

REPETITIVE transcranial magnetic stimulation (rTMS) is a promising new treatment for patients with major depression. However, the mechanisms underlying the antidepressive action of rTMS are widely unclear. Rapid eye movement (REM) sleep has been shown to play an important role in the pathophysiology of depression. In the present study we demonstrate that rTMS delays the first REM sleep epoch on average by 17 min (102.6 ± 22.5 min *vs* 85.7 ± 18.8 min; $p < 0.02$) and prolongs the nonREM–REM cycle length (109.1 ± 11.4 min *vs* 101.8 ± 13.2 min, $p < 0.012$). These rTMS-induced changes in REM sleep variables correspond to findings observed after pharmacological and electroconvulsive treatment of depression. Therefore, it is likely that the capability of rTMS to affect circadian and ultradian biological rhythms contributes to its antidepressive action. *NeuroReport* 9: 3439–3443 © 1998 Lippincott Williams & Wilkins.

Key words: Depression; Polysomnography; Rapid eye movement sleep; REM sleep; Repetitive transcranial

High-frequency repetitive transcranial magnetic stimulation delays rapid eye movement sleep

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Introduction

Among the first and the most frequent symptoms of depression are subjective sleep complaints. These are reflected for the majority of patients with major depression by polysomnographically verifiable sleep disturbance. One of the most robust, though not specific features of sleep in depressed patients is a reduced REM latency.¹ Several of the neurobiological hypotheses of depression are at least partially based on the observation of a shortened REM latency: the REM pressure hypothesis,² the phase advance hypothesis,³ the deficiency of the process S in the two process model of sleep,⁴ as well as the cholinergic–aminergic imbalance hypothesis.⁵ The shortened REM sleep latency in depressive patients is normalized by treatment with antidepressive drugs⁶ and electroconvulsive therapy. A prolongation of REM latency after the first dose of a tricyclic antidepressant⁶ or electroconvulsive therapy⁷ is predictive of a favourable treatment response.

There is growing evidence from clinical studies that the above mentioned strategies for the treatment of

depression will be expanded by repetitive transcranial magnetic stimulation (rTMS). Transcranial magnetic stimulation facilitates non-invasive and painless stimulation of the cerebral cortex by a transient magnetic field of about 1.5–2.5 T, which is produced by a powerful and rapidly changing current passing a small coil of wire placed on the scalp. Currently used stimulators and coils are thought to activate cortical neurons at a depth of 1.5–2 cm directly underneath the coil⁸ and trans-synaptically at some distance from the stimulation site.⁹ Stimulators capable of discharging series of repetitive pulses at high frequencies of up to 60 Hz were applied successfully to humans without significant side-effects, provided that safety margins for stimulus parameters were obeyed.¹⁰

In addition to multifaceted scientific and diagnostic purposes, rTMS was shown to have therapeutic potential in Parkinson's disease¹¹ and in obsessive-compulsive disorder.¹² The most remarkable work, however, was done in patients with depression. Slow-frequency rTMS studies^{13–16} and studies employing high-frequency rTMS to the left prefrontal cortex^{17–20} indicated that rTMS has antidepressive

effects. The high-frequency rTMS studies considered two issues that probably are conceptually relevant for the treatment of depression. First, slow-frequency rTMS at 1 Hz induced a post-stimulation inhibition of the underlying cortex²¹ while high-frequency rTMS at 10–20 Hz increased cortex excitability.²² Second, neuroimaging studies suggested that the pathophysiology of depression is linked to reduced blood flow and cerebral metabolic rate, particularly in the left prefrontal cortex.^{23,24}

Despite the promising therapeutic results from these rTMS trials, the mechanisms of the antidepressive action of rTMS are unclear. On the basis that REM sleep is abnormal in depression, we hypothesized that rTMS induces its antidepressive effect through changes in human REM sleep. In order to find experimental support for this view, we investigated, as a first step, the effects of high-frequency rTMS on REM sleep in healthy human volunteers.

