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The influence of the repetitive transcranial magnetic stimulation on sleep quality in depression

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Summary

Aim. Repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. In this study we investigated whether the depression-related insomnia is modulated by this therapeutic method.

Methods. We examined 13 patients (mean age 50.6±13.9; 11 women) with bipolar or unipolar depression. During 20 consecutive days, excluding Saturdays and Sundays, they underwent 20 daily sessions of 10 Hz rTMS over the left dorsolateral prefrontal cortex (DLPFC). Outcome measurement included the Clinical Global Impression (CGI), the 21-item Hamilton Depression Rating Scale (HDRS), the Athens Insomnia Scale (AIS) as well as sleep diary and actigraphy.

Results. After rTMS, the CGI and HDRS total score decreased significantly. Also, the insomnia-related items of HDRS improved. The AIS showed trend towards decrease. No significant changes were present in sleep diaries and actigraphy.

Conclusions. The beneficial effect of rTMS on the mood in depression has been confirmed. The rest of the results suggest high frequency rTMS to the left DLPFC does not have strong effects on sleep quality in patients with depression. Additional interventions or modification of the rTMS protocol should be considered to improve insomnia in these patients.

Key words: insomnia, left dorsolateral prefrontal cortex, actigraphy

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Introduction

During the last decade, the repetitive transcranial magnetic stimulation (rTMS) became a well established therapeutic method for the drug-resistant depression [1–3]. The stimulation over the left dorsolateral prefrontal cortex (DLPFC) with frequency between 5 and 20 Hz is now considered to have a definite (evidence level A) antidepressant effect [4]. This statement is based mainly on two multisite large studies [5, 6]. Active stimulation is clearly superior to placebo with the effect size amounting to 0.87 in the methodologically best studies [7]. The appropriate government agencies of about ten countries accepted this method to treat the drug-resistant depression [4]. However, some authors question these results pointing out that the placebo stimulation perfectly imitating the therapeutic one is virtually impossible [8]. Moreover, the Polish researchers did not confirm antidepressant potential of rTMS [9].

While majority of rTMS studies focused on the overall effectiveness in the depressive syndrome, its influence on the particular symptoms has usually been beyond their scope. Among these symptoms are sleep disturbances. The most frequent of them is sleeplessness, reported by 83% of depressive patients from the large (> 8,000) sample examined in the UK [10]. Hypersomnia, found in 10 to 40% of patients, is less frequent but also important [11, 12]. Sleep disorders independently decrease quality of life [13] and increase the risk of suicide [14]. Similarly to lowered mood, sleep disorders often do not respond to pharmacotherapy [15]. The aim of this study is, therefore, to investigate whether rTMS has the therapeutic effect on insomnia associated with depression.

Material

This was a prospective, open study. Investigations were made between 2010 and 2014. All patients included in the study provided written informed consent. The study protocol has been accepted by the appropriate bioethics committee.

Inclusion criteria were as follows:

- diagnosis of depressive episode associated with major depressive disorder (MDD) or bipolar affective disorder (BD) according to 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10);
- lack of response to pharmacological treatment – in patients with MDD defined as failure to respond to two different, adequate therapy trials of antidepressant medication and for BD with concomitant use of mood stabilizer [16];
- age between 18 and 70;
- insomnia defined as the score of ≥ 6 points in the Athens Insomnia Scale (AIS) [17].

Exclusion criteria were as follows:

- seizure-like changes in the EEG performed not earlier than three months before inclusion;
- contraindications to rTMS listed by the International Federation of Clinical Neurophysiology (IFCN), i.e., seizure in the past, pregnancy, metal in the body (except dentures and titanium), cochlear implants, implanted neurostimulator, cardiac pacemaker, intracardiac lines, medication infusion device, surgical procedures to the spinal cord in the past, complications associated with the past TMS or MRI [18];
- severe unstable neurological or internal diseases;
- psychotic features during the current episode;
- suicidal ideations;
- history of substance abuse or addiction.

