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Brief report

Mood effects of repetitive transcranial magnetic stimulation of left prefrontal cortex in healthy volunteers

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Abstract

This study investigated the effect of high-frequency repetitive transcranial magnetic stimulati(HF-rTMS) of the left prefrontal cortex (LPFC) on mood in a sham-controlled crossover design. Twenty-five healthy male subjects received HF-rTMS of the LPFC in real and sham conditions. Forty trains (frequency 20 Hz, stimulation intensity 100% of individual motor threshold, train duration 2 s, intertrain interval 28 s) were applied in each session. Mood change from baseline was measured with five visual analog scales (VAS) for sadness, anxiety, happiness, tiredness and pain/discomfort. We were unable to demonstrate significant mood changes from baseline on visual analog scales after either sham or real stimulation of LPFC. There is insufficient evidence to support the general conclusion that HF-rTMS of LPFC has mood effects in healthy volunteers. Future studies should be sham-controlled, have larger sample sizes, and strictly stimulate one single region per session in order to exclude interaction effects with the previous stimulation. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Visual analog scales; Affect; Transcranial magnetic stimulation; Prefrontal cortex

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1. Introduction

It is of obvious importance to elucidate the exact structural and functional bases of affect to understand the neurobiology of and putative therapeutic approaches to human disorders like depression and mania. Today it is widely accepted (George et al., 1995) that the system mediating emotion consists of several brain regions that are reciprocally interconnected. Among them, the limbic system integrates external stimuli with internal drives and is part of a distributed neural network that imbues stimuli and events with positive or negative value (Damasio et al., 1991; Saver and Damasio, 1991; Aggleton, 1993). In addition, mood has been mapped to prefrontal cortex, although with considerable variability (Pardo et al., 1993; George et al., 1995; Gemar et al., 1996; Lane et al., 1997; Paradiso et al., 1997). Focal limbic (anterior cingulate), paralimbic (ventral frontal, anterior insular cortex) and neocortical (prefrontal, parietal) abnormalities have also been identified in affective disorders (Robinson et al., 1984; Baxter et al., 1989; Bench et al., 1992).

Of considerable interest for the understanding of the basic neurophysiology of mood generation and modulation are recent studies of non-invasive high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) in healthy subjects. Five studies (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997; Cohrs et al., 1998; Nedjat et al., 1998) investigated the effect of prefrontal HF-rTMS on mood systems in normal volunteers. In three studies (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997) HF-rTMS over the left prefrontal cortex (LPFC) transiently induced a decrease in self-rated happiness and an increase of sadness compared to the effects of right prefrontal cortical HF-rTMS. In none of those studies, however, were mood changes clinically apparent to either the investigators or the subjects themselves. Two more recent studies (Cohrs et al., 1998; Nedjat et al., 1998) failed to demonstrate any mood effects in healthy volunteers.

The aim of this study was to reproduce previous findings in a larger number of subjects who were more homogeneous than previous study groups with respect to gender, age, handedness and nicotine consumption. To avoid interaction of mood changes of two different stimulation sites and to exclude interaction of the previous stimulation, only the LPFC was stimulated and only one stimulation was performed per session. A sham-controlled crossover design was used to exclude non-specific effects such as discomfort and noise.

2. Methods

Thirty male subjects were recruited for this study by advertisements. Included were male, right-handed, non-smoking subjects with an age between 20 and 25 years, all of whom were naive to the rTMS method. Exclusion criteria were current or past history of head surgery, epilepsy, any psychiatric disorder, or the intake of any drug. Psychiatric disorders were assessed by the PRIME-MD interview (Spitzer et al., 1994) and an in-depth clinical interview with a board-certified psychiatrist before the subject's inclusion in the study.

