RESEARCH PAPER

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The use of MR-less MNI based neuronavigation for 10 Hz rTMS depression therapy: electrophysiological and clinical implications

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

[1] Republican Vilnius Psychiatric Hospital, Vilnius, Lithuania, [2] Vilnius University, Department of Neurobiology and Biophysics, Vilnius, Lithuania, [3] Vilnius University, Psychiatry Clinic, Vilnius, Lithuania,
** Email: vladas.valiulis@gmail.com*

Repetitive transcranial magnetic stimulation (rTMS) is a popular and effective treatment for drug resistant depression. However, there is considerable variability in clinical outcomes, in previous studies and between patients. Because of high requirements for the use of fMRI based neuronavigation, many practitioners of rTMS still choose to use a standard 5 cm rule for rTMS coil placement which leads to large variations in which brain regions are being stimulated. We decided to test the possibilities of a MNI based MR-less neuronavigation system in rTMS depression treatment, by comparing the physiological effects and clinical outcomes of 3 distinct stimulation targets. Forty-six patients (thirty-three female, thirteen male) from the Republican Vilnius psychiatric hospital, all with drug resistant depressive disorder, participated in the study. All patients received high frequency (10 Hz) stimulation for 10 to 15 daily rTMS sessions. However, before the treatment they were randomly sorted into 3 groups according to stimulation target in MNI map: Group 1 received rTMS at point -40; 48; 35; Group 2 received rTMS at point -46; 45; 38; Group 3 received rTMS at point -38; 44; 26. Electroencephalography (EEG) recordings and clinical tests were obtained the day before the rTMS course and after the last session. There were some notable differences in physiological changes between the groups, with the largest EEG band spectral power increases found in Group 1 patients and the lowest in Group 2 patients. There was a significantly larger decrease of the Hamilton Depression Rating Scale (HAM-D) scores in the Group 3 (66.94%) compared to Group 1 (57.52%) and Group 2 (56.02%). This suggests it is possible to achieve higher clinical efficacy and less physiological impact on the brain when using different targets in a neuronavigated MNI based MR-less rTMS system.

Key words: transcranial magnetic stimulation, depression, EEG, neuronavigation, MNI, MR-less

INTRODUCTION

According to the World Health Organization around 350 million of people suffer from depression worldwide (Morvai et al. 2016). However, less than one third of depression patients reach remission after 12 weeks of initial pharmacological treatment (Trivedi et al. 2006), some produce unwanted side effects (Teng et al. 2017), whilst around 30% of major depressive disorder patients are diagnosed with drug treatment resistant disorder (Bewernick and Schlaepfer 2015, Fitzgerald et al. 2003, Silverstein et al. 2015). Currently, depression which fails to find a pharmacological treatment is treated with repetitive transcranial magnetic stimulation (rTMS), which has proven itself to be clinically effective in drug resistant depression therapy, surpassing the placebo effect (Avery et al. 2006, Blumbergeret al. 2016, Concerto et al. 2015, Filipcic et al. 2017, Fitzgerald et al. 2003, Kito et al. 2016, O'Reardon et al. 2007, Sehatzedeh et al. 2016, Teng et al. 2017). However, the therapeutic effect of rTMS therapy tends to vary significantly between studies and between individuals, even when similar protocols are applied, so there is a strong need for better optimization of rTMS parame-

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ters as well as better insights into possible therapeutic markers (Kobayashi et al. 2017, Luber et al. 2017, Zyss et al. 2015).

With rTMS pulse parameters being standardized and easily replicated in multiple cases, and with stimulation intensities being tailored to the individual motor threshold values, most technical variability should arise from differences in coil placement over the brain. Since its origin as a treatment for depression, the coil placement in the clinical rTMS application has been a standard or blind protocol which attributes left hemisphere prefrontal dorsolateral cortex (DLPFC) to a fixed point 5 to 6 cm anterior of a right hand thumb muscle motor area (Ahdab et al. 2010). However, since individual brain size and shape can vary significantly, this method leads to a great dispersion of actual stimulation targets (Luber et al. 2017, Mir-Moghtadaei et al. 2015, Pommier et al. 2017) and therefore can severely limit efficacy. Studies have shown that when using 5 cm standard coil positioning rule, up to 68% of patient cases might actually result in a miss of the DLPFC area, instead hitting the dorsolateral premotor cortex or orbitofrontal cortex (Herwig et al. 2001, Luber et al. 2017). Based on the fact that the focality of a typical figure of eight TMS coil is modeled to be around 5 cm^2 (Deng et al, 2013, Thielscher and Kammer 2004), it could be that the application of a standard 5 cm anterior to the motor cortex rule yields a great variety of clinical responses in different patients and studies as it does not take in account absolute differences in head anatomy (George et al. 2013) and thus results in administering the most effective stimulation to different cerebral areas for each patient. Currently the highest precision in anatomically and physiologically based stimulation targeting can be achieved when using findings of functional brain imaging studies together with precision neuronavigation tracking (Luber et al. 2017, Mir-Moghtadaei et al. 2015). The best results can be achieved with individual measurements and better insights into antidepressant rTMS mechanisms through research.

