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Add-on rTMS for treatment of depression: a pilot study using stereotaxic coil-navigation according to PET data

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Abstract

Objective: Repetitive transcranial magnetic stimulation (rTMS) is regarded as a potentially new tool to treat depression. In a double-blind, randomized, sham-controlled pilot study we investigated the efficacy of neuronavigated rTMS, guided according to the prefrontal metabolic state determined by positron emission tomography (PET). Methods: 25 patients with major depression were included. Prior to rTMS, PET scans were obtained. For the real stimulation condition, the dorsolateral prefrontal cortex (DLPFC) with lower metabolic activity compared to the contralateral hemisphere was selected, if detected by prior PET. Stimulation parameters were 15 Hz, 110% motor threshold (MT), 3000 stimuli/day, for 10 days. A neuronavigational system was used to place the magnetic coil above each individuals' selected cortical region (real condition: DLPFC, sham: midline parieto-occipital, intensity 90% of MT). RTMS was administered add-on to medication. Depression-related symptoms were rated with Beck's, Hamilton's (HAM-D), and Montgomery–Asberg's (MADRS) depression rating scales. Results: Real stimulation improved depression according to HAM-D and MADRS moderately but significantly better compared to sham at the end of the stimulation sessions. In the real condition, four out of 13 patients responded with a mean improvement in HAM-D and/or MADRS of at least 50%, whereas none responded to sham. Antidepressant effects of stimulation of the relatively hypometabolic DLPFC were comparable to stimulation in absence of metabolic differences. Conclusions: A moderate improvement of depressive symptoms after rTMS was observed. Our preliminary data show that stimulation of prefrontal hypometabolism may not be advantageous to stimulation irrespective of the metabolic state.

Keywords: Transcranial magnetic stimulation; Depression; Neuronavigation; PET; Prefrontal cortex

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been evaluated as a potentially new tool for treatment of depression (George et al., 1999; Wassermann & Lisanby, 2001). RTMS administered over the scalp evokes a current in the cortex beneath the coil and induces neuronal depolarization locally and in transsynaptically connected brain areas. When applied to cortical areas supposed to be involved in the pathophysiology of depression it may exert therapeutic effects by for instance releasing certain neurotransmitters, neurotrophic factors or hormones (Post & Keck, 2001). After initial high expectations, the current state of investigation, based on several studies with fundamental differences in design and use of stimulation parameters, points to only modest effects (consider recent meta-analyses: Martin et al., 2002; Burt et al., 2002; Kozel & George, 2002). Open questions include (1) where exactly the coil should be placed, (2) which stimulation parameters like frequency and intensity should be applied, and (3) which neurobiological parameters may mediate the effect of rTMS.

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The dorsolateral prefrontal cortex (DLPFC) has been proposed as target for stimulation (George et al., 1995). One argument for its selection were findings of depression related hypometabolism in this region that disappeared after successful treatment, revealed by positron emission tomography (PET) and single photon emission computed tomography (SPECT) (overview in Soares and Mann, 1997). The antidepressant effect of rTMS was reasoned to be based upon increasing the excitability of hypoactive or hypometabolic cortical areas (George et al., 1995; Pascual-Leone et al., 1996). PET studies have shown that rTMS can influence regional cerebral blood flow (rCBF), and that it can modulate rCBF in transsynaptically connected areas as well (Paus et al., 1997; Siebner et al., 2000). The therapeutic response to rTMS and the effect of different stimulation parameters may be related to cerebral baseline metabolism or to changes of prefrontal metabolism (Kimbrell et al., 1999; Speer et al., 2000). Further support for the choice of the DLPFC as a target site for rTMS are neuropsychological findings after lesions of this area which can produce depression related symptoms, such as drive deficiency, disordered attention and planning, and loss of interest and motivation (Fuster, 1999; Ottowitz et al., 2002).

All recent studies selected the DLPFC for antidepressant rTMS (Wassermann & Lisanby, 2001). In order to locate the stimulation site for the DLPFC, most studies applied a positioning method by which an area 5 cm anterior to the motor cortex is identified. The resulting region was thought to be appropriate for stimulation of the DLPFC ('5-cm rule'), specifically Brodmann areas 9 and 46 (Pascual-Leone et al., 1996). However, this procedure does not take into account the considerable variations of individual cortical morphology, and it does not target the DLPFC reliably (Herwig et al., 2001a,b).