Before the study all patients underwent a detailed interview and neurological investigation, as well as ECG and routine laboratory test, including: TSH, liver enzymes and electrolytes, were performed. EEG and neuroimaging (magnetic resonance imaging or computer tomography) were performed in every patient not earlier than three months before rTMS.

Method

rTMS

Stimulation was done with the Magstim Super Rapid^2 stimulator (Magstim Company Ltd, Whitland, South West Wales, UK) connected to a figure of eight, air cooled coil with peak magnetic field of 0.93 Tesla. Stimulated area was the left DLPFC. According to previous studies, this area was identified as the point located 5 cm anteriorly to the "hot spot" for the right abductor digiti minimi muscle. "Hot spot" for a given muscle is the site on the scalp where TMS pulses produce motor evoked potentials (MEP) of maximum amplitude recorded by the electrode located on the body of the muscle (and the corresponding reference electrode) [19, 20]. The stimulation strength was 110–120% of the resting motor threshold (RMT). RMT is the weakest stimulus intensity which is able to produce MEP of amplitude ≥ 50 μV after at least five of ten elicited TMS stimuli in the "hot spot" [21].

The therapy included 20 sessions performed on the subsequent week days. A single session contained 3,000 pulses elicited with 10 Hz frequency, divided into 75 trains; each train contained 40 pulses. The trains were separated with intervals lasting 26 seconds. During sessions, the subjects were in semi-recumbent position, in a comfortable armchair. They were provided with ear plugs to protect them against the noise of the stimulator and the coil-cooling machine. Antidepressant pharmacotherapy has

been maintained unchanged from at least four weeks prior to rTMS beginning until the assessment after the last session. In general, the stimulation protocol was similar to previously used ones [22, 23].

Assessment of depressive symptoms and sleep quality

Before the first and after the last rTMS session, patients filled out the AIS, which is an eight-item scale concerning the sleep quality and its derivatives, i.e., the quality of wellbeing, physical and mental fitness, and daytime sleepiness. In the AIS, the increasing score means the worse sleep quality and the maximum score is 24 [17]. The raters (psychiatrists experienced in affective disorders) performed assessment with the Clinical Global Impressions (CGI) [24] and with the 21-item Hamilton Depression Rating Scale (HDRS) [25]. Severity of depression has been assessed on the basis of total score of the items 1 to 17. Items 4 to 6 which examine the sleep quality were analyzed separately.

Five to seven days before the first and the same period after the last rTMS session, the patients kept sleep logs which contained time of going to bed and getting up, subjective sleep onset latency, subjective assessment of sleep length and information about unusual events and medications not included in the pharmacotherapeutic plan. Along with keeping the sleep log, patients wore an actigraph (Actiwatch AW4, CamNtech Ltd., Cambridge, UK) on the non-dominant wrist. Actigraph is a small and light accelerometer which is able to register movements of the extremity. In this experiment acceleration counts were accumulated every 30 seconds. Patients were instructed to remove the actigraph only for shower, bath or swimming.

Analysis of the collected activity measurements was done with appropriate software – Sleepwatch (CamNtech Ltd., Cambridge, UK). On the basis of this analysis we calculated the following sleep parameters: sleep onset latency (SOL), sleep efficiency (SE), fragmentation index (FI), mean 24 h activity (M24hA), mean daytime activity (MDA), and mean nocturnal activity (MNA). SOL is the time from lights out to the beginning of sleep. SE is the percentage of the time spent asleep to the whole time spent in bed. FI is the mean number of the sleep fragmenting events (physical activity) per hour of sleep. M24hA is the mean number of acceleration counts per minute during 24 h. MDA is the mean number of acceleration counts per minute during the time out of bed. MNA is the mean number of acceleration counts per minute during the time in bed.

Statistics

The HDRS total score (items 1 to 17), subscores of the three items concerning sleep quality (sleep initiation, sleep maintenance, early morning awakening), the CGI and the AIS score, as well as the parameters derived from sleep log and actigraphy

measurements before and after rTMS were compared using the Wilcoxon signed-rank test. Calculations were made with the StatSoft, Inc. (2008) STATISTICA data analysis software system, version 12.0. All values are expressed as the mean and standard deviation (*SD*). The significance level was $p < 0.05$.