Another important piece of the rTMS therapy puzzle is finding the most suitable biomarkers to help predict the clinical response and better understand the mechanisms underlying antidepressant rTMS treatment. Suggested markers range from quantitative changes in brain activity, measured by simple baseline electroencephalography (EEG) or baseline functional magnetic resonance imaging (fMRI); to specific cognitive priming or functional connectivity studies, using complex algorithms and integrated systems; to studies of molecular factors and individual gene polymorphisms (Kito et al. 2016, Kobayashi et al. 2017, Luber et al. 2017, Noh 2016, Sale et al. 2015, Silverstein et al. 2015). Major depressive disorder is usually characterized by functional impairments in the fronto-mezo-lymbic system network (Pulcu et al. 2014), manifesting itself in asymmetry of activity in the prefrontal cortex between brain hemispheres (Henriques and Davidson 1991, Lubar et al. 2003) and an increase of metabolic activity in the subgenual anterior cingulate (Mayberg et al. 2000, 2005). Since individual fMRI is often found to be too expensive and complicated to be used in a daily clinical rTMS practice, many studies into the treatment of depression with rTMS markers are carried out using separate EEG systems or integrated rTMS-EEG systems. Experiments support the use of EEG in various TMS studies as a reliable indicator of cortical excitability changes, as EEG activity is a sensitive measure to subtle TMS induced changes (Canali et al. 2014, Thut and Pascual-Leone 2010), ranging from short event-related potential (ERP) like phenomenon to a more robust long-term potentiation/depression (LTP/LTD) based change, especially in the motor and prefrontal cortices (Lioumis et al. 2009). Previously, much emphasis was placed on the frontal alpha band asymmetry theory (Henriques and Davidson 1991). However, later studies have proved it to be of limited diagnostic value with a high degree of variability (Funk and George 2008, van der Vinne et al. 2017). As in the studies examining the clinical effectiveness of rTMS, studies examining the effect of rTMS on EEG have also been quite variable, and are hard to replicate beyond the original study population (Widge et al. 2013). When various authors have tried to measure a basic rTMS effect on EEG profile, many have failed to find consistent changes in alpha band power, supporting the alpha asymmetry theory. Some have found a notable increase of alpha power in the occipital area (Melnikova et al. 2015), whilst others have observed no alpha band power change at all (Funk and George 2008, Loo et al. 2001, Spronk et al. 2008). The most robust baseline EEG findings were an increase in slow delta wave power after prefrontal cortex rTMS (Griškova et al. 2006, Spronk et al. 2008, Valiulis et al. 2012). Increased delta band power has also been observed after rTMS application over the motor cortex (Assenza et al. 2015) and after depression treatment with electroconvulsive therapy (ECT) (Sackeim et al. 1996). However, no cases, except for the delta increase in the prefrontal cortex after ECT (Sackeim et al. 1996), have produced significant correlations with clinical changes. It seems that the rise in delta band power, although not clearly related to any underlying depression mechanisms and therefore of questionable therapeutic value, can be regarded as a physiological stamp of the impact of rTMS on the brain. While some EEG variability might arise from differences in the time between the rTMS procedure and EEG recording (Thut and Pascual-Leone 2010) (many EEG changes tend to return to the baseline after 15–70 minutes) the delta power changes can be very robust and long lasting (Vali-

ulis 2014), even after a complete therapy course. Therefore, the question remains; could delta power changes also be influenced and probably minimized by TMS coil placement precision?

