HF-rTMS Treatment in Medication-Resistant Melancholic Depression: *Results from ^{18}FDG-PET Brain Imaging*

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ABSTRACT

Introduction: High frequency repetitive transcranial magnetic stimulation (HF-rTMS) of the left dorsolateral prefrontal cortex (DLPFC) might be a promising strategy to treat depression, but not all patients show a positive outcome.

Objective: In this open study, we evaluate whether a favorable HF-rTMS treatment outcome could be predicted by baseline prefrontal brain glucose metabolism (CMRglc), measured by ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET).

Methods: A sample of 21 antidepressant-free, treatment-resistant depression (TRD) patients of the melancholic subtype received 10 sessions of HF-rTMS delivered on the left DLPFC. Patients underwent a static ^{18}FDG-PET before and after HF-rTMS treatment.

Results: Forty-three percent of the patients showed a reduction of at least 50% on their Hamilton Rating Scale for Depression scores. Higher baseline metabolic activities in the DLPFC and the anterior cingulate cortex (ACC) were associated with better clinical outcome. Successful HF-rTMS treatment was related to metabolic changes in subdivisions of the ACC (Brodmann areas 24 and 32).

Conclusion: This biological impact of HF-rTMS on regional brain CMRglc explains to some extent how HF-rTMS may improve moods in TRD patients. Larger sham-controlled HF-rTMS treatment studies are needed to confirm

FOCUS POINTS

- Distinguish prefrontal fronto-cingulate network models in unipolar depression.
- Identify by ^{18}fluorodeoxyglucose positron emission tomography brain neuroimaging metabolic changes in this network related to clinical high frequency repetitive transcranial magnetic stimulation (HF-rTMS) outcome.
- Comprehend the biological impact of HF-rTMS on regional brain glucose metabolism and how these influences might be related to improve moods in treatment-resistant depressed patients.

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these results.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) has been put forward as a promising new technique to treat major depression.[1,2] Currently, the physiological influence and treatment effects of repetitive TMS (rTMS) are under investigation.[3-5] As a focused cortical intervention, the majority of all treatment studies in depression target the dorsolateral prefrontal cortex (DLPFC) as the area of interest for rTMS.[6,7] However, it remains unclear which TMS parameters can produce the most benefits.[8,9] Besides having an effect on neuroendocrinology[10] and on neurotransmitters, such as dopamine and serotonin,[11,12] rTMS may also alter regional cerebral blood flow (rCBF) in stimulated regions and those connected to them.[13,14]

Preliminary clinical results suggest that antidepressant responses to rTMS might vary as a function of stimulation frequency and may depend on pre-treatment prefrontal brain metabolism.[15-17] Additionally, the anterior cingulum cortex (ACC) has not only been described as a possible predictor of treatment response,[18] but left prefrontal rTMS also seems to influence its metabolic activity status.[19-22] Should such observations be confirmed, it may then be possible to use these baseline measures to choose the optimal TMS stimulus parameters in individuals to maximize antidepressant responses.[23]

The primary objective of this open ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) study is to explore whether basal brain glucose metabolism (CMRglc) in the frontocingulate circuit could predict favorable outcome of high frequency rTMS (HF-rTMS) treatment in major depression, as postulated by other authors.[13,24-26] To avoid heterogeneity in our sample, we selected only unipolar treatment-resistant melancholically depressed patients. Melancholic depression is clinically characterized by anhedonia, psychomotor difficulties, excessive guilt or hopelessness, and appetite and weight disturbances.[27,28] Furthermore, we expected that after treatment HF-rTMS responders would show metabolic changes in prefrontal cortical and ACC activity,[6] whereas in non-responders no significant changes should be observed in any of the predefined regions of interest.

METHODS

Subjects

Our group consisted of 21 antidepressant-free unipolar depressed patients of the melancholic subtype (Female:Male=13:8; 47.1±9.6 years of age). With the exception of benzodiazepines, after a washout period from all psychotropics, such as antidepressants, antipsychotics, and mood stabilizers, all patients were antidepressant free for at least two weeks before stimulation started. During the washout period, patients had contact with their physicians on a regular basis. Pharmacological changes during the stimulation sessions were considered as drop-out from the study, but not from HF-rTMS treatment.

