VILNIUS UNIVERSITY

Vladas Valiulis

THE EFFECT OF TRANSCRANIAL MAGNETIC STIMULATION ON BRAIN BIOELECTRICAL ACTIVITY

Summary of doctoral dissertation
Biomedical sciences, Biophysics (02 B)

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VILNIAUS UNIVERSITETAS

Vladas Valiulis

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CONTENTS

ABBREVIATIONS

ANOVA – analysis of variance

AsF – frontal asymmetry

AsT – temporal asymmetry

BDI – Beck depression inventory

Cen – Central cortical area

EEG – electroencephalography

ECT – electroconvulsive therapy

FrL – left frontal cortical area

FrR – right frontal cortical area

HAM-D – Hamilton depression scale

MADRS – Montgomery-Asberg depression rating scale

MNI – Montreal Neurological Institute

Ocp – occipital cortical area

Par – parietal cortical area

PFDLC – prefrontal dorsolateral cortex

rTMS – repetitive transcranial magnetic stimulation

RVPH – republican Vilnius psychiatric hospital

SD- standard deviation

SPECT- single photon emission computer tomography

TmL – left temporal cortical area

TmR – right temporal cortical area

TMS – transcranial magnetic stimulation

WHO – world health organisation

1. INTRODUCTION

Affective disorders are among the most pervasive psychiatric disorders of current times. According to WHO calculations around of 350 million people suffer from depression annually (Pellicciani et al, 2013). Conventional treatment methods of the disease, such as pharmaceutical treatment or psychotherapy, does not always yield satisfactory results, therefore they are being supplemented or even replaced by alternative therapeutic means. Transcranial magnetic stimulation (TMS) is one such optional method, rapidly gaining popularity in depressive disorder, especially drug resistant, treatment. TMS therapy can be described as a non invasive mean to alter the activity of cerebral cortex (Pascual-Leone et al, 1998). In drug resistant psychiatric disorder treatment TMS is usually used as an alternative to older and more conventional electroconvulsive therapy (ECT). However, unlike the ECT, TMS does not require patient to undergo anaesthesia and does not produce notable cognitive impairment (Cusin and Dougherty, 2012).

Although the majority of studies, analysing the effect of several week TMS therapy course on depression symptoms, have showed considerable clinical improvement, surpassing the placebo effect (Padberg and George, 2009), there are some patients to whom TMS therapy proves to be ineffective when using generally standardized TMS protocols. *Situation is being complicated by the fact that exact neurophysiological mechanism of TMS therapy, causing alleviation of depressive symptoms, remains unknown, the most common measure of TMS efficacy being estimations of sole changes in clinical test scores.* Without the firm physiological base there are difficulties in choosing the right TMS parameters, suitable for each depressive patient, and the possibility of objective and thorough evaluation of the treatment becomes compromised.

The most commonly used TMS protocols in depression treatment and studies are high frequency (10 Hz) stimulation over the left prefrontal dorsolateral cortex (PFDLC)(George et al, 2000) and low frequency (1 Hz) stimulation over the right PFDLC (Klein et al, 1999). Usually chosen by psychiatrist according to pervasive depressive disorder symptoms, these two protocols on the average are proven to be equally effective clinically in most studies (Fitzgerald et al, 2003; Hoppner et al., 2003, Isenberg et al, 2005; Fitzgerald et al., 2009; Valiulis et al, 2012), despite initially

opposite physiological effect they produce (high frequency rTMS locally increases cortical activity, whereas low frequency stimulation inhibits targeted cortical area)(George and Belmaker, 2007).

Studies, exploring the neurophysiological changes in the brain, produced by previously mentioned rTMS protocols, are scarce and controversial. Results usually tend to vary greatly, however there have been observations of a notable increase in EEG delta band power across several brain areas after the rTMS session (Spronk et al, 2008; Griškova et al, 2006). It is worth to mention that most researchers studied only the neurophysiology of 10 Hz rTMS protocol over the left PFDLC. *There is a serious shortage of 1 Hz rTMS physiology and both protocol physiology comparison studies. Moreover, physiological changes, caused by rTMS, are usually being measured after single procedure and not the whole therapy course.*

There is a notion that at least some of the electrophysiological variance and differences in clinical effect for individual patients after rTMS therapy can be caused by the variations in procedure, including location of stimulation target and positioning of TMS coil (Rusjan et al, 2010). Standard TMS positioning method defines stimulation area in the brain by constant distance to other particular functional cerebral area (commonly the motor cortex). When using such positioning method, stimulation target localization error usually accounts to 1-2 cm between subjects (Ahdab et al, 2010), at some cases even exceeding the 2 cm mark (Nauczyciel et al, 2011). Stimulation target accuracy in the clinical TMS field can be improved by using neuronavigation system. This system allows to set TMS target according to precise coordinates in the individual brain map, thus eliminating the influence of individual anatomical variations and decreasing target localization error to 1-2 mm. *Majority of clinical studies support higher therapeutic rTMS efficacy when using neuronavigation system (Dell'osso et al, 2009), however it remains unknown how this methodological advancement affects electrophysiological changes in the brain.*

Thorough analysis of physiological changes can help to evaluate not only the efficacy of the therapy, but safety as well. Although it is generally accepted, that in their adequate intensities both TMS and modern ECT are safe methods, complicated physiological mechanisms of these therapies and uncertainties regarding long term bioelectrical changes they produce in the brain still raise concerns (Padberg and George,

