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Electrophysiological differences between high and low frequency rTMS protocols in depression treatment

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Repetitive transcranial magnetic stimulation (rTMS) is a rapidly expanding mean in drug resistant depression treatment. Yet, despite vast research in this field, exact neurophysiological mechanism of rTMS therapy still remains unclear. This results in difficulties choosing suitable rTMS parameters in advance and compromises thorough evaluation of efficacy after the treatment. In order to obtain more explicit assessment of rTMS therapy in the psychiatric field, we evaluated and compared the influence of two most widely used antidepressive rTMS protocols on EEG band power spectrum and relation to clinical test scores (MADRS, BDI, HAM-D17). Forty-five patients (12 male, 33 female, mean age 52.16 years) participated in the study. Twenty-three patients received high frequency (10 Hz) stimulation, the rest 22 were stimulated using low frequency (1 Hz) protocol. Both groups received 10 to 15 daily rTMS sessions. EEG recordings and clinical tests were obtained the day before rTMS course and same day after the last session. Majority (57.78%) of patients showed considerable improvement after the treatment. There were no notable differences in clinical test score drop between the two rTMS protocols. However, we found that different protocols resulted in significantly different electrophysiological changes. High frequency (10 Hz) rTMS resulted in widespread changes off EEG band power, including delta power increase on the left hemisphere and alpha power growth on the right. Theta power increase was also obtained in parietal-occipital areas. Low frequency (1 Hz) rTMS showed to have no major effect on basic EEG band power, however we found a notable shift of frontal alpha power asymmetry towards the right hemisphere, which correlated with the clinical outcome. Our study results suggest that two widely used rTMS protocols strongly differ in their electrophysiological mechanisms. Low frequency stimulation finesse on frontal alpha power asymmetry shift, whereas high frequency protocol acts on wider electrophysiological changes in the brain.

Key words: Transcranial magnetic stimulation, TMS, depression, EEG, high frequency, low frequency, electrophysiological differences

INTRODUCTION

Affective disorders currently are few of the most prominent mental health issues. World Health Organization estimates around 121 million people suffering from severe depression to date. Regular treatment of depression by psychotherapy sessions and pharmacological agents does not always yield satisfactory results, therefore it is often being complemented or even replaced by alternative treatment methods. One of those methods – repetitive transcranial magnetic stimulation (rTMS) is spreading widely as a therapeutic mean in depression, especially treatment - resistant.

Despite the recent popularity of rTMS clinical usage and exponential growing number of studies, exact neurophysiological rTMS mechanisms, responsible for depressive symptom alleviation, still remains complicated and unclear. This uncertainty results in difficulties choosing the right rTMS parameters, suitable for the patient, as well as complicates thorough evaluation of the treatment efficacy.

From the clinical standpoint, although data still remain somewhat controversial, most studies indicate,

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that rTMS is indeed an effective method in depression treatment. More so, from the clinical research it has been shown, that two rTMS protocols, commonly used in treating depression – high frequency stimulation over the left prefrontal dorsolateral cortex (PFDLC) (George et al. 2000) and low frequency stimulation over the right PFDLC (Klein et al. 1999), are equally matched in their efficacy despite the initially opposite physiological action they produce on the cerebral cortex (Fitzgerald et al. 2003, 2009, Hoppner et al. 2003, Isenberg et al. 2005).

Neurophysiology of depression

Studies aimed at bioelectrical brain activity changes in depression yield variable and controversial results. Depression is often associated with asymmetrical slow wave activity in the frontotemporal area, decreased inter hemisphere coherence in delta and theta bands (Lieber 1988), resulting overall increase in delta and theta power in the right hemisphere (Kwon et al. 1996). On the contrary, Pozzi and coauthors (1995) describes depression as a disorder, manifesting itself by theta wave increase exclusively in the posterior areas. Different from Kwon and colleagues (1996) study, Pozzi and others (1995) states that delta power is decreased in every cortical area in the case of depression. It is important to note, that depression patients can also display general increase in alpha band power (Kemp et al. 2010) or on the opposite an alpha power decrease (Price et al. 2008) along with some changes in the beta frequency band (Kemp et al. 2010). Grin-Yatsenko and coworkers (2009) study revealed that in the early stages of depression patients display an increase in beta (along with alpha and theta) power in parietal and occipital cortices. Although it is usually accepted that depression results in a decrease of general brain activity, manifesting itself by slower wave – theta and alpha – power increase, it is clear that the actual brain activity picture is much more complex. It is possible that beta power increase might be correlated to the present anxiety symptoms.

