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The Influence of Repetitive Transcranial Magnetic Stimulation on Sleep in Parkinson's Disease

JAKUB ANTCZAK[1,*], MARIA RAKOWICZ[1], MARTA BANACH[1], MIROSŁAWA DEREJKO[1], JAKUB SIENKIEWICZ[2], URSZULA ZALEWSKA[1], MAŁGORZATA WIĘCŁAWSKA[1], WOJCIECH JERNAJCZYK[1]

[1] *Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland*
[2] *Department of Neurology, Medical University of Warsaw, Warsaw, Poland*

Sleep disturbance is common in Parkinson's disease (PD). In this study we investigated the effect of a novel therapeutic tool, repetitive transcranial magnetic stimulation (rTMS) on sleep quality in PD patients. The study group consisted of 11 PD patients who underwent ten daily rTMS sessions at 15 Hz. Their sleep patterns were monitored with polysomnography. After the stimulation, non-REM stage-1 sleep and the number of nocturnal arousals decreased, thus improving sleep quality. These changes were probably related to the improvement of motor symptoms observed in UPDRS and in the 9 Hole peg test.

K e y w o r d s: Parkinson's Disease, repetitive transcranial magnetic stimulation, sleep, polysomnography, motor symptoms

1. Introduction

Complaints of disordered sleep are reported in 60 to 98% of Parkinson's disease (PD) patients [1], being one of the most frequent non-motor symptoms and contributing significantly to the decreased quality of life in PD [2]. While, usually having no problem falling asleep [3], PD patients suffer mostly from impaired sleep maintenance and increased sleep fragmentation [4]. The nocturnal recurrence of motor symptoms, including rigidity and dystonia, is one of the factors contributing to poor sleep quality [5]. Among other causes are PD related neurodegeneration, which involves the

* Correspondence to: Jakub Antczak, EMG Laboratory, Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, ul. Sobieskiego 9, 02–957 Warsaw, Poland, e-mail: antczak@ipin.edu.pl
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sleep specific areas in brainstem and hypothalamus [6], and the arousing effect of the dopaminergic medication [7]. Finally, an increased prevalence of periodic limb movements, REM sleep behaviour disorder (RBD) and other sleep-disturbing conditions have been documented in PD [8, 9].

Repetitive transcranial magnetic stimulation (rTMS) is a relatively novel non-invasive therapeutic tool in which repetitive pulses of magnetic field are applied over assigned cortical areas. In PD, the stimulation of primary motor cortices has resulted in significant improvement in motor symptoms lasting approximately six weeks [10, 11]. A positive effect was also found for PD associated depression and cognitive dysfunction when stimulation was applied over prefrontal cortex [12, 13]. The effect on sleep was investigated with a self assessment scale by Khedr and colleagues [14] who found improvement after the stimulation applied over primary motor cortex (PMC). A more recent study reported objective improvement of patients' sleep profile after the stimulation over parietal cortex but not over PMC [15]. However in that study sleep was recorded with actigraphy, a diagnostic tool considered to be less sensitive than nocturnal polysomnography (PSG), especially in determining the percentage of particular sleep stages, occurrence of EEG arousals and the presence of sleep-related breathing disorders [16, 17]. The improvement of sleep quality after the stimulation over parietal cortex was explained by documented involvement of this area in sleep regulating processes [18]. The stimulation of PMC may improve sleep as an outcome of the alleviation of motor symptoms.

The aim of our study was to analyse the influence of rTMS on sleep quality in patients with Parkinson's disease using nocturnal polysomnography.

2. Material and Methods

2.1. Patients

We investigated 11 PD patients who were recruited from the neurological outpatient clinic and from the First Neurologic Department of the Institute of Psychiatry and Neurology in Warsaw, and from the Medical University Hospital Bródno (Warsaw) from June 2007 to March 2009. All patients fulfilled the criteria of the U.K. Parkinson's Disease Brain Bank Criteria for idiopathic PD [19] and were in a disease stage from I to III according to Hoehn & Yahr [20]. The patients were examined in the "ON" stage, since their antiparkinsonian medication remained unchanged during the month preceding the stimulation and throughout the whole period of the stimulation. Patients were not included in the study if they had changes in neuroimaging suggesting symptomatic Parkinsonism, cognitive deficits (MMSE<26), or contraindications for rTMS, i.e., metallic implants and a positive history of seizure. The demographic and clinical data are summarized in Table 1.