The aim of this study was to investigate aspects of the antidepressant efficacy of rTMS. Depressed patients were randomly assigned to a real or a sham stimulation and received a PET scan prior to treatment. TMS was targeted to the DLPFC in the real condition. The laterality of the real condition—left or right DLPFC—was chosen according to the PET data. If the PET indicated a relatively lower metabolic DLPFC, compared to the DLPFC of the other hemisphere, this site was stimulated. Sham stimulation was applied with lower intensity over the midline parieto-occipital transition. In all patients (real and sham), a stereotaxic neuronavigational system was used to guide the coil to the intended cortical area and to monitor the coils' position online during the stimulation procedure. We hypothesized, that real stimulation would have a better therapeutic outcome than sham stimulation, and that TMS of the DLPFC with relatively lower metabolism would exert a better effect than stimulation irrespective of the metabolic state.

1.1. Methods

1.1.1. Subjects

Twenty-five patients fulfilling the diagnostic criteria of moderate or severe major depression according to ICD 10 (F 32.1-2, F33.1-2) and DSM IV (296.2, 296.3) were enrolled in the study. Exclusion criteria were current neurological or other psychiatric disorders, as well as a history of epileptic seizures, substantial brain damage or neurosurgical operation, according to established safety criteria (Wassermann, 1998). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the institutional ethics committee of the University of Ulm. Written informed consent was obtained after full description of the study to the subjects.

1.1.2. PET

Patients underwent a static ^{18}Fluor-deoxy-glucose positron emission tomography (^{18}FDG-PET) (intravenous application of 370 MBq ^{18}FDG) prior to the stimulation sessions. PET-scans were performed with a CTI ECAT-EXACT HR+™ Tomograph (Siemens, Erlangen, Germany). In-plane resolution was 5 mm full width at half maximum (FWHM), transverse resolution was 4.6 mm FWHM, and axial resolution was 4.3 mm FWHM. Planes (63) were scanned with a slice thickness of 2.25 mm. Visual and software based individual region-of-interest (ROI)-analysis of metabolic differences between the right and left DLPFC were performed. The analysis consisted in a coregistration of the PET with the individual MR using the software tool RView™ 8.0w (Colin Studholme), which was followed by the ROI-analysis using Medx and ANALYZE™ 3.0 (Mayo Foundation). For the determination of the DLPFC-ROIs, the middle frontal gyrus (MFG) anteriorly to the precentral sulcus was plotted on the individual MRIs, oriented anatomically according to the Talairach atlas (Talairach and Tournoux, 1988), including the MFG parts of Brodmann Areas 9 and 46. The left and the right DLPFC were chosen as ROIs, and the values reflecting their metabolic activity were compared. In order to state a DLPFC as relatively hypometabolic, it had to show at least 5% lower activity in its mean value compared to the other side. Further, the mean values of the ROIs in the slices of interest on both sides had to be significantly different in a paired t-test (comparing the values of each right and left DLPFC slice within a subject). When these criteria were fulfilled, the site with the relatively lower metabolism was stimulated in the real condition. If no difference was detected, patients were assigned alternating to either a left or a right sided stimulation.

A Statistical Parametric Mapping (SPM) analysis of the PET was performed for all patients afterwards (when methodologically established at the end of the

study). For the last three patients of the study it was performed prior to the real stimulation for determination of the stimulation site replacing the ROI-analysis. For SPM analysis, image data were converted to ANALYZE, and automated spatial normalization was performed with SPM99 (Wellcome Department of Cognitive Neurology, London) in order to realign the dataset according to the 3D stereotaxic grid by Talairach and Tournoux (1988). Prior to voxel-based statistical analysis, images were smoothed using a 10×10×10 mm Gaussian kernel. The global cerebral metabolic rate for glucose (gCMRGlc) was normalized to an arbitrary mean of 50 μmol/100 ml/min by a group-wise analysis of covariance (ANCOVA) (Friston et al., 1990).

The normalized FDG-PET data of each individual patient as well as the whole patient group were compared to a normal data base constituted from 12 healthy subjects without morphological or neurological pathology by computing pixel by pixel *t*-statistics for detection of a priori hypo- or hypermetabolic areas (Juengling et al., 2000; Signorini et al., 1999). The activity of injected FDG and the time delay between injection and start of acquisition were defined as confounding covariates. Only voxel clusters were kept that exceeded *t*-values corresponding to $P<0.05$ corrected for multiple comparisons (single patient vs. normals), *t*-values corresponding to $P<0.001$ corrected (patient group vs. normals), and a minimal cluster size of 30 voxels. The *t*-statistics was transformed to normal statistics yielding a *Z*-score for each pixel. The *Z*-score voxel clusters were projected onto the standard MRI data set provided by SPM99 for visualization of the *Z*-score statistics, using the SPM projection routine which additionally displays the Talairach coordinates, allowing anatomic identification.