If we assume that rTMS can restore or optimize neural activity from a pathological state (Paus and Barret 2004, Sale et al. 2015) by hitting the right target with the right stimulus parameters, we should at all costs avoid oversimplification of our therapeutic models and always take into account, not just the activity of a target region, but rather the state of the whole neural network (Fox et al. 2012). Although traditional rTMS coils are unable to reach and therefore alter the activation of subcortical areas relevant for depression treatment like the subgenual cingulate directly, this could be achieved in an effective manner when targeting cortical network areas with the strongest possible connectivity. Generally, left hemispheric prefrontal cortex areas have a notable functional connection to the fronto-mezo-limbic system, including deeper limbic areas (Padberg and George 2009). However, not all rTMS therapy neuroimaging studies show equal strength of this connection measured by changes in the subgenual cingulate (Kito et al. 2011). It puts an additional interest in high precision rTMS targeting, based on individual cortical-subcortical connectivity evaluation. Since neuronavigated rTMS coils theoretically can be placed with an accuracy of less than 1 mm over the cortical target, it would makes sense to find an exact point of the left DLPFC with the strongest connection to the subgenual cingulate (Fox et al. 2013).

Literature provides several brain coordinates to be used as precise rTMS targets in left DLPFC to be used in depression therapy. SPECT studies have provided us with possible rTMS stimulation target areas based on blood perfusion differences (Jha et al. 2016, Teneback et al. 1999), by distinguishing blood flow patterns in left prefrontal dorsolateral cortex areas of responders (-40; 48; 35;) *vs.* non responders (Teneback et al. 1999). Other possible precise rTMS targets (-46, 45, 38) can be averaged from empirical clinical effectiveness when using fMRI based rTMS neuronavigation (Fitzgerald et al. 2009b). Fox et al. (2012) argue that the differences in clinical effectiveness when stimulating left PFDLC might arise from differences of connection strength to the subcortical areas. fMRI studies have shown that when comparing stimulation of different left DLPFC targets to the activity changes of the subgenual cingulate, the highest negative correlation is found when using rTMS target coordinates of -38; 44; 26 (Fox et al. 2013). As such, stimulation placement so to achieve indirect subgenual cingulate activity alteration should provide the best clinical results.

However, despite the enormous potential of neuroimaging studies, the biggest drawback of applying ultra-precise individual fMRI based neuronavigated rTMS in clinical practice is the high monetary and time costs, given it would require sophisticated equipment and solid neuroanatomical skills for operators to identify individual targets for each patient (Pommier et al. 2017). This results in most clinical practitioners still using a standard, highly imprecise rTMS coil placement method, instead of incorporating neuroimaging research data findings into their practice. Optional Beam F3 method, although more adaptive to head size differences, also proves to be less precise than neuronavigation as it is based entirely on head landmarks, rather than functional connectivity data (Mir-Moghtadaei et al. 2015, Pommier et al. 2017). Mir-Moghtadaei et al (2015) found that a discrepancy of coil placement between MRI-Guided placement and Beam F3 scalp site can vary between 0.65 cm and 1.36 cm for most patients, and in some cases this can reach close to 2 cm. Another benefit of neuronavigation systems is an ability to accurately track coil positions during the procedure in real time. Possible upgrades in this situation could be the use of MR-less MNI model based neuronavigation systems, which enable practitioners to place the rTMS coils over an exact brain coordinate without the need of an individual MRI scan, thus providing less dispersion of stimulation targets than previous methods (Pommier et al. 2017) and enabling easy incorporation of functional connectivity study findings into a standardized semi-blind design. However, such applications are still quite rare. Therefore, in our study we decided to compare how different rTMS targets, provided by previous neuroimaging studies and applied in the MNI model based MR-less neuronavigation system, would affect basic physiological EEG changes in the brain, as well as how they would affect clinical outcomes.

METHODS

Subjects

46 inpatients (33 female, 13 male, mean age 51.28 years, SD=12.62 years) from the Republican Vilnius psychiatric hospital with drug resistant depressive disorder (without anxiety symptoms) participated in the study. Before the treatment each patient signed a written consent. During the rTMS course, previously unsuccessful pharmaceutical treatment was continued at steady stable doses. None of the patients were treated with tricyclic antidepressants.

Patients were randomly assigned to three groups according to stimulation site in the MNI map: Group 1 (20 patients); Group 2 (11 patients); Group 3 (11 patients).

All the patients were treated with high frequency (10 Hz) rTMS over the left PFDLC. Procedures were carried out daily, five days per week, for two to three weeks (10–15 procedures overall).

Equipment and 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. The rTMS protocol consisted of 20.8 second trains of 10 Hz frequency impulses, applied at 100% motor threshold intensity (1600 impulses overall).