It is also worth mentioning, that studies indicate a very important role of prefrontal cortex alpha band power in relation to depressive symptoms. Henriques and Davidson (1991) proved that depression results in an increase of alpha power in the left prefrontal cortex, indicating hypo activity in this area. At the same time right prefrontal cortex is hyperactive, which is observable by alpha power decrease [alpha band power negatively correlates with metabolic activity (Cook et al. 1998)]. The fact, that depression results in frontal alpha asymmetry has been proved by later studies as well (Lubar et al. 2003). Numerous PET studies also sup-

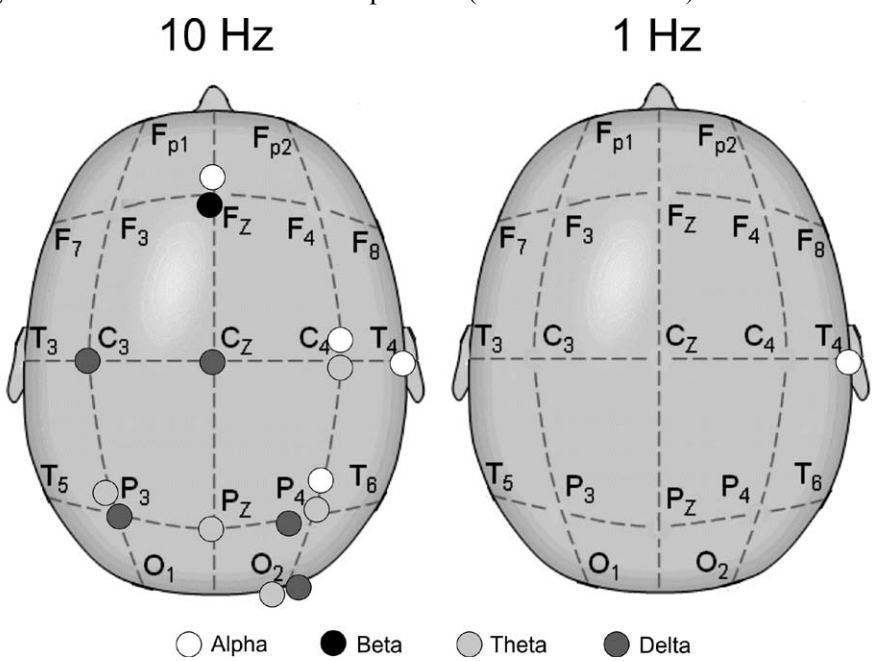

Fig. 1. Regional differences between different frequency rTMS protocols. This figure shows electrophysiological changes in particular EEG electrodes after 10 Hz and 1 Hz rTMS therapy. Accentuated dots indicate statistically significant (P<0.05) increase of band power after the treatment.

port the hypothesis of left prefrontal cortex hypoactivity in depression (Ebert et al. 1991, Bench et al. 1993). Increasing interest in depressive patient frontal alpha asymmetry lead to a number of research, studying it's usage for diagnostic and prognostic purposes. It was proven, that frontal alpha asymmetry is a constant trait, remaining stable for up to 16 weeks. Also it is a valid marker for affective psychopathology risk, going beyond just depressive disorders (Allen et al. 2004).

Moreover, alpha asymmetry can be used for treatment prognosis. Rosenfeld and coauthors (1996) study showed that the direction of change in frontal activity asymmetry during the treatment course could help evaluating overall outcome of the treatment. Correlation between frontal alpha asymmetry and clinical test score was also found in Diego and colleagues (2001) study. Bruder and coworkers (2001) study showed that patients for whom twelve week course of flouxetine was ineffective had significantly higher right hemisphere activity than on the left, before the treatment compared to those patients for whom the course was successful.

However, not all studies support the notion that depression clinical symptoms and frontal alpha asymmetry universally correlate. Allen and others (2004) failed to prove statistically significant link between frontal alpha asymmetry and change in clinical outcome. Gotlib (1998) also did not found statistically significant difference between patients suffering from depression and those in the state of remission. Some authors postulate, that frontal alpha asymmetry is an absolutely constant depression trait, remaining stable even after a successful pharmaceutical treatment (Baehr et al. 1997).

Flor-Henry and coauthors (2004) study results absolutely contradicted frontal alpha asymmetry theory. They registered activity increase in the left prefrontal cortex and decrease on the right. Differences in frontal asymmetry between depressive patients and healthy controls were not observed in Hoppner and colleagues (2006) and Suhhova and others (2008) studies. Martin and coworkers (2001) also failed to find the difference of left and right prefrontal cortex metabolism in depressive patients.

Considering parietotemporal alpha asymmetry role in depression, studies and notions are even more variable and contradictory (Pozzi et al. 1995, Reid et al. 1998, Moratti et al. 2008, Kemp et al. 2010). However it seems that depression without anxiety symptoms usually results in lower right hemisphere temporal cortex activity compared to one on the left, whereas patients suffering from anxious depression showed higher right hemisphere frontal and temporal cortex activity (Bruder et al. 1997). These results were also duplicated in Kentgen and coauthors (2000) study.

Neurophysiology of rTMS

It is widely known, that rTMS is able to alter bioelectrical activity of cerebral cortex. That is an important fact in drug resistant depression treatment, because it allows to try and restore pathophysiological changes, associated with depressive disorders, usually involving decrease in left prefrontal cortex activity and higher than normal right prefrontal cortex activity.