1.1.3. Stimulation procedure

Patients were randomly assigned to real or sham treatment. The real condition consisted in a stimulation of the relatively hypometabolic DLPFC, or alternating of the left and right DLPFC in case of no detectable hypometabolism, in order to obtain equivalent group sizes. rTMS was performed with a MagPro™ stimulator (Dantec) using a figure-of-8-coil (MC-B70). Thirteen patients obtained real stimulation and 12 received sham stimulation.

Motor threshold (MT) was determined as the lowest stimulation intensity, with the coil held over the optimal scalp position, that evoked a motor potential (MEP) of at least 50 μV in at least three out of six stimulations recorded by surface EMG (Keypoint Portable™, Medtronic) from the resting right M. abductor pollicis brevis (APB) (Rossini et al., 1994).

In the real condition, the magnetic coil was navigated to the DLPFC as visualized on the computer screen of the navigational system. Real stimulation was performed using the following parameters: Intensity at 110% of the individual MT, frequency of 15 Hz, 30 pulses in 2-s-trains, an intertrain interval of 4 s and a total of 100 trains per day, resulting in 3000 impulses per day. These parameters were within the safety regulations, considering an extrapolation of the safe parameters given for 10 and 20 Hz by Chen et al. (1997). rTMS was performed on ten consecutive working days with a total of 30 000 impulses. Sham stimulation was applied using the same parameters, but with an intensity of 90% MT, located in the midline at the parieto-occipital transition, where no antidepressant effect was expected.

The stimulation sessions were performed as add-on, i.e. parallel to conventional antidepressant therapy, with stable antidepressant medication for at least 3 weeks prior to stimulation onset (in one patient 18 days, no responder). In six cases (three real and three sham stimulated) the stimulation was commenced on the day of onset of a new antidepressant medication, the effect of which would generally be expected later than the possible stimulation effect. The patients were permitted to be prescribed other medication in a naturalistic manner, such as low dose hypnotics in case of severe insomnia, low dose olanzapine as antidepressant augmentation, or prophylactic medication (e.g. lithium).

1.1.4. Neuronavigation

In all patients, real and sham stimulated, neuronavigation was applied. A neuronavigational system commonly used in neurosurgery (Surgical Tool Navigator™, STN, Zeiss Oberkochen), was adapted to navigate the coil according to the individual anatomy (Herwig et al., 2001a,b) as visualized by high resolution structural T1-weighted MRI (magnetization prepared rapid echo sequences, TE 4 ms, TR 9.7 ms, FA 8°, isotropic voxels 1×1×1 mm, 1,5 T Magnetom Vision MR Scanner™, Siemens, Germany). Based on frameless stereotaxy, thereby avoiding head fixation, the STN allows the visualization of the stimulated brain area in real time on a computer screen. A 3D-camera system detects infrared light emitting diodes (LED), three mounted on the subjects head using a latex swimming cap and three fixed on the magnetic coil. A referencing procedure using anatomical landmarks allows the coregistration of the head and the coil in the coordinate system of the MR image of the brain. The reliability was confirmed by navigating the reference pointer to identifiable landmarks (nasion, inion, ears) before and after the stimulations. The peak electric field beneath the center of the magnetic coil is visualized as a line running perpendicular through the midpoint of the coil towards the cortex, relative to the MRI on the computer screen in all three axes and in a 3D-reconstruction of the head surface. The line can be virtually prolonged until the visualized cortex is reached after about 12–24 mm. The magnetic coil was targeted to the DLPFC in the medial part of the middle frontal gyrus either in the right or the

left hemisphere (Fig. 1). The coil position was monitored online during the stimulation.

1.1.5. Data collection

Depressive symptoms were assessed using the interviewer rating scales Hamilton Depression Rating Scale (HAM-D, 21 item version) and Montgomery–Asberg Depression Rating Scale (MADRS). Beck's Depression Inventory (BDI) was performed as a self-rating instrument. To be included in the study as moderately or severely depressed, at least two of the ratings of the subjects should have had at least 17 points. Responders were defined by a 50% reduction of the mean of the HAM-D and MADRS ratings ($\text{mean}_{\text{HAM-D}} + \text{mean}_{\text{MADRS}}/2$). The ratings were performed 5 times: (1) before stimulation, (2) after four stimulations, (3) after seven stimulations, (4) at the end of the stimulation sessions, and (5) in responders 2 weeks after the stimulation sessions (for all ratings ± 1 day depending on the weekday and rater availability). In this double-blinded design, neither the raters nor the patients were informed about the stimulation condition.