2009; Ahdab et al., 2010; Fosse et al, 2013). It has been shown that overly intense TMS application can evoke a motor seizure (George and Belmaker, 2007). Overdose in ECT can cause even more serious consequences. Animal experiments have demonstrated that too intense and frequent ECT usage, exceeding the recommended 8-12 procedure course can be sufficient enough to cause pathological changes in the brain, including swelling, gliosis, atrophy and necrosis (Zyss et al, 2000). Moreover, physiological studies indicate that TMS and ECT methods, even when using at or below considered safe intensities, are able to cause long term bioelectrical changes in the brain, which can be related to pathological mechanisms, such as an increase of EEG delta and theta band power (Fosse et al, 2013). *Despite their similarities, comparative studies of TMS and ECT electrophysiology are rare, there are no trials to compare the physiology of both methods in the single study. There is also a void in TMS studies, exploring the dynamics of evoked physiological changes during several months after the therapy.*

Correlative studies between EEG band power spectrum and depressive symptom change are scarce and produce inconsistent results. There is a lack of practical knowledge on how TMS and ECT evoked EEG changes influence the clinical outcome. Another potent electrophysiological marker – auditory evoked potential P300, widely used in psychiatric disorder identification and evaluation practice, has also been somewhat neglected in the depression therapy. P300 parameters credibly show the status of cognitive functions and their changes. In the RVPH P300 potential has been used to evaluate ECT and other therapeutic means in treating schizophrenic spectrum disorders where it proved itself to be potential therapeutical effect marker (Dapšys, 2011). Studies show that depressive spectrum disorder can also manifest in P300 potential changes (Isintas et al, 2012; Jandl et al, 2010). Some authors have found out that initial parameters of P300 potential can in part help to prognosticate the later success of TMS therapy (Arns et al, 2012). *Anyhow, in general TMS-P300 relation studies remain limited and heterogeneous (Rego et al, 2012). Also, there are no studies found, evaluating and comparing the influence of different rTMS protocols and coil positioning methods on P300 potential.*

1.1. Aim and objectives.

The main aim of the study was to evaluate the effect of rTMS therapy course on bioelectrical brain activity and compare it to alternative electrophysiological drug resistant psychiatric disorder treatment effect.

Main objectives of the study were:

1. To compare the two most common antidepressive rTMS protocol influence on EEG band power spectrum.
2. To study how different TMS coil positioning methods affect EEG band power spectrum.
3. To compare the EEG band power spectrum changes, caused by different parameter rTMS therapy to changes, produced by ECT.
4. To study the temporal dynamics of TMS evoked EEG band power spectrum changes by measuring and evaluating EEG of returning patients.
5. To study the influence of different parameter rTMS therapy on auditory evoked potential P300.
6. To study the relationship between bioelectrical brain activity (EEG band power spectrum and P300 potential) changes and clinical effect using depression rating scales.

1.2. Actuality and scientific novelty.

Scientific novelty:

1. For the first time in Lithuania the analysis of TMS physiological effect in depressive affective disorder treatment was carried out.
2. For the first time in the world a quantitative comparison of long term electrophysiological changes, produced by two different rTMS protocols and coil positioning techniques was included in the single study.
3. For the first time in the world a comparative study of TMS and ECT long term physiological effects was carried out.
4. For the first time in the world TMS evoked long term bioelectrical brain activity dynamics was studied in several months time.

Practical value:

1. Popular and successful rTMS protocols (Classical 10 Hz and Klein‘s 1 Hz), being used in psychiatric practice abroad, were tested and installed in Lithuania.
2. TMS therapy coil positioning methods, ranging from standard anatomical metrics to Talairach coordinate based neuronavigation system were installed and corrected in Lithuania.
3. TMS patient physiological evaluation protocols, involving the measurement and analysis of resting state EEG band spectrum power and evoked potential P300, were installed in Lithuania.

Practical recommendations:

1. When treating drug resistant depressive disorders it is advisable to choose therapeutic methods in succession of physiological effects from the mildest (1 Hz rTMS > 10 Hz rTMS > ECT).
2. For the higher accuracy and clinical effectiveness it is recommended to use neuronavigation system in all TMS procedures.
3. P300 potential parameters can be used as a TMS therapeutic efficacy marker, therefore it is suggested to measure P300 potential several times during the TMS course.
4. EEG recordings before and after TMS course can be useful in determining the level of physiological side effects of the therapy.

1.3. Statements to be defended:

1. Changes in EEG band power spectrum, caused by high and low frequency rTMS protocols, differ significantly.
2. The use of neuronavigation system in TMS therapy causes fewer physiological side effects, measured by EEG band power spectrum and more pronounced clinical effect.
3. Changes in EEG band power spectrum, produced by TMS therapy, differ in it‘s intensity from ECT caused changes and therefore can be used as an argument in choosing the therapy method.
4. Changes in EEG band power spectrum, caused by TMS therapy, are dynamic and return to the baseline in few months time.

5. TMS therapy of different parameters produces variable changes to auditory evoked potential P300.

6. Some changes to EEG band power spectrum and auditory evoked potential P300 correlate to clinical effect of TMS therapy and can be used as a treatment efficacy marker.

2. METHODS

For all studies the consent of Medical ethics committee of Republican Vilnius Psychiatric Hospital Nr. V5-2, 2011-10-10 was received. All the calculations were carried out using Microsoft Office Excel 2003 and SPSS Statistics 17.0 software packages.

2.1. Study of high and low frequency rTMS therapy effect on EEG band power spectrum.

2.1.1. Subjects.

50 subjects (37 women, 13 men, mean age 51,6 years, SD = 11,6 years), with diagnosed drug resistant depressive disorder (41 patient) or depressive type schizoaffective disorder (9 patients) participated in the study. Before participation each patient gave a written consent. Chosen patients were free of tricyclic antidepressant treatment. Ineffective pharmacological treatment prior to rTMS course was continued at steady doses during the rTMS therapy.

