In search of optimal site for 10 Hz rTMS depression treatment: a clinical and physiological comparison

Vladas Valiulis[1], Karolina Valavičiūtė[2], Kastytis Dapšys[1], Giedrius Gerulskis[1], Aldona Šiurkutė[1,3], Valentinas Mačiulis[1,3]

1 Republican Vilnius Psychiatric Hospital, Vilnius, Lithuania

2 Department of Neurobiology and Biophysics, Vilnius University, Vilnius, Lithuania

3 Psychiatry Clinic, Vilnius University, Vilnius, Lithuania

*Email of corresponding author: vladas.valiulis@gmail.com

1. Introduction

10 Hz rTMS over the left dorsolateral prefrontal cortex (DLPFC) is one of the most popular treatment options for drug resistant depression. However, despite much research, the exact mechanism of how a focused facilitative stimulation over the DLPFC results in a clinical improvement still remains elusive, while measured efficacy between the studies tend to vary greatly. With increasing efforts to standardize 10 Hz rTMS protocol most variability seems to arise from the stimulation site selection. That is because differences in patient head sizes lead to great dispersion of stimulation sites in previously standard 6 cm rule and there is still an ongoing debate over which exact coordinate for DLPFC to use in a neuronavigated rTMS. In order to clarify the possible choices for TMS coil placement we decided to study three homogenous groups of patients in the same setting using three neuronavigated DLPFC sites suggested by previous studies. Patients with diagnosed drug resistant depressive disorder selected for 10 Hz rTMS treatment were randomly assigned to 3 groups differing in sites of stimulation. To account both factors of clinical effectiveness and physiological impact before the treatment course and after it patients were evaluated using MADRS, HAM-D and BDI clinical tests as well as an analysis of resting state EEG power spectrum.

2. Methods

2.1. Subjects

42 subjects (30 women, 12 men, mean age 52.43 years, SD=12.82 years), with diagnosed recurrent treatment resistant depressive disorder participated in the study.

Patients were treated with high frequency (10 Hz) rTMS over the left DLPFC. Procedures were applied five times per week for two to three weeks (10-15 procedures overall in rTMS treatment course).

2.2. Subject groups

Patients were randomly assigned to three groups according to stimulation site in a MNI map: 1. -40.0; 48.0; 35.0 (Teneback et al, 1999)(20 patients); 2. -46.0; 45.0; 38.0 (Fitzgerald et al, 2009)(11 patients); 3. -38.0; 44.0; 26.0 (Fox et al, 2012)(11 patients)(Fig. 1).

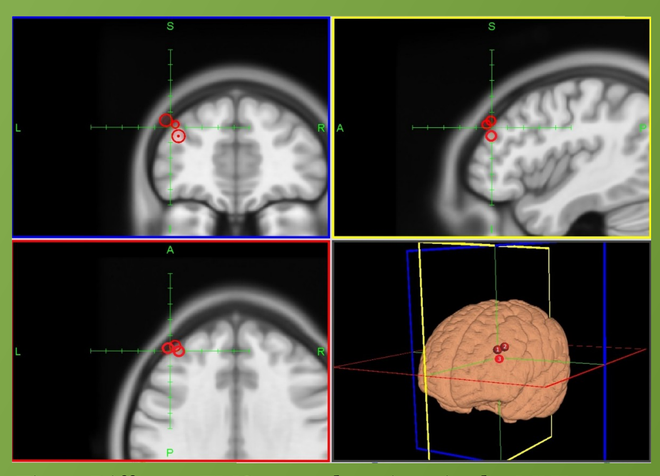

Fig. 1. Different TMS target locations in the MNImap.

2.3. TMS procedure

TMS procedures were applied using MagVenture Magpro X100 TMS stimulator with MagVenture Cool Coil B65 liquid cooled figure eight coil. During the stimulation 280 μs biphasic impulses were used. rTMS protocol consisted of 20 8s trains of 10 Hz frequency impulses, applied at 100% motor threshold intensity (1600 impulses overall). Stimulation targets were managed on MNI model brain using Localite TMS Navigator system.

2.4. EEG measurement

For EEG recording EBNeuro Galileo Mizar apparatus was used. EEG was recorded before rTMS course and 20-30 minutes after the last procedure in the electrically shielded booth. Over the head of the patient 20 round bridge type Ag/AgCL electrodes were placed according to international 10-20 system and secured with the special cap. Fpz electrode was used as a ground, ear electrodes acted as a reference.

Electrode impedance was maintained lower than 5 kΩ. Resting state EEG was recorded for 10 minutes with the patient sitting eyes closed. EEG record was filtered using low frequency (0.53 Hz), high frequency (70 Hz) and notch (50 Hz) filters. Data was digitized at 256 frequency 12 bit rate. For further analysis 30 s EEG intervals without artefacts was used. Hanning window was applied for 2 s epochs. EEG spectrum S(ω) mean power values (μV2) was calculated by fast Fourier transformation (FFT) method. Absolute power values were calculated for delta (1,00-3,50 Hz), theta (3,50-8,00 Hz), alpha (8,00-12,00 Hz) and beta (12,00-32,00 Hz) frequency band intervals.