Table 1. Demographic and clinical data

No	Gender	Age	Disease duration (years)	Dom. hand	Initial side	Dom. sympt.	LDOPA (mg)	Other PD medication (mg)
1	f	74	11	dex	dex	tremor	800	
2	f	75	13	dex	dex	mixed	600	Amantadine 100
3	f	70	2	dex	dex	tremor	0	
4	f	66	6	dex	dex	rigidity	1440	Ropinirole 6
5	f	50	14	dex	dex	rigidity	950	
6	m	48	2	dex	dex	mixed	0	
7	m	73	5	dex	sin	rigidity	600	Amantadine 200
8	m	71	4	sin	dex	mixed	0	Ropinirole 9
9	m	54	4	dex	sin	rigidity	400	Ropinirole 6, Amantix 200, Selegiline 10
10	m	61	10	dex	dex	rigidity	1500	Piribedil 15
Mean		64.2	7.1				629.0	
SD		10.3	4.5				556.7	

2.2. Clinical Investigation

The subjective sleep assessment was done with the Parkinson's Disease Sleep Scale – PDSS [21]. The motor function was evaluated using the Unified Parkinson's Disease Rating Scale – UPDRS [22] (Parts II–IV) and the 9 Hole Peg Test (Handy Healthcare Ltd. UK), a tool to examine the fine motor performance in which a subject is instructed to fit nine pegs into holes of 5 mm diameter as quickly as possible. Two attempts for each hand were timed and the total completion time was averaged.

The potential mood changes under rTMS were assessed with the Hamilton Depression Rating Scale (HDRS) [23]. All examinations were conducted one to three days before rTMS started and one to six hours after the 10^{th} session of rTMS finished.

Patients were examined in the "ON" stage. Medication was not changed during the month preceding the stimulation and during the whole period of the stimulation.

2.3. Polysomnography (PSG)

The nocturnal PSG was done during the night preceding the rTMS treatment and during the night following completion of the stimulation. Six patients received unattended ambulatory polysomnographies (PSGs) recorded on an Aura PSG amplifier (Grass Telefactor USA). The remaining subjects received attended PSGs that were

obtained in the Department of Clinical Neurophysiology of the Institute of Psychiatry and Neurology with the use of the Aura PSG or Comet XL amplifier (Grass Telefactor USA). A consistent mode of the PSG examination was used for each patient before and after the stimulation. One unrecorded "adaptation night" was included before the start of PSG.

All recordings included an electroencephalogram from C3, C4, O1, O2 electrodes, an electrooculogram and EMG activity from the mentalis muscle. Air flow was monitored with the nasal prongs and the respiratory effort was measured with either inductance bands (Comet XL) or piezo inductive bands (Aura PSG), placed around the thorax and abdomen. Nocturnal oxygen saturation was measured with a finger oximeter. The motor leg activity was monitored using the tibialis anterior EMG recorded with surface electrodes.

The recording time for analysis was 8 hours (960 epochs) following lights out, defined as the time in bed (TIB). All recordings were scored manually for sleep stages according to the modified standard criteria [24]. Sleep efficiency (SE) was defined as the percentage of time spent asleep compared to TIB, sleep onset latency (SOL) as the time from the lights out to the first epoch of the sleep stage N2. The definition of REM latency was the time from the lights out to the first epoch of REM sleep minus SOL. The wake after sleep onset (WASO) was defined as the time spent awake after the first epoch of the sleep stage Non-REM 2 (N2). The REM%, N1%, N2% and N3% were defined as the ratio of the time spent in a given sleep stage to the total sleep time (TST). TST was calculated as the TIB minus WASO. An arousal from sleep was scored when a sudden change in EEG activity occurred that lasted more than three seconds and less than half of the epoch [25]. Nocturnal respiration was assessed according to the American Academy of Sleep Medicine (AASM) criteria [26] and motor activity of the lower limbs using the International Restless Legs Syndrome Study Group (IRLSSG) criteria [27].

2.4. Repetitive Transcranial Magnetic Stimulation

The rTMS stimulation was performed using a Magstim Super Rapid^2 stimulator (Magstim Company Ltd, Whitland, South West Wales, UK), with a figure of eight air cooled coil with peak magnetic field of 0.93 Tesla.