Treatment resistance was assessed with the Thase and Rush criteria.[29] All participants were right-handed and considered at least stage III treatment resistant in that they had had a minimum of two unsuccessful trials of selective serotonin reupake inhibitor/nonadrenalin serotonin reupake inhibitor treatment and one failed trial with tricyclic antidepressants as described by Rush and colleagues.[30] Right-handedness was assessed with the Van Strien Questionnaire.[31] Psychiatric disorders were assessed using the Mini-International Neuropsychiatric Interview.[32] Severity of depression was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D)[33] and the 21-item Beck Depression Inventory (BDI).[34,35] A certified psychiatrist, unrelated to the study, rated depression symptoms and depression severity before and after HF-rTMS treatment. Mean HAM-D scores before entering the study were 25.24±3.90 and mean BDI scores were 33.48±11.50, indicating severe depression. Patients with suicide attempts during the current depressive episode or alcohol/drug dependence and/or abuse were not included. Eleven participants were current in-patients during HF-rTMS treatment. This study was part of a larger project investigating the influence of HF-rTMS on different neuro-cognitive markers. The same treatment resistant depression (TRD) patients were tested before and after treatment with a battery of neurocognitive tests. Further, besides the ^{18}FDG-PET assessment, all patients also received a single photon emission computed tomography (SPECT) scan before and after HF-rTMS treatment, examining the serotonergic system. These data will be published elsewhere. The ethics committee of the University Hospital

of the Free University of Brussels (UZBrussel) approved the study. All subjects gave written informed consent.

Data Collection

The day before the first HF-rTMS session (T1) and within two days after the last treatment (T2), patients received a static ^{18}FDG-PET scan. Patients had to lie supine with their eyes closed. No cognitive tasks or other instructions were given. Before entering the study, each patient was asked to rate her/his depressive symptoms, using the BDI. On the same day, a certified psychiatrist, unrelated to the study, rated depression symptoms and depression severity using the HAM-D. The HAM-D and BDI were re-administered 2–3 days after 10 sessions of HF-rTMS. We defined clinical response as a 50% reduction of the baseline HAM-D score. Demographic and clinical characteristics of the patients are summarized in Tables 1 and 2.

Repetitive Transcranial Magnetic Stimulation

For the application of rTMS we used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK), connected to a specially designed figure-of-eight-shaped double 70 mm coil. The coil was held tangentially to the skull, the coil handle pointing 45° antero-medial. Before each application, the resting motor threshold (MT) of each individual was determined using motor evoked potentials (MEP). A stimulation intensity of 110% of the subject's MT of the right abductor pollicis brevis muscle was used. To accurately target the left DLPFC also known as Brodmann area 9/46, the precise stimulation site and position of the coil were determined using magnetic resonance imaging (MRI) non-stereotactic guidance (Philips Intera, Best, The Netherlands). To obtain individual anatomical information, all subjects underwent a T1-weighted MRI (3D-TFE, voxel size 1x1x1 mm) of the brain using a 1.5T Intera MRI scanner (Philips, Best, the Netherlands). All post processing was done on a ViewForum console (Philips, Best, the Netherlands). We located the left DLPFC visually on the 3D surface rendering of the brain based on the known gyral morphology and marked the central part of the middle prefrontal gyrus as the center of the left DLPFC. Perpendicular to this point, the precise stimulation site on the skull was marked and stimulated.[36] In each high-frequency (10 Hz) stimulation session, subjects received forty trains of 3.9 s duration, separated by an intertrain interval of 26.1 s. Each session, therefore, lasted 20 minutes (1,560 pulses per session). The treatment protocol of 10 daily HF-rTMS sessions was spread over two weeks. The International Society of Transcranial Magnetic Stimulation safety guidelines were followed.[37-39]