It has been shown that low frequency (~1 Hz) stimulation action on cerebral cortex is inhibitory, whereas high frequency (>5 Hz) stimulation facilitates cortical activity (George and Belmaker 2007). In their study Speer and collagues (2000) used 20 Hz stimulation over left PFDLC in depressive patients and found increase in cerebral blood flow in prefrontal cortex (left>right), cingulate gyrus (left>right), left amygdala, as well as both hemisphere insula, basal ganglia, uncus, hipocampus, thalamus and cerebellum (registered 72 hours after the last rTMS session). The use of low frequency rTMS (1 Hz) diminished blood flow in right prefrontal and left temporal cortices, left basal ganglia and amygdala. Kimbrell and coauthors (2002) studied brain metabolism changes after rTMS in

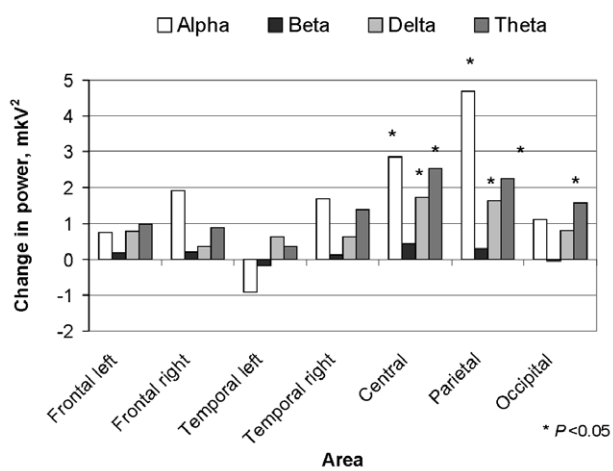

Fig. 2. 10 Hz rTMS influence on EEG band power. This figure shows changes of EEG band power in certain brain areas after 10 Hz rTMS therapy.

Table I

Mean clinical test score drop after the treatment (*P<0.05)

Protocol	MADRS	BDI	HAM-D
10 Hz	48.20%	49.45%	56.35%
1 Hz	48.10%	45.27%	47.83%
Both	48.14%	47.50%	52.21%

healthy subjects. They found that 30 minutes of 1 Hz rTMS over left PFDLC decreases glucose metabolism in contralateral prefrontal cortex, basal ganglia in both hemispheres, sACC, hypothalamus, midbrain and cerebellum. High frequency rTMS course over the left PFDLC as been shown in Baeken and others (2009) study increases ACC area metabolic activity in depressive patients.

Despite mentioned research of rTMS influence on local activity changes, rTMS studies aimed at more complex bioelectrical brain function modulation in depression treatment are scarce and controversial. Loo and coworkers (2001) and Spronk and others (2008) in their studies tried to evaluate 10 Hz rTMS over the left PFDLC influence on EEG of depressive patients, however failed to find any universally significant or specific changes. However it is worth noting that in Spronk and colleagues (2008) study many patients displayed delta power increase in the right hemisphere after the treatment. These findings coincide with Griskova and coauthors (2007) high frequency rTMS study results, using healthy volunteers. Although

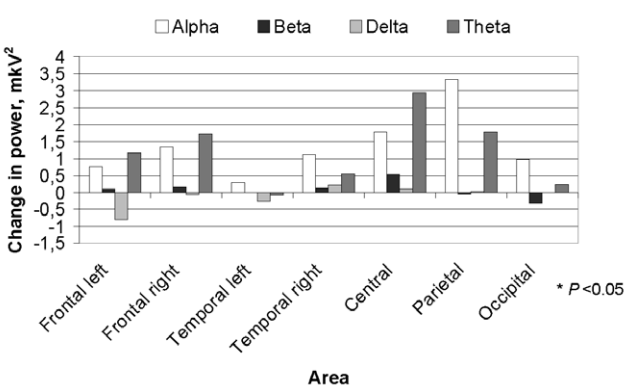

Fig. 3. 1 Hz rTMS influence on EEG band power. This figure shows changes of EEG band power in certain brain areas after 1 Hz rTMS therapy.

Spronk and others (2008) study failed at finding significant change in alpha asymmetry, general alpha band power increase was observed and it also was slightly larger on the right hemisphere. Price and coworkers (2008) measured general alpha power and asymmetry changes after each high frequency rTMS procedure. Observed changes were insignificant and opposite to the alpha asymmetry theory. On the contrary Funk and George (2008) in their 10 Hz rTMS proved that TMS course actually diminishes hemisphere asymmetry in all frequency bands, taking into account that their patients had strong asymmetry tendency towards higher power on the right before the treatment.

Aims and objectives

Previous studies suggest that rTMS therapy success might depend on initial EEG characteristics like wave band power asymmetry. It is worth to note, that in relation to different starting position, chosen rTMS protocol might also produce different effect as the final result. Although there are many published studies on high as well as low frequency rTMS efficacy on depressive clinical symptoms, not many tried to compare effects of different rTMS protocols in a single study. Mentioning the few it is worth noting Fitzgerald and coworkers (2003) (comparison between 10 Hz and 1 Hz rTMS), Hoppner and colleagues (2003) (20 Hz and 1 Hz), Isenberg and coauthors (2005) (20 Hz and 1 Hz) and Fitzgerald and others (2009) (10 Hz and 1 Hz) studies, yet none of this research was in any way directed at electrophysiological differences between the rTMS protocols, concentrating only on clinical tests. All of these authors in their conclusions state, that both stimulation protocols display higher efficacy than placebo stimulation, although they failed to show any notable differences between high frequency rTMS over the left PFDLC and low frequency rTMS over the right PFDLC at least considering the clinical effect.