For neuronavigated coil placement, the Localite TMS Navigator MR-less system was used. This neuronavigation system utilizes a standard the Montreal Neurological Institute (MNI) (MNI ICBM152 non-linear symmetric T1 Average Brain) brain map. MNI brain map deformations for each patient head are calculated using anatomical markers and points from the head surface: 1) root of the nose (nasion); 2) left corner of the eye (left exocanthion); 3) right corner of the eye (right exocanthion); 4) anterior point on the left auditory canal (left preauricular point); 5) anterior point on the right auditory canal (right preauricular point); 6) occipital prominence (inion); 7) surface at the back of the head from the most posterior point; 8) surface at the top of the head from the most superior point. Left PFDLC targets were placed in the MNI map according to these coordinates: 1) Group 1 -40; 48; 35; (Teneback et al. 1999); 2) Group 2 -46; 45; 38 (Fitzgerald et al. 2009b); 3) Group 3 -38; 44; 26 (Fox et al. 2014) (Fig. 1).

EEG measurement

For EEG recording, EBNeuro Galileo Mizar apparatus was used. EEG was recorded before the rTMS course and 20–30 minutes after the last procedure in an 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 a cap.

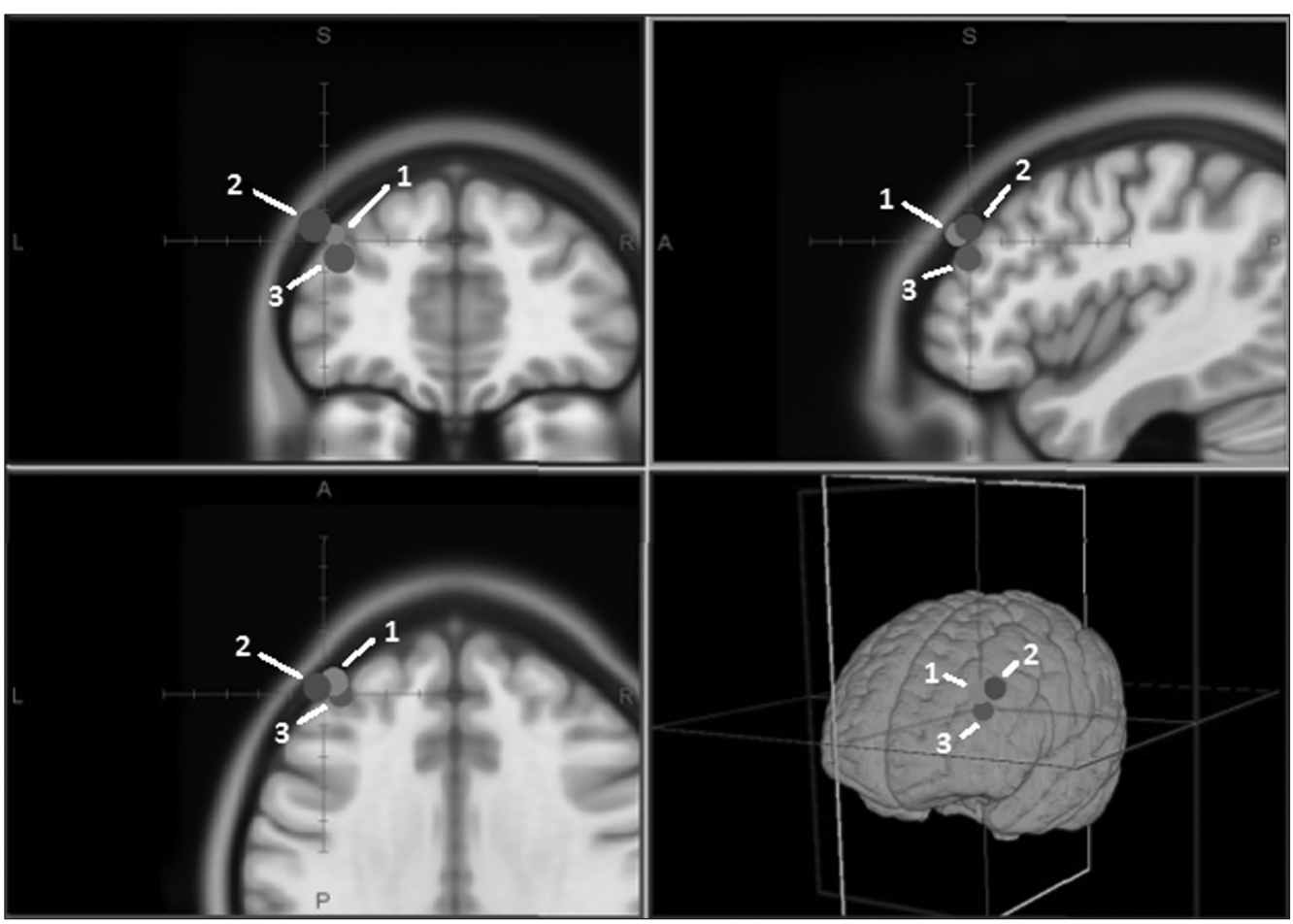

Fig. 1. TMS target coordinates in the MNI brain model for three patient groups.