^{18}FDG-PET Brain Imaging

Patients underwent a static ^{18}FDG-PET (intravenous application of 222 MBq ^{18}FDG) prior to the stimulation sessions and after the last of the 10 daily sessions of HF-rTMS. We performed PET-scans with an Ecat Acell (Siemens) 30 minutes after tracer administration. Emission data were obtained in 3D mode over 10 minutes. For transmission, germanium-68 sources (3x185 MBq; decay corrected) were used and data were acquired in 2D mode over 3 minutes. Emission data were reconstructed iteratively (OSEM 10 iterations, 32 subsets) and a post-reconstruction filter (6 mm Gauss) was applied. We used filtered back reconstruction for the transmission, and these data were subsequently segmented into regions with similar attenuation factors. This segmented image was then forward projected to obtain attenuation correction factors for each line of response. The pixel size is 2,57 mm transaxial and 3,38 mm axial. Each scan was projected onto a normalized brain template with the SPM2 (Statistical Parametric Mapping, Welcome Department of Imaging Neuroscience, University College of London, UK) software.[40]

We defined regions of interest (ROI) by using the WFU PickAtlas Tool Version, 2.4.[41] The following ROI's were defined for both hemispheres: the dorsolateral prefrontal cortex (DLPFC; Brodmann area (BA) 9/46) and the ACC, with its subdivisions (BA 24, BA32, BA25) (Figure 1). Whereas the dorsal regions of the ACC (BA24) seem to be associated with cognition, the ventral regions of the ACC (BA32, BA25) are more related to affect.[42,43] Medians of the ^{18}FDG-PET CMRglc values were computed per region of interest over the scans. We further analyzed the median values of each ROI with SPSS 15 (Statistical Package for the Social Sciences). To overcome a possible non-linear relationship between brain imaging results and clinical outcome, non-parametric (Spearman) correlation tests may be more appropriate.[44]

Changes in mood were defined as the difference between mood assessment before and after HF-rTMS treatment (ΔHAM-D and ΔBDI). To investigate the relationship between CMRglc and clinical outcome, we used HAM-D scores as a relevant clinical response parameter to define responders versus non-responders. We calculated the lateralization index for each hemispheric ROI to evaluate contra- and ipsilateral changes in activities, related to treatment response. The lateralization index was calculated by the median CMRglc in the specific regions of interest: ([ROI right – ROI left] / [ROI right + ROI left]) x 100. A negative value corresponds with a higher median CMRglc in the left ROI and a positive value indicates the reverse.

We performed many different ROI analyses. First, we used a continuous method. We calculated the correlation between the baseline CMRglc (^{18}FDG-PET) in the predefined ROI's and

TABLE 1.
Demographic Data and Individual Rating Scores of the Hamilton Rating Scale for Depression and the Beck Depression Inventory

Patient	Gender	Age	Hospital/ Ambulatory	Thase and Rush stage	Duration current episode (years)	ECT trial	HAM-D Pre	HAM-D Post	BDI Pre	BDI Post
Non-responders										
1	M	56	A	5	1.5	+	16	9	11	8
2	F	55	H	3	12	-	24	22	16	19
3	F	48	A	3	3	-	27	25	53	40
4	F	47	H	3	12	-	30	25	51	47
5	M	40	A	4	2.5	-	26	23	43	46
6	F	58	H	5	3	+	24	26	29	38
7	F	52	A	3	5	-	23	17	32	36
8	F	55	H	5	4	+	33	23	43	35
9	M	39	A	3	1	-	27	26	31	22
10	M	25	A	3	2	-	22	25	31	32
11	F	54	A	3	2		21	15	37	32
12	M	34	A	3	11	-	22	18	25	36
Ratio	7:5									
Mean±SD		46.92±10.32			4.92±4.21		24.58±4.44	21.17±5.32	33.5±12.79	32.58±11.29
Responders										
1	F	49	H	3	3	-	32	16	50	31
2	M	34	H	5	7	+	21	6	23	17
3	F	48	A	3	5	-	26	9	38	23
4	M	38	H	3	0.5	-	27	6	17	6
5	F	50	A	3	2	-	27	10	26	21
6	F	61	H	3	0.5	-	27	10	41	24
7	F	42	H	3	4	-	23	9	32	19
8	F	45	H	3	1.5	-	25	8	33	10
9	M	60	H	5	20	-	27	12	41	16
Ratio	6:3									
Mean±SD		47.44±9.06			4.83±6.08		26.11±3.06	9.56±3.09	33.44±10.28	18.56±7.50

