prescriptions of patients did not differ across subgroups, it is unlikely that these effects would have confounded the results of direct comparison of responders with nonresponders. Moreover, the metabolic findings are consistent with findings of other studies of untreated depressed patients (Teneback *et al*, 1999).

Third, in a few studies, resistance to TMS has been associated with previous medication resistance, or anxiety comorbidity (Fregni *et al*, 2006; Brakemeier *et al*, 2008; Lisanby *et al*, 2009). In this study, medication resistance was comparable across responders and nonresponders to TMS. Regarding comorbid anxiety, the number of patients with a comorbid anxiety disorder was similar in both groups, and anxiety scores before scanning were similar across groups, and did not correlate with PET measures, which suggests that nonresponse parameters did not depend on anxiety comorbidity in this group.

Fourth, the pooling of patients with unipolar resistant depression and with resistant depression in the context of history of bipolar disorder may be considered as a limitation. At variance with most previous reports, the present study aimed at assessing [^{18}F]-FDG in highly treatment-resistant patients notwithstanding the UP/BP dichotomy, rather than to compare UP or BP subgroups. In addition, many imaging studies indicate increased resting-state metabolism in the amygdala in Major Depressive Disorder as well as in BP depression (Savitz and Drevets, 2009). Regarding OFC, resting-state activity has generally been found similarly increased in both UP and BP depressives (Drevets, 2000), although in more severely ill or TRD patients, studies have found no change or decreased function (Mayberg *et al*, 1994; Savitz & Drevets, 2009). Thus, putative differences in functional pattern reported in the literature between BP and UP patients are not clearcut.

In addition in the present study, the UP/BP ratios were similar in both responder and nonresponder subgroups, and no difference was found between UP and BP patients regarding improvement rates or depression history, or when comparing UP and BP groups using a similar image analysis, within the same regions of interest and at the same statistical threshold as in the responder/nonresponder analysis. Regarding the responder/nonresponder comparisons, and although the groups were much smaller, the same left amygdala function and left OFC gray matter pattern still distinguished responders from nonresponders within each subgroup. In both the BP and UP subgroups, nonresponders had significantly higher amygdala gluMI (Wilcoxon test, BP: responders, mean (SD) $= -1.36$ (1.86), nonresponders mean (SD) $= 9.49$ (2.04), $\chi^2 = 5.63$, $p = 0.02$; UP: responders, mean (SD) $= -2.19$ (1.65), nonresponders mean (SD) $= 5.21$ (1.82), $\chi^2 = 6.48$, $p = 0.01$). Similarly, BP and UP nonresponders had significantly lower GM in OFC than their responder counterparts (Wilcoxon test, BP: responders, mean (SD) $= 0.04$ (0.02), nonresponders mean (SD) $= -0.03$ (0.02), $\chi^2 = 5.63$, $p = 0.02$; UP: responders, mean (SD) $= 0.01$ (0.01), nonresponders mean (SD) $= -0.04$ (0.02), $\chi^2 = 5.73$, $p = 0.02$). In addition, the differential relation between amygdala and OFC gluMI according to treatment response (responders and nonresponders) was maintained in both the UP and BP diagnostic subgroups (gluMI $\times$ group interactions, UP: $t = 2.13$, $p = 0.05$; BP: $t = 2.40$; $p = 0.05$).

In summary, the results suggest that alterations in brain metabolism and structure influence the response to TMS. Response to prefrontal TMS might depend on OFC volume and amygdala functioning. Further research is needed to determine the predictive value of such a functional pattern determined at an individual level in patients with resistant depression referred to TMS therapy.

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DISCLOSURE

The authors declare no conflict of interest. Over the past 3 years, Dr Paillère Martinot has received compensation from Bristol-Meyers-Squibb, Lilly, and Sanofi companies. Dr Artiges has received compensation from Janssen Laboratory; and Dr Galinowski from Ardix, Lilly, and Sanofi companies.

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