Subjects and Methods

Subjects: Thirteen healthy, drug-free males (mean age 26.9 ± 2.3 years) were carefully screened for physical or mental disease before inclusion into the study. The study was approved by the local ethics committee. Each subject gave written informed consent and was paid an honorarium equivalent of US\$400.

Methods: For transcranial magnetic stimulation a Dantec high-frequency magnetic stimulator (Dantec Medical A/S, Magpro, Skovlunde, Denmark) and a focal 8-shaped coil (outer diameter of each wing 5 cm, maximum magnetic field intensity 1.1 T) were used. Each subject participated in six rTMS sessions, each 5–7 days apart. Sessions started around 18.00 h. In each session, rTMS was applied in 160 trains of five stimuli (20 Hz, intertrain interval 8 s) at an intensity of 120% of the motor threshold of the resting abductor digiti (ADM) muscle. In a single session, one of the following scalp positions was stimulated: (1) Left prefrontal, 5 cm anterior from the optimal site over the left motor cortex to elicit motor evoked potentials in the right ADM; (2) right prefrontal, 5 cm anterior from the optimal site over the right motor cortex to elicit motor evoked potentials in the left ADM; (3) left inferior parietal (P3); (4) right inferior parietal (P4); (5) mid-occipital (Oz); and (6) sham stimulation over the vertex (Cz) with the coil angled at 90° and only the edge of the coil resting on the scalp. All positions except the prefrontal ones were determined according to the 10/20 international electroencephalographic system. The order of stimulation sites was randomized across subjects.

The stimulus parameters used in the present study conform to the currently accepted safety guidelines.¹⁰

All subjects underwent polysomnographic recordings for one night following each rTMS session. The polysomnography included electroencephalography (C3/A2), electrooculogram, submental electromyogram, electrocardiogram, and electromyogram of the anterior tibial muscles. Subjects were allowed to go to bed at their usual bedtime and to get up at their convenience. Sleep was recorded at a paper speed of 10 mm/s on a 21 channel polysomnograph (Nihon Kohden, Japan) and scored according to the standard criteria of Rechtschaffen and Kales²⁵ in 30 s epochs. REM latency was defined as the time between sleep onset (first three epochs of sleep stage 1 or one epoch of any other sleep stage) and the time between lights out and the first REM epoch. The average nonREM–REM cycle length was determined from the first three cycles, the maximum number of cycles exhibited by all subjects during all nights. It included the time between the beginning of nonREM sleep and the end of a REM period. If a REM period was interrupted for less than 15 min by another sleep stage the following REM sleep was considered to belong to the same REM period. Time spent in REM sleep was calculated as percentage of total sleep time.

The study was performed in a double-blinded manner. The two investigators who performed and analysed the sleep recordings were blind for the type of stimulation (active or sham, site of stimulation). The investigator who performed rTMS was blind for polysomnographic recordings and sleep stage analyses. All subjects were naive to the purposes and the hypothesis of this study.

As in previous studies,²⁶ the volunteers rated their mood immediately after the end of each rTMS session, using five 100 mm visual analog scales labeled sadness, anxiety, happiness, tiredness, and pain/discomfort.

Statistics: For descriptive statistics of sleep variables, means and s.d. were calculated. To test for normal distribution, the Kolmogorov–Smirnov test was applied. To determine the overall effect of rTMS on REM sleep variables in comparison to sham stimulation, the mean of all active conditions was calculated and compared with the sham stimulation by a two-tailed paired *t*-test. For comparison of sleep variables between the five stimulation sites and the sham condition, the Friedman repeated measures analysis of variance (ANOVA) on ranks was chosen if the Kolmogorov–Smirnov test showed non-normally distributed data, otherwise a repeated measures ANOVA was applied to all six conditions. For all calculations, the level of significance was set at $p < 0.05$.