ECT=electroconvulsive shock therapy: (+) received (unsuccessful) treatment in the past, (-) no ECT treatment in the past; HAM-D=Hamilton Rating Scale for Depression; BDI=Beck Depression Inventory; H=hospitalized TRD patients during HF-rTMS treatment; A=ambulatory TRD patients during HF-rTMS treatment; SD=standard deviation; TRD=treatment-resistant depression; HF-rTMS=high frequency repetitive transcranial magnetic stimulation.

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the observed mood changes, using non-parametric Spearman correlation analyses. Second, we used a categorical approach of treatment responder identification. A patient that showed a 50% reduction in her/his baseline HAM-D score was defined as a HF-rTMS responder. To detect different baseline CMRglc patterns between responders and non-responders, we used the non-parametric Mann Whitney U test. Third, to detect the influence of 10 sessions of HF-rTMS in the different ROI's for the whole group, and for responders and non-responders separately, we performed non-parametric Wilcoxon Signed Ranks tests. Significance threshold was set at a two-tailed probability of $P \leq .05$.

TABLE 2.
Psychopharmacologic Patient Data

Patient	Last antidepressant medication before washout	Medications during HF-rTMS treatment (dose/day)
Non-responders		
1	Clomipramine	Alprazolam 2mg, Flurazepam 27 mg
2	Trazodone	Lorazepam 5mg, Lormetazepam 2 mg
3	Clomipramine	no
4	Amytriptiline	Bromazepam 24 mg
5	Paroxetine	Alprazolam 1 mg
6	Trazodone	Lormetazepam 1 mg
7	Amytriptiline	no
8	Venlafaxine	no
9	Clomipramine	no
10	Clomipramine	no
11	Clomipramine	no
12	Clomipramine	no
Responders		
1	Amytriptiline	Lormetazepam 2 mg
2	Fenelzine	no
3	Venlafaxine	no
4	Clomipramine	no
5	Nortryptiline	no
6	Clomipramine	Alprazolam 2 mg, Flurazepam 27 mg
7	Clomipramine	no
8	Dosulepine	Flunitrazepam 1mg
9	Fenelzine	Dikaliumclorazepaat 50 mg

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RESULTS

Clinical Responses

Responders did not differ from non-responders in age (t=.12, df=19, P=.90) or gender ($\chi 2$ (1, n= 21)=1.19, P=.28). Duration of the current depression episode was similar for both groups (t=.04, df=19, P=.97). Depression severity at baseline was not different between responders and non-responders (HAM-D: t=.88, df=19, P=.27; BDI: t=.13, df=19, P=.43). A paired t-test for the whole group showed that rating scores significantly decreased after HF-rTMS for the HAM-D (t=5.73, df=20, P<.01) and for the BDI (t=3.62, df=20, P=.02). As expected by design, the BDI rating scores before and after HF-rTMS treatment were significantly different for responders (t=6.44, df=8, P<.01), but not for non-responders (t=1, df=11, P=.34).

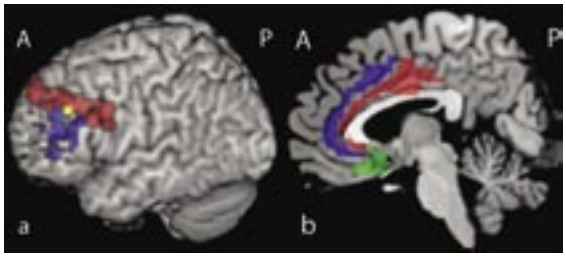
Nine of the 21 patients (43%) showed a 50% reduction in the initial HAM-D score after the 10 sessions of HF-rTMS, indicating a clinical response at that time. Mean HAM-D and BDI rating scores are listed in Table 1.