Twenty-five subjects (mean age 22.4 ± 1.9) satisfied criteria for inclusion in the study; five of the initially evaluated subjects were excluded before randomization because they did not meet inclusion criteria. Subjects were compensated with US$50 (75 sFr). Safety guidelines of the International Society of Transcranial Magnetic Stimulation (ISTS) were followed (Wassermann, 1998). The Institutional Review Board of the medical faculty of the University of Bern approved of the study, and all subjects gave written informed consent.

All stimulations were performed using a Magstim high-speed stimulator (Magstim Company Limited, Wales, UK) by the same investigator (U.M.) with a figure-8-shaped air-cooled coil. Motor threshold (MT) was determined individually before real and sham stimulation. Stimulation intensity was 100% of MT of the right abductor pollucis brevis muscle, frequency was 20 Hz and intertrain interval was 30 s. Forty trains were applied in 20 min (1600 pulses per session). The LPFC was defined as the location 5 cm anterior

and 2 cm on the left of the parasagittal plane from the location of the motor threshold of the right abductor pollucis brevis muscle. Real and sham stimulation were performed at the same place on the scull, but for the sham stimulation the figure&shaped coil was held at an angle of 90° and the edge of the coil was put on the LPFC.

All subjects were stimulated in the time interval from 14.00 to 16.00 h. There was a delay of 2-3 days between the two stimulation sessions. Volunteers rated themselves before the stimulation (baseline T_0) and 20 min after HF-rTMS (T_{20}) on five 100-mm visual analog scales (VAS). Similar to the procedures followed in previous studies, sadness, anxiety, happiness, tiredness and pain/discomfort were assessed with the VAS (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997; Cohrs et al., 1998; Nedjat et al., 1998). To avoid interference among the different scales, each scale was presented on an individual cardboard card in randomized order. For descriptive statistics, the mean and S.E. distances (mm) of the changes from baseline ratings were calculated for each VAS for real vs. sham stimulation. Two-way repeated measures analysis of variance (ANOVA) with the main effects sham/real stimulation and order effect was used and the interaction of these effects was tested.

3. Results

No subject had to be excluded after randomization. Five of the 25 subjects complained of a mild headache 20 min after the stimulation. Four subjects recovered spontaneously, one after a single dose of paracetamol, 500 mg. No obvious mood changes were observed. Fig. 1 shows the mean change from baseline (mm) and S.E. of all VAS for real and sham stimulation. Two-way repeated measures ANOVA did not reject the null hypothesis of each VAS (e.g. happiness, sadness, tiredness, pain/discomfort) for the main effects mood change after sham/real stimulation and order effect. Furthermore, no significant interaction of these effects was detected.

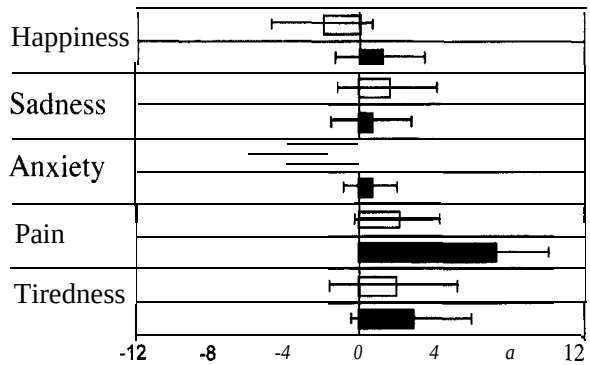

Fig. 1. Mean change from baseline with S.E. (mm) of five different visual analog scales (VAS) after HF-rTMS of left prefrontal cortex. Positive changes indicate increase, and negative changes indicate decrease of the variable. Empty bars represent sham HF-rTMS stimulation, filled ones real HF-rTMS.