26 patients were treated with high frequency (10 Hz) rTMS over the left hemisphere PFDLC, remaining 24 patients received low frequency (1 Hz) rTMS over the right hemisphere PFDLC. Particular protocol for each patient was prescribed by a psychiatrist according to prevailing symptoms: adynamic depression was treated with high frequency rTMS, anxious depression was treated with low frequency rTMS. Procedures were applied five times per week for two to three weeks (10-15 procedures overall in rTMS course).

2.1.2. TMS procedure.

TMS procedures were applied using Medtronic Magpro X100 TMS stimulator with MagVenture Cool Coil B65 liquid cooled figure eight coil. During the stimulation 280 μs biphasic impulses were used. Stimulation target area was placed by standard distance from the motor cortex: 1) left hemisphere PFDLC 6 cm anterior to right hand thumb muscle (abductor pollicis brevis) motor area for high frequency rTMS; 2) right hemisphere PFDLC 6 cm anterior to left hand thumb muscle (abductor pollicis

brevis) motor area for low frequency rTMS. High frequency rTMS protocol consisted of twenty 10 Hz frequency impulse trains, lasting for 8 seconds each, divided by 40 second intervals (1600 impulses overall), applied at 100% motor threshold intensity. Low frequency protocol consisted of two 1 Hz frequency impulse trains, lasting for 60 seconds each, divided by 3 minute interval (120 impulses overall), applied at 120 % motor threshold intensity.

2.1.3 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 screened 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 (Fig. 2.1).

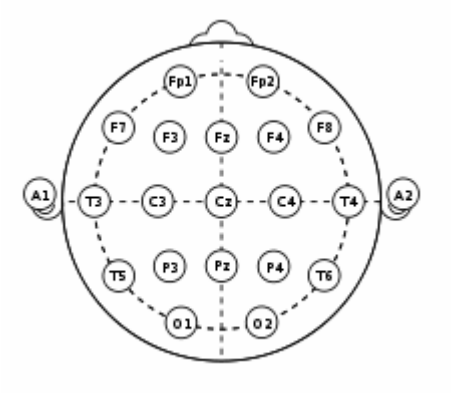

Fig. 2.1. Electrode placement for EEG recording.

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 $S(\omega)$ mean power values (μV^2) 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.

EEG band power was averaged in the following areas: 1) frontal left (FrL)(Fp1, F7, F3 electrode average); 2) frontal right (FrR)(Fp2, F4, F8 electrode average); 3) temporal left (TmL)(T3, T5 electrode average); 4) temporal right (TmR)(T4, T6 electrode average); 5) central (Cen)(C3, Cz, C4 electrode average); 6) parietal (Par)(P3, Pz, P4 electrode average); 7) occipital (Ocp)(O1, Oz, O2 electrode average)(Fig. 2.2).

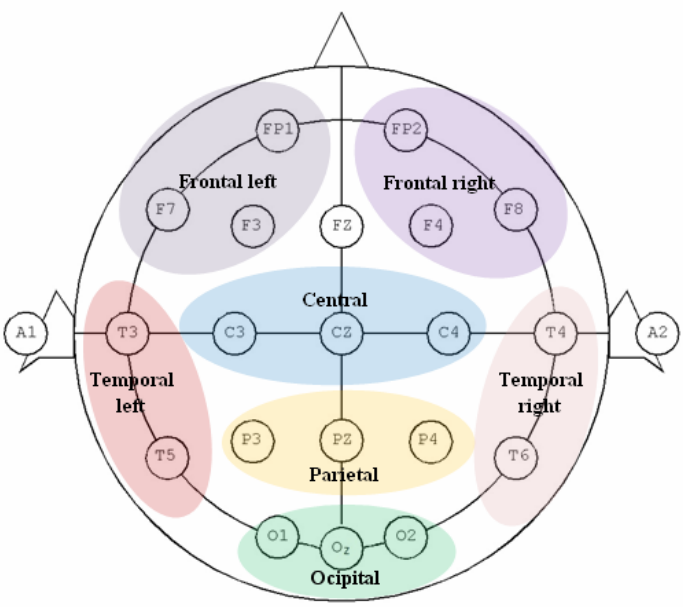

Fig. 2.2. Cerebral areas for EEG band power spectrum calculations.

Cerebral hemisphere EEG asymmetry coefficient was calculated according to these formulas (Griškova et al, 2007):

1) Frontal asymmetry (AsF) = (FrL-FrR)/(FrL+FrR);

2) Temporal asymmetry (AsT) = (TmL-TmR)/(TmL+TmR).

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

2.1.4 Statistical analysis.

Resting state EEG tends to display great individual differences (Smit et al, 2005). Kolmogorov-Smirnov test showed that EEG band power spectrum data in this study did not match the normal distribution curve. Therefore, to analyse the changes of

this data, nonparametric statistical tests were applied. To measure the significance of EEG band power spectrum and asymmetry coefficient change after the rTMS course, Wilcoxon test for two related samples was used. To explore the physiological homogeneity of different rTMS protocol patient groups before the treatment EEG band spectral power and asymmetry coefficient differences were compared using Mann-Whitney U test for two independent samples. To study the differences of physiological changes between rTMS protocols and brain areas, additional analysis of variance (ANOVA) for repeated measures was applied. Within subject variable was measurements before rTMS course and after it (Procedure factor). Between subjects factors were rTMS Protocol (1 Hz vs. 10 Hz) and brain Area (FrL, FrR, TmL, TmR, Cen, Par, Ocp).