Results

Active rTMS induced a significant prolongation of REM latency by on average 16.8 ± 21.6 min for the lights out definition (102.6 ± 22.5 min *vs* 85.7 ± 18.2 min, $t = 2.8$, $df = 12$, $p < 0.02$; paired *t*-test), and 13.9 ± 19.9 min for the sleep onset definition (91.6 ± 22.1 min *vs* 77.7 ± 17.4 min, $t = 2.5$, $df = 12$, $p < 0.03$; paired *t*-test) compared with sham stimulation (Fig. 1). The Friedman repeated measures ANOVA on ranks showed no significant difference for both definitions between any of the stimulation sites or the sham condition. Nevertheless, the strongest effect was seen after left prefrontal stimulation (114.5 ± 41.2 min for the lights out definition with a difference of 28.8 ± 37.0 min from the sham condition and 102.3 ± 43.3 min for the sleep onset definition with a difference of 24.6 ± 37.7 min from the sham condition; Table 1). Effects tended to be more pronounced after left hemispheric stimulation than after right hemispheric stimulation (Table 1).

Active rTMS showed a significant prolongation of the nonREM–REM cycle length compared with sham stimulation (109.1 ± 11.8 min *vs* 101.8 ± 13.8 min, difference 7.3 ± 8.8 min; $t = 3.0$, $df = 12$, $p < 0.012$, paired *t*-test; Fig. 1). Friedman repeated measures ANOVA on ranks for the effect of stimulation site just missed significance ($p = 0.057$).

Total sleep time (ANOVA and paired *t*-test) as well as REM sleep percentage (ANOVA and paired *t*-test) of total sleep time were unaffected by rTMS. REM percentage remained stable at 24% of total sleep time independent of stimulation condition (Table 1).

None of the mood self-ratings on the visual analog scales that were filled out by 12 subjects after stimulation of active sites showed a significant difference to sham stimulation analysed by Friedman repeated measures ANOVA on ranks or after pooling the data and comparing the average of the verum conditions of each subject with the sham condition with the paired *t*-test (Table 2).

One subject experienced a transient mild tension headache after right prefrontal stimulation that stopped after the end of the rTMS session. No other adverse side effects were observed.

Discussion

The major finding of this study is that high-frequency rTMS delayed REM latency and prolonged nonREM–REM cycle length in humans. These results indicate for the first time a marked change in the rather robust system of circadian REM sleep and ultradian nonREM–REM sleep organization by magnetic stimuli applied to the human brain. Due to stimulation of five different brain areas and therefore lack of statistical power, it was not possible to identify a significant effect of one specific rTMS stimulation site on REM sleep parameters. Nevertheless, it is important to point out that the strongest effects on REM latency and nonREM–REM cycle length were seen after stimulation of the left prefrontal cortex. High-frequency rTMS at this site was found to be uniquely effective for the treatment of nonpsychotic and psychotic, monopolar and bipolar as well as medication-resistant patients with major depression.^{17–20}