^{18}FDG-PET ROI CMRglc Analyses

Baseline CMRglc as possible predictor of response to HF-rTMS treatment

Spearman correlation analysis between base-

FIGURE 1.
a) Left dorsolateral prefrontal cortical region of interest* b) Subdivisions of the anterior cingulate cortex†



* In red Brodmann area 9 and in blue Brodmann area 46. The yellow circle represents the HF-rTMS stimulation site (Talairach coordinates: -50, 34, 34).

† In blue Brodmann area 24, in red Brodmann area 32, and in green Brodmann area 25.

All regions of interest were defined by using the WFU PickAtlas Tool Version, 2.4 41, implemented on a MRI template of the MRIcron version beta 7 (www.mricro.com).

A=anterior; P=posterior.

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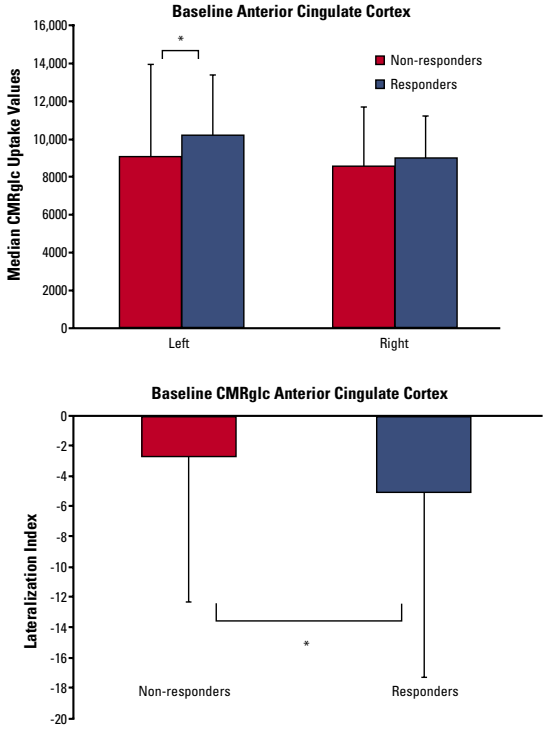
line DLPFC CMRglc and treatment outcome (ΔBDI) was significant (left: rs=.56, n=21, *P*<.01; right: rs=.54, n=21, *P*=.01), but not for ΔHAM-D (left: rs=.35, n=21, *P*=.12; right: rs=.35, n=21, *P*=.12). No lateralization pattern was observed (HAM-D: rs=–.41, n=21, *P*=.86 and BDI: rs=–.17, n=21, *P*=.46). Mann Whitney U tests showed no differences in DLPFC baseline CMRglc when comparing responders to non-responders (left: U=29, n1=12, n2=9, *P*=.08; right: U=29, n1=12, n2=9, *P*=.08).

By looking at the entire anterior cingulum cortex, we found that a higher bilateral baseline ACC CMRglc was associated with a better treatment outcome, however only with ΔBDI (left: rs=.63, n=21, *P*<.01; right: rs=.48, n=21, *P*=.03). The correlations between ACC metabolic activity and ΔHAM-D were not significant (left: rs=.39, n=21, *P*=.08; right: rs=.32, n=21, *P*=.16). However, Mann Whitney U tests showed that responders had significantly higher left sided ACC CMRglc compared to non-responders (left: U=26, n1=12, n2=9, *P*=.05; right: U=40, n1=12, n2=9, *P*=.35). Furthermore, baseline lateralization index of responders differed significantly from that of non-responders (U=25, n1=12, n2=9, *P*=.04): responders had a higher left–to-right gradient (Figure 2).

