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HF-rTMS treatment decreases psychomotor retardation in medication-resistant melancholic depression

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List of abbreviations:

DLPFC: Dorsolateral Prefrontal Cortex
rTMS: repetitive Transcranial Magnetic Stimulation
HF-rTMS: High-Frequency Repetitive Transcranial Magnetic Stimulation
HDRS: Hamilton Depression Rating Score
DRRS: Depressive Retardation Rating Scale
AD: antidepressant
MT: motor threshold
3D-MRI: Three Dimensional Magnetic Resonance Imaging
ANOVA: Analysis of Variance
ANCOVA: Analysis of Covariance
SPSS: Statistical Package for the Social Sciences
F: female
M: male
mg: milligram

Abstract

Repetitive Transcranial Magnetic Stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC) might be a promising treatment strategy for depression. As one of the key features of melancholic depression are disturbances in psychomotor activity, we wanted to evaluate whether HF-rTMS treatment could influence psychomotor symptoms. Twenty antidepressant-free unipolar melancholic depressed patients, all at least stage III medication-resistant, were studied. All were treated with 10 sessions of High-Frequency (HF)-rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) under MRI guidance. Forty percent of the patients showed a reduction of at least 50% on their initial 17-item Hamilton Depression Rating Score (HDRS) scale and were defined as clinical responders. Regardless of clinical outcome HF-rTMS treatment resulted in significant decreases on the Depressive Retardation Rating Scale (DRRS) scores. Although this was an open study in a relatively small sample, our results suggest that HF-rTMS might act on the 'psychomotor' level and these findings could add some further information as to why this kind of treatment can be beneficial for severely depressed patients of the melancholic subtype.

Keywords: HF-rTMS, melancholic depression, psychomotor retardation

Introduction

Currently, the physiological influences and treatment effects of repetitive Transcranial Magnetic Stimulation (rTMS) in psychiatric patients are under investigation (Burt et al., 2002; Hallett, 2007). However, the underlying neurobiological mechanism as to how this non-invasive technique can alter depressive states remains unclear (Post and Keck, 2001; George et al., 2003). Recently, Hoeppner and colleagues published an interesting paper examining psychomotor retardation and agitation in combination with infrathreshold high-frequency (HF)-rTMS in a depressed sample (Hoeppner et al., in press). Besides a trend in reduction of agitation, they found no significant influence of HF-rTMS on psychomotor symptoms. Although this was a well carried-out sham-controlled HF-rTMS study, some methodological issues and the concomitant pharmacological antidepressant therapy on the start of their HF-rTMS study might have biased the results (Martin et al., 2003).

In this study, we wanted to investigate whether suprathreshold HF-rTMS treatment affects psychomotor symptoms in a homogeneous sample of unipolar medication-resistant and antidepressant-free depressed patients, all of the melancholic subtype. As psychomotor retardation is one of the key features of this type of depression (Sobin and Sackeim, 1997; Gold and Chrousos, 2002; Pier et al., 2004), this group should be in particular suitable to evaluate psychomotor changes in rTMS paradigms. Because a higher level of psychomotor retardation has been associated with reduced metabolic activities in the left dorsolateral prefrontal cortex (DLPFC) - suggesting an important role of this cortical area on psychomotor functioning (Schrijvers et al., 2008) – we targeted this prefrontal cortical area under MRI guidance. We expected that psychomotor retardation symptoms only would improve in clinical HF-rTMS responders.

Methods and Materials

The study was approved by the ethics committee and all subjects gave written informed consent. Our study group consisted of twenty antidepressant-free unipolar depressed patients of the melancholic subtype (age 47.05±9.20; 13 females), selected by using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). All were right-handed and were considered at least stage III treatment resistant, as described by Rush et al (2003). Exclusion criteria were current or past history of epilepsy, neurosurgical interventions, having a pacemaker or metal or magnetic objects in the brain, alcohol dependence and suicide attempts within 6 months before the start of the study. Because concomitant antidepressant treatment can confound outcome results, all patients went through an antidepressant (AD) washout before entering the study and they were AD free for at least two weeks before HF-rTMS treatment. Only habitual benzodiazepine agents were allowed. For details see Table 1. However, all psychopharmacological changes during the stimulation sessions were considered as drop-out from the study.