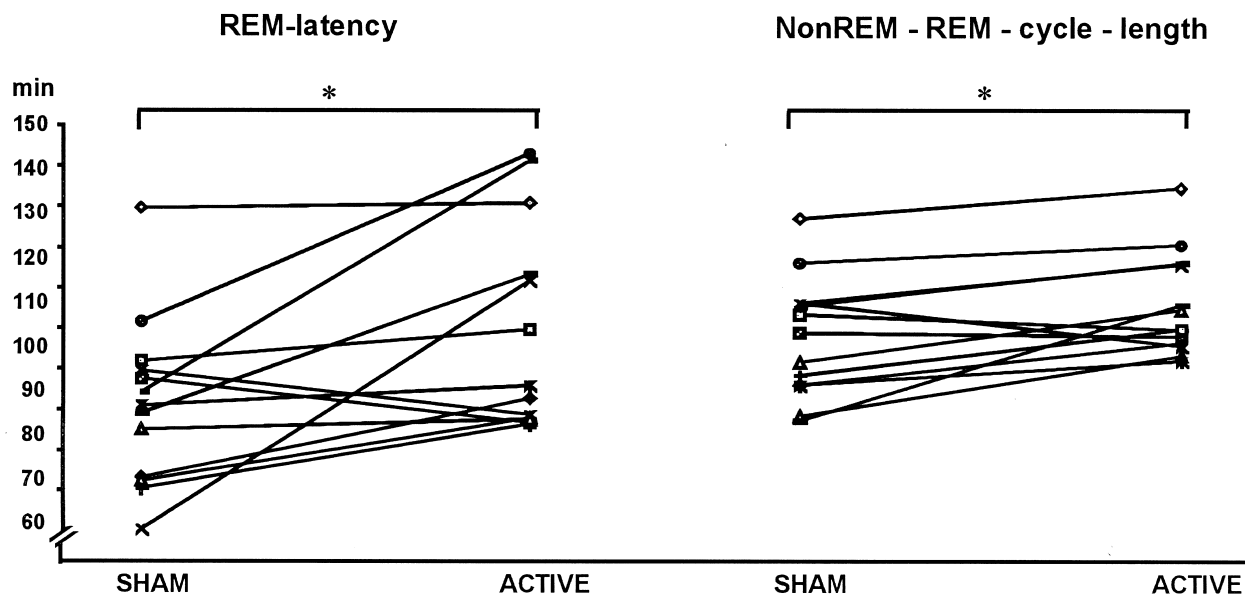


FIG. 1. Comparison of individual REM latency and nonREM–REM cycle length after active rTMS and sham stimulation. Active: pooled data across left prefrontal, right prefrontal, left inferior parietal (P3), right inferior parietal (P4), and midoccipital (Oz) rTMS. Sham: data after rTMS at the vertex (Cz) with the stimulating coil angulated away from the scalp. All data are from 13 healthy subjects. $*p < 0.05$

Table 1. REM sleep parameters (mean \pm s.d.) after active rTMS to different brain regions and sham stimulation.

	Sham	LEPF	RIPF	P3	P4	Oz
REM latency (SO) (min)	77.7 \pm 17.0	102.3 \pm 43.3	87.1 \pm 23.5	99.0 \pm 52.5	90.2 \pm 41.5	79.2 \pm 14.8
REM latency (LO) (min)	85.7 \pm 18.8	114.5 \pm 41.2	100.4 \pm 27.1	106.8 \pm 55.8	100.9 \pm 43.9	90.3 \pm 18.3
NonREM-REM cycle length (min)	101.8 \pm 13.2	115.6 \pm 17.0	111.0 \pm 9.9	107.4 \pm 23.0	109.0 \pm 17.5	102.3 \pm 10.5
REM (%TST)	24.0 \pm 5.8	24.4 \pm 4.7	25.0 \pm 4.2	24.0 \pm 4.0	24.2 \pm 4.4	24.3 \pm 5.5
TST	434.8 \pm 42.8	444.5 \pm 51.8	442.6 \pm 41.4	438.3 \pm 42.5	454.9 \pm 46.1	431.4 \pm 37.5

REM latency defined as the occurrence of REM sleep after sleep onset (SO) or after 'lights out' (LO) in minutes, NonREM-REM cycle length in minutes, and percentage REM sleep of total sleep time (TST). All data are averages from 13 healthy subjects after sham stimulation and stimulation of left prefrontal (LEPF), right prefrontal (RIPF), left inferior parietal (P3), right inferior parietal (P4), and midoccipital (Oz) region.

Table 2. Mood self ratings (mean \pm s.d.) on 100 mm visual analog scales after active rTMS to different brain regions and sham stimulation.

