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Repetitive TMS Optimized by SPECT Control in Refractory Depression

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is effective in the treatment of major depression. Here, we used quantitative SPECT to individually target rTMS site. 12 in patients suffering from pharmacoresistant major depression and a control group were given high frequency rTMS (10 Hz) on identical cortical regions with hypoactivation with a stimulation intensity of 80% of the motor threshold and a simple circular coil. 11 of the 12 patients showed significant (p=0.001) improvement in their depressive symptoms. The method is effective and easily applicable. But further studies should control the findings in larger sample groups and also give impetus to better definitions of hypoactivation areas and their influence on rTMS effects.

Keywords: rTMS; SPECT; Therapy resistant depression; Hypoactivation; Hyperactivation

Introduction

High frequency and low frequency repetitive transcranial magnetic stimulations (rTMS) are effective in the treatment of refractory major depression according to several studies [1-4]. Usually, the left prefrontal dorsolateral cortex is the application site of high frequency rTMS [4]. On the other hand, there have also been positive results after the application of low frequency rTMS on the right prefrontal cortex [4-6]. Recently, TMS was focused on different regions of the brain with both methods: the design was based on an intra individual comparison of four regions of interest (ROI) with hypoactivation (3% decrease compared with other ROI) which were stimulated by high frequency rTMS (20 Hz) [7]. Regions with hyperactivation (increase in activation of 3% in comparison with other ROI) were stimulated by low frequency rTMS [7]. However, no additional advantages were obtained by this individually-defined combination method. Therefore, in the present study 12 inpatients suffering from treatment-resistant major depression were exclusively given high frequency rTMS on cortical regions with hypoactivation as determined by SPECT compared with a control group. We used the method of quantitative SPECT which allows an interindividual quantitative comparison (percentage ranges 0 – 100%) between identical cortical regions in patients and healthy controls.

Methods

Subjects

After giving written consent, 12 inpatients (mean age 53.3 ± 12.8 years), 10 women (mean age 53.1 ± 14.0 years) and 2 men (mean age 54.0 ± 7.1 years) fulfilling the diagnostic DSM IV criteria (APA 1987) for unipolar major depression of recurrent, severe, non-psychotic subtype without seasonal pattern were enrolled in the study (see table 1, 2). The local Ethics Committee approved the study (Nr. 2878). No further diagnoses on axes I, II, and III were ascertained. All 12 patients were rated as treatment resistant, which was defined by at least two different drug treatments in vain using adequate dosages and lasting at least 4 weeks each. A tricyclic antidepressant have been administered in one of the two regimens. The last medication was carried on when patients received rTMS on 10 days in succession. Patients following a psychotherapeutic program were also advised to continue their program as usual. All patients were right-handed. Exclusion criteria beside any other mental disease were a personal or family history of seizures, implanted pacemaker (e.g. VNS-systems), inner ear prosthesis, neurosurgical procedures in the past, and pregnancy. Age, gender, first episode, number of episodes, 24-item Hamilton Depression Rating Scale [8] Beck Depression Index [9] and SPECT were recorded (see Table 2, subjects` characteristics). The control group was recruited from 10 inpatients (6 male,4 female) with major depression who were all treated at the department of psychiatry with standardized left sided DLPFC rTMS (pre/post rTMS-outcome see table 3).

For calculations data were analyzed using linear regression models and a parametric t-test. (SPSS 14, SPSS Inc).

Repetitive TMS

For the rTMS, we used the commercial Dantec magnetic stimulator MagPro MC 125®, a circular coil with an outer diameter of 12 cm, an inner diameter of 2 cm, generating a magnetic field of maximum 1.9 Tesla. It was stimulated at 80% of the motor threshold of the right abductor pollicis brevis muscle (APBM), which was detected optically by application of single impulses over the left precentral gyrus (M1). Dependent on areas with hypoactivation (see SPECT methods), the coil was centred on the midpoints of the temporal, parietal and frontal lobes with respect to the 10-20 electrode system [10,11]. Each patient received 1000 impulses with 50 impulses per train, 25 s intertrain interval, 10 Hz rate per train, and 20 trains per session. During the rTMS, patients had their eyes open and were at rest. The treatment was split into two blocks of 5 days each with a break of 2 days. Study patients and control subjects were treated with identical stimulation parameters (see table 3).