Therefore in our study we set a goal to evaluate electrophysiological mechanisms of both high and low frequency rTMS protocols, including their influence on EEG power band spectrum and frontal - temporal hemisphere asymmetry. Another important variable was the correlation between evoked electrophysiological changes and the clinical outcome. The general hope of the study therefore was to try and discover initial

Table II

Mean EEG band power before and after 10 Hz rTMS treatment (*P<0.05)

10 Hz rTMS		Alpha	Beta	Delta	Theta
Frontal left	Before	8.26 ± 6.86	2.05 ± 1.57	7.37 ± 4.49	7.68 ± 6.48
	After	8.99 ± 6.24	2.23 ± 1.94	8.15 ± 5.10	8.67 ± 7.98
Frontal right	Before	8.58 ± 6.65	2.10 ± 1.54	7.22 ± 4.33	8.02 ± 7.06
	After	10.51 ± 7.37	2.31 ± 1.31	7.57 ± 3.50	8.91 ± 6.31
Temporal left	Before	10.41 ± 12.31	2.12 ± 2.06	3.75 ± 2.18	5.38 ± 3.59
	After	9.49 ± 7.91	1.94 ± 1.74	4.37 ± 3.03	5.73 ± 4.98
Temporal right	Before	10.67 ± 9.02	2.05 ± 1.48	4.05 ± 2.74	5.80 ± 5.26
	After	12.37 ± 10.51	2.18 ± 1.48	4.68 ± 2.60	7.18 ± 6.44
Central	Before	14.59 ± 15.02*	2.73 ± 1.79	6.47 ± 4.20*	9.62 ± 8.77*
	After	17.44 ± 12.16*	3.16 ± 2.03	8.22 ± 5.31*	12.14 ± 11.15*
Parietal	Before	21.43 ± 23.75*	2.70 ± 1.60	5.82 ± 4.12*	8.09 ± 7.03*
	After	26.12 ± 20.15*	2.99 ± 1.89	7.46 ± 4.88*	10.35 ± 8.34*
Occipital	Before	18.45 ± 24.08	2.25 ± 1.21	4.03 ± 2.53	5.63 ± 3.44*
	After	19.57 ± 18.67	2.19 ± 1.07	4.83 ± 2.74	7.22 ± 5.06*

Table III

Mean EEG band power before and after 1 Hz rTMS treatment (*P<0.05)

1 Hz rTMS		Alpha	Beta	Delta	Theta
Frontal left	Before	8.59 ± 7.78	2.91 ± 1.72	7.80 ± 4.95	5.36 ± 4.11
	After	9.35 ± 8.50	3.02 ± 2.06	7.01 ± 5.12	6.53 ± 6.71
Frontal right	Before	8.73 ± 8.64	3.14 ± 2.27	7.03 ± 4.42	5.07 ± 3.58
	After	10.06 ± 8.26	3.31 ± 2.17	6.98 ± 3.88	6.80 ± 6.25
Temporal left	Before	10.04 ± 10.93	2.72 ± 1.74	3.88 ± 3.30	4.00 ± 3.78
	After	10.34 ± 9.36	2.72 ± 1.87	3.61 ± 3.23	3.92 ± 3.08
Temporal right	Before	11.22 ± 12.90	2.83 ± 2.13	3.27 ± 1.74	3.55 ± 2.77
	After	12.33 ± 10.95	2.95 ± 2.18	3.50 ± 1.59	4.10 ± 2.71
Central	Before	16.08 ± 17.55	4.56 ± 3.04	5.61 ± 3.23	6.29 ± 4.54
	After	17.85 ± 15.25	5.09 ± 3.52	5.73 ± 2.49	9.23 ± 12.41
Parietal	Before	22.13 ± 23.34	4.55 ± 3.58	4.73 ± 2.70	5.40 ± 4.28
	After	25.45 ± 26.28	4.49 ± 3.08	4.76 ± 2.04	7.18 ± 8.29
Occipital	Before	22.50 ± 30.13	3.45 ± 2.71	3.56 ± 2.15	4.24 ± 3.45
	After	23.48 ± 28.48	3.13 ± 2.48	3.55 ± 1.55	4.49 ± 3.30

differences in EEG activity before rTMS treatment and different courses of physiological changes, related to different rTMS protocols, potentially serving as new guidelines for the protocol choice in order to achieve the best possible clinical outcome.

METHODS

Subjects

Forty-five subjects (33 female, mean age 52.16 years, SD = 11.9 years) with diagnosed drug resistant major depressive episode participated in the study. Each gave a written consent before participation. Selected patients were free of tricyclic antidepressant treatment. Previously failed pharmacological treatment used before rTMS was maintained at steady doses during the course.

Twenty-three subjects received high frequency rTMS (10 Hz) over the left PFDLC while 22 subjects received low frequency rTMS (1 Hz) over the right PFDLC. Different protocols were prescribed by psychiatrist based on whether depressive episode was adynamic (high frequency) or anxious (low frequency). Selected treatment protocol was applied five days per week for two to three weeks (10–15 procedures).