2.2 Study of neuronavigated TMS therapy effect on EEG band power spectrum.

2.2.1 Subjects .

55 subjects (41 women, 14 men, mean age 47,6 years, SD = 13,5 years), with diagnosed drug resistant depressive disorder (46 patient) or depressive type schizoaffective disorder (9 patients) participated in the study. Before participation each patient gave a written consent. Chosen patients were free of tricyclic antidepressant treatment. Ineffective pharmacological treatment prior to rTMS course was continued at steady doses during the rTMS therapy.

34 patients were treated with high frequency (10 Hz) rTMS over the left hemisphere PFDLC, remaining 21 patient received low frequency (1 Hz) rTMS over the right hemisphere PFDLC. rTMS protocol choice for each patient was determined by a psychiatrist according to prevailing symptoms: adynamic depression was treated with high frequency rTMS, anxious depression was treated with low frequency rTMS. Procedures were applied five times per week for two to three weeks (10-15 procedures overall in rTMS course).

2.2.2 Neuronavigated TMS procedure.

Neuronavigated rTMS procedures, like the standard coil positioning procedures, were carried out using Medtronic Magpro X100 stimulator with MagVenture

Cool Coil B65 figure eight coil and 280 µs biphasic impulses. rTMS protocols also matched protocols described in chapter 2.1.2. For neuronavigated coil placement Localite TMS Navigator MR-less system was applied. In the neuronavigation system standard MNI dataset (MNI ICBM152 non-linear symmetric T1 Average Brain) was used. Deformations of MNI map for each patient head were calculated using fixed anatomical landmarks and head surface points registered using the navigation system pointer: 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. PFDLC targets were placed in the MNI map according to Talairach coordinate system, based on Teneback et al (1999) rTMS SPECT study coordinates (-40 ; 48 ; 32) for left hemisphere PFDLC (Fig. 2.3) and symmetrical coordinates (40; 48; 32) for right hemisphere PFDLC.

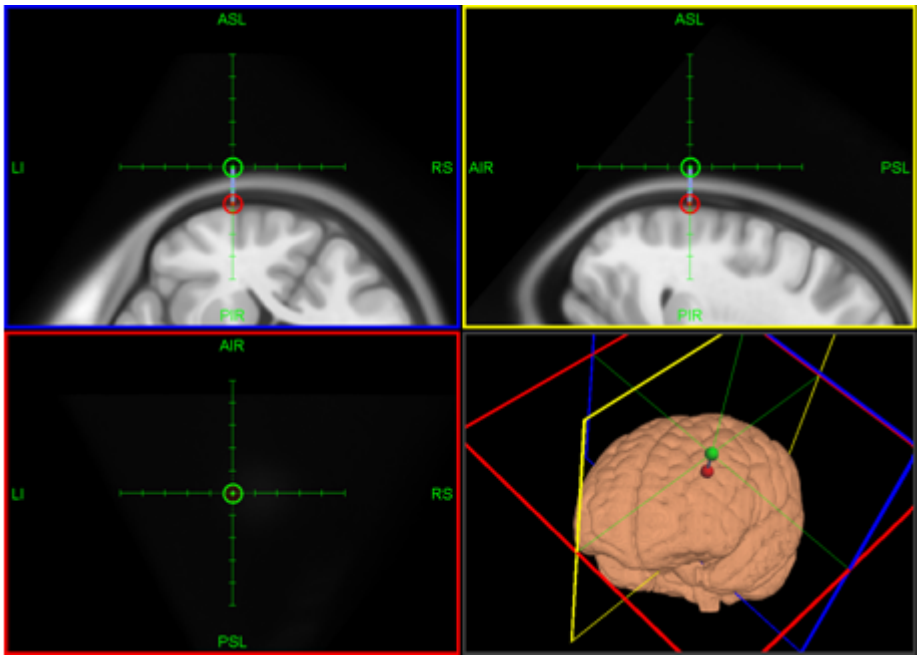

Fig. 2.3. Location of left PFDLC in the neuronavigation system brain model according to Talairach coordinates (-40; 48; 32).

2.2.3 Measurements and statistical analysis.

EEG was recorded in the same way as for the study of high and low frequency rTMS therapy effect on EEG band power spectrum (Chapter 3.1.3). Significance of electrophysiological changes after the rTMS course was calculated using Wilcoxon test for two related samples. To explore the physiological homogeneity of different study group EEG band spectral power and asymmetry coefficient differences before the treatment for 10 Hz and 1 HZ rTMS protocol groups were compared using Mann-Whitney U test for two independent samples. Using this test initial physiological differences between 10 Hz standard and neuronavigated positioning rTMS as well as 1 Hz standard and neuronavigated positioning rTMS were also studied. Repeated measures ANOVA was used to compare the effect of neuronavigated rTMS with the previous standard coil placement rTMS as well differences between rTMS protocols and brain areas. Within subject variable was measurements before rTMS course and after it (Procedure factor). Between subjects factors were TMS coil Positioning (neuronavigated vs. standard), rTMS Protocol (1 Hz vs. 10 Hz) and brain Area (FrL, FrR, TmL, TmR, Cen, Par, Ocp).

2.3 Study of ECT effect on EEG band power spectrum.

2.3.1 Subjects.

15 subjects (4 women, 11 men, mean age 37,2 years, SD = 12,5 years), with diagnosed recurrent depressive disorder (3 patients), depressive type schizoaffective disorder (2 patients) or paranoid schizophrenia (10 patients) participated in the study. Before participation each patient gave a written consent.