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 recordings were 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 second EEG intervals without artifacts were used. Hanning window was applied for 2 second epochs. EEG spectrum S (ω) mean power values (μV^2) were 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.

EEG band power averages for particular brain areas were calculated by combining data from these electrodes: a) Frontal left (Fp1, F7, F3 electrode average); b) Frontal right (Fp2, F4, F8 electrode average; c) Temporal left (T3, T5 electrode average); d) Temporal right (T4, T6 electrode average); e) Central (C3, Cz, C4 electrode average); f) Parietal (P3, Pz, P4 electrode average); g) Occipital (O1, Oz, O2 electrode average) (Fig. 2).

Clinical evaluation

Clinical evaluation was carried out by a psychiatrist before rTMS treatment and day after the last rTMS session. It consisted of the Montgomery-Asberg Depression Scale (MADRS) (Montgomery and Asberg 1979), the Hamilton Depression Rating Scale (HAM-D) (Williams 1989) and the Beck Depression Inventory (BDI) scale (Beck et al. 1988). General clinical efficacy was based on percentage changes of MADRS scale and divided into three distinct groups: 1) weak effect (<10% decrease); 2) medium effect (10%–50% decrease); 3) significant effect (>50% decrease) (Fitzgerald et al. 2009b). Remission was achieved when MADRS score after the therapy was <10 points (Fitzgerald et al. 2006).

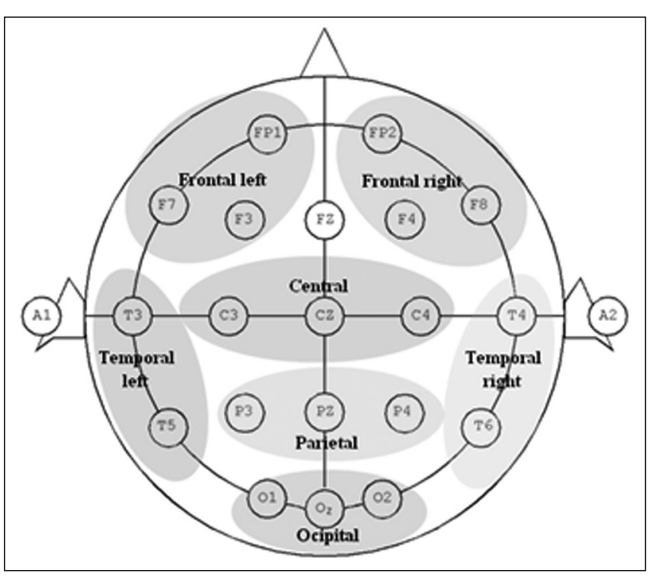

Fig. 2. EEG electrodes averaged according to brain areas.

Statistical analysis

Statistical analysis was carried out using Microsoft Excel 2010 and SPSS statistics v17 software. To measure the significance of EEG band power spectrum changes 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 variables were the measurements before the therapy course and after it (Procedure factor). Between subjects factors were the Group and brain area. Differences between patient groups in clinical test reduction were analyzed using One-Way ANOVA. Correlations between EEG band power changes and clinical changes were calculated using Pearson correlation coefficient.

RESULTS

After EEG band spectral power changes were averaged, an increase in delta and theta band power for Group 1 patients became apparent (Fig. 3). For the same patients, alpha band power had decreased slightly in all brain areas except for the left temporal area and occipital area. Beta power had increased slightly across the brain, except for the right frontal area (Fig. 3). Wilcoxon testing showed statistically significant (P<0.05) changes in the delta band power in both frontal areas, temporal right, central, parietal and occipital areas

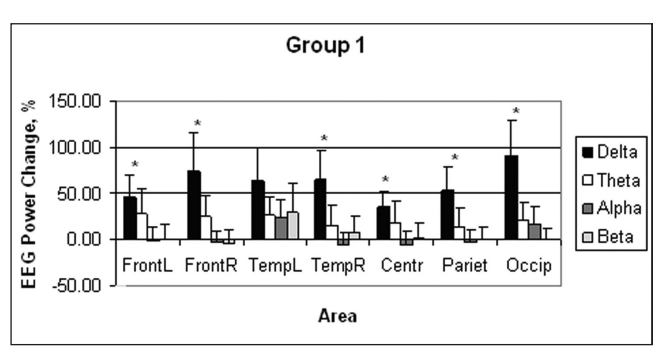

Fig. 3. Changes of EEG band power spectrum in Group 1 patients. * P≤0.05 in Wilcoxon test.