Psychometric measurements

All patients were rated by a treating physician on day 0 of the study and after the rTMS series application with the 24-item HDRS.

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HAMD ratings were done for all patients. On days 0 and 12 of the study, patients did self-ratings using the BDI. Only 11 of the 12 patients did the BDI rating after the rTMS treatment. These patients were excluded for calculations of BDI scores (see tables 1,2).

SPECT

For each patient, functional brain imaging measured by a 140 keV SPECT, applying the isotope technique of ^{99m}Tc HMPAO at rest, was carried out before day 1 and after day 12 of the rTMS treatment. SPECT was used to find the region for magnetic stimulation defined as the area of hypoperfusion. By consensus of all investigators and according to literature, hypoperfusion was defined by a) the decrease of the intensitiy of the colour red (see figure 1, tables 1-3) b) the quantitative measurable decrease of the intensity of perfusion of at least 3 percentage points compared with a reference collective of healthy subjects without major depression [12].

The regional cerebral blood flow distribution in each subject was recorded and analysed using a program recently developed by the department of nuclear medicine at the University Hospital of Erlangen. It allows a quantitative analysis of cerebral blood flow, which is separated in percentage ranges from 0-100%. These were obtained by SPECT recordings in a group of patients who were screened to exclude strokes and showed no pathological findings (see also table 3).

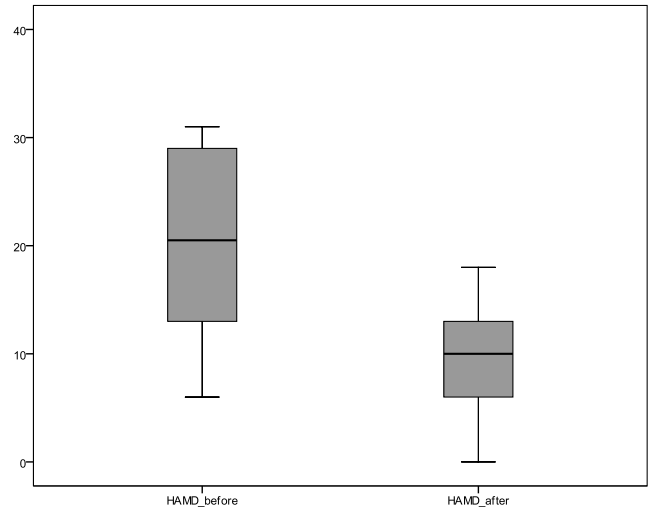

Figure 1: Boxplots of distributions before and after rTMS treatment: *left HAMD* (n = 12), *right BDI* (n = 11), *HAMD* n = 12, y-scale 0-40, *BDI* n = 11, *y-scale* 0-63.

Results

Using the SPECT technique, regional hypoperfusion could be found out in 9 out of 12 patients in our baseline investigations. Not only patients with hypoperfusion benefit from the treatment. Hyperperfusion was not found in any case. Hypoperfusion was found in the left frontal region, in the left parietal and in the left temporal and left frontal region (see also table 1,2). All 12 patients finished the study as planned and showed significant improvements in their depressive symptoms. The patients with no hypoperfusion were stimulated in the left prefrontal region.

Mean decrease of HAMD was 10.57 (SD = 5.61) scores. The scores dropped from a mean HAMD of 20.1 (SD = 8.4) before treatment to a mean HAMD of 9.6 (SD = 5.7) after treatment. Individual decreases for each patient varied from 4 to 21 points. As well as the clinicians assessment, self-rated BDI scores showed a mean decrease of 11.36 (SD = 9.9). The scores dropped from a mean BDI 33.0 (SD = 13.9) before treatment to a mean BDI 21.6 (SD = 12.6) after treatment. The individual reduction of BDI scores varied from 0 to 30. Figure 1 and table3 illustrate the different distributions of psychometric scores before and after rTMS series.

