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Influence of repetitive transcranial magnetic stimulation on special symptoms in depressed patients

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Abstract. Since various studies, including multi-centre studies, investigating the effect of repetitive transcranial magnetic stimulation (rTMS) in depression have shown different results, it is now important to research, which symptoms of depression are most responsive to this kind of non-invasive brain stimulation. Furthermore, an increasing interest of rTMS as a potential tool for treatment of neurological and psychiatric disorders should be recorded. Therefore, it is critical to investigate dopaminergic functional interactions in the prefrontal cortex, and in particular, the effect of dorsolateral prefrontal cortex stimulation on clinical symptoms depending on dopaminergic concentrations in various brain regions. This short review summarizes important preliminary data, which focus on the symptom-oriented effects of rTMS in depression.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) was introduced as a promising new treatment option for depression and showed beneficial effects in single-centre studies (Burt et al., 2002; Kozel and George, 2002; Loo and Mitchell, 2005). To date, numerous open and controlled clinical trials have demonstrated that high-frequency (> 5 Hz) rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) (means high frequency left – HFL) and low-frequency (< 1 Hz) rTMS applied over the right DLPFC (means low fre-

quency right – LFR) have antidepressant effects (Gershon et al., 2003). However, it remains difficult to draw general conclusions about the antidepressant efficacy of rTMS because of heterogeneous study designs, variable stimulation parameters and low sample sizes (Martin et al., 2003). In recent years, two important multi-centre studies (MCS) on higher number of included depressive patients were published (Herwig et al., 2007; O'Reardon et al., 2007). The aim of these multi-centre trials was to evaluate whether the application of rTMS in a routine clinical setting as a complementary treatment to standard antidepressant medication (Herwig et al., 2007), or as a single treatment in drug resistant patients (O'Reardon et al., 2007), would have an effect compared with a sham treatment regarding the number of responders and the decrease in depression rating

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scores. Presumably due to the distinct study designs, different results were found (see Schönfeldt-Lecuona et al. in this special issue). Within the European Multi-Centre Study, we did not find beneficial effects of rTMS compared to a sham stimulation condition with regard to responder rates or changes in the rating scores (Herwig et al., 2007).

In conclusion, it is still a matter of debate, whether HFL rTMS could be useful in treating depression. Apart from methodological problems including stimulation parameters and inclusion criteria, it is hypothesized, that rTMS has effects on specific depressive symptoms, which are difficult to assess with standard diagnostic instruments for depression severity. Most of the studies on rTMS in depression have investigated the effect on treatment response rate or the effect on depression rating scales as a global measure of depressive symptoms. The influence on selective symptoms, however, has rarely been investigated up to now.

The present article aims to give an overview of some specific effects of rTMS on typical depressive symptoms. The most frequently investigated symptoms influenced by rTMS, regardless of the underlying disorder, are attention and motor signs, which are closely related to brain dopamine (DA) dysfunction. DA is implicated in the regulation of movement, attention, reward and learning, and plays an important role in neuropsychiatric disorders such as Major Depression (MD) (Khedr et al., 2006) and Parkinson's Disease (PD). Therefore, this article refers to rTMS effects on dopaminergic dysfunctions in both disorders.

2. Parkinson's disease and depression

From a pathophysiological and clinical view, PD and MD are closely related clinical conditions. Results of several studies indicate that depressive symptoms appear in an early stage of PD, that depression is associated with a high risk for PD, and that depressive disorders are often associated with PD-like motor dysfunction. With this background, central findings of recent studies in the field are summarized as follows:

First: MD is a frequent comorbid condition in PD, prevalent in 31% of PD patients (Brooks and Doder, 2001), and may precede the diagnosis of PD by 10–20 years (Shiba et al., 2000). Large register studies have shown that, compared to non-depressed controls, depressed patients have a 2.2 to 3.1-fold higher risk for developing PD (Leentjens et al., 2003; Nilsson et al., 2001; Schuurman et al., 2002).