Table I. EEG band power spectrum percentage change averages and standard deviations in all patient groups (Group 1 n=20, Group 2 n=13, Group 3 n=13) * $P \leq 0.05$ in Wilcoxon test.

Group	EEG band	Brain Area						
		FrontL	FrontR	TempL	TempR	Centr	Pariet	Occip
1	Delta	44.92± 24.50*	73.24± 42.53*	63.74± 36.00	65.38± 32.07*	34.59± 17.48*	53.07± 26.09*	90.87± 37.81*
	Theta	27.77± 26.72	25.05± 22.57	25.85± 19.11	14.52± 22.22	17.95± 22.94	13.55± 20.32	20.03± 20.23
	Alpha	-1.34± 14.99	-2.43± 11.95	23.48± 18.53	-6.26± 12.98	-5.53± 13.37	-3.54± 13.28	16.89± 18.01
	Beta	0.52± 16.37	-3.85± 14.02	30.14± 29.76	6.97± 18.52	1.59± 15.35	0.73± 12.60	0.28± 10.93
2	Delta	51.14± 41.01	47.87± 30.47	59.62± 42.17	48.10± 33.59	21.42± 21.46	32.01± 23.78	20.61± 23.21
	Theta	1.64± 10.63	20.88± 24.46	4.75± 19.08	47.22± 54.69	4.92± 12.39	17.41± 16.18	19.16± 17.06
	Alpha	3.80± 15.96	14.14± 20.73	4.03± 21.54	30.38± 27.43	10.15± 16.77	15.68± 17.01	31.92± 30.50
	Beta	-16.27± 10.62	-12.51± 10.12	-7.54± 12.41	13.32± 17.95	-2.08± 11.59	-0.87± 13.27	10.91± 19.06
3	Delta	48.17± 25.39	36.22± 17.61*	203.90± 146.36	41.65± 32.18	36.12± 14.38	45.67± 14.87*	37.26± 15.16*
	Theta	36.21± 14.24	18.90± 13.68	65.30± 13.74*	32.14± 29.75	41.14± 17.97	36.53± 16.12	40.40± 17.54
	Alpha	27.70± 19.30	24.01± 17.57	37.68± 28.43	10.67± 27.40	35.54± 17.50	52.43± 43.07	16.73± 9.71
	Beta	8.60± 11.21	19.92± 14.22	16.65± 17.25	-8.36± 13.26	20.69± 24.31	19.96± 21.82	18.55± 9.03

(Table I). Group 2 patients showed an increase in delta, theta and alpha band power in all brain areas and a decrease in beta band power across the whole brain, except for right temporal and occipital areas (Fig. 4). However, none of these changes were statistically significant according to the Wilcoxon test (Table I). Group 3 patients showed an increase in all EEG band powers across the whole brain, with the only exception being a beta band power reduction in the right temporal area (Fig. 5). Statistically significant changes were found in the right frontal, parietal and occipital areas in delta band power and in the left temporal area for theta band power (Table I).

Repeated measures ANOVA's were carried out to test the differences in results between the groups and brain areas, as well as a combined therapy effect for different EEG bands (procedure factor within groups). This data showed that 'everything combined' rTMS therapy has an effect on delta, theta and alpha band power and statistically significant differences can be found between different areas in each EEG power band (Table II). There are also considerable differences between the groups

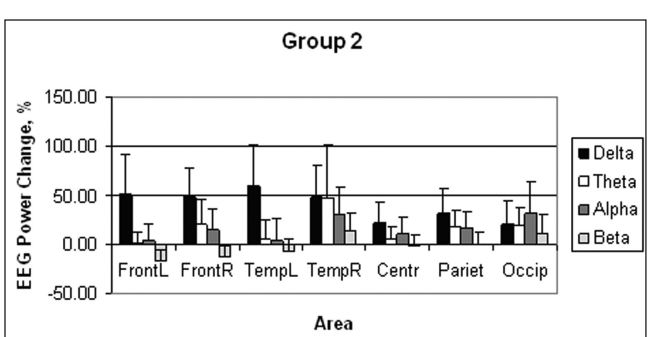

Fig. 4. Changes of EEG band power spectrum in Group 2 patients. * $P \leq 0.05$ in Wilcoxon test.