Results

We included 13 patients (mean age 50.6 ±13.9; 11 women). All patients suffered from depressive episode in major depressive disorder or bipolar affective disorder, not due to a medical condition or induced by a substance. Their characteristics are presented in Table 1. Except two, they were inpatients. It was difficult to define precisely the number of previous depressive episodes, especially in bipolar patients (due to highly changing course of the illness). The mean number of prior hospitalizations was 5.3 ± 4.1. Patients failed to respond to 3.5 ± 1.94 adequate antidepressant trials during the current episode. Two patients had comorbid personality disorder (F60.9 according to ICD-10). The AIS was not performed in one patient.

Table 1. **Sociodemographic and clinical characteristics of the study group**

No.	Age	Gender	Age at the illness onset	Duration of the last episode (months)	Diagnosis	Pharamcotherapy
1.	43	M	23	36	MDD	venlafaxine 300 mg
2.	54	F	26	4	BD	lamotrigine 75 mg, lithium 750 mg, olanzapine 5 mg, escitalopram 10 mg, promethazine 100 mg
3.	34	F	19	2	MDD	reboxetine 10 mg, risperidone 3mg
4.	52	F	37	5	BD	amitriptyline 250 mg, lithium 500 mg, memantine 10 mg
5.	26	M	18	24	MDD	citalopram 40 mg, lamotrigine 100 mg
6.	41	F	31	14	MDD	venlafaxine 150 mg
7.	69	F	59	7	BD	reboxetine 6 mg, olanzapine 5 mg, zolpidem 10 mg, promethazine 75 mg
8.	37	F	20	21	BD	amitriptyline 100 mg, lithium 1,250 mg
9.	55	F	50	5	MDD	paroxetine 30 mg, mirtazapine 15 mg

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10.	54	F	40	7	BD	fluoxetine 20 mg, olanzapine 10 mg, promethazine 50 mg
11.	67	F	58	7	BD	vortioxetine 10 mg, mirtazapine 30 mg, bupropion 300 mg, valproate 600 mg, lorazepam 1 mg, promethazine 25 mg
12.	71	F	57	5	MDD	reboxetine 12 mg, olanzapine 5 mg
13.	55	F	38	2	BD	lithium 750 mg, venlafaxine 225 mg, olanzapine 15mg, estazolam 2 mg, promethazine 50 mg
m*	50.6	11 F	36.6	10.6	6 MDD	
SD*	13.9	2 M	15.4	10.3	7 BD	

*where appropriate; m – mean; SD – standard deviation; F – female; M – male; MDD – major depressive disorder; BD – bipolar affective disorder

After rTMS, the HDRS and CGI scores decreased. Also the HDRS items concerning the sleep quality also decreased. The AIS showed a trend towards improvement. No significant changes were present in parameters derived from sleep diary and from actigraphy. All results obtained before and after intervention are presented in Table 2.

Table 2. **Results**

	All participants				MDD		BD	
		Mean	SD	p	Mean	SD	Mean	SD
HDRS	before rTMS	19.5	4.2		18.3	4.2	20.4	4.2
	after rTMS	11.2	7.2	<0.01	14.2	8.2	8.7	5.7
	change in %	-43%			-22%		-57%	
Item 4 – sleep initiation	before rTMS	1.2	0.9		1.0	0.9	1.3	1.0
	after rTMS	0.7	0.9	<0.05	0.7	1.0	0.7	0.8
	change in %	-40%			-33%		-44%	
Item 5 – sleep maintenance	before rTMS	0.8	0.8		0.8	0.8	0.9	0.9
	after rTMS	0.4	0.8	<0.05	0.5	0.8	0.3	0.8
	change in %	-55%			-40%		-67%	
Item 6 – early morning awakening	before rTMS	0.9	0.9		0.7	0.8	1.1	0.9
	after rTMS	0.2	0.4	<0.05	0.3	0.5	0.1	0.4
	change in %	-75%			-50%		-88%	