1.1.6. Statistical analysis

In order to test antidepressant effects, the non-parametrical Mann–Whitney *U* test (MWU) was used, considering the relative changes of the scores in each scale in percent in the course of the stimulation (end score relative to initial score). We selected a non-parametric test because the absolute initial rating scores were not consistently normal distributed (one of six of the initial rating score/condition groups, MADRS sham, was not normally distributed according to the Lilliefors test), and because the rating scales do not have a continuous character according to biometrical requirements. We compared (1) real and placebo stimulation outcomes irrespective of the metabolic state, (2) leftsided vs. rightsided stimulation irrespective of the metabolic state, and (3) hypometabolism-guided stimulations with prior ROI-analysis, hypometabolism-guided stimulations as revealed with post-hoc SPM analysis, and stimulation outcome in lateralized hypometabolic versus non-hypometabolic patients.

Fisher's exact test was used to test the influence of medication (stable at least 3 weeks before stimulation vs. new medication started at stimulation onset) on responder rate in the real stimulations. It was further used to reveal possible interactions between responder status and the stimulation site.

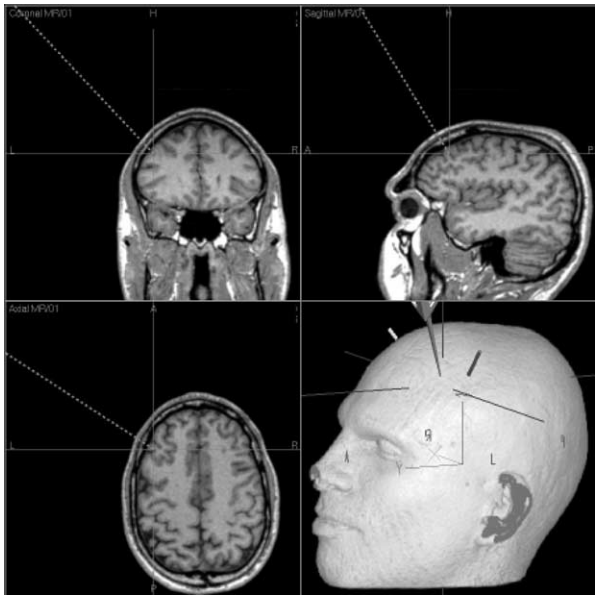

Fig. 1. Real time visualization with the Surgical Tool Navigator during the stimulation in the three axes and a 3D-surface rendered MR image of the head. The dotted line represents a line perpendicular through the center of the coil prolonged by about 2 cm towards the cortex, where the peak of the magnetic field is estimated. The magnetic coil was guided to the dorsolateral prefrontal cortex.

2. Results

Twenty-five patients (15 female, age range 22–60, 19 inpatients, six outpatients) were included in the study (Table 1). All patients tolerated the stimulation well. Severe side effects were not observed. Three patients complained about mild and local headache after stimulation, but did not need medication. The neuronavigation was easily and comfortably applicable and reliable in its precision.

2.1. PET

In five of the 13 real stimulated patients (four rightsided and in one left-sided), a relative hypometabolism was determined prior to the stimulation. These results were confirmed except one by post-hoc SPM analysis. The SPM analysis revealed in seven of the real stimulated patients a hypometabolism, in six patients in the region of the right DLPFC and in one patient on the left side. Right-sided hypometabolism concerning SPM was found in five of eight scanned sham stimulated patients. In four patients assigned for sham stimulation we decided to commence TMS despite a PET scan was not available for technical reasons.

The post-hoc SPM group analysis of all patients compared to a normal control group (Juengling et al., 1999) revealed a right sided prefrontal hypometabolism, as well as hypometabolism in the left orbitofrontal and in the cingulate regions (Fig. 2).

2.2. Rating outcome

The initial rating scores of the sham and the real stimulated patients, as well as the ages of both

Table 1
Individual data of the patients with sham (1–12), and real stimulation (13–25)[a]