Using a single pulse TMS, researchers located the optimal stimulation area for the contralateral abductor digiti minimi muscle (ADM) and established the resting motor threshold (RMT). Intensity of RMT (measured in percentage of the maximum stimulator output) was equal to the lowest stimulus intensity that was able to generate the motor evoked potential from the contralateral abductor digiti minimi muscle (ADM) in an amplitude range between 50 and 120 μV in at least five out of ten consecutive stimulations [29].

Motor evoked potential (MEP) amplitude and central silent period (CSP) from the contralateral ADM prior to and after the rTMS sessions were evoked

with a single pulse TMS at an intensity of 125% of RMT. The MEP of the highest amplitude after four stimulations was selected for analysis. The CSP was defined as the period of voluntary EMG activity suppression after the TMS. The value presented here was the length of the suppression period averaged from three stimulations.

The treatment protocol consisted of ten consecutive daily sessions of 15 Hz rTMS applied bilaterally over the primary motor areas at an intensity of 120% of the resting motor threshold (RMT) unless the RMT exceeded 67%. In those cases, the rTMS was set to 80% intensity of the maximum stimulator output. rTMS consisted of 40 trains of 50 pulses each, separated by 10-second intervals. Each session contained 4000 pulses. The stimulation and the measurements of cortical excitability were done in the "ON" stage as previously described. During the stimulation, the patients rested in a comfortable, semi-recumbent position and were protected with ear plugs from the noise created by the cooling device.

2.5. Statistical Analysis

Results from the clinical investigation and from PSG obtained prior to and after rTMS were compared. We also compared the MEP and CSP results from the first and tenth sessions after averaging the values for both ADM and for pre-and post- rTMS measurements of the appropriate hemispheres. The descriptive results are expressed as mean value and SD (±).Statistical analysis was conducted using the Wilcoxon test with the STATISTICA V. 8.0 software (StatSoft, U.S.A.). The confidence level was set at $P < 0.05$.

2.6. Ethics

All patients gave written informed consent. The study protocol had been previously approved by a local ethics committee.

3. Results

3.1. Changes in Motor Symptoms, Mood and Cortical Excitability After rTMS

Ratings of the motor function decreased on Part II of the UPDRS after the stimulation but not on Part III or Part IV (12.2 ±5.3 to 7.4 ±3.7 $p < 0.03$). Also the summarized score of parts II–IV decreased from 28.7 ±12.7 to 19.5 ±10.6 ($p < 0.03$). Scores on the 9-Hole Peg Test improved for the non-dominant hand (20.5 ±3.3 vs 18.3 ±2.8 sec $p < 0.05$). Mood as measured by the HDRS did not change under rTMS (Table 2). Cortical excitability altered in terms of the increased MEP amplitude (from 1.5 ±0.9 mV to 2.5 ±1.3 mV $p < 0.01$) without any accompanying change in CSP (Table 2).

Table 2. Changes in motor signs, mood and cortical excitability after rTMS

	Before rTMS	After rTMS	Significance
UPDRS part:			
II	12.2 ± 5.3	7.4 ± 3.7	$p<0.03$
III	11.6 ± 7.5	8.2 ± 6.6	ns
IV	4.9 ± 3.1	3.9 ± 3.2	ns
II-IV	28.7 ± 12.7	19.5 ± 10.6	$p<0.03$
9 Hole Peg Test (sec)			
Dominant hand	18.4 ± 3.9	17.5 ± 3.6	ns
Nondominant h.	20.5 ± 3.3	18.3 ± 2.8	$p<0.05$
HDRS	6.7 ± 5.4	5.9 ± 4.7	ns
MEP (mV)	1.5 ± 0.9	2.5 ± 1.3	$p<0.01$
CSP (ms)	96.7 ± 35.7	97.3 ± 26.0	ns

rTMS – repetitive transcranial magnetic stimulation; UPDRS – Unified Parkinson's Disease Rating Scale; HDRS – Hamilton Disease Rating Scale; MEP – motor evoked potential; CSP – central silent period

3.2. Changes in Polysomnographic Parameters and in Subjective Sleep Assessment Under rTMS

The rTMS reduced episodes of light sleep (N1%) (20.0 ±8.4 vs 12.0 ±5.7 % $p < 0.01$) and the arousal index (AI) (12.2 ±9.0 vs 8.7 ±6.3 $p < 0.04$). The rTMS also improved the subjective sleep assessment as reflected by the increase in PDSS score (95.8 ±23.4 vs 106.4 ±24,6 $p < 0.02$) (Table 3). There were no changes after the stimulation to other polysomnographic parameters including the nocturnal respiration and the leg movements (Table 3).