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CGI	before rTMS	4.2	0.6		3.9	0.5	4.4	0.5
	after rTMS	2.8	1.2	<0.01	3.4	1.1	2.2	1.0
	change in %	-34%			-13%		-50%	
AIS	before rTMS	11.3	3.9		12.4	4.5	10.6	3.5
	after rTMS	9.7	5.3	=0.07	12.0	4.8	8.0	5.3
	change in %	-15%			-3%		-24%	
Data from sleep diaries								
SOL	before rTMS	0.9	0.6		0.8	0.6	1.0	0.6
	after rTMS	1.1	0.5	ns	0.8	0.5	1.3	0.5
	change in %	16%			1%		27%	
Total sleep duration	before rTMS	7.3	1.9		6.4	1.3	7.8	2.1
	after rTMS	7.5	1.4	ns	6.8	0.7	8.2	1.5
	change in %	4%			5%		5%	
Data from actigraphy								
SOL	before rTMS	28.0	12.3		23.8	4.7	31.6	15.8
	after rTMS	29.2	11.8	ns	27.0	8.1	31.0	14.6
	change in %	4%			13%		-2%	
SE	before rTMS	83.5	5.7		83.1	6.2	83.8	5.8
	after rTMS	83.6	6.0	ns	83.8	6.4	83.5	6.2
	change in %	0%			1%		0%	
FI	before rTMS	31.7	13.2		32.6	15.0	30.9	12.6
	after rTMS	33.3	12.8	ns	29.5	13.0	36.6	12.6
	change in %	5%			-9%		19%	
M24hA	before rTMS	177.4	82.7		200.1	114.2	157.9	43.1
	after rTMS	173.8	70.6	ns	167.8	95.2	179.0	48.6
	change in %	-2%			-16%		13%	
MDA	before rTMS	274.0	118.8		299.9	168.1	251.8	58.5
	after rTMS	270.1	107.7	ns	252.5	143.7	285.2	73.6
	change in %	-1%			-16%		13%	
MNA	before rTMS	20.4	11.3		21.3	13.8	19.6	9.9
	after rTMS	20.1	10.7	ns	19.7	12.7	20.4	9.8
	change in %	-1%			-7%		4%	

MDD – major depressive disorder; BD – bipolar affective disorder; HDRS – Hamilton Depression Rating Scale; CGI – Clinical Global Impressions; AIS – Athens Insomnia Scale; SOL – sleep onset

latency (in hours); SE – sleep efficiency; FI – fragmentation index; M24hA – mean 24 h activity (per minute); MDA – mean daytime activity (per minute); MNA – mean nocturnal activity (per minute).

Due to similar amount of patients with MDD and BD (6 vs. 7), we performed a post hoc comparison of the influence of rTMS within both sub-groups. Their small size allowed only descriptive comparison, which is presented in Table 2. Another post hoc comparison included the influence of rTMS on severity of groups of depressive symptoms extracted from the HDRS according to Cole and Motivala model [26]. They include the core symptoms (items 1–3), insomnia (items 4–6), anxiety (items 9–13, 15), and "somatic" factor (items 7, 8, 14, 16, 17). Statistical analysis showed improvement within all four groups of symptoms. It is summarized in Table 3.

Table 3. **Influence of rTMS on severity of groups of depressive symptoms extracted from the HDRS according to Cole and Motivala model [26]**

	before rTMS		after rTMS		p
	Mean	SD	Mean	SD	
Core symptoms (items 1–3)	4.6	1.1	2.3	1.8	0.003
Insomnia (items 4–6)	2.9	2.3	1.3	2.0	0.028
Anxiety (items 9–13, 15)	7.0	1.6	4.0	3.0	0.012
"Somatic" factor (items 7, 8, 14, 16, 17)	5.1	1.4	3.6	1.8	0.021

HDRS – Hamilton Depression Rating Scale

Discussion

The results indicate that rTMS rather does not have a potential to improve the objective sleep quality in depression. The beneficial effect of rTMS on depressive symptoms has been confirmed. Improvement observed in the group of symptoms related to the sleep quality in the HDRS as well as the trend towards improvement in the AIS should be attributed rather to the subjective sleep perception.