Apparatus

Medtronic Magpro X100 stimulator with MagVenture Cool Coil B65 figure 8 coil for rTMS procedure and EBNeuro Galileo Mizar EEG apparatus for EEG recording were used.

Procedures

rTMS

During the stimulation biphasic 280 μs impulses were used. Stimulation targets were left PFDLC (6 cm anterior to right abductor pollicis brevis motor area) for high frequency stimulation or right PFDLC (6 cm anterior to left abductor pollicis brevis motor area) for low frequency stimulation. High frequency rTMS consisted of twenty 10 Hz stimulation trains lasting 8 seconds each, spaced at 40 second interval, applied at 100% motor threshold value. Low frequency rTMS consisted of two 1 Hz stimulation trains lasting 60 seconds each, spaced at 3 minute interval, applied at 120% motor threshold value.

EEG was recorded before rTMS course and 25 min after the last session. Electrodes were placed according to 10-20 system. Fpz electrode was used as a ground, ear electrodes were used as a reference. Impedance was maintained lower than 5 kΩ. Baseline EEG was recorded for 10 min while the patient was sitting with eyes closed. EEG was filtered using low frequency (0.53 Hz), high frequency (70 Hz) and notch (50 Hz) filters. Data was digitized at 256 frequency and 12 bit rate. Thirty-second EEG interval without artefacts was used for further analysis. Hanning window was applied for 2 s epochs. Power spectrum $S(\omega)$ mean EEG intensity ($\mu V^2/Hz$) was evaluated by means of fast Fourier transformation (FFT). Absolute power was evaluated in 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 bands.

The averages of EEG band power were calculated from the data to the following areas: (a) Frontal left (FrontL) (Fp1, F7, F3 electrode averages); (b) Frontal right (FrontR) (Fp2, F4, F8 electrode averages); (c) Temporal left (TempL) (T3, T5 electrode averages); (d) Temporal right (TempR) (T4, T6 electrode averages); (e) Central (C3, Cz, C4 electrode averages); (f) Parietal (P3, Pz, P4 electrode averages); (g) Occipital (O1, Oz, O2 electrode averages).

Hemispherical asymmetries were calculated according to these formulas:

(a) Frontal (FrontL-FrontR)/(FrontL+FrontR);

(b) Temporal (TempL-TempR)/(TempL+TempR).

Therefore positive asymmetry coefficient indicates higher band power on the left hemisphere, whereas negative coefficient shows higher power on the right.

Clinical data

Before rTMS course and day after clinical symptoms were evaluated using The Montgomery-Åsberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression (HAM-D) tests.

Statistical analysis

All calculations were carried out using SPSS 11.0.0 software. Kolmogorov-Smirnov test showed that some data did not match the normal distribution. Therefore we used nonparametric tests for our further data analysis. Electrophysiological changes before and after rTMS course were analyzed using Wilcoxon test for two related samples. Electrophysiological differences

Table IV

Mean EEG band power asymmetry before and after 10 Hz rTMS treatment (*P<0.05)

10 Hz rTMS		Alpha	Beta	Delta	Theta
Frontal asymmetry	Before	−0.02 ± 0.13	−0.02 ± 0.15	0.00 ± 0.14	−0.01 ± 0.13
	After	−0.06 ± 0.14	−0.05 ± 0.15	0.01 ± 0.17	−0.02 ± 0.15
Temporal asymmetry	Before	−0.03 ± 0.26	−0.01 ± 0.23	−0.03 ± 0.19	0.04 ± 0.22
	After	−0.09 ± 0.26	−0.07 ± 0.24	−0.04 ± 0.19	−0.06 ± 0.26

between patients of different rTMS protocols and patients with different clinical outcome were calculated using Mann-Whitney test for two independent samples. Additional analysis of variance (ANOVA) for repeated measures was performed separately for values of power in each EEG frequency bands. Within subjects variables were measured before and after stimulation (procedure factor). Between subjects factors were protocol (1 Hz vs. 10 Hz) and area (frontal left, frontal right, temporal left, temporal right, central, parietal and occipital) factors. Correlations between the electrophysiological changes and clinical progress were evaluated using Spearman correlation coefficient. Bonferroni correction was applied for confidence interval adjustment.

RESULTS

After the treatment 40 patients (88.89%) showed at least some signs of improvement (MADRS test score reduction >10%), 26 patients (57.78%) considerable improvement (MADRS test score reduction >50%), 11 patients (24.44%) achieved full remission (MADRS test score after the treatment <10 points) in both study groups. Table I shows mean score reductions in both as well as separate rTMS protocol groups. Mann-Whitney test failed to show significant differences in clinical test score change between the high (10 Hz) and low (1 Hz) frequency rTMS protocols.

Statistically significant (P<0.05) physiological changes in local band power after rTMS course show that high frequency (10 Hz) rTMS protocol gives much larger and wider electrophysiological changes, compared to the low frequency stimulation (Fig. 1).