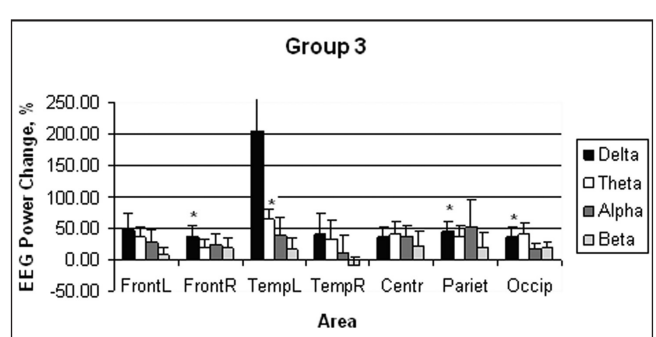

Fig. 5. Changes of EEG band power spectrum in Group 3 patients. * $P \leq 0.05$ in Wilcoxon test.

Table II. Repeated measures ANOVA.

EEG band	Factors	*F*	*P* value
Delta	Procedure	20.131	0.0001*
	Group	5.982	0.003*
	Area	2.316	0.034*
Theta	Procedure	20.74	0.0001*
	Group	4.952	0.001*
	Area	2.012	0.064
Alpha	Procedure	6.7	0.01*
	Group	0.478	0.621
	Area	9.112	0.000*
Beta	Procedure	0.041	0.839
	Group	2.651	0.072
	Area	3.955	0.001*

in the delta and theta bands (Table II). The later result, when taken together with Wilcoxon test findings, suggests that Group 2 patients had the least physiological changes after the treatment, Group 1 had the most notable and widespread increase in the delta band power whereas Group 3 had a more sporadic increase in delta band power and a slight increase in the theta band power (Figs 3–5, Table II).

Percentage decreases in clinical test scores show a very similar outcome between Group 1 and Group 2 patients, but Group 3 patients had the largest reduction in all three (MADRS, BDI and HAM-D) clinical test scores (Table III). Moreover, when ANOVA's were applied, the HAM-D test showed statistically significant changes between the three groups (Table IV). Pearson correlations between the EEG power changes and clinical changes failed to show any significant relationships.

DISCUSSION

After rTMS therapy there was a notable tendency for a slow EEG wave (delta and theta) power increase in all study groups which was not limited to specific brain areas. This coincides with several previous studies which have showed an increase in slow wave activity after electrophysiological antidepressant therapy (Griškova et al. 2006, Spronk et al. 2008). However, these changes do not correlate to a clinical improvement and tend to show a very basic brain reaction to an outside electrical stimulation (Valiulis 2014). Alpha and beta power changes were less pronounced and more variable. It is important to note that endeavors to find specific changes in the alpha band frequency, although initially promising from the clinical point of view, also failed in a numerous previous studies (Funk and George 2008, Widge et al. 2013, van der Vinne et al. 2017).

Group 1 patients displayed the most widespread increase in delta band power across the brain. This indicates the largest physiological changes of the three groups. The coordinates for stimulation in this group were based on Teneback et al. (1999), a SPECT study which showed an increase in brain activity in that region after rTMS therapy. Our EEG results did not show any substantial increase in beta band power in the left frontal area, or in any brain region for that matter.

Table III. Average decreases of clinical test scores among the patient groups (Group 1 n=20, Group 2 n=13, Group 3 n=13).

Group	MADRS	BDI	HAM-D
1	54.96%	47.89%	57.52%
2	56.75%	44.14%	56.02%
3	62.9%	55.22%	66.94%

Table IV. One Way ANOVA results for clinical test scores.

Test	*F*	*P* value
MADRS	1.675	0.191
BDI	1.44	0.241
HAM-D	3.929	0.022*

Group 2 patients showed the mildest increases in slow wave EEG band power of all study groups. There was also no evidence of activation of the left frontal area from the beta band power standpoint. Fitzgerald et al. (2009b), who proposed these coordinates for rTMS treatment, did not provide EEG activity change measures in his study. However, an fMRI comparison highlighted that the Fitzgerald et al. (2009b) target did show two times stronger anti-correlation with subgenual cingulate cortex activity, when compared to a 5 cm anterior to motor cortex standard rTMS target (Fox et al. 2012b).

Group 3 patients, whose stimulation targets were based on the Fox et al. (2012a) study, produced a middling effect when measuring EEG band power changes. Slow wave power increases were apparent but were limited to several brain areas when compared to the Group 1 patients. However, like in previous cases, this stimulation target provided no benefit when considering activity increases via the beta band power rise.