4. Discussion

It is controversial whether high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) of the prefrontal cortex has an influence on mood. This study investigated the effect of left prefrontal cortical (LPFC) HF-rTMS on mood with five visual analog scales (VAS) in a sham-controlled crossover design and failed to demonstrate significant mood changes from baseline at 20 min after real and sham stimulation. Two other studies (Cohrs et al., 1998; Nedjat et al., 1998) also failed to demonstrate mood effects in healthy volunteers after prefrontal HF-rTMS. However, several cases of clinically observable mood changes as side effects (Nedjat et al., 1998) of rTMS have been reported. Furthermore, three studies specifically designed to study mood (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997) found mood changes after HF-rTMS of prefrontal cortex that were not clinically apparent to either the investigators or the subjects themselves.

Table 1 summarizes our own findings and the findings of previous studies using HF-rTMS for comparison and discussion: study goals and designs were slightly different. The subjects in our study were homogeneous with respect to gender, age, handedness and nicotine consumption. Three

Table 1
Summary of HF-rTMS mood studies in healthy subjects[a]

	Pascual-Leone et al. (1996)	George et al. (1996)	Dearing et al. (1997)	Nedjat et al. (1998)	Cohrs et al. (1998)	Mosimann et al. (2000)
Study goal	Influence of rTMS on mood	Influence of rTMS on mood, hormone, reaction time	Influence of rTMS on mood (two coil shapes)	Influence of rTMS on mood	Influence of rTMS on REM sleep, mood	Influence of rTMS on mood
Design	Crossover	Crossover	Crossover	Parallel group	Crossover	Crossover
N	10	10	9	50	12	25
Sex ratio (M:F)	6:4	6:4	5:4	*	13:0	25:0
Age	22-27	35 ± 8.1	33 ± 7	*	26.9 ± 2.3	22.4 ± 1.9
Handedness	*	Right	Right	*	*	Right
Site of stimulation	RPFC/LPFC/ midfrontal	RPFC/LPFC/ midfrontal/occipital/ cerebellum	RPFC/LPFC	LPFC	RPFC/LPFC/ right left inferior parietal/midoccipital	LPFC
Site of sham stimulation	None	None	RPFC, coil angled 45°/90°	None	Vertex, coil angled 90°	LPFC, coil angled 90°
Stimulated sites per session	6	1	3	*	1	1
Shape of the coil	Figure 8	Figure 8	Figure S/teardrop	Figure 8	Figure 8	Figure 8
Intensity (%MT)	110	120	80	80	120	100
Frequency (Hz)	10	5	20	10 and 20	20	20
No. of trains	10	10	20	20	160	40
Train duration	5	10	2	5 and 2	0.25	2
Intertrain interval	25	120	58	60	8	30
Pulses per site	500	500	800	1000 and 800	800	1600
Time of mood rating ($T_{minutes}$)	T_0, T_1	$T_0, T_{30}, T_{60}, T_{90}, T_{180}, T_{>480}, T_{1440}$	*	T_0, T_1, T_{1440}	T_1	T_0, T_{20}
Effect of LPFC stimulation**	Happiness ↓ Sadness ↑	Happiness ↓ Sadness ↑	Happiness ↓ Sadness ↑	*	*	Happiness ↑ Sadness ↑
Effect of RPFC stimulation**	Happiness ↑ Sadness ↑	Happiness ↑ Sadness ↓	*	*	*	
Conclusion ($P < 0.05$)	rTMS to LPFC: Happiness ↓ Sadness ↑	rTMS to LPFC: Happiness ↓	rTMS to LPFC: Happiness ↓	No mood effects	No mood effects	No mood effects

'Notes. * not reported; **relative change from baseline. MT, individual motor threshold of contralateral abductor brevis muscle; LPFC, left prefrontal cortex; RPFC, right prefrontal cortex; T_0, mood rating at baseline before the stimulation; T_1, mood rating immediately after the stimulation; $T_{minutes}$, mood rating after n minutes after the stimulation (e.g. T_{20} mood rating 20 min after the stimulation).

studies (George et al., 1996; Pascual-Leone et al., 1996; Nedjat et al., 1998) were not sham-controlled, although sham control is particularly important in rTMS studies to control for the marked non-specific effects of the procedure, such as discomfort and noise. In the controlled studies (Dearing et al., 1997; Cohrs et al., 1998), comparison is difficult because sham stimulation was performed with different methods (i.e. angles of the coil 45° or 90°) and consequently with different putative influences on scalp and brain. Sham stimulation in our study was different from that used in the study of Dearing et al. (1997) in order to ensure that no magnetic stimulation of the brain occurred.