2.3.2 ECT procedure.

ECT procedures were carried out using Somatics Inc. (USA) Thymatron DGx apparatus with DualGraph EEG registration device. ECT procedures were applied every other day. The total number of procedures depended on clinical effect achieved as well as patient status before the treatment and ranged from 10 to 12 procedures. Before ECT procedure the patient was anaesthetized using short duration anaesthetics (sodium

thiopental solution 2-5 mg/kg), evoked motor seizures were suppressed using myorelaxant (suxamethonium chloridum 0,5-1 mg/kg).

ECT electrodes were placed at bipolar scheme on temporal areas. For generalized seizure evaluation, during the procedure one EEG channel was recorded with two electrodes placed above the left and right eyebrows. For stimulation 1 ms short biphasic square wave impulses were used. Impulse current was fixed at 0,9 A. During the procedure the current was applied from 0,47 to 4 seconds at 70 Hz frequency and 55-100% energy value. Initial energy value for each patient was prescribed by psychiatrist according to the age of the patient (energy percent = patient age ± 5 percent). In case of failure to induce a generalized seizure, stimulation was repeated using higher energy value.

2.3.3 Measurements and statistical analysis.

EEG before and after ECT course was recorded in the same way as for the study of high and low frequency rTMS therapy effect on EEG band power spectrum (Chapter 3.1.3). Significance of electrophysiological changes after the treatment course was calculated using Wilcoxon test for two related samples. To study the physiological homogeneity of rTMS and ECT patient groups before the treatment EEG band spectral power and asymmetry coefficient differences were measured using Mann-Whitney U test for two independent samples. Repeated measures ANOVA was used to compare the effect of ECT with previous rTMS therapy as well differences between rTMS protocols and brain areas. Within subject variable was measurements before treatment course and after it (Procedure factor). Between subjects factors were Method (ECT, 10 Hz standard positioning rTMS, 1 Hz standard positioning rTMS, 10 Hz neuronavigated rTMS and 1 Hz neuronavigated rTMS) and brain Area (FrL, FrR, TmL, TmR, Cen, Par, Ocp).

2.4 Study of EEG band power spectrum long term dynamics for rTMS patients

2.4.1 Subjects.

20 patients (17 women, 3 men, mean age 45,9 years, SD = 11,7 years), recurrent depressive disorder (15 patients) or depressive type schizoaffective disorder (5 patients), returning for additional rTMS course, participated in the study. Each patient

gave a written consent for participation. Time interval from the end of a previous rTMS therapy course to the beginning of a new one ranged from 3 to 42 months (Mean 14 months).

2.4.2 Measurements and statistical analysis.

EEG was recorded in the same way as for the study of high and low frequency rTMS therapy effect on EEG band power spectrum (Chapter 3.1.3). Significance of electrophysiological changes was calculated using Wilcoxon test for two related samples, however EEG band power spectrum change was measured between the end of a previous rTMS course and EEG recorded before the new rTMS course.

2.5 Study of TMS therapy effect on evoked potential P300.

2.5.1 Subjects.

82 patients (63 women, 19 men, mean age 49,5 years, SD = 12,7 years), with diagnosed drug resistant depressive disorder (65 patients) or depressive type schizoaffective disorder (17 patients) participated in the study. Before participation each patient gave a written consent. Chosen patients were free of tricyclic antidepressant treatment. Ineffective pharmacological treatment prior to rTMS course was continued at steady doses during the rTMS therapy.

42 patients were treated with standard coil positioning TMS, 40 patients received neuronavigated TMS. From the former group 21 patient was treated with high frequency (10 Hz) rTMS over the left PFDLC, remaining 21 received low frequency (1 Hz) rTMS over the right PFDLC. In the neuronavigated TMS group 24 patients were treated with high frequency (10 Hz) rTMS over the left PFDLC, remaining 16 received low frequency (1 Hz) rTMS over the right PFDLC. Particular protocol for each patient was prescribed by a psychiatrist according to prevailing symptoms: adynamic depression was treated with high frequency rTMS, anxious depression was treated with low frequency rTMS. Procedures were applied five times per week for two to three weeks (10-15 procedures overall in rTMS course). Apparatus used for procedures and rTMS protocols are described in chapters 2.1.2 and 2.2.2.

2.5.2. Evoked potential P300 registration.

Evoked potentials were recorded using EBNeuro Galileo Mizar EEG apparatus. P300 registration was standartized according to International and American clinical neurophysiology societies recomendations (Duncan et al, 2009). Active electrodes for registering P300 potential were placed over the head according to 10-20 system in Fz, Cz and Pz points. Fpz electrode was used as a ground, ear electrodes were used for a reference (Fig. 2.4). Evoked potential P300 was recorded before rTMS course and 30-40 minutes after the last procedure.

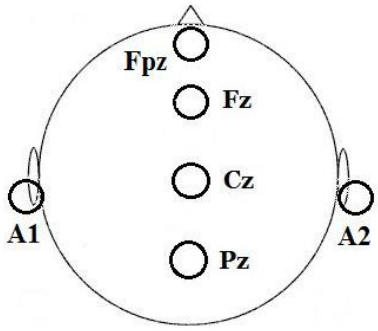

Fig. 2.4. Electrode placement for P300 registration.

To evoke P300 potential „odd-ball paradigm“ method was used. Parameters for P300 generation and registration were based on the earlier research practice in the RVPH (Korostenskaja et al, 2000). Subject received two types of auditory stimuli in random succession: 1) 1000 Hz „frequent“ (chance of appearance 80%); 2) 2000 Hz „rare“ (chance of appearance 20%). Auditory stimuli were produced via high quality audiometric headphones „Telephonics TDH-39P“. Patient was asked to count the rare (significant) stimuli produced while ignoring the frequent (insignificant) ones. In registration system software responses to significant and insignificant stimuli were averaged separately. Therefore on the screen two types of curves were produced: 1) standard lenght latency auditory evoked potential with sensory complex P1-N1-P2 (response to insignificant stimulus); 2) wave set, consisting of sensory (P1-N1-P2) and cognitive (N2-P3-N3) complex (response to significant stimulus). For further analysis 2 parameters of the cognitive complex were measured in all three areas (Fz – frontal area, Cz – central area, Pz – parietal area): 1) P300 wave latency; 2) P300 wave amplitude

(difference between N2 and P300 wave amplitudes, measured from the baseline). Measured parameters in the three brain areas later were averaged together.