Before and after treatment, depression severity was assessed with the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) by a certified psychiatrist, unrelated to the study. Mean HDRS scores before entering the study were 25.05±5.40. A trained psychiatric nurse, also unrelated to the study, assessed psychomotor symptoms and retardation with the Depressive Retardation Rating Scale (DRRS; Widlöcher, 1983). The DDRS is a well validated 15-item rating instrument to assess the severity of psychomotor retardation, especially in depressed samples. Mean DDRS scores were 30.75±8.47, showing a marked degree of psychomotor retardation. After the assessment, all received 10 sessions of HF-rTMS delivered on the left DLPFC. All patients were re-assessed after HF-rTMS treatment.

For the application of HF-rTMS we used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK), connected to a figure-of-eight-shaped coil. Before each application, the resting motor threshold (MT) of each individual was determined using electromyography. A stimulation intensity of 110 % of the subject's MT of the right abductor pollicis brevis muscle was used. In order to accurately target the left DLPFC, the precise stimulation site was determined using three dimensional Magnetic Resonance Imaging (3D-MRI) (see also Peleman et al., in press). In each high-frequency (10 Hertz) stimulation session, subjects received forty trains of 3.9 seconds duration, separated by an intertrain interval of 26.1 seconds (1560 pulses per session).

All collected data were analyzed with SPSS 15 (Statistical Package for the Social Sciences). The significance level was set at $p \leq 0.05$ for all analyses. A two-way ANOVA was performed with psychomotor symptoms (DDRS before and after treatment) as within subjects factor and treatment response (responder vs. non-responder) as between-subjects factor.

Results

Data from one patient were missing and due to a suicide attempt in the second week of HF-rTMS treatment, one patient did not complete the study. Seven of the 18 remaining patients were considered as HF-rTMS responders (7 responders, 5 females; 11 non-responders, 6 females), as defined as 50% reduction of the baseline HDRS score. See also Table 1. Responders did not differ from non-responders in age ($t(17)=0.03$, $p=0.98$), duration of the current depressive episode ($t(17)=0.04$, $p=0.70$), gender ($\chi 2(19)=0.33$, $p=0.66$) or the use in benzodiazepines ($\chi 2(19)=1.03$, $p=0.38$). No baseline differences on HDRS ($t(17)=1.60$, $p=0.13$) or DDRS ($t(17)=1.06$, $p=0.28$) scores between the two groups were observed.

A two-way ANOVA with psychomotor symptoms (DDRS before and after treatment) as within subjects factor and treatment response (responder vs. non-responder) as between-subjects factor showed a significant main effect of psychomotor symptoms ($F(1,17)= 71.03$, $p< 0.01$), but no main effect of response ($F(1,17)= 0.01$, $p= 0.98$). The interaction effect between psychomotor symptoms and treatment response was significant ($F(1,17)= 9.44$, $p< 0.01$). See also Fig 1. However, post hoc paired *t*-tests revealed that DDRS scores significantly decreased after HF-rTMS treatment for responders ($t(6)= 7.99$, $p< 0.01$) as well as for non-responders ($t(11)= 4.21$, $p< 0.01$). Independent *t*-tests also revealed that the level of psychomotor retardation symptoms was not significantly different between these two groups before but also after HF-rTMS treatment ($t(17)=1.31$, $p=0.21$).

To further examine whether the main effect of psychomotor retardation could not be attributed to a general improvement of depressive symptoms we re-analyzed the model with ANCOVA, with psychomotor symptoms (DDRS before and after treatment) as within subjects factor and treatment response (responder vs. non-responder) as between-subjects factor and delta HDRS (pre HDRS minus post HDRS) as covariate. Again, we found a main effect of psychomotor symptoms ($F(1,15)= 7.06$, $p= 0.02$) and no main effect of response ($F(1,15)= 0.01$, $p= 0.97$). Importantly, we found no significant interaction effect between psychomotor symptoms and response ($F(1,15)= 2.78$, $p= 0.12$) and between psychomotor symptoms and delta HDRS ($F(1,15)= 0.12$, $p= 0.74$).

Discussion

First of all, the observed 40 % of clinical responders is consistent with other open HF-rTMS treatment studies in depression (Pridmore et al., 2000). Our results indicate that HF-rTMS treatment improves psychomotor symptoms in TRD patients of the melancholic subtype irrespective of their treatment response as measured with the HDRS. One could argue that the decrease in psychomotor symptoms would be merely a side effect of a general decrease in depressive symptoms; however the effect of HF-rTMS on psychomotor retardation (pre versus post) remains significant after controlling for the decrease in depression severity (pre minus post HDRS scores).