All but one patient reported differences before and after rTMS treatment that indicates an improvement in depressive symptoms. We conducted a Wilcoxon-Test to examine the likeliness of such a finding under the hypothesis that rTMS treatment is of no use and no other influences was active. This non-parametric test was used due to the small sample size which does not allow for parametric testing. The Z-value for HAMD scores was -3.3 (p = 0.001) based on positive ranks, which suggests that the improvements in HAMD scores is not random. The same is true for BDI scores. We found a Z-value of -2.8 (p = 0.005). Table 1 shows subjects characteristics, HAMD and BDI scores before and after treatment and positive and negative ranks and linkages of the Wilcoxon-Test.

Discussion

Our results show significant improvements of depressive symptoms measured by HAMD and BDI within both study and also control group. Thus, the generally-defined criteria for treatment response are fulfilled. Study patients were treated with region-specific rTMS series, while control subjects with major depression were treated with standardized DLPFC- rTMS. The given improvements are highly unlikely under the assumption that treatment is not effective. Thus, region-specific

Patient ID	Sex	Age	Hypoperfusion-area	HAMD_before	HAMD_after	Wilcoxon rank	BDI_before	BDI_after	Wilcoxon rank
1	f	75	left parietofrontal	24	13	negative	51	27	negative
2	f	52	left fronto-basal	26	9	negative	22	21	negative
3	f	51	both sides front-temp-parietal	15	9	negative	35	30	negative
4	f	63	right cerebellär	20	13	negative	49	49	linkage
5	f	31	right PF hyperperfusion	13	3	negative	29	22	negative
6	f	65	both sides high-frontal	30	16	negative	52	22	negative
7	f	38	no hypoperfusion	12	0	negative	14	3	negative
8	f	65	no hypoperfusion	31	10	negative	39	16	negative
9	f	40	left- temporal	6	0	negative	13	3	negative
10	f	51	no hypoperfusion	30	18	negative	25	19	negative
11	m	49	left fronto-temporal	15	11	negative	33	25	negative
12	m	59	left frontal	10	6	negative	49	22	m.v.

Table 1: Subjects characteristics, psychometric scores, Wilcoxon ranks.

Patient ID	HAMD end score	HAMD difference	BDI end score	BDI difference
1	13	11	27	24
2	9	17	21	1
3	9	6	30	5
4	13	7	49	0
5	3	10	22	7
6	16	14	22	30
7	0	12	3	11
8	10	21	16	23
9	0	6	3	10
10	18	12	19	6
11	11	4	25	8
12	6	4	22	27.
Mean ± SD	9.0 ± 5.8	10.3 ± 5.3	21.6 ± 12.6	11.4 ± 10.0

Table 2: Improvements in depression scores after rTMS.

Control ID	Age	Sex	HAMD before	HAMD after	BDI before	BDI after
1	36	M	26	14	51	43
2	51	F	24	19	47	36
3	47	F	23	16	46	30
4	45	M	25	18	50	38
5	32	F	23	12	42	34
6	48	M	24	15	48	37
7	32	M	25	20	46	36
8	51	F	21	14	47	34
9	45	M	24	16	50	42
10	34	M	23	14	51	41

Table 3: Control characteristics (n =10), psychometric scores.

application of rTMS seems to be powerful treatment of depression, especially within the sub diagnosis of TRD. A meta-analysis of the rTMS studies in major depression published to date (10 open, 7 sham controlled) comprising more than 300 patients revealed antidepressive effects of 6 to 60% improvement (mean 37%) of the HADS vs. 12% following sham rTMS [3]. Therefore, in our opinion, there can be little doubt that the overall good improvements of depressive symptoms in our study are due to effects from rTMS, especially because we used rather strict criteria of therapy resistance compared to other authors. It cannot be completely ruled out that the good treatment response might be due to the relatively young age of 53.3 yrs, which has often been described as a predictor of a better outcome in rTMS studies [3]. However, regarding the 4 patients aged over 60, it appears that 3 of them have improvements of more than 45 % in HRDS. Likewise, effects of time can not completely be ruled out. But then the examined patients were treatment resistant, meaning they showed no improve in depressive symptoms over a period of four weeks with at least two drug treatments. This suggests that improvement in depressive symptoms as we found them may not be due to just time. Nevertheless, further studies should compare rTMS treatment in larger sample and control groups to be able to make certain conclusions. From this considerations we also conduct that region-specific rTMS was the factor that contributed to decrease in depressive symptoms. Several studies with different functional imaging techniques (fMRI, PET) revealed a hypoperfusion effect mainly in the dorsolateral frontal gyrus in patients with major depression [13,14] but also other regions like left frontal gyrus , the left temporal and parietal gyrus may be involved in the discussion of the hypoperfusion model. All patients with no hypoperfusion benefit from rTMS which is a surprising finding. Therefore the standardized rTMS treatment on the left DLPFC-region must still be discussed critically.