Figures 2 and 3 show the direction of band power change in the previously described brain areas. High frequency (10 Hz) rTMS results in an increase of alpha and delta power in the central and parietal areas as well as an increase in theta power, which also expands to the occipital area (Fig. 2, Table II). Low frequency (1 Hz) rTMS influence on central and parietal alpha and theta power, although statistically insignificant, is similar to high frequency rTMS, whereas there is no visible effect on delta power in those areas (Fig. 3, Table III). Additional look at the local changes (Fig. 1) indicates alpha power increase in the right hemisphere, delta power in the left and theta power being increased across the whole brain. However not statistically significant, there is also a difference in delta power change direction between high and low frequency

Table V

Mean EEG band power asymmetry before and after 1 Hz rTMS treatment (* P<0.05)

1 Hz rTMS		Alpha	Beta	Delta	Theta
Frontal asymmetry	Before	0.02 ± 0.14*	−0.02 ± 0.14	0.04 ± 0.16	0.02 ± 0.13
	After	−0.05 ± 0.11*	−0.06 ± 0.11	−0.03 ± 0.17	−0.05 ± 0.12
Temporal asymmetry	Before	−0.04 ± 0.18	0.01 ± 0.25	0.01 ± 0.27	0.03 ± 0.24
	After	−0.11 ± 0.22	−0.05 ± 0.19	−0.04 ± 0.21	−0.04 ± 0.22

rTMS protocols in some areas. Whereas high frequency rTMS tends to raise delta power in all regions, especially in the left hemisphere, low frequency rTMS acts on the complete opposite actually diminishing delta power in the left frontal and temporal areas.

There were noted changes in EEG band power between patients of different rTMS protocol groups before as well as after treatment (Tables I and III). It is apparent, that low frequency patients before the rTMS course displayed higher beta power in frontal, central, parietal and left temporal areas, which also remained higher after the treatment. Additional Mann Whitney test proved these differences to be statistically significant (P<0.05).

We also checked the change and direction of frontal and temporal power asymmetry. Both protocols seem to shift band power towards the right hemisphere. However, only low frequency (1 Hz) rTMS show statistically significant (P<0.05) increase of frontal alpha power asymmetry towards the right hemisphere (Figs 4 and 5, Tables IV and V).

ANOVA testing showed a significant effect of procedure (after vs. before) on alpha power ($F_{1.00}$=5.708, P=0.018), delta power ($F_{1.00}$=5.273, P=0.022) and theta power ($F_{1.00}$=18.258, P=0.000). Additional factor of protocol showed significantly higher delta after high frequency stimulation ($F_{1.00}$=8.369, P=0.004).

Correlations between electrophysiological changes and clinical improvement, expressed in percentage of clinical test score decrease after the treatment are shown in Tables VI and VII. After high frequency (10 Hz) rTMS treatment there is a significant relation between occipital beta power increase and BDI test score as well as delta power increase on the frontal left region and clinical improvement, measured by BDI and HAM-D tests. Notable delta power changes in central and parietal areas, together with alpha and theta power increase appeared to correlate little or even slightly negatively to the clinical improvement. Correlations between beta power increase on the left frontal area and all clinical tests scores, delta power increase on the right frontal area and BDI test scores as well as alpha power asymmetry shift and BDI test scores were found after low frequency (1 Hz) rTMS course. However, since the asymmetry shift towards the right is expressed by negative number, this particular correlation actually meant worse test scores after larger shift.

DISCUSSION

From the clinical perspective, we found no notable differences between the test scores of both patient groups. Low frequency and high frequency rTMS protocols proved to be equally effective treatment options, matching the results of previous studies (Fitzgerald et al. 2003, 2009, Hoppner et al. 2003, Isenberg et al. 2005).

Notable differences were found in the physiology of different rTMS protocols. Electrophysiological differences between the two patient groups before treatment already show an obvious tendency of higher beta power in low frequency rTMS group. That is expected, taken into account that low frequency rTMS is prescribed for patients, suffering from depression with anxiety symptoms. Grin-Yatsenko and coworkers (2009) also have observed increase in beta power in their study, especially

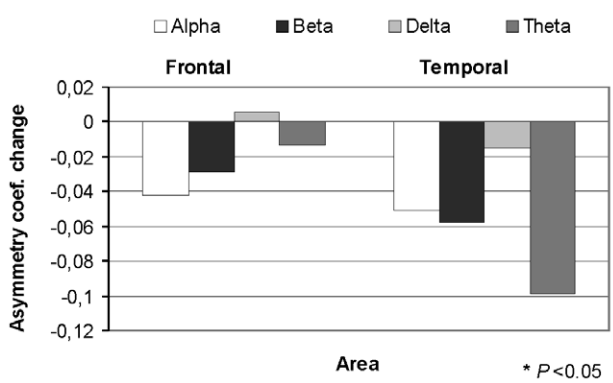

Fig. 4. 10 Hz rTMS influence on EEG band power asymmetry. This figure shows changes of EEG band power asymmetry after 10 Hz rTMS therapy.