FIGURE 2.
Baseline metabolic differences and lateralization index



Top: Baseline CMRglc differences between HF-rTMS responders and non-responders for the entire ACC (Left). Baseline ACC CMRglc is significantly higher in responders compared to non-responders (non-parametric Mann Whitney U test) (Right).

Bottom: Responders displayed significantly higher left-to-right lateralization compared to non-responders. A negative value of the lateralization index corresponds with a higher median CMRglc in the left ACC compared to the right. CMRglc values are expressed as medians and interquartile ranges.

* Significance threshold was set at a two-tailed probability of *P*≤.05.

CMRglc=brain glucose metabolism; HF-rTMS=high frequency repetitive transcranial magnetic stimulation; ACC=anterior cingulate cortex.

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By looking at the subdivisions of the ACC, no significant correlations between baseline CMRglc and treatment outcome were observed. For BA25: ΔHAM-D: left: rs=.03, n=21, *P*=.89; right: rs=.01, n=21, *P*=.96; ΔBDI: left: rs=.21, n=21, *P*=.37; right: rs=.16, n=21, *P*=.49. For BA32: ΔHAM-D: left: rs=.11, n=21, *P*=.62; right: rs=.05, n=21, *P*=.83; ΔBDI: left: rs=.14, n=21, *P*=.55; right: rs=.05, n=21, *P*=.82. For BA24: ΔHAM-D: left: rs=.13, n=21, *P*=.58; right: rs=.09, n=21, *P*=.70; ΔBDI: left: rs=.06, n=21, *P*=.80; right: rs=.01, n=21, *P*=.96. Mann Whitney U tests (responders versus non-responders) revealed a trend that higher right-to-left baseline BA 24 asymmetry was associated with better treatment outcome (U=27, n1=12, n2=9, *P*=.06). The other ACC subdivisions showed no lateralization patterns (BA 32: U=52, n1=12, n2=9, *P*=.92; BA25: U=52, n1=12, n2=9, *P*=.92).

Evaluating the impact of HF-rTMS treatment on CMRglc

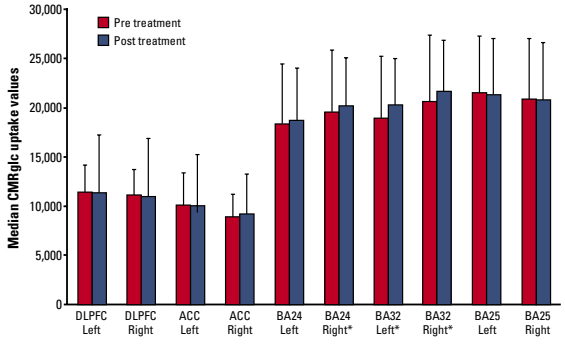
Wilcoxon paired t-tests showed no significant differences in CMRglc pre-post treatment for the DLPFC and the entire ACC, neither for the group analyses (DLPFC: left: z=–2.26, n-ties=21, *P*=.82; right: z=–2.26, n-ties=21, *P*=.82; ACC: left: z=–2.44, n-ties=21, *P*=.66; right: z=–2.44, n-ties=21, P=.66), nor for responders (DLPFC: left: z=–.41, n-ties=21, *P*=.68; right: z=–.53, n-ties=21, *P*=.59; ACC: left: z=–.65, n-ties=21, *P*=.51; right: z=–.89, n-ties=21, *P*=.37) or non-responders separately (DLPFC: left: z=–.78, n-ties=21, *P*=.94; right: z=–.16, n-ties=21, *P*=.86; ACC: left: z=–.31, n-ties=21, *P*=.75; right: z=0, n-ties=21, *P*=1).

However, when including all TRD patients, Wilcoxon paired t-tests showed a significant difference in pre-post treatment for the left BA32 (left: z=–2.03, n-ties=21, *P*=.04; pre HF-rTMS, median=18887, post HF-rTMS, median=19412), indicating an increase of metabolic activity after 10 daily ses-

sions. For the right BA32, we found a similar trend in metabolic increases post HF-rTMS (z=–1.86, n-ties=21, *P*=.06; pre HF-rTMS, median=20591, post HF-rTMS, median=21097).