Pat #	Gender	Age	Stim. Cond.	SPM Hyp.	Medication	BDI (end%/in.)	HAM (%)	MAD (%)	Th.-res./ TMS-rsp.	n-epis.	dur. epis. (months)
1	F	56	S	–	Mir45* Li1000	100	86	111	Yes	> 5	3
2	F	57	S	–	Reb4 Tri200 Li800 Zop7.5	96	97	88	No	> 5	2
3	M	59	S	ri	Ven225* Zop7.5	40	92	75	No	3	1.5
4	F	58	S	–	Cit60 Ola10	65	88	112	No	> 5	2
5	M	49	S	ri	Ven150	81	92	88	No	3	1
6	M	48	S	ri	Mir45 Li800 Ola5	108	65	123	Yes	3	> 3
7	M	60	S	l = r	Dox100 Ven300 Dkc20	108	152	111	Yes	> 5	> 3
8	F	28	S	–	Cit60 Tri100 Lor0.5	115	105	111	No	3	2
9	F	54	S	ri	None	81	85	84	No	5	2
10	F	41	S	l = r	Cit60 Val750 Ola10	92	107	130	Yes	5	3
11	F	33	S	l = r	Ven300 Val1200 Ola2.5	125	90	93	No	4	1
12	F	31	S	ri	Ven75* Lor0.5	77	115	111	No	4	2
Mean sham		47.8				90.7	97.8	103.1			
13	F	35	R-le	l = r	Ven225 Lor1	98	75	81	Yes	> 5	> 3
14	M	48	R-ri	ri	Amy75	94	89	65	Yes	5	3
15	M	22	R-ri-g	ri	Mir45 Li1400 Ola10	41	28	39	No/Rsp.	4	2
16	F	30	R-ri-g	ri	Ven225* Car450 Li1000	46	64	71	No	> 5	2
17	M	41	R-ri	ri	Nef600	91	92	83	No	> 5	1.5
18	F	55	R-le	ri	Dox150* Mir45 Ris2	89	85	74	No	> 5	2
19	F	51	R-le	l = r	Mir45* Ven225 Lor0.5 Ola10	71	48	41	Yes /Rsp.	5	> 3
20	M	52	R-le	l = r	Cit40	61	45	51	No/Rsp.	> 5	1
21	M	43	R-ri	l = r	Ven225 Tri100 Car400	74	83	78	Yes	3	3
22	F	59	R-le	l = r	Hyp900 Zop7.5	11	37	35	No/Rsp.	> 5	1.5
23	M	43	R-le-g	li	Cit80 Mir45 Ola7.5	97	100	97	Yes	3	3
24	F	37	R-ri-g	ri	Mir45 Lor1.5	81	82	69	No	3	2
25	F	25	R-ri-g	l = r	Ven375 Mir45	100	65	79	No	2	1
Mean real		41.6				73.4	68.7	66.4			
Mann–Whitney *U* test sham versus real (S vs. R)						$P = 0.11$	$P = 0.002$	$P < 0.001$			

[a] Mentioned are the relative changes in scores at the end of stimulations, with the initial scores normalized to 100%. Abbreviations: Pat # = Patient number, Stim. cond. = stimulation condition, S = sham, R-ri/le = real right/left DLPFC, -g = PET-guided by prior detected hypometabolism, SPM Hyp = hypometabolism according to SPM analysis,% = end rating in percent of initial rating, l = r = no hypometabolism, ri = right sided hypometabolism, le = left sided hypometabolism, - = no PET obtained, BDI = Beck's Depression Inventory, HAM = Hamilton Depression Rating Scale, MAD = Montgomery-Asberg Depression Rating Scale, Th.-res. = therapy resistant before stimulation, TMS-rsp. and Rsp. = responder to TMS, n-epis. = number of previous episodes of depression. Medication: Ven = Venlafaxin, Mir = Mirtazapin, Dox = Doxepin, Par = Paroxetin, Reb = Reboxetin, Cit = Citalopram, Amy = Amitryptiline, Nef = Nefazodon, Hyp = Hypericum, Ola = Olanzapine, Ris = Risperdal, Li = Lithium, Car = Carbamazepine, Val = Valproat, Dkc = Dikaliumclorazepat, Lor = Lorazepam, Zop = Zoplicon, * = medication started with onset of TMS.

groups, did not differ as tested with the Mann–Whitney *U* test.

The rating scores of the 13 real stimulated patients and the 12 sham stimulated patients were compared firstly irrespective of the metabolic state (Table 1, Fig. 3). In the real condition group, mean (percentage) changes in the end ratings were as follows: BDI −8.8 points (73.4% of the initial score), HAM-D −6.9 (68.7%), MADRS −9.5 (66.4%). The changes in the sham condition group were: BDI −2.3 (90.7%), HAM-D −0.9 (97.8%), MADRS +0.3 (103.1%). The MWU test revealed significant differences between sham and real stimulation concerning the relative rating values in percent in HAM-D ($P = 0.002$) and MADRS ($P < 0.001$) but not for the selfrating (BDI $P = 0.1$). The rating score differences between real and sham after seven stimulations already indicated the upcoming improvement which was present at the end of the real stimulations (Fig. 4).