Some of the discrepancies in psychomotor retardation results between the Hoeppner et al (in press) and our study could be related to differences in patient sampling, because we only included patients of the melancholic subtype. Pier and co-workers (2004) suggested that differences in psychomotor functioning between melancholic and non-melancholic depressed patients could imply different underlying neurobiological disturbances in these subtypes of major depression. Other important differences between our and the Hoeppner study (in press) which could explain the divergent results could be that instead the use of infrathreshold stimulation, we used suprathreshold HF-rTMS thought to increase clinical outcome (Gershon, 2003). Furthermore, the imprecise TMS-coil positioning method to target the left DLPFC (Sparing et al., 2008; Peleman et al., in press), the more heterogeneous sampling of depressed patients (not all treatment-resistant), and the concomitant pharmacological antidepressant therapy on the start of their HF-rTMS study might have biased their results (Martin et al., 2003; Herwig et al., 2007).

On a neurobiological standpoint of view, it has been hypothesized that a possible working mechanism of action of this kind of treatment could be on the dopaminergic system as several studies point to an rTMS-related release in endogenous dopamine when stimulating prefrontal cortical areas (Strafella et al., 2001; Pogarell et al., 2006, 2007). Without co-concomitant brain imaging techniques is speculative to assume that our clinical HF-rTMS effects on psychomotor improvement are associated with a 'hypodopaminergic state'. In addition, whether these effects on psychomotor retardation are mediated by dysfunctions within fronto-cingulate networks or by the spreading of neuronal activity to the (pre)motor cortical areas remains to be answered (Knoch et al, 2006; Baeken et al., 2009).

It cannot be ruled out that placebo effects have interfered with the end results. However, when the effects would be merely placebo-related, it would be unlikely that general

symptoms (HDRS) would not decrease in 60 % of our TRD patients, whereas psychomotor retardation symptoms significantly decreased after HF-rTMS treatment in responders as well as in non-responders. This would mean that the general placebo effect would only emerge on the psychomotor symptoms, and not on the depression severity (HDRS). Moreover, because our study sample consisted of medication-resistant depressive patients who were confronted with multiple failures of antidepressant treatment in the past, spontaneous clinical responses would be unexpected. Nevertheless, due to the open design, the interpretation of our data should be done cautiously. A major advantage of our study was that all patients were two weeks AD-free before and during HF-rTMS treatment. On the other hand, although all included patients in our analysis continued with exactly the same benzodiazepine concentrations in the AD-free period before stimulation, the use of benzodiazepines in our sample might have been a confounding variable. (Pier et al., 2004).

Due to an attempted suicide one female patient did not complete the study. Although before inclusion in this study recent suicide attempts were considered as a contra indication, suicide attempts in the past and actual suicidal thoughts were not. In spite that this patient was known with a severe history of suicidal behavior and attempted suicides in the past, she was included in the study because there were no recent suicide attempts. When asked about her current suicidal behavior, she expressed feelings of hopelessness when not experiencing mood improvement in the second week of stimulation. Although rTMS induced acute psychiatric changes such as psychotic symptoms, anxiety, agitation, mania and suicidal ideation have been reported (Zwanzger et al., 2002; Janicak et al., 2008), it remains unknown whether these occur at higher rates compared to the natural course of disease, or compared with other interventions (Rossi et al., 2009). Presently, no reports of suicides due to the rTMS application have been reported (Rachid and Bertschy, 2006; Rossi et al., 2009) and rTMS has been suggested as a treatment option to prevent suicide (Yoshimura, 2007). Nevertheless, future studies should carefully evaluate suicidal ideation and behaviors during this kind of treatment as high dopaminergic and low serotonergic activity has been associated with a higher level of impulsiveness and suicide risk (van Heeringen, 2003; Ryding et al., 2008; Carver et al., 2009). However, besides effects on the dopaminergic system (e.g. Pogarell et al., 2006), it has been demonstrated that HF-rTMS increases serotonin concentrations as well (e.g. Ben-Shachar et al., 1999).

In summary, our results indicate that HF-rTMS treatment affects psychomotor functioning regardless of clinical response. In support of the conclusions of Hoeppner and colleagues (in press), future sham-controlled studies might indeed do well to include

psychomotor scales to evaluate whether or not the clinical effects of HF-rTMS treatment are related to (psycho)motor processes.