A 72-year-old man was removed from the study after developing a myocardial infarction, after completion of the fifth rTMS session. Prior to rTMS he had no documented history of cardiac problems except for occasional chest pain, which was recorded in the study admission interview, and had presented no signs of cardiac failure. On admission to the clinic, before the start of rTMS, his ECG and laboratory tests had been normal. In the morning that followed the fifth session (done between 9:00 and 10:00 a.m.) he started to complain about chest pain, which was initially reactive to nitrates, and presented with the normal cardiac panel and ECG. The further rTMS sessions were suspended. During the next three days, the symptoms worsened, i.e., increased chest pain and ischemic changes in the ECG; however, the patient refused the heart catheterization. On the fourth day after his last rTMS session, the ECG showed an evolving infarction and the patient was transported to a cardiac intensive care unit.

All other subjects who underwent the stimulation completed the study with good tolerance of the rTMS and without adverse events.

Table 3. Changes in polysomnography and PDSS after rTMS

	Before rTMS Mean ± SD	After rTMS Mean ± SD	Significance
TST (min)	284.9 ± 96.9	293.9 ± 112.4	ns
SOL (min)	51.5 ± 44.2	45.5 ± 40.2	ns
WASO (min)	133.7 ± 38.9	119.9 ± 59.4	ns
SE (%)	59.8 ± 18.9	62.1 ± 21.7	ns
REM latency (min)	163.7 ± 104.7	102.6 ± 62.2	ns
N1%	20.0 ± 8.4	12.0 ± 5.7	$p < 0.01$
N2%	45.2 ± 11.2	48.5 ± 11.3	ns
N3%	21.4 ± 13.2	23.7 ± 15.6	ns
REM%	13.4 ± 10.0	15.8 ± 11.3	ns
Arousal index	12.2 ± 9.0	8.7 ± 6.3	$p < 0.04$
AHI	1.9 ± 4.5	2.2 ± 3.5	ns
min SaO_2	89.8 ± 1.0	89.2 ± 3.5	ns
PLM index	3.6 ± 7.3	2.5 ± 4.3	ns
PDSS	95.8 ± 23.4	106.4 ± 24.6	$p < 0.02$

rTMS – repetitive transcranial magnetic stimulation; TST – total sleep time, SOL – sleep onset latency; WASO – wake after sleep onset; SE – sleep efficiency; N1%, N2%, N3%, REM% – percentage of time spent in particular sleep stages to TST, Arousal index – mean number of arousals per one hour of TST, AHI – apnea hypopnea index, min SaO2 – minimal oxygen saturation during time in bed, PLM index – number of periodic limb movements per hour of TST, PDSS – Parkinson Disease Sleep Scale, SD – standard deviation.

4. Discussion

This study has documented the effects of rTMS on sleep in the PD patients, using the nocturnal PSG for the first time. Improvements to sleep were seen in a decrease in light sleep (N1), which is known to be less regenerative than other sleep stages, and in a decrease in nocturnal awakening (AI). Although limited to two parameters, this improvement supported the positive results observed in the questionnaires on sleep quality used in this study, and also by Khedr and colleagues [14], as more than a placebo effect. As well, our results did not specifically contradict the actigraphic data inVan Dijk et al. [15], despite their finding of no improvement in sleep quality after stimulation of PMI. The explanation lies in the fact that the occurrence of N1 and other sleep stages is not detected by actigraphy. Also the arousal index cannot be compared to the fragmentation index used by Van Dijk, since in our study arousal was defined by transient changes in EEG and was not necessarily associated with motor activity.

The decrease of AI after rTMS may result from an improvement in the motor symptoms, in particular of their recurrence at the night. There was a significant

improvement in scores on the peg board test for the non-dominant hand, as well as in the UPDRS–Part II and the global UPDRS (parts II–IV). Part II in particular refers to nocturnal PD symptoms as difficulties, e.g., turning in bed or nocturnal drooling, and may therefore explain the polysomnographic improvement. The motor symptoms that appear or may be recurrent at night are addressed in detail in the PDSS, which contains questions about restlessness of limbs, fidgetting in bed or painful muscle cramps, and which also improved significantly after the rTMS.