When analyzing responders and non-responders separately, Wilcoxon paired t-tests showed that only responders presented a similar pattern in left BA32 CMRglc, (z=–2.19, n-ties=9, *P*=.03; pre HF-rTMS, median=19048, post HF-rTMS, median=20326) and for the right BA 32 (z=–1.96, n-ties=9, *P*=.05; pre HF-rTMS, median=20787, post HF-rTMS, median=21724). Comparable results of metabolic increases post treatment were obtained for the right BA 24 in responders (left: z=–1.48, n-ties=21, *P*=.14; pre HF-rTMS, median=18485, post HF-rTMS, median=18774; right: z=–1.96, n-ties=9, *P*=.05; pre HF-rTMS, median=19628, post HF-rTMS, median=20194). No pre-post treatment differences in CMRglc were observed for non-responders (BA 32: left: z=–.86, n-ties=21, *P*=.39; BA 32 right: z=–.78, n-ties=9, *P*=.43; BA 24: left: z=–.47, n-ties=21, *P*=.64; BA 24 right: z=–.31, n-ties=9, *P*=.75) and all analyses for the subgenual part of the ACC (BA 25) were not significant (responders; BA 25: left: z=–1.24, n-ties=21, *P*=.21; BA 25 right: z=–.89, n-ties=9, *P*=.37; non-responders BA 25: left: z=–.78, n-ties=21, *P*=.94; BA 25 right: z=–.47, n-ties=9, *P*=.64)(Fig 3).

FIGURE 3.
The impact of HF-rTMS treatment on the predefined regions of interest in responders (n=9)



Analysis pre and post treatment were performed with non-parametric Wilcoxon Signed Ranks test. CMRglc values are expressed as medians and interquartile ranges.

*Significance threshold was set at a two-tailed probability of *P*≤.05.

HF-rTMS=high frequency repetitive transcranial magnetic stimulation; CMRglc=brain glucose metabolism; DLPFC=dorsolateral prefrontal cortex; ACC=anterior cingulate cortex; BA=Brodmann area.

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DISCUSSION

In agreement with other open clinical studies examining rTMS efficacy in depressed samples, we observed a clinical response rate of 43%, as defined by a 50% reduction of initial HAM-D scores.[45] Several clinical parameters might affect treatment success, such as the absence of psychosis, age, and/or length of the current depressive episode.[23,46-49] In our study, neither gender, age, depression severity,[50] nor duration of the current episode predicted successful outcome.

Our results suggest that higher baseline bilateral DLPFC metabolic activity was associated with a better clinical outcome as measured by the self-reported BDI score. Although some studies report increased dorsolateral metabolic activities after successful treatment,[19,51-53] in line with other HF-rTMS interventions,[54] in our study successful HF-rTMS treatment resulted in no significant metabolic changes in this area. It may be possible that the limited duration of HF-rTMS treatment was too short to induce metabolic changes in the DLPFC: in a 99mTc-HMPAO SPECT study, Catafou and colleagues[55] reported in a comparable HF-rTMS design that the magnitude of rCBF changes was <10% in all cerebral regions and ~3% in the prefrontal cortex.

Successful HF-rTMS treatment did not result in significant ACC metabolic decreases, as proposed by several TMS authors.[19,56] On the other hand, Luborzewski and colleagues[22] failed to demonstrate neurochemical ACC alterations post HF-rTMS and Loo and colleagues[57] demonstrated that one session of LF-rTMS seemed rather to deactivate the ACC than to activate it. Further, (persistent) ACC asymmetries upon depression recovery are reported[58] and other studies have observed that HF-rTMS treatment resulted in higher ACC CMRglc,[13,16,59] just as we did. Importantly, we found that a positive HF-rTMS treatment response was associated with a higher level of baseline ACC CMRglc. These results are in line with pharmacological and sleep deprivation studies that report on higher baseline ACC CMRglc being a positive predictor of an antidepressant effect.[60,61] Our data differ with brain imaging findings from electroconvulsive shock therapy (ECT) in depressed patients, as ECT results in prefrontal and ACC metabolic decreases.[62-64] Although both non-pharmacological techniques affect neuronal circuits, the mechanism of action to achieve changes in mood in TRD patients might not be the same.[4]