Second: Psychomotor symptoms similar to typical motor signs in PD are very common in patients with MD, have been found to correlate with anhedonia (Lemke et al., 1999), and can be assessed with the Motor Agitation and Retardation Scale (MARS) (Sobin et al., 1998). Psychomotor retardation symptoms rated as items of the MARS are very similar to Parkinson symptoms, including motor slowness, reduced voice volume, abnormal gait, lack of facial expressivity, delayed onset of speech, and monotone speech. Psychomotor agitation symptoms include items such as increased axial truncal movements, abnormal hand, foot and lower leg movements, tension of the mouth, increased blinking. Compared to patients without psychomotor signs, patients with such signs tended to be more severely ill and have a more complicated course of the depressive disorder (Angst et al., 2009). From a pathophysiological perspective, an association to DA neurotransmission was shown in MD patients with psychomotor symptoms. In [¹¹C]raclopride PET investigations, Meyer et al. found an elevated putamen D(2)-receptor binding potential in psychomotor retarded depressed patients (Meyer et al., 2006). Furthermore, functional neuroimaging findings also suggest an involvement of the same DA-related neuroanatomical substrates in patients with MD as in patients with PD (e.g. striatum, ventrolateral prefrontal and orbitofrontal cortex) (Tremblay et al., 2005).

In our research group, transcranial brain sonography (TCS) was used to investigate associations between abnormalities in substantia nigra (SN) and clinical motor functions in depressive patients. TCS has previously proved reliable in detecting abnormalities of SN and basal ganglia in PD (Becker et al., 1995; Walter et al., 2003). In about 90% of PD patients, TCS reveals characteristic SN hyperechogenicity, which remains stable during the course of the disease and is discussed to reflect increased amounts of iron, bound to proteins other than ferritin, but not the progressive neurodegeneration in the SN (Berg et al., 2005; Berg et al., 2002; Walter et al., 2004; Walter et al., 2003). SN hyperechogenicity in non-parkinsonian subjects was found to be associated with a malfunction of the nigrostriatal dopaminergic system (Berg et al., 1999; Berg et al., 2001; Sommer et al., 2004; Walter et al., 2004). In patients with depressive disorders, SN hyperechogenicity is found with threefold increased frequency compared to non-depressed controls (Walter et al., 2007). In our study on 56 depressed patients, we studied whether SN hyperechogenicity in depressed subjects is already related to mild motor abnormalities suggestive of early stages of PD (Höppner et al., 2009). TCS data in

Fig. 1. Results of a TCS study in 56 depressed patients. Correlation between SN echogenic size in patients with depressive disorder and right-to-left tapping asymmetry index, estimated by division of larger by smaller tapping score of both hands. SN echogenic size was correlated with tapping asymmetry index in the group of all patients ($r = 0.35$, $P = 0.017$; dashed line), and even stronger if only patients at ages ≥ 50 years were considered ($r = 0.52$, $P = 0.007$; continuous line) but not among patients at ages < 50 years ($P = 0.70$; dotted line).

this study shows, that SN hyperechogenicity is related to motor asymmetry (measured with the finger tapping test), as a characteristic finding of preclinical PD stage (Fig. 1). This relationship is independent from age, yet stronger in patients 50 years and older, and stronger in patients with reduced brainstem raphe (BR) echogenicity. Reduced BR echogenicity in depressed subjects has been shown to relate to alteration on MRI of the dorsal raphe nucleus, and to better responsiveness to serotonin reuptake inhibitors (Becker et al., 2001; Walter et al., 2007). The underlying mechanisms of motor asymmetry in depressive patients might be (a) an alteration of nigral dopaminergic neurons, indicated by SN hyperechogenicity, and/or (b) impaired serotonin-mediated regulation of striatal DA transmission (Alex et al., 2005), indicated by reduced BR echogenicity.

Third: Patients with PD and MD show similarities in prefrontal brain dysfunctions. The prefrontal cortex (PFC) is important for screening distractions, sustaining attention, shifting/dividing attention in a task-appropriate manner, and is critical for regulating behaviour, especially for inhibiting inappropriate emotions, impulses and habits. The PFC is needed for allocating/planning goals and organizing behaviour/thought, and it regulates attention and behaviour through networks of interconnected pyramidal cells. These networks excite each other and are highly dependent on their neurochemical environment, for example, changes in DA can have marked effects on

PFC function (Arnsten, 2009). Due to the dysfunction in the DLPFC, depressed patients are impaired in the ability to shift their focus of attention (Silton et al., 2009). It has been proposed that a dorsal circuit plays an important role in the interaction between emotional and attentional processing. Neuroimaging studies have shown the engagement of the left DLPFC in executive functioning (Johnson et al., 2007), emotion regulation (Domes et al., 2010; Ochsner et al., 2004) and its crucial involvement in depression (Koenigs and Grafman, 2009). Individuals with PD also demonstrate impairments on tasks relying on the PFC, regarding the loss of dopaminergic neurons in the SN and the ventral tegmental area, with degeneration of their striatal terminals, and the resulting dysfunction of the intimate connections between the striatum and the frontal lobes (Drag et al., 2009).