The responder rate was four of 13 in the real group and 0 of 12 in the sham group. The correlation between responder status and real stimulation was with this small *n* on the border to significance (Fisher's exact test, one-tailed $P = 0.057$). Three out of 13 real stimulated patients, and three out of 12 patients in the sham group, were stimulated parallel to starting new antidepressant medication. In the real group one of them responded, in the sham group none. We did not find a relationship between the responder status and the factor "medication start" using Fisher's exact test.

The analysis of the antidepressant effects of the left ($n = 6$, 3 responders) versus the right ($n = 7$, 1 responder) real stimulations, not taking into account the metabolic state, did not reveal significant difference (Fisher's exact). However, there were more responders after stimulation of the left DLPFC. Both, left and right real stimulation, had significantly better rating scores except BDI compared to sham stimulation (left versus sham:

BDI $P=0.2$, HAM-D $P=0.01$, MADRS $P=0.003$; right versus sham: BDI $P=0.2$, HAM-D $P=0.01$, MADRS $P<0.001$).

Five of the 13 real stimulated patients showed a relatively lower DLPFC metabolism in the ROI-analysis and were stimulated accordingly. Only one of them was a responder. This PET-guided stimulation showed no difference in antidepressant efficacy compared to the non PET-guided stimulation (MWU: BDI $P=0.9$, HAM $P=0.8$, MAD $P=0.7$).

The post-hoc SPM analysis revealed prefrontal hypometabolism that was not detected in the ROI analysis in three additional verum stimulated patients, and did not confirm the prior analysis in one patient, resulting in seven patients with lateralized hypometabolism. Accordingly, additional statistical testing was performed by comparing the patients that had been stimulated on the hypometabolic site as revealed afterwards by SPM and those that were stimulated over a non-hypometabolic hemisphere. Again there were no differences of both stimulation conditions (MWU: BDI $P=1.0$, HAM $P=0.3$, MAD $P=0.7$). Further, those patients showing a lateralized hypometabolism according to SPM, irrespective of the stimulation site, did not have a better stimulation outcome than patients showing no hemispheric differences (MWU: BDI $P=0.9$, HAM $P=0.1$, MAD $P=0.6$).

The ratings performed 2 weeks after the stimulation sessions in the four responding real stimulated patients showed a persisting effect with a mean HAM-D of 48% and mean MADRS of 44% of the initial rating scores.

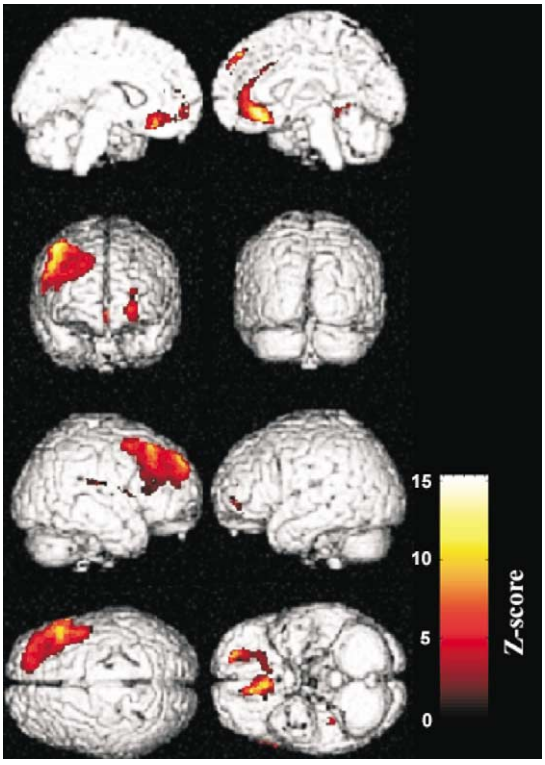

Fig. 2. The group effect in the SPM-analysis ($n=21$, $P<0.001$, corrected for multiple comparisons, cluster threshold 30) of hypometabolic areas of depressed patients prior to the stimulation sessions showed a right sided prefrontal hypometabolism, as well as hypometabolism in the left orbitofrontal and in the cingulate regions.