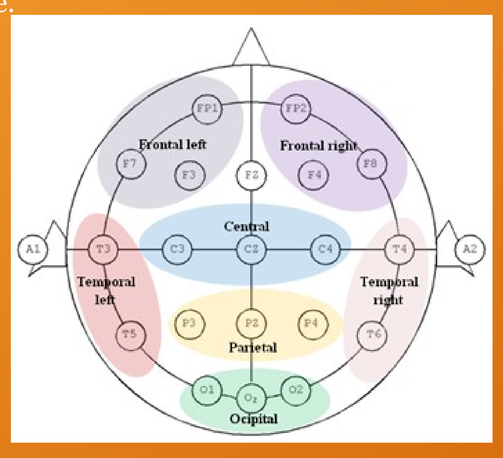

Fig. 2. Areas where EEG band power was averaged

2.5. Statistical analysis

To measure the significance of EEG band power spectrum change after the therapy course, Wilcoxon test for two related samples was used. To study the differences of physiological changes between patient groups and brain areas, additional analysis of variance (ANOVA) for repeated measures was applied. Within subject variable was measurements before therapy course and after it (Procedure factor). Between subjects factors were patient Group and brain Area. Differences between patient groups in clinical test changes were analysed using One-Way ANOVA.

3. Results

3.1. EEG changes after rTMS course

A considerable physiological difference in effect to the resting state EEG power was found between the groups. While Group 1 patients showed a significant increase of Delta band power in almost all brain areas, EEG power changes in Group 2 patients were all statistically insignificant. Group 3 patients revealed a significant increase of slow wave (Delta and Theta band) power over the left temporal area (Fig. 3).

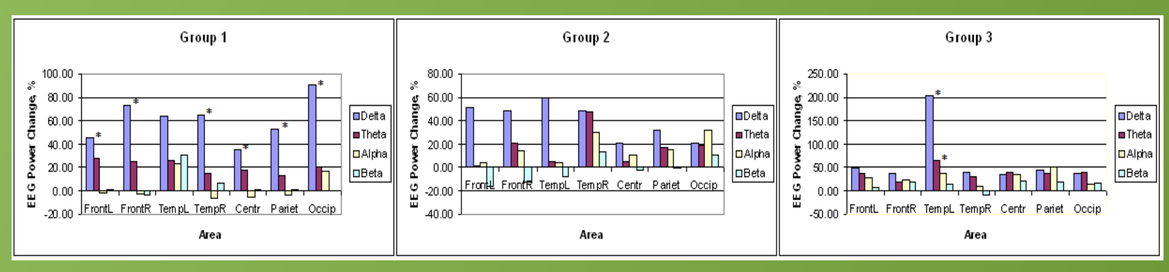

Fig. 3. Percent changes of EEG band spectrum power after rTMS treatment (* p<0.05 in Wilcoxon 2 related samples test).

Table 1. Analysis of variance for EEG band power spectrum between different patient groups and brain areas.

Band	Factors	F	p value
Delta	Procedure	4.364	**0.038***
	Group	3.046	**0.049***
	Area	2.144	**0.049***
Theta	Procedure	0.449	0.503
	Group	0.632	0.532
	Area	2.281	**0.036***
Alpha	Procedure	4.188	**0.042***
	Group	1.368	0.256
	Area	7.695	**0.000***
Beta	Procedure	2.030	0.155
	Group	5.761	**0.004***
	Area	3.388	**0.003***

According to repeated measures ANOVA there was a general significant effect on Delta and Alpha band power after a rTMS course. Patient groups differed significantly in the changes of Delta and Beta band power, the former also evident in the different results of Wilcoxon test. Also a combined significant differences were measured between the separate brain areas in all EEG frequency bands (Table 1).

3.2. Clinical changes after rTMS course

After the treatment a largest decrease in clinical test (MADRS, BDI and HAM-D) scores were found in the Group 3 patients (59.46%-71.14% mean decrease), compared to Group 1 (47.89%-57.52% mean decrease) and Group 2 (44.09%-58.87%) patients. However One-Way ANOVA failed to show statistical significancein differences between the groups (Table 2).

Table 2. Percental reduction of clinical test scores between patient groups.

		N	Mean decline, %	Std. Deviation	F	p value
MADRS	Group 1	20	54,96	19,15	1,78	0,19
	Group 2	11	58,76	9,99		
	Group 3	11	70,86	23,45		
	Total	42	59,03	19,65		
BDI	Group 1	20	47,89	28,41	0,60	0,56
	Group 2	11	44,09	17,20		
	Group 3	11	59,46	32,02		
	Total	42	49,90	27,15		
HAM-D	Group 1	20	57,52	18,59	1,77	0,19
	Group 2	11	55,86	17,62		
	Group 3	11	71,14	19,72		
	Total	42	60,30	19,08		

Conclusions

Our study results suggest that there are significant differences in physiological response to 10 Hz rTMS treatment dependent on stimulation site selection, especially in the EEG Delta band power. Clinical efficacy results may also vary a bit according to properly chosen TMS target coordinates. Considering both clinical efficacy and mild physiological effect it would be advisable to use MNI coordinates -38.0; 44.0; 26.0 or -46.0; 45.0; 38.0 for 10 Hz rTMS depression treatment. However it should be noted that the sample in this study so far has been rather small. Further investigation is required to support these findings.

References

1. Teneback CC, Nahas Z, Speer AM, Molloy M, Stallings LE, Spicer KM, et al. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. Journal of Neuropsychiatry and Clinical Neurosciences. 1999; 11:426.
2. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, Bailey M, Been G, Kulkarni J, Daskalakis ZJ. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. Neuropsychopharmacology. 2009; 34:1255–1262.
3. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of TMS targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biological Psychiatry. 2012 1; 72(7): 595–603.