This result may be seen as unexpected since rTMS improved sleep in Parkinsonian patients [27]. In depressive patients it was reported that rTMS locally enhances EEG delta activity and delays REM sleep [28, 29]. Such changes allowed expecting that rTMS can improve sleep continuity, normalize sleep architecture and enhance restorative value of sleep.

We consider several reasons to explain why our results did not meet these expectations. The first one can be the genetic factors, in particular the altered expression of genes which code the modulation of the endogenous circadian cycle (e.g., miRNA-182). These genes interact with the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus and which is considered to be the main synchronizer of the human circadian rhythm [30]. To the best knowledge of the authors, the influence of

rTMS on SCN has never been assessed. However, considering the known fact that the magnetic field induced by rTMS does not excite the subcortical structures [21], we speculate that the alteration of the circadian rhythm induced by SCN cannot be influenced by rTMS.

Moreover, the increase of the metabolic activity of the left prefrontal cortex, which is likely to occur along with the high frequency stimulation of this area [31], may attenuate the possible sleep-promoting effect of rTMS. This speculation is derived from the observation that in healthy individuals the cerebral metabolism decreases during the NREM sleep in frontal, parietal and temporal areas [32]. In depressive patients the influence of sleep on metabolism in these areas is significantly smaller [33]. By increasing the metabolic rate, rTMS may aggravate the previously described abnormality present in patients with depression. In this light, the alternative stimulation protocol for depression, which involves the low frequency stimulation of the right DLPFC, might be associated with better outcome.

Another explanation for lack of improvement in objective sleep quality may be related to the fact that in many patients insomnia is precipitated not by illness-related factors but, first of all, by behavioral factors, e.g., low physical activity during the day and long time spent in bed [34]. In our study, variables related to this behavior, e.g., low motor activity during the day as well as decreased sleep efficacy did not change despite improvement of depressed mood. Those factors should be addressed by cognitive-behavioral interventions for successful insomnia treatment. However, one should be aware that the subjective improvement of sleep quality seen in our patients also contains therapeutic value. The subjective sleeplessness is a very frequent problem in the Polish and general population, significantly reducing daily performance [35].

Due to the small sample sizes, the analysis of the effect of rTMS within subgroups with MDD and BD has only speculative character. RTMS seems to have greater impact on mood and subjective sleep quality in BD patients. Regarding actigraphic measurements, rTMS seems to increase the motor activity in the BD and decrease it in the MDD group. These results need, however, to be replicated on the groups of proper size.

Limitations of the study

The small size of the sample might decrease the sensitivity to the possible beneficial effect of the intervention on sleep. Especially the observed trend towards reduction of insomnia in the AIS could convert into significant change after recruitment of more patients. No trends were, however, observed in the actigraphic measurements. Treatment with sleep-promoting medication and mood stabilizers during stimulation could further reduce the sensitivity of the measurements and effect of treatment. However, it must be emphasized that despite the treatment, the severity of sleep disturbances assessed

using the AIS was similar to baseline diagnosis of insomnia and the used medication was therefore insufficient. Moreover, we have not done a follow up. It is theoretically possible that an assessment of the sleep quality several weeks after rTMS could reveal different results than those measured directly after the intervention. This speculation is based on the experiences with several antidepressants (e.g., venlafaxine) which, similarly to rTMS, increase the activity of the left DLPFC. According to some reports, they initially worsen the sleep quality but after several weeks interval improve it [36]. Finally, the lack of the control group makes it impossible to separate the therapeutic effect from the placebo one, as well as from the effect of the regression towards the mean which may be associated with spontaneously remitting episode.

Conclusions

This study confirmed the potential of high frequency rTMS to the left DLPFC in improving the mental condition of depressive patients (although without placebo control). The objective sleep quality of depressive patients was not observed. Neurobiological mechanisms, such as lack of the effect of rTMS on SCN as well as a tendency to increase the metabolic rate of DLPFC by the stimulation protocol used in the study along with the behavioral factors precipitating insomnia are the possible reasons of this negative outcome. Likely, the small size of the study group may also contribute to the observed lack of the effect of rTMS on subjective sleep quality.

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