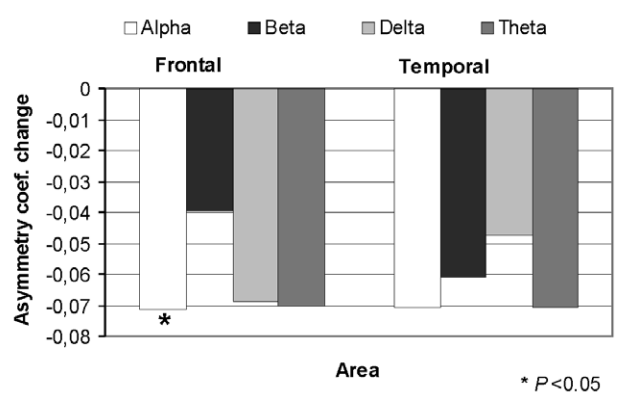

Fig. 5. 1 Hz rTMS influence on EEG band power asymmetry. This figure shows changes of EEG band power asymmetry after 1 Hz rTMS therapy.

Table VI

Correlations between electrophysiological changes and clinical improvement in 10 Hz rTMS treatment (*P<0.05)

	Alpha			Beta			Delta			Theta		
	MADRS	BDI	HAM-D	MADRS	BDI	HAM-D	MADRS	BDI	HAM-D	MADRS	BDI	HAM-D
Frontal left	−0.10	−0.17	−0.05	−0.10	0.20	0.24	0.24	0.51*	0.49*	0.37	0.36	0.39
Frontal right	0.12	−0.14	0.07	0.29	0.14	0.22	0.10	0.20	0.24	0.35	0.03	0.17
Temporal left	0.14	0.31	0.38	0.13	0.44	0.35	−0.05	0.14	0.16	0.36	0.26	0.43
Temporal right	0.29	0.03	0.14	0.39	0.18	0.23	−0.03	−0.23	0.00	0.34	0.01	0.18
Central	−0.21	−0.18	−0.05	0.28	0.41	0.38	−0.08	0.00	−0.01	0.33	0.27	0.34
Parietal	−0.16	−0.21	−0.11	0.17	0.33	0.22	−0.07	−0.11	−0.10	0.29	0.15	0.24
Occipital	−0.14	−0.17	−0.12	0.21	0.57*	0.30	0.22	0.12	0.33	0.42	0.32	0.41
Frontal asymmetry	−0.14	0.11	−0.16	−0.38	−0.06	−0.16	0.19	0.22	0.18	0.10	0.39	0.15
Temporal asymmetry	−0.04	0.22	0.00	−0.07	0.28	0.07	−0.03	0.34	0.14	−0.02	0.27	0.17

during the early stages of depression. The fact, that beta power differences remained unchanged after the treatment course suggests, that low frequency rTMS relieves anxious symptoms by mechanism other than simply diminishing the beta band power.

rTMS induced changes in electrophysiology differed greatly between two protocol groups as well. Results show that the effect of low frequency rTMS on the brain manifests itself mostly on frontal alpha asymmetry shift towards the right hemisphere. Several previous researchers have noticed and studied frontal alpha asymmetry and its change as a depression trait and a possible prognosis marker (Henriques and Davidson 1991, Rosenfeld et al. 1996, Diego et al. 2001, Lubar et al. 2003). Henriques and Davidson (1991) stated that frontal alpha asymmetry towards the left indicates left hemisphere hypoactivity, however it might also be caused by an overly excessive activation on the right. Before our study Bruder and colleagues (2001) noticed, that depressed patients, unresponsive to fluoxetine treatment had significantly higher right hemisphere activity than one on the left. They also expressed an idea that higher right hemisphere frontal and temporal cortex activity is mostly common in patients, suffering from anxious depression. In our study we found that low frequency rTMS protocol, aimed at diminishing the activity of right hemisphere per se, resulted in largest frontal alpha asymmetry shift. However, this change seemed to have an adverse effect. Our results proved, that larger frontal alpha asymmetry shift towards the right hemisphere can result in lesser self observed improvement. It seems that although frontal alpha asymmetry plays an important role in anxious depression due to right hemisphere hyperactivation, diminishing its activity well below the left hemisphere level can also create negative reaction. Rosenfeld and others (1996) stated that the direction of change in frontal activity asymmetry during the treatment course could be helpful evaluating overall outcome of the treatment. Our study indicates that for the best clinical outcome frontal alpha asymmetry should be maintained closest to equilibrium.

For high frequency rTMS group, alpha asymmetry remained unchanged after the treatment. It could be said that in this group it has preserved status quo as a constant depression risk trait, same way as in Baehr and coauthors (1997) and Allen and others (2004) studies suggested. Same as those author findings, our results proved, that alpha asymmetry remained constant after a successful high frequency rTMS treatment. On the other hand it might be due to a near even alpha band power in both hemispheres before the rTMS course, since Funk and George (2008) have shown that 10 Hz rTMS diminishes hemisphere asymmetry in all bands only as long as patients initially display higher power on the right hemisphere.