We speculate that the good treatment results are attributable to the special method of finding the optimal brain area for TMS. So far, only one other study has been published that used SPECT for defining individual treatment regions [7]. The differences between the definitions of cortical hypoactivation were the intraindividual comparison of identical regions in both hemispheres [7,15,16] and the interindividual comparison of cortical areas of depressive patients at different times in our study. It still remains unclear how hypoactivation must be defined especially because literature findings are still inconstant [14]. Additionally, we did not stimulate with low TMS on regions with cortical hyperactivation, since none were found in our group. Moreover, the two study groups were not identical, because depressive symptoms in our patients were mild to moderate, whereas the Spanish group mainly had severe courses. Another interesting aspect to examine would have been to compare the treatment outcome of patients with respect to different regions of hypoperfusion. In our sample most of the patients showed hypoperfusion in the left frontal region. Other regions were underrepresented in terms of hypoperfusion. Having more even numbers of patients with different regions of hypoperfusion would allow for group comparisons regarding the benefit of region-specific TMS. From such an examination one could conclude which patients are most likely to experience relieve of depressive symptoms due to region-specific TMS. The present method shown in this study seems to provide a relatively easy way of finding the ROI of hypoperfusion within the cortex. The effectiveness is based on the findings that hypofrontality seems to play a major role in depressive disorders, with hypoperfusion and reduced glucose uptake in distinct frontal or (para-) limbic structures being reversed during effective antidepressive treatments [17,18]. More sham-controlled studies with different patient samples (severe, moderate depressive symptoms) are required to confirm the hypothesis. Anyhow also patients with no signs of hypofrontality got benefits from the treatment. This fact should be controlled in upcoming larger studies.

The patients included were generally suffering from only slight to moderate depressive symptoms according to the mean Hamilton baseline score, whereas the BDI reflects a more severe form of depressive symptomatology. Provided that a systematic bias of a very critical rater is excluded here, it seems possible that patients with a relatively high proportion of "neurotic" self perception were included in the study, perhaps reflecting the admission situation of a university hospital with the possibility of selecting its patients. Another explanation could be general negative thinking as a bias due to prolonged depressive symptoms in the area of cognition. Yet, the most important fact is that a wide range of depressed patients – from objectively moderate symptoms to great subjective suffering – seem to profit from rTMS. In this study, we used a stimulation intensity of only 80% of the motor threshold, despite recommendations of studies with negative results using low stimulation energy. The good improvements in our study contradict that hypothesis. So using the standardized rTMS treatment on the left DLPFC-region must be discussed critically.

The positive effect that no patient complained about adverse reactions, the higher safety impact, further supports the notion of using lower intensities, which seem to be effective as well. In contrast to the widely used figure 8 coils, a simple circular coil was applied in the present study. The technique was easy to install and much less cost intensive than a comparable figure 8 coil. This fact seems especially important with respect to the increasingly widespread use as routine psychiatric therapy.

Conclusion

The present open study demonstrates a noticeable improvement

in objective and subjective symptoms of refractory major depression during rTMS (1000 impulses, 20 trains of 10 Hz, 2 series of 5 days each, and 80% of the motor threshold) with a circular coil. In contrast to all studies available, SPECT was used to find out the individual region of left cortex hypoperfusion, which was then used for stimulation. This might be a reason for the good treatment outcome. Anyhow upcoming examinations should contribute to clarification of still inconsistent findings in the definition and role of hypoactivation areas in rTMS because our findings of improvement in non-hypoactivated areas are surprising. So further randomized and sham-controlled studies with larger patient groups and defined SPECT activation localisations should be performed.

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