2.5.3 Statistical analysis.

Evoked potentials are a standardized physiological measure, fitting a normal distribution curve within distinctive age groups (Korostenskaja et al, 2003). Therefore, for evoked potential data analysis parametric statistical tests were used. Parameters of P300 before rTMS course and after it were compared using paired samples T test. Differences between rTMS protocols and coil positioning techniques were compared using repeated measures ANOVA. Within subject variable were measurements before and after rTMS course (Procedure factor). Factors between subjects were Method (10 Hz standard rTMS, 1 Hz standard rTMS, 10 Hz neuronavigated rTMS, 1 Hz neuronavigated rTMS) and brain Area (Fz, Cz and Pz electrodes).

2.6 Study of relationship between bioelectrical brain activity and depression symptoms.

2.6.1 Subjects.

82 patients (63 women, 19 men, mean age 49,5 years, SD = 12,7 years), included in the studies of rTMS effect on EEG band power spectrum and evoked potential P300, participated in the study.

2.6.2 Clinical tests.

Before the rTMS course and day after the last procedure depressive symptoms of the patients were measured using Montgomery-Åsberg depression rating scale (MADRS), Beck depression inventory (BDI) and Hamilton depression rating scale (HAM-D) clinical tests. Clinical efficacy groups were divided according to percent changes in MADRS test scores: 1) weak effect (<10% decrease); 2) significant effect (10%<decrease<50%); 3) considerable effect (>50% decrease) (Fitzgeral et al, 2009). State of remission was achieved when after the therapy MADRS rating scale score was <10 points (Fitzgerald et al, 2006).

2.6.3 Statistical tests.

Percent changes of clinical test score scales between different rTMS therapy groups (10 Hz standard rTMS, 1 Hz standard rTMS, 10 Hz neuronavigated rTMS, 1 Hz neuronavigated rTMS) were compared using one way ANOVA. Different categories of clinical effect and remission between different rTMS therapy groups compared using Mann-Whitney U test. Relationship between percent changes of clinical test scores and bioelectrical activity changes was measured using Pearson correlation coefficient.

3. RESULTS

3.1. Study of high and low frequency rTMS therapy effect on EEG band power spectrum.

After 10 Hz rTMS therapy course EEG spectral power was increased in all frequency bands (Fig. 3.1.1). According to Wilcoxon test, statistically significant ($p<0,05$) changes were found in central brain area for delta and alpha band powers, in parietal area for delta, theta, alpha and beta band powers and in occipital area for delta and theta band powers (Table 3.1.1). Cerebral activity asymmetry in the frontal areas after 10 Hz rTMS course shifted to the right hemisphere side for delta, theta, alpha and beta bands, as well for theta and beta bands in the temporal areas. Temporal asymmetry for delta and alpha bands shifted towards the left cerebral hemisphere (Fig. 3.1.2). None of these changes were statistically significant according to Wilcoxon test (Table 3.1.2).

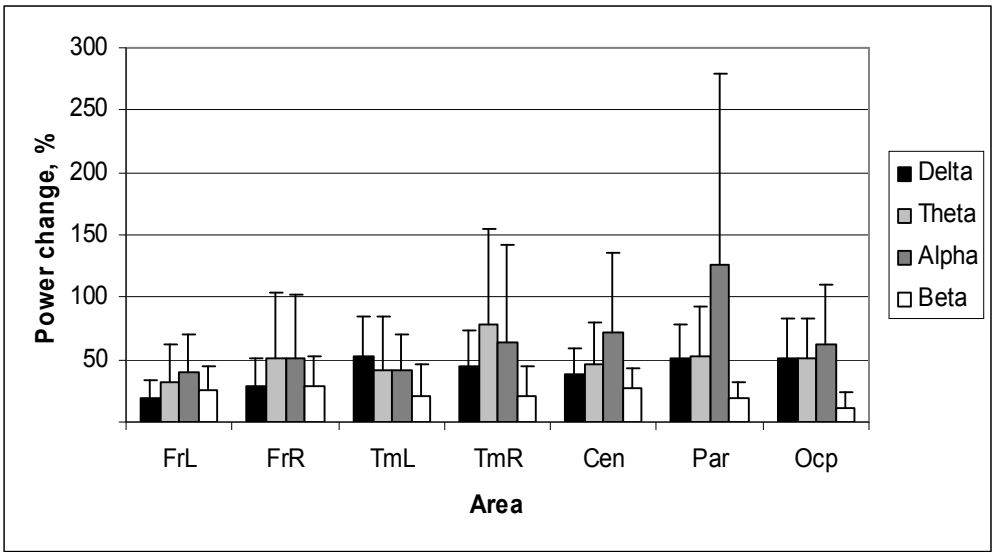

Fig. 3.1.1. Percent changes of EEG band spectrum power after 10 Hz rTMS therapy (N=26).