Table VII

Correlations between electrophysiological changes and clinical improvement in 1 Hz rTMS treatment (*P<0.05)

	Alpha			Beta			Delta			Theta		
	MADRS	BDI	HAM-D	MADRS	BDI	HAM-D	MADRS	BDI	HAM-D	MADRS	BDI	HAM-D
Frontal left	0.23	0.38	0.29	0.46*	0.57*	0.60*	0.03	0.46	0.12	−0.13	0.07	−0.16
Frontal right	0.16	0.11	0.27	0.39	0.29	0.46	0.34	0.67*	0.30	−0.21	0.08	−0.27
Temporal left	0.22	0.09	0.30	0.20	0.26	0.42	0.08	0.16	0.31	−0.22	−0.03	−0.14
Temporal right	0.18	0.10	0.08	0.43	0.37	0.23	0.23	0.46	0.19	−0.10	0.09	0.01
Central	0.29	0.00	0.34	0.34	0.49	0.39	0.09	0.49	0.07	−0.28	−0.10	−0.35
Parietal	0.39	0.14	0.25	0.19	0.30	0.22	−0.20	0.40	−0.07	−0.18	−0.05	−0.19
Occipital	0.23	0.16	0.13	0.08	0.15	0.12	−0.10	0.42	−0.14	−0.09	0.07	−0.03
Frontal asymmetry	0.26	0.61*	0.20	0.32	0.47	0.40	−0.24	−0.09	−0.11	0.05	0.19	0.19
Temporal asymmetry	0.04	0.25	0.45	−0.20	−0.02	0.17	0.12	−0.02	0.30	−0.28	−0.24	−0.11

Opposite to low frequency rTMS which has not produced notable changes in local EEG band power, high frequency stimulation resulted in a significant increase of alpha, theta and delta power across the brain. Delta power increase after high frequency stimulation was proved to be significantly greater overall by ANOVA test. It is important to note, that delta power increase after high frequency rTMS coincides with results of Griskova and coauthors (2007) study results, obtained from healthy subjects. Spronk and colleagues (2008) also noted an increase of delta band power, but only on the right hemisphere, which contradicts our study results, showing most of delta power gain on the left. It is also important to note, that the role of delta band power in depression is generally controversial. Pozzi and colleagues (1995) stated that depression results in an overall decrease of delta power in every cortical area, whereas Kwon and coworkers (1996) noted actual delta power increase on the right hemisphere in case of depression. Considering alpha band power, both Spronk and others (2008) and our study showed an increase on the right hemisphere, suggesting indirect inhibition, although frontal and temporal alpha asymmetry remained unchanged using high frequency rTMS.

There were significant differences in correlations between clinical tests and electrophysiological changes, indicating possibly different therapeutic mechanisms. As mentioned above, low frequency rTMS physiological effect mostly manifests on frontal alpha asymmetry shift towards the right, which actually results in lesser clinical improvement as it grows larger. Correlations between clinical improvement and delta power increase on the frontal right hemisphere as well as beta power growth on the left were also found it this group, despite the fact that the actual changes in power were small and insignificant. Using high frequency rTMS protocol therapeutic gain was strongly related to delta power increase on the left hemisphere, especially in the frontal lobes. However, despite the stimulation being targeted at those areas, largest delta power increases were found in central and parietal lobes. Here it is important to note, that as the previous studies suggest, delta band power role in depression can be rather complex (Pozzi et al. 1995, Kwon et al. 1996). Generally it seems that under adynamic depression without anxiety symptoms left hemisphere delta power increase produces beneficial results and should be endeavored. Our results suggest that anxious depression on the other hand could be alleviated with the increase of delta power on the right, which is contradictory to Kwon and coauthors (1996) notion, stating that high right delta power is a malicious depression trait.

Overall, when it comes to choosing the right rTMS protocol, Fitzgerald and colleagues (2003) prescribed

low frequency rTMS as a first strategy in drug resistant depression treatment, because of better overall proportion in safety, tolerability and efficacy terms. Our study proves it to be less intrusive physiologically and equally effective clinically, as long as frontal alpha band asymmetry does not become overly excessive towards the right hemisphere.

Our study suggests the possibility to use alpha asymmetry differences and delta power differences between the hemispheres as markers for choosing the right rTMS protocol. Large frontal alpha asymmetry towards the left hemisphere and relatively high delta power would encourage using the low frequency rTMS protocol. In other cases (low delta power and right shifted or near even frontal alpha asymmetry) high frequency protocol might be a better option. Observing EEG changes during rTMS course could also help predict overall outcome, especially when using low frequency rTMS protocol.

The main limitation of our study is the large sample of physiological variables measured and numerous correlations tested. It may be argued that some of these relations could be accidental, however others (frontal alpha power and delta power) have been discovered and studied to some extent by previous authors, investigating depression mechanisms, and the latter was additionally confirmed by ANOVA testing. Therefore it would be beneficial to study these physiological parameters and their relation to clinical status further, using larger study groups or additional treatment techniques (ECT, drug therapy, etc.) Electrophysiological changes should also be measured more frequent to observe the earliest reactions. Another limitation is a lack of control or healthy subject group. For the future studies it would be beneficial to use sham stimulation or include measurements of healthy test subjects as well, to be used as a standard reference group.

CONCLUSIONS

High and low frequency rTMS protocols differ in their electrophysiological mechanisms, despite the equally matched therapeutic effect. Low frequency rTMS protocol acts on subtle changes in frontal alpha asymmetry. High frequency rTMS protocol initiates vast bioelectrical changes in the brain, of which delta power increase on the left hemisphere correlates with positive clinical effect.

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