3. rTMS effects on dopaminergic neurotransmission

Concerning the above mentioned observations, it is critical to investigate dopaminergic functional interactions in the PFC and in particular the effect of DLPFC stimulation on DA concentration in various brain regions. In a first study in PD patients, the influence of rTMS on DA and homovanillic acid (HVA) levels in the lumbar cerebrospinal fluid (CSF), in addition to

clinical effects was investigated. The results show that patients receiving frontal rTMS have a significant decrease in clinical PD scores and significantly reduced CSF levels of HVA, which suggest that rTMS may exert its effect via the dopaminergic systems (Shimamoto et al., 2001). In animal studies, an elevation of extracellular DA in the striatum has been shown after frontal rTMS (Keck et al., 2002). In humans, a PET study with healthy subjects shows that rTMS on the left DLPFC induced a significant reduction in the [(11)C]FLB 457 binding potential (BP) in the ipsilateral subgenual anterior cingulate cortex (ACC), pregenual ACC and medial orbitofrontal cortex (Cho and Strafella, 2009). There were no significant changes in [(11)C]FLB 457 BP following right DLPFC rTMS. This study provides evidence of extrastriatal DA modulation in the PFC following acute rTMS of left DLPFC. It is concluded, that the increase in dopaminergic neurotransmission contributes to the effects of rTMS in the treatment of MD and PD. Accordingly, a [123I] iodobenzamide (IBZM) SPECT study with depressed patients found a reduction of specific striatal IBZM binding to DA D2 receptors after HFL rTMS (Pogarell et al., 2006).

Further, combining neuroimaging and TMS-studies might help to identify the neurobiological effects of TMS for the treatment of different neurological and psychiatric diseases. In sum, the results of these investigations suggest that left prefrontal rTMS stimulates the release of endogenous DA, and thereby exerts modulation of mesolimbic and mesostriatal dopaminergic pathways. Based on this conclusion, effects of HFL rTMS on DA related clinical symptoms should be expected.

4. rTMS effects on motor/psychomotor symptoms

Independent of the above discussed findings of rTMS effects on dopaminergic neurotransmission, motor symptoms have been the focus of investigations on clinical TMS effects in PD since 1985 (Elahi et al., 2009). In a meta-analysis on the effects of rTMS on motor signs in PD, the mean effect size for 10 included studies on the Unified Parkinson's Disease Rating Scale (UPDRS) was calculated. Pooling of the results yielded an average effect size of -0.58 for HF rTMS studies and no significant effects for LF rTMS studies (Elahi et al., 2009). However, since the clinical presentation of PD is related to abnormal neuronal activity within the basal ganglia and cortical regions, including the primary motor cortex, the premotor cortex, and the

PFC, the studies have used different rTMS procedures including different stimulation regions.

As already mentioned above, depression is a frequent comorbid condition in PD. Therefore, the influence of prefrontal rTMS on motor symptoms in addition to its effects on depressive symptoms became the object of investigations. Helmich et al. reviewed TMS studies investigating therapeutic effects on mood and motor function in PD patients and highlighted methodological inconsistencies, including the difficulty to define the most effective protocol for rTMS or to establish an appropriate placebo condition (Helmich et al., 2006). The results on the HFL rTMS effects in PD patients are inconsistent. While some HFL rTMS studies have shown that prefrontal stimulation may be beneficial for depressed PD patients in multiple functional domains, i.e. depression scores, anxiety, movement scores, and some neuropsychological measures (Epstein et al., 2007), others could not confirm these results (del Olmo et al., 2007) and concluded that prefrontal rTMS has no effect on motor functions and clinical motor status, and that the observed improvement in performance of motor tasks could only be attributed to the effects of practice (del Olmo et al., 2007).

So far, some results in the literature suggest that rTMS might have a positive effect on clinical symptoms associated with striatal dopaminergic dysfunction. In MD the clinical effects of rTMS on psychomotor symptoms has been rarely investigated up to now. Our group's aim is to devote time and research to this question.