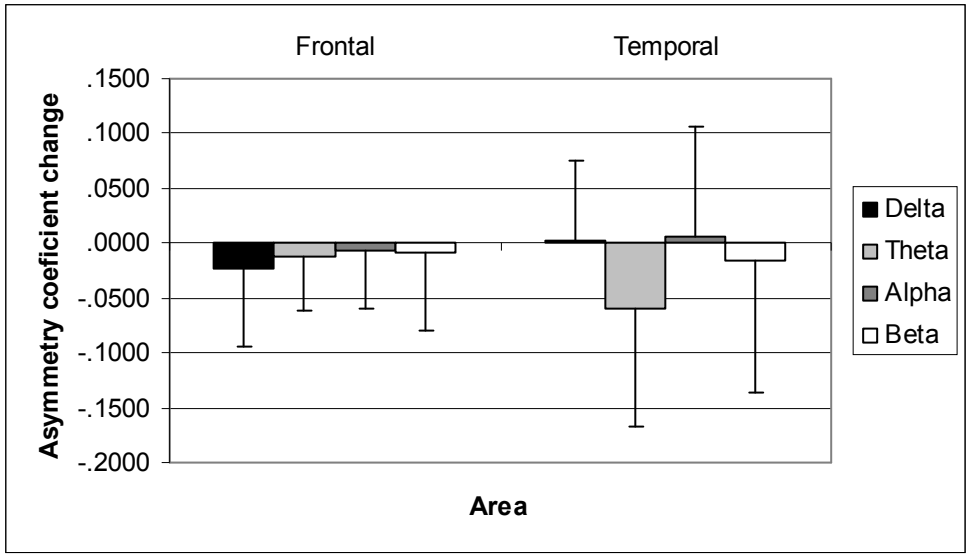

Fig. 3.1.2. Changes of cerebral hemisphere EEG activity asymmetry coefficient after 10 Hz rTMS therapy (N=26).

Table 3.1.1. EEG band spectrum power (μV^2) averages before and after 10 Hz rTMS therapy course (N=26; * $p<0,05$ according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal left FrL	Before TMS	8,96±9,34	7,76±6,36	8,00±6,57	2,01±1,48
	After TMS	10,32±12,71	8,52±7,69	9,08±6,09	2,31±1,84
Frontal right FrR	Before TMS	7,88±6,08	7,85±6,79	8,27±6,37	2,07±1,45
	After TMS	9,50±10,26	8,58±6,18	9,93±7,15	2,31±1,23
Temporal left TmL	Before TMS	3,67±2,08	5,07±3,52	10,23±11,97	2,05±1,96
	After TMS	4,90±3,92	5,51±4,74	10,31±9,46	2,01±1,66
Temporal right TmR	Before TMS	3,84±2,65	5,37±5,08	10,13±8,68	1,97±1,41
	After TMS	4,77±2,86	6,63±6,25	11,67±10,21	2,09±1,42
Central Cen	Before TMS	**6,33±4,03***	9,16±8,40	**14,26±14,53***	2,72±1,68
	After TMS	**8,20±5,25***	11,30±10,77	**16,91±12,05***	3,15±1,92
Parietal Par	Before TMS	**5,59±3,92***	**7,66±6,75***	**21,37±23,55***	**2,69±1,50***
	After TMS	**7,55±4,86***	**9,73±8,07***	**26,39±21,79***	**3,03±1,80***
Occipital Ocp	Before TMS	**3,89±2,42***	**5,32±3,38***	19,00±24,11	2,24±1,15
	After TMS	**5,05±2,94***	**6,89±4,89***	19,84±18,84	2,24±1,03

Table 3.1.2. Averages of cerebral hemisphere EEG activity asymmetry coefficient before and after 10 Hz rTMS therapy (N=26; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal	Before TMS	0,030±0,147	0,010±0,131	-0,017±0,122	-0,024±0,145
	After TMS	0,006±0,164	-0,002±0,150	-0,025±0,171	-0,032±0,153
Temporal	Before TMS	-0,008±0,185	0,042±0,224	-0,037±0,267	-0,013±0,239
	After TMS	-0,007±0,209	-0,017±0,272	-0,032±0,291	-0,029±0,262

After the course of 1 Hz rTMS therapy EEG spectral power of all bands was increased over the brain (Fig 3.1.3.). However none of the changes were statistically significant according to Wilcoxon test (Table 3.1.3). Cerebral activity asymmetry in frontal and temporal areas after 1 Hz rTMS therapy shifted to the right hemisphere side fro delta, theta, alpha and beta bands (Fig. 3.1.4). Alpha band asymmetry change in the frontal area was statistically significant (p<0,05) according to Wilcoxon test (Table 3.1.4).

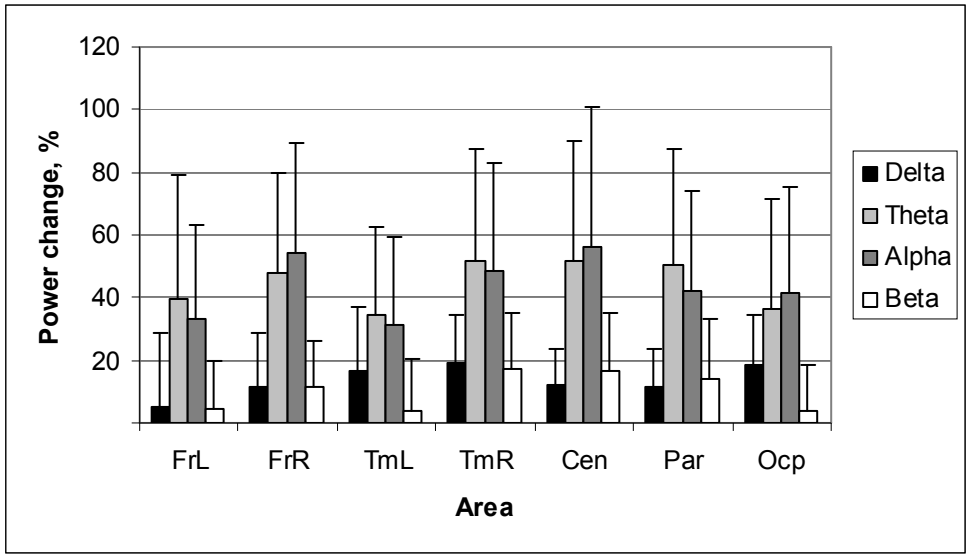

Fig 3.1.3. Percent changes of EEG band spectrum power after 1 Hz rTMS therapy (N=24).