Despite the fact that our patients were on optimal antiparkinsonian medication, their sleep improved. We suppose the advantage of rTMS over pharmacological treatment may lie in continuity of its therapeutic effect. This is of particular importance at night when medication is less frequently administered, often leaving the patients in an "OFF" state.

The decrease in N1% in our patients is a consequence of the lower AI. According to the standard rules of sleep-scoring [24], the presence of arousal indicates a change from N2 to N1. Taking into consideration the high prevalence of N2 in the normal sleep profile and also in our patients (45% of the total sleep time before the stimulation) the close association between arousal and N1% is to be expected. This is supported by earlier data of Askenasy and colleagues [5] who described greater prevalence of arousals during light sleep in PD patients. The lack of change in periodic limb movements (PLM) and sleep-related breathing disorders supports the opinion that the AI improvement was related to the improvement in motor symptoms of PD, rather than in the improvement to these sleep specific disorders.

Another possible explanation for the polysomnographic improvement may be the modulation of cortical excitability by rTMS, which has a direct influence on the physiologic mechanisms of sleep. Cortical excitability in our group increased after the rTMS, an effect documented by the increase of MEP amplitude. In healthy subjects, changes in cortical excitability after rTMS have been associated with changes in subsequent PSG: after 20 Hz stimulation Graf and colleagues observed a reduction in the percentage of N1 sleep, a finding similar to ours. However, the site of the stimulation was located over the left dorsolateral prefrontal cortex [29]. When rTMS in the paired associative protocol was applied to PMC, an enhancement of the slow wave activity occurred without producing any change in the parameters of sleep macrostructure that were examined in our study [30]. A standard 5 Hz rTMS applied over PMC in a protocol similar to the paired-associative method induced an increase in the slow wave activity. However, in that study only the first sleep cycle was recorded, and therefore the effect on the sleep macrostructure could not be assessed [31]. Based on these data, we believe that the sleep improvement seen in our subjects was not directly caused by changes in the cortical excitability but resulted from the motor improvement. Another possible factor might be the influence of rTMS on mood that was described in other PD patients [13, 32]. As the HDRS did not change after rTMS, we believe that this was not a factor for our patients.

5. Study Limitations

The rTMS in the protocol used in our study is known to improve significantly the motor symptoms in PD [10], therefore the lack of improvement in the UPDRS-Part III in our patients was unexpected. One explanation may be that the patients were examined in the "ON" stage, while receiving medication. One previous study of rTMS in PD also reported no significant improvement in the patients who were in the "ON" stage [33]. According to Fregni and colleagues the effect of medication may mask that of rTMS due to a ceiling effect [10]. Another limitation in our study was the lack of a placebo group, which would have been necessary to confirm the observed effects. Finally, the sleep assessment was limited by the insufficient video monitoring since some of our patients received an ambulatory PSG. This limited the analysis of incidence of the REM sleep behaviour disorder (RBD), which is a significant factor contributing to disturbed sleep in PD patients. The analysis of available video data did not indicate the presence of RBD in any of our subjects and during interviews none of the group reported typical RBD symptoms in the previous months. Despite the negative interview data, without complete video data we cannot completely rule out the presence of RBD in our group and therefore the possibility that it was modulated by rTMS, which in turn contributed to the reported sleep changes.

5.1. Complications

To our knowledge, rTMS is unlikely to cause any adverse cardiac events [34]. In particular, we found no reports of myocardial infarction described as a side effect of rTMS. There was one report of arrhythmia caused by rTMS, but with the coil situated directly over the left heart ventricle and with stimulus intensity far exceeding those usually applied to stimulate the cortex [35]. In this light, the infarction that led to one of our patients leaving the study could have arisen during rTMS by chance. Nevertheless, since this complication, we have monitored every patient at cardiac risk with repetitive ECG to exclude any possible causal relationship.

6. Conclusions

The main finding of this study is that 10 sessions of 15–Hz rTMS applied over both PMC improved the subjective as well as the objective sleep quality as reflected by a decrease of frequency in arousal from sleep and in Non-REM–1 stage sleep. This improvement was probably associated with alleviation of the nocturnal symptoms by rTMS rather than any modulation of the mood or the motor cortex excitability.

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