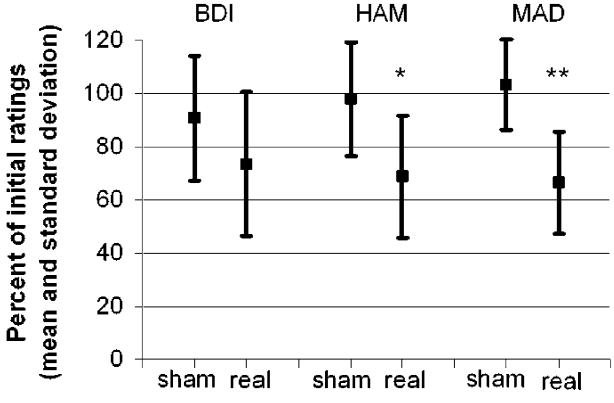

Fig. 3. Means and standard deviations of the end ratings relative to the initial ratings. BDI, HAM, MAD = see legend for Table 1. The differences between real and sham are significant (MWU) for HAM-D *$P=0.002$ and MADRS **$P<0.001$, not for BDI ($p=0.11$). "sham" represents the 12 patients with a sham stimulation, "real" are the 13 patients with a real stimulation.

3. Discussion

The principle finding of the presented study is a moderate antidepressant efficacy according to HAM-D and MADRS of the neuronavigated dorsolateral prefrontal rTMS, which does not seem to depend on the

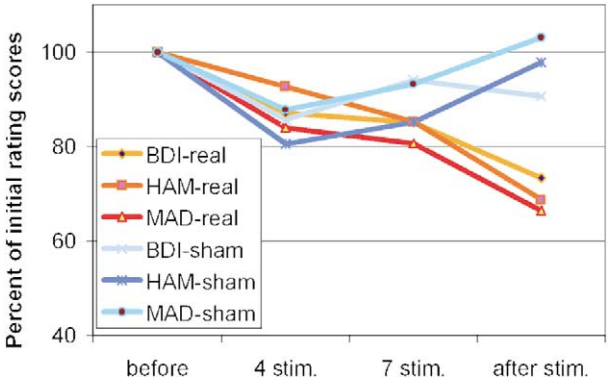

Fig. 4. Course of the ratings in percent of the initial ratings. The course of the ratings goes parallel during the first stimulations, but divides towards a significant improvement at the end of the real stimulation sessions compared with the sham stimulations. For standard deviations of the end ratings see Fig. 3. BDI, HAM, MAD = see legend for table 1, "sham" represents the 12 patients with a sham stimulation, "real" are the 13 patients with a real stimulation, "before" = initial ratings normalized to a relative baseline of 100%, "4 stim." = ratings after four applied stimulation sessions, "7 stim." and "after stim.", respectively.

prefrontal metabolic state. Four of 13 patients responded to real stimulation with an improvement by more than 50% of the interviewer rating scores. The mean response of all real stimulated patients was more than 30%. This moderate therapeutic effect is within the range of the findings of other groups (George et al., 1997; Avery et al., 1999; Triggs et al., 1999; Figiel et al., 1998; Berman et al., 2000; George et al., 2000; Padberg et al., 2002). Being in line with other reports (meta-analysis in Martin et al., 2002), the selfratings showed despite a trend no significant improvement. This may be due to the common clinical finding that the observation of improvements of depressed symptoms by other persons precede the patients subjective estimations. None of 12 sham stimulated patients responded, and the mean response showed no improvement. The effect in the responder group persisted at least two weeks after the end of the stimulation sessions.

Considering the progressive improvement of the scores in the course of the stimulation, longer and/or more stimulation blocks may have to be recommended in order to increase therapeutic efficacy in future studies. The effects of our stimulation parameters support the trend in literature to apply higher intensities, higher frequencies, higher total amount of stimuli, and to stimulate the left DLPFC. However, other parameters like low frequency stimulation above the right DLPFC had been reported to be effective as well (Klein et al., 1999). Thus, general recommendations for stimulation parameters are not yet established.

It is noteworthy, that in this study both, right- and left-sided stimulations irrespective of hypometabolism, did not differ statistically in their effectiveness and led both to an improvement compared to sham. Left-sided real stimulation led to more responders, supporting the selection of the left DLPFC for stimulation.

Most rTMS studies to treat depression have been of an add-on type, i.e. investigated the effect of rTMS applied in addition to standard antidepressant pharmacotherapy. In such a framework, any new additional therapy has to have considerable efficacy to produce significant results, in particular given the small patient numbers involved. The sum of the evidence so far points to a possible therapeutic effect that should be further evaluated in larger scale multicenter studies. Whilst the current study also employed rTMS as an add-on to antidepressant medication, and the design allowed other concomitant medication which may have led to higher heterogeneity of results, the stable antidepressant dosage and the balanced amount of patients with a start of medication parallel to stimulation makes it less likely that the observed improvements compared to the sham group were attributable to medication.