Mood effects of prefrontal HF-rTMS were observed with stimulation intensities both above and below the motor threshold. In our study, the stimulation intensity (100% of motor threshold) was in the middle range of the intensities used in the three previous studies (range 80–120%) that reported mood effects (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997). The number of pulses per stimulation site was considerably larger in our study (our study 1600 pulses, previous studies 500-1000 pulses).

In two studies that reported effects on mood (Pascual-Leone et al., 1996; Dearing et al., 1997), different sites were stimulated in the same session. In one study, the number of stimulations per session was not reported (Nedjat et al., 1998). To avoid interaction of mood changes of two different stimulation sites and to exclude interaction of the previous stimulation, only one location should be stimulated per session.

In two of three studies that reported a decrease of happiness after HF-rTMS of LPFC (George et al., 1996; Pascual-Leone et al., 1996), the effect was always reported in comparison to a relative increase of happiness after HF-rTMS of the right prefrontal cortex (RPFC). In the third study (Dearing et al., 1997), the decrease of happiness was only found when comparing HF-rTMS of LPFC with HF-rTMS of RPFC, not by comparing HF-rTMS of LPFC and sham RPFC stimulation. Our data, together with these observations, suggest the interpretation that the reported decrease of happiness after HF-rTMS of the LPFC (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997) is rather a consequence of an interaction of two different prefrontal stimulations than a specific effect of HF-rTMS of the LPFC. For the rating of sadness, the same interaction (i.e. increase of sadness after HF-rTMS of LPFC and decrease of sadness after HF-rTMS of RPFC) has not been found consistently.

All studies investigating mood effects in healthy volunteers have used visual analog scales (VAS) to measure mood changes. However, only two studies (Pascual-Leone et al., 1996; Dearing et al., 1997) found mood changes on VAS by comparing HF-rTMS of the LPFC with HF-rTMS of the RPFC. In one study (George et al., 1996), VAS-assessed mood changes were not observed, and mood effects were apparent only with the modified version of the National Institute of Mental Health (NIMH) mood scale, which includes explicit questions about sadness and happiness.

Although the VAS were the same in all studies (George et al., 1996; Pascual-Leone et al., 1996; Dearing et al., 1997; Cohrs et al., 1998; Nedjat et al., 1998), the time of rating was different. Two studies (George et al., 1996; Dearing et al., 1997) showed that mood ratings are dependent on the time interval after baseline rating. Multiple testing and non-specific effects (e.g. different sensory inputs: events during the course of the day, watching TV, caffeine consumption) can influence mood rating during the day (Rogers and Dernoncourt, 1998) and the interpretation of ratings at long intervals after the stimulation can be difficult. To avoid these biasing effects of VAS rating and because the study of Dearing et al. (1997) found the largest mood changes 20 min after stimulation, mood was rated before and 20 min after stimulation in our study. To exclude possible interaction effects of the five VAS, the scales in our study were presented on individual cardboard cards.

In conclusion, there is insufficient evidence to support the general conclusion that HF-rTMS of the left prefrontal cortex has an effect on mood in healthy volunteers. The mood effects reported in previous studies are small and clinically insignificant, and appear to be a consequence of two different effects of left and right prefrontal stimu-

lation. HF-rTMS would be an extremely useful tool in the assessment of the location of brain circuits involved in the control of mood due to its relative non-invasiveness and its ability to stimulate specific cortical regions. Unfortunately, the body of data published to date does not yet support such use, although variation of parameters such as stimulation amplitude and frequency might lead to that ultimate goal in the near future.

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