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Patients	**Age (years)**	**Gender**	**Duration (years)**	**HDRS before**	**HDRS after**	**DRRS before**	**DRRS after**	**Medications during HF-rTMS (dose/day)**
Non-responders								
1	56	M	1.5	16	9	27	25	Alprazolam 2mg, Flurazepam 27mg
2	48	F	3	27	25	27	17	none
3	47	F	12	30	25	23	10	Alprazolam 1mg, Flurazepam 27mg
4	40	M	2.5	26	23	13	20	Alprazolam 1mg
5	46	F	2	25	16	25	14	none
6	61	M	14.5	31	18	39	32	Prazepam 20mg
7	58	F	3	24	26	32	17	none
8	55	F	6	33	23	33	20	none
9	39	M	1	27	26	35	30	none
10	31	F	1	21	13	24	18	none
11	39	F	6	31	-	38	34	none
12	51	M	6	27	20	39	23	none
Mean (*SD*)	47.58 (9.09)	7F:5M	4.88 (4.36)	26.5 (4.72)	20.36 (5.73)	29.58 (7.86)	21.67 (7.38)	
Responders								
1	48	F	7	25	12	36	22	Lormetazepam 2mg
2	34	M	7	21	6	16	7	none
3	61	F	0.5	27	10	46	27	Alprazolam 1mg, Flurazepam 27mg
4	42	F	4	23	9	36	13	none
6	45	F	1.5	25	8	30	15	Flunitrazepam 1mg
6	60	M	20	27	12	35	10	Potassium clorazepate 50mg
7	44	F	1	10	3	39	25	none

Mean (*SD*)	47. 71 (9.74)	5F: 2M	5.86 (6.80)	22.57 (5.94)	8.57 (3.26)	34.00 (9.29)	17.00 (7.72)	
Missing								
1	36	F	1	-	-	22	9	none
All patients	47.05 (9.20)	13F: 7M	5.03 (5.17)	25.06 (5.40)	15.78 (7.62)	30.75 (8.47)	19.40 (7.84)	

Table 1: Clinical assessment. Data are presented as means and standard deviations. HDRS= 17-item Hamilton Depression Rating Scale. DRRS= Depressive Retardation Rating Scale. Clinical response is defined as 50% reduction of the baseline HDRS score. F= female. M= male. (-) represent missing values. mg= milligram

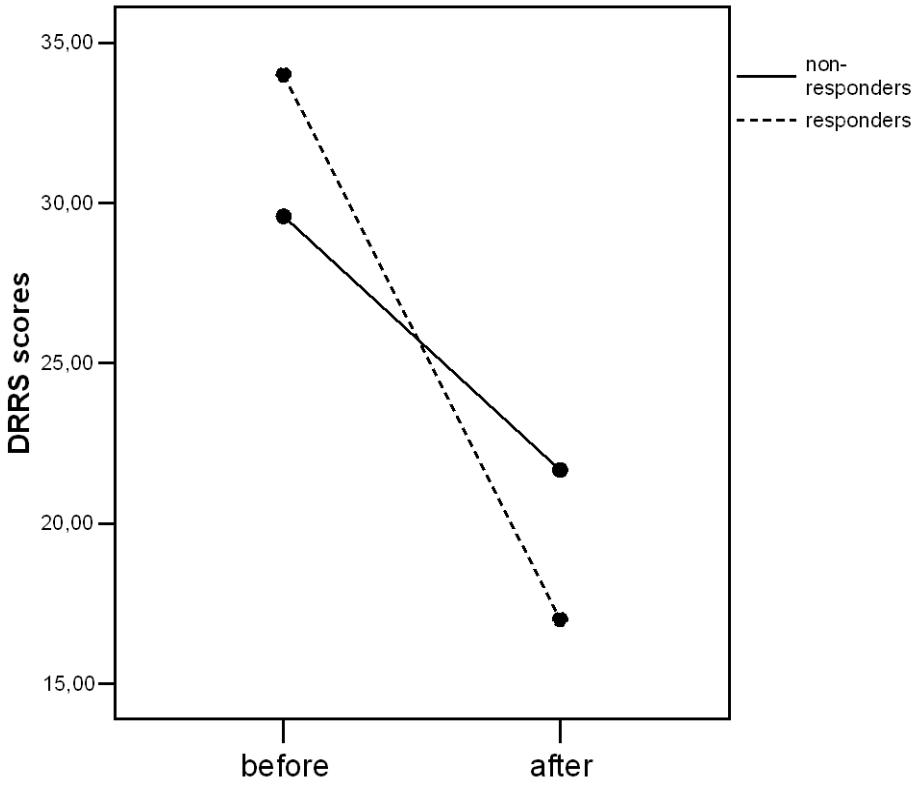

Fig 1: Graphical representation of the two-way ANOVA data with psychomotor symptoms (DDRS before and after treatment) as within subjects factor and treatment response (responder vs. non-responder) as between-subjects factor. DRRS= Depressive Retardation Rating Scale.