As stated in the previous literature, overall delta power increase is often a consequence of electrophysiological brain stimulation, including both rTMS and ECT (Assenza et al. 2015, Griškova et al. 2006, Sackeim et al. 1996, Spronk et al. 2008, Valiulis et al. 2012). Theoretically, it can be regarded as both a marker of neuroplastic processes and brain lesions (Assenza et al. 2015). Therefore it makes sense to try and limit its manifestation where it is not proved to serve a particular clinical benefit.

Patients in Group 1 and Group 2 displayed a 50% decrease in MADRS and HAM-D clinical test scores. This correlates with data from Teneback et al. (1999), the study which Group 1 patients rTMS target coordinates were based on. Similar decrements in clinical test scores were also found in other studies (George et al. 2013, Filipcic et al. 2017, Tarhan et al. 2012).

Group 2 patients clinical results in MADRS and BDI tests have exceeded previous Fitzgerald et al. (2003) rTMS study results: MADRS – 32.2 ± 9.0; BDI – 27.2 ± 10.8 (Fitzgerald et al. 2003).

Group 3 patients displayed the largest clinical improvement in MADRS and HAM-D clinical test scores, averaging a 60% decrease. The rTMS target coordinates used for this group were based on the Fox et al. (2012a) study, which also showed the highest anti-correlation to subgenual cingulate, three times larger than using a standard 5 cm anterior to motor cortex rule and 1.25 larger than when using a target suggested by Fitzgerald et al. (2003). Our study findings support the rationale of using the left DLPFC point with the highest anti-correlation to subgenual cingulate in order to achieve the best clinical results, even when calculated in the averaged MNI map.

No significant correlations were found between clinical changes and baseline EEG band power changes. This contradicts the findings of the ECT study conducted by Sackeim et al (1996), which found prefrontal region delta power increases, indicative of depressive symptom improvement. However, it conforms to previous rTMS research, which reported that delta power had no influence on the clinical or the neuroplastic improvement (Assenza et al. 2015, Spronk et al. 2008, Valiulis et al. 2012). In our study, EEG spectral power changes can be regarded as a generalized quantitative measurement of brain reaction to rTMS therapy, without considerable clinical value. Therefore, in this case, the rTMS influence on slow EEG band power seems to be relevant only from the perspective of slight changes the different MNI targets have had on brain physiology and thus is worth applying when small disturbances in brain activity would be considered in the choice of rTMS parameters. For a more detailed look at clinical rTMS mechanisms, more complex EEG algorithms involving more specific and immediate brain excitability changes should be used, including standardized low-resolution brain electromagnetic tomography (sLORETA) (Canali et al. 2014, Noh 2016, Kito et al. 2016).

To summarize, minute changes in rTMS coil placement when using precision navigation can lead to significant differences in physiological and clinical aspects. This rule can also be applied when using a MNI brain model. This supports the use MR-less MNI based neuronavigation for rTMS coil placement in clinical practice as a superior option to standard blind or Beam F3 methods (Mir-Moghtadaei et al. 2015, Pommier et al. 2017). For the best clinical results it is advisable to use MNI coordinates -38; 44; 26 (Fox et al. 2012a). However, these data should be taken with a slight caution, as the patient groups in this study were rather small and should be enlarged for the future studies. Also it would be beneficial to try and recreate the results using different rTMS protocols, like the FDA recommended 120% motor threshold (MT) intensity 37 minute 10 Hz protocol (O'Reardon et al. 2007) or intermittent theta burst stimulation (iTBS) (Huang et al. 2011). It could be proposed that using longer treatment courses, for example six weeks instead of three, may highlight differences between groups. For higher relevance and comparison purposes in the future it would also be useful to register metabolic changes in the DLPFC and the subgenual cingulate, together with more specific EEG changes. It would also be interesting to do a direct clinical comparison of MR-less MNI based neuronavigated rTMS and individual fMRI based neuronavigated rTMS, because although complicated and expensive, individual fMRI still provides us with individual brain anatomy and the possibility to manipulate additional important variables like cognitive priming (Luber et al. 2017).

CONCLUSIONS

1. Lowest physiological changes in EEG power spectrum were observed when using -46; 45; 38 MNI coordinates, highest - when using -40; 48; 35 MNI coordinates.
2. Highest clinical gain was observed when using -38; 44; 26 MNI coordinates.
3. Considering both physiological imprint and clinical efficacy it is advised to use -38; 44; 26 MNI coordinates.

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