In an initial rTMS study from our laboratory, we investigated 30 MD patients using two different rTMS procedures (HFL 20 Hz: 20 Hz rTMS over the left dorsolateral prefrontal cortex; LFR 1 Hz: 1 Hz rTMS over the right dorsolateral prefrontal cortex) compared to sham stimulation (e.g. the coil was placed with an angle of 90° in relation to the head, stimulation intensity was reduced – for details see: (Hoeppner et al., 2003)) (10 patients in each group) over 10 days (Hoeppner et al., 2003). We measured the effect on depressive rating scales and the effects on psychomotor functioning. Psychomotor impairments were assessed with the MARS (Sobin et al., 1998). Patients of the sham-stimulated group show, on average, no reduction of psychomotor functions. Within the 20 Hz rTMS group, the improvement of MARS score was statistically significant after 5 days ($t = 3.33$; $p < 0.001$), with a further improvement at the end of rTMS-treatment ($t = 6.98$; $p < 0.001$). The MARS-scores of the patients of the 1 Hz rTMS group show a reduction exclusively

Fig. 2. Comparison of pre- to post-treatment MARS scores in our first rTMS study using two different rTMS procedures (high frequency left = HFL 20 Hz/low frequency right = LFR 1 Hz) compared to a sham stimulation. One-sample t-test showed, that in the group receiving 20 Hz rTMS over the left dorsolateral prefrontal cortex (HFL 20 Hz) the improvement of MARS sum score was statistically significant between baseline and endpoint score ($t = 6.98$; $p < 0.001$). The MARS score of the patients of the group receiving the 1 Hz rTMS over the right dorsolateral prefrontal cortex (LFR 1 Hz) showed a less statistical powerful reduction ($t = 2.73$; $p = 0.023$), whereas the reduction was not statistically significant in the sham stimulated patients group. * $p \leq 0.05$; *** $p \leq 0.001$.

after 10 days ($t = 2.73$; $p = 0.023$) (Fig. 2). However, no differentiation is drawn between psychomotor agitation and retardation (Hoepfner et al., 2003). In addition, the groups were not comparable regarding their antidepressant medication. Patients were left on their antidepressant medication on which they failed to show clinical effects. The medication was not changed two weeks before and during the rTMS procedure.

The aim of our second study was to investigate the effect of HFL (10 Hz) rTMS on psychomotor dysfunction, and in addition, to investigate the differential influence on psychomotor retardation and on psychomotor agitation in MD patients (Hoepfner et al., 2009). The data were collected as part of a recent randomized, double-blind, sham-controlled, multi-center trial investigating the antidepressant effects of augmentative rTMS (Herwig et al., 2007) (see also in Schoenfeldt-Lecuona et al. in this special issue). Based on our initial findings, we hypothesize that rTMS will improve both psychomotor agitation and retardation.

Inclusion criteria were: age 18–75 years, a moderate or severe major depressive episode according to ICD-10 and DSM-IV (SCID), and a score of 18 points or more in at least two of the three depression rating scales: Beck's Depression Inventory (BDI), Hamilton Depression Scale (HAM-D 21-items version), Montgomery-Åsberg Depression Rating-Scale (MADRS). Thirty patients (18 females, mean age: 52.3 ± 11.9 years) were investigated at two participating centers of the multi-

center study (Psychiatric Departments of the Universities of Rostock and Munich). The patients were randomly assigned to either a real stimulation or a sham stimulation group. Details regarding the inclusion and exclusion criteria have been described previously (Herwig et al., 2007). In order to integrate rTMS in a naturalistic routine clinical setting, and for ethical and safety reasons, rTMS was applied parallel to a standardized antidepressant medication. The stimulation sessions were started together with a venlafaxine or mirtazapine treatment, both selected because of their combined serotonergic and noradrenergic profile in order to rule out neurotransmitter-specific confounding effects. Other antidepressants, neuroleptics or anticonvulsants were not allowed, lorazepam was only permitted as an exceptional crisis medication. Both groups did not differ either in terms of age, clinical baseline characteristics, in concomitant antidepressant medication, in dosage of antidepressants nor in the severity of depression. Unfortunately, but accidentally, there were significantly more women in the real, than in the sham stimulation group (real: 13/sham: 5) ($\chi^2 = 8.89$, $p = 0.01$). Again, the MARS was used to evaluate psychomotor symptoms. Group differences were tested with Student's t-test (one tailed) for independent samples. As the main result, we found a significant reduction of the agitation after real compared to sham stimulation ($t = -1.8$, $p = 0.045$; single-tailed), although the real stimulation group showed higher pre-treatment scores

Fig. 3. Relative change in % of the MARS sumscore, agitation and retardation subscores. Comparison between real (10 Hz HFL) and sham stimulation groups. Significant reduction of the agitation after real compared to sham stimulation (one tailed t-test: $p = 0.045$), no statistical significant differences in MARS sumscore and retardation score.