We decided to use a subthreshold parieto-occipital stimulation for the sham condition. One may argue, that this stimulation is less painful than the real condition and that therefore a stronger placebo-effect may have occurred in the real condition. However, except for target location and intensity, stimulation and neuronavigational procedure was exactly the same in both conditions, so that the issue of comfort was only a minor part of the whole setting. Further, the "classical" sham condition with the coil angled 45 or 90° to sagital midline over the DLPFC, is less painful compared to real stimulation as well, thus having the same disadvantage. Additionally, the "classical" sham condition has the major problem of being possibly effective too, thus representing an attenuated real condition (Loo et al., 2000; Lisanby et al., 2001). This, of course, cannot be ruled out completely in our condition but it seems to be less likely. Therefore, we suppose that our sham condition is suitable for a placebo-controlled study design.

The SPM-analysis of the PET revealed more right-sided than left-sided hypometabolism. This, on the one hand, contrasts with some previous reports of more left-sided hypometabolism that increased after treatment of depression (Baxter et al., 1989; Martinot et al., 1990; Bench et al., 1993; overview in Soares and Mann, 1997). On the other hand, the findings are in accordance with reports of lower right prefrontal metabolism in depression (Hurwitz et al., 1990) and relatively higher left-sided prefrontal metabolism in familial depression (Drevets et al., 1992). Mayberg et al. (1999) described decreases in right-sided DLPFC metabolism in depressed patients, which increased with recovery from depression. Kimbrell et al. (2002) reported as well decreased absolute metabolism in right-sided prefrontal cortex and other regions in depressed patients.

The data basis concerning cerebral metabolism and antidepressant therapy with rTMS is still small. Kimbrell et al. (1999) reported a trend to correlation between cerebral global baseline metabolism prior to stimulation in depressed patients and the antidepressant effect of different stimulation frequencies. Speer et al. (2000) demonstrated an increase of prefrontal metabolism, and of other regions, after a stimulation period with 20 Hz, and a decrease after 1 Hz stimulations, in depressed patients (left DLPFC, 100% MT, 10 days, total of 16 000 stimuli). However, they did not report any therapeutic effect using these parameters.

We tested if a stimulation of the hypometabolic DLPFC would lead to better antidepressant outcome. Our results do not support this hypothesis. This was found for the PET-analysis prior to stimulation as well as for the post-hoc SPM-analysis. However, though we navigated the stimulation reliably to the DLPFC, in future studies the individual target of navigation could be even more precise the exact region of hypometabolism within the DLPFC or in the neighborhood, leading to possible better outcome. The results are as well to be interpreted in consideration of the small sample size in

our study. However, they indicate that the metabolic state may not be a predictor of therapy response. The pathophysiological meaning of hypometabolism, which may be an epi-phenomenon, and the modulating effect of the rTMS on the local cortical metabolism need further study.

The presented results show that stereotaxic navigated stimulation of the DLPFC has therapeutic benefit in depression. However, we have not directly tested if the navigational approach leads to better outcome than the '5 cm rule', and our effect was not better than reported in earlier studies most of which used this rule (e.g. George et al., 1997; Avery et al., 1999; Triggs et al., 1999; Figiel et al., 1998; Berman et al., 2000; George et al., 2000; Padberg et al., 2002). The optimal stimulation site for antidepressant treatment, which may not be the DLPFC, should be evaluated by comparing the stimulation effect of different regions within the prefrontal cortex. For precise stimulation targeting, neuronavigational devices and neuroimaging on an individual basis are recommended.

In our view, rTMS is suited to tailoring of individual patient therapy planning. The approach to find neurobiological markers that possibly predict therapy response and to reveal the mode of rTMS efficacy in depression remains a major issue in future TMS research. Alterations of local and distant cerebral metabolism as revealed by PET that have been reported after cortical TMS (Paus et al., 1997; Siebner et al., 2000; Strafella et al., 2001), or findings of transmitter and neuroendocrine alterations in animal models that are relevant in depression (Ben-Shachar et al., 1999; Juckel et al., 1999; Keck et al., 2000, Post & Keck, 2001) may be candidates. Measuring altered cortical excitability with the paired-pulse paradigm (Maeda et al., 2000), or the cortical silent period (Steele et al., 2000), reflecting neural network modulations, or specific cortical activations measured by functional MRI during neuropsychological tasks may be further candidates.

In conclusion, our preliminary results indicate that rTMS of prefrontal hypometabolism may not be advantageous to stimulation irrespective of the metabolic state. However, our results support previous findings of an add-on antidepressant effect of rTMS applied to the dorsolateral prefrontal cortex.

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