Our observation of a trend in right-to-left baseline BA 24 CMRglc asymmetry is in line with recent

findings about the involvement of in particular the right BA 24 as a possible predictor of antidepressant response to HF-rTMS treatment.[18] Our data extend these findings, as successful HF-rTMS treatment resulted in metabolic increases in this area. Electrophysiological imaging studies found that the rostral part of the ACC is not only implicated as a predictor of response in depression, but that differential ACC activity (higher>lower) is also associated with gradations of response.[65] Further, in our TRD patients (in particular treatment responders), HF-rTMS resulted in metabolic increases in predominantly the left BA 32 area, being the affective part of the ACC. Our results are in line with a recent open 99mTc-ECD SPECT study, treating male TRD patients with a similar HF-rTMS protocol, which also found rCBF increases in the ACC (BA 24 and BA 32).[66]

Although the BA25 area is frequently reported to be involved the pathophysiology of major depression,[67] we could not demonstrate metabolic changes in this area after HF-rTMS treatment such as reported in the Kito and colleagues.[66] However, in this study all TRD patients were taking antidepressant medication during the stimulation protocol, and treatment response was defined as a 25% decrease of the initial 17-item HAM-D score. It should be noted, that although in our study 43% of the participants could be identified as a responder (a 50% decline of baseline HAM-D scores), only five patients reached the criteria of remission (which is 24% of the total study group). The other "responders" were still considered as being mildly depressed. Nevertheless, all our TRD patients were antidepressant-free at the time of brain imaging protocol, which can be considered as a major advantage of the study.

There are some major limitations that have to be mentioned: sample size, duration of stimulation, and no sham condition. First of all, our conclusions are based on a group of only nine responders versus twelve non-responders. Second, in spite that melancholically depressed patients do not tend to react well to placebo treatment,[25,68] and that our participants were severely depressed patients who were documented resistant to a number of medical interventions, without the inclusion of a sham treatment condition, we cannot exclude that placebo responses could have interfered with our results. The fact that in our study the number of responders was relatively higher in the hospitalized group could indicate a partial placebo effect. In addition, some sham-controlled HF-rTMS studies found placebo responses.[17,55] Moreover, we observed some dissimilarities between the results obtained by the self-report BDI versus the clinical interview data obtained with the HAM-D. Although both measures assess depressive symptoms based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria, reliability and validity of these measures might differ between patients.

Another limitation could be the number of stimulation sessions: non-rTMS interventions, such as pharmacological trials or cognitive behavioral therapy and interpersonal psychotherapy, are spread over longer periods of time (>6–15 weeks) and metabolic changes after less than two weeks of treatment were not demonstrated.[58,61,69] Furthermore, recent data suggest that two weeks of rTMS could be too short a period for patients to reach remission and that probably three to four weeks of treatment are necessary.[23,70] Finally, due to the exploratory nature of the study, rigorous alpha correction for multiple testing was not applied.

CONCLUSION

Higher baseline metabolic activities in the DLPFC and the ACC were associated with better clinical outcome. Successful clinical responses resulted in metabolic increases in those subdivisions of the ACC (BA24, BA 32), which are strongly interconnected with BA 9/46 areas.[6] Our observations correspond with pathophysiological models of major depression that are based on dysfunctions within fronto-cingulate networks[71] and extend recent brain imaging findings in medicated TRD patients studies treated with HF-rTMS.[18,66] If these findings of our open pilot study can be substantiated in larger sham-controlled rTMS studies, then the ACC could be the region of interest to evaluate or to predict rTMS effects. ***CNS***

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