($t = 2.19$, $p = 0.037$) (Fig. 3). When considering the course of scores within the groups, we found a significant difference between pre- and post-stimulation scores in the real stimulation group ($p = 0.002$), which was not the case in the sham group ($p = 0.061$). The Mann-Whitney-U exact test revealed a trend towards an enhanced improvement (pre- to post-agitation scores) in the group comparison ($p = 0.053$, one tailed). Analyzing effect sizes, we found a medium effect of rTMS on agitation compared to sham stimulation (absolute change; Cohen's $d = 0.66$). There were no group differences for the total and the retardation score of the MARS. Furthermore, there were no significant differences between patients who received venlafaxine ($n = 14$) and those who received mirtazapine ($n = 16$) on the absolute changes of psychomotor symptoms irrespective of the rTMS condition (MARS sum score: $t = -0.73$, $p = 0.47$; agitation score: $t = -0.08$, $p = 0.93$; retardation score: $t = -1.03$, $p = 0.31$). Regarding the depression rating scales, there were no significant differences in clinical ratings of depression severity, measured with BDI, HDRS and MADRS.

5. Discussion and summary

Starting from our own neurobiological studies on psychomotor dysfunctions in depressive patients, which suggest alterations of nigral dopaminergic neurons, indicated by SN hyperechogenicity in TCS (Hoeppner et al., 2009; Walter et al., 2007), and numerous other investigations on this topic, and from an-

imal and human studies, which show an influence of HFL rTMS on dopaminergic neurotransmission, we investigated the effect of rTMS on underlying clinical symptoms such as psychomotor dysfunctions.

Although we did not observe significant differences between real and sham stimulation conditions with regard to the overall severity of depression in both of our rTMS studies (Hoeppner et al., 2009; Hoeppner et al., 2003), a trend toward the overall improvement of psychomotor symptoms after real, especially after HFL rTMS, compared to sham stimulation (Hoeppner et al., 2003), and in addition, a significant reduction of a certain domain of psychomotor functioning (psychomotor agitation) was found after real rTMS compared to sham stimulation (Hoeppner et al., 2009).

Based on the results of our second rTMS study (Hoeppner et al., 2009), that differentiated between special psychomotor dysfunction in depressed patients, and shows reduction in agitation but not, as was expected, in retardation, other pathways, different from release of endogenous DA, should be discussed. In addition, serotonin neurotransmission deficits are thought to be involved in agitation and hyperactivity (Brus et al., 2004). Neurochemical investigations have shown an effect of rTMS on serotonergic neurotransmission: high-frequency frontal rTMS in rats resulted in an increase of extracellular 5-HT concentration in the prefrontal cortex (Kanno et al., 2003). Furthermore, dysfunctions of the hypothalamic-pituitary-adrenocortical (HPA) axis should be discussed. Rubin et al. have shown that agitation in depression correlates with increased HPA activity (Rubin et al., 1987), and rTMS

has been reported to suppress post-dexamethasone cortisol levels in rTMS-responsive MD patients (Zwanzger et al., 2003). Hence, modulation of HPA and serotonergic functioning by rTMS could be responsible for the influence of HFL rTMS on psychomotor agitation.

Some methodological problems in both of our rTMS studies should be mentioned, which are most likely due to the fact that the studies were conducted in a real common sample of depressed in-patients. We should mention the small sample sizes. In clinical routine settings and in single-centre trials, it is obviously challenging to recruit large samples of patients who fulfill the inclusion criteria, agree to the study conditions, and do not take anticonvulsants, neuroleptics and benzodiazepines. In addition, the different gender ratio (more female patients in the real compared to the sham rTMS group) and the use of two different antidepressant medications in our second rTMS study (Hoëppner et al., 2009) should be critically discussed.

Nevertheless, our findings provide new evidence that psychomotor symptoms in depression could be responsive to HFL rTMS. The mechanism of action, however, has to be elucidated in more detail. For further studies it would be of great interest to investigate specific symptoms of depression, which depend on certain neurobiological alterations and pathophysiologic brain dysfunctions. Therefore, combining rTMS, clinical, neuroimaging and neurochemical investigations might be a promising approach.

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