	Sham	LEPF	RIPF	P3	P4	Oz
Sadness	49 \pm 5	45 \pm 13	52 \pm 8.4	48 \pm 3.6	50 \pm 5.7	48 \pm 6.7
Anxiety	49 \pm 2.8	46 \pm 5.8	50 \pm 4.4	47 \pm 3.1	49 \pm 3.9	48 \pm 2.2
Happiness	49 \pm 5.2	49 \pm 7.0	47 \pm 8.4	49 \pm 4.7	48 \pm 8.0	48 \pm 7.6
Tiredness	57 \pm 16	53 \pm 9.7	54 \pm 9.6	58 \pm 13	55 \pm 10	57 \pm 8.7
Pain/Discomfort	48 \pm 6.7	49 \pm 3.5	53 \pm 10	50 \pm 9.2	49 \pm 4.6	52 \pm 3.8

Data are from 12 healthy subjects after sham stimulation and stimulation of left prefrontal (LEPF), right prefrontal (RIPF), left inferior parietal (P3), right inferior parietal (P4), and midoccipital (Oz) region.

The fact that rTMS in the present study induced REM-sleep changes in healthy subjects indicates that these effects *per se* are independent of pre-existing psychiatric disease. rTMS changed the REM-sleep architecture in the same direction as reported for antidepressant drugs in healthy subjects²⁷ and in patients with major depression.²⁸ Therefore, it is probable that rTMS like antidepressant drugs affect the human REM-sleep system in the above mentioned way in healthy subjects as well as in patients with major depression.

Most antidepressants increase aminergic neurotransmission, and some decrease cholinergic neurotransmission. These drugs therefore affect REM sleep according to the reciprocal interaction model of nonREM-REM sleep regulation.²⁹ Since REM latency is either prolonged by enhancing aminergic neurotransmission or by diminishing cholinergic activity the delay in REM sleep in our sample of normal volunteers may have well been due to an rTMS-induced increase of monoaminergic transmission. Concordant with this hypothesis, recent work showed that whole brain rTMS in rats markedly increased the turnover rate of monoamines in the frontal cortex and increased serotonin and its metabolite 5-hydroxyindolacetic acid in the hippocampus.³⁰ Changes in monoaminergic activity play a key role in the widely proven cholinergic-aminergic hypothesis of affective psychosis,⁵ which postulates a neurochemical imbalance in patients with depression in favour of the cholinergic over the aminergic system. Therefore, it is attractive to speculate that rTMS

induces changes in the balance of the monoaminergic-cholinergic system that are important for both the changes in REM sleep found in this study and the antidepressant effects of rTMS.

Further evidence indicates that the prolongation of REM latency by rTMS is likely of crucial importance for its antidepressant effect. It has been stated that the treatment effect of some antidepressant medication is accompanied by a resynchronization of internal circadian rhythms. This is reflected by a normalization of sleep parameters, especially REM latency.⁶ It was also shown that the response to antidepressant drugs⁶ and electroconvulsive therapy⁷ in depression is linked to a prolongation of REM latency. In addition, the present study demonstrated a significant prolongation of the average nonREM-REM cycle after rTMS. Therefore, rTMS affected not only circadian but also ultradian rhythms. We suggest that rTMS mediates its antidepressant effect at least partially by a prolongation of the ultradian period length. This is supported by severely depressed patients in whom not only the REM latency but also the nonREM-REM cycle length was found to be shortened.³¹

We are aware of recent findings that high-frequency rTMS in healthy subjects decreased happiness and increased sadness after left prefrontal stimulation, and decreased sadness after right prefrontal stimulation.^{26,32} In the present study, rTMS did not affect mood ratings, indicating that the observed effects of rTMS on REM sleep were not due to acute changes in mood. The reason for the

discrepancy between our study and the previous two reports is currently unclear, but may be related to differences in the rTMS equipment and the stimulus parameters used, and different experimental settings.

Conclusion

The observed changes in REM sleep provide suggestive evidence that therapeutic effects of rTMS in depression are based on measurable biological mechanisms. It is likely that the capability of rTMS to affect circadian and ultradian biological rhythms contributes to its antidepressive action. Future studies in patients should clarify whether the effect of rTMS on sleep parameters is essential for treatment efficacy and treatment prognosis in major depression.

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