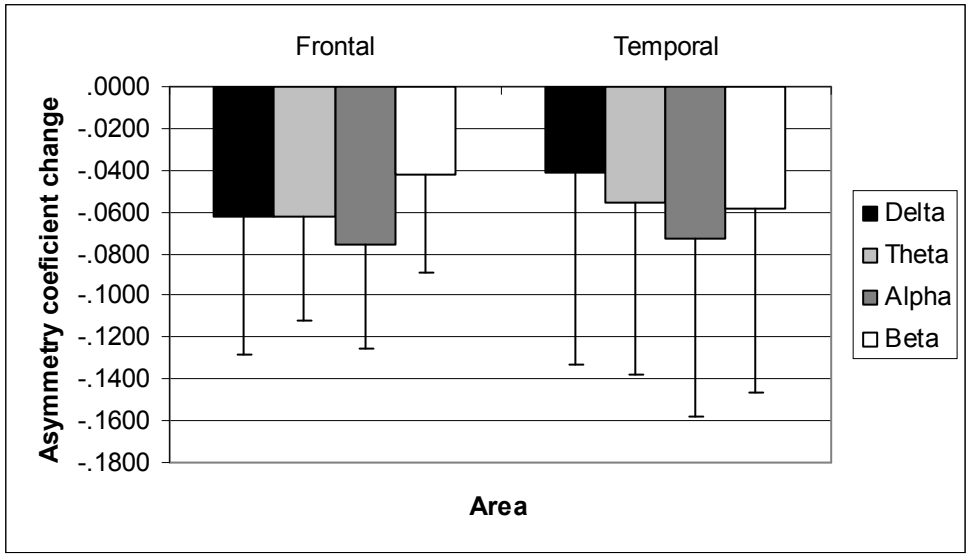

Fig. 3.1.4. Changes of cerebral hemisphere EEG activity asymmetry coefficient after 1 Hz rTMS therapy (N=24).

Table 3.1.3. EEG band spectrum power (μV^2) averages before and after 1 Hz rTMS therapy course (N=24; * $p<0,05$ according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal left FrL	Before TMS	8,13±5,23	6,47±7,36	8,51±7,67	2,91±1,65
	After TMS	7,13±5,08	7,34±7,97	9,43±8,50	2,92±2,01
Frontal right FrR	Before TMS	7,46±4,83	5,71±5,18	8,51±8,42	3,09±2,18
	After TMS	7,16±4,04	7,36±7,13	10,40±8,81	3,19±2,13
Temporal left TmL	Before TMS	4,18±3,65	4,21±4,01	9,67±10,57	2,69±1,68
	After TMS	3,90±3,24	4,47±4,17	10,19±9,04	2,63±1,82
Temporal right TmR	Before TMS	3,37±1,82	3,76±3,14	10,65±12,52	2,75±2,06
	After TMS	3,71±2,10	4,78±4,83	12,24±10,87	2,84±2,13
Central Cen	Before TMS	6,08±4,12	6,86±5,76	15,46±17,01	4,48±2,92
	After TMS	6,16±3,31	9,98±12,91	17,59±14,94	4,86±3,46
Parietal Par	Before TMS	5,47±4,64	5,89±5,27	21,32±22,63	4,48±3,44
	After TMS	5,30±3,31	7,73±8,75	24,86±25,43	4,33±3,00
Occipital Ocp	Before TMS	4,26±4,35	4,75±4,62	21,72±29,10	3,35±2,61
	After TMS	4,18±3,59	5,48±6,33	24,09±28,41	3,08±2,39

Table 3.1.4. Averages of cerebral hemisphere EEG activity asymmetry coefficient before and after 1 Hz rTMS therapy (N=24; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal	Before TMS	0,029±0,159	0,029±0,132	**0,025±0,135***	-0,011±0,138
	After TMS	-0,033±0,166	-0,033±0,124	**-0,050±0,110***	-0,053±0,117
Temporal	Before TMS	0,020±0,267	0,037±0,233	-0,013±0,197	0,018±0,252
	After TMS	-0,021±0,243	-0,019±0,240	-0,086±0,249	-0,041±0,216

Mann-Whitney U test showed that 10 Hz and 1 Hz rTMS groups before the treatment were homogeneous in delta, theta and alpha bands for EEG spectral power and in all frequency bands for asymmetry coefficient (Table 3.1.5). Significant differences were found in the beta frequency band spectral power, evident in frontal, left temporal, central and parietal areas (Table 3.1.5), where initial spectral power was greater for 1 Hz rTMS patient group compared to 10 Hz rTMS patients (Table 3.1.1; Table 3.1.3).

Table 3.1.5. 10 Hz and 1 Hz rTMS patient group comparison before therapy using Mann-Whitney U test p values (N=50).

Band	FrL	FrR	TmL	TmR	Cen	Par	Ocp	AsF	AsT
Delta	0,907	0,884	0,938	0,683	0,641	0,509	0,727	0,985	0,560
Theta	0,177	0,140	0,187	0,303	0,303	0,286	0,244	0,587	1,000
Alpha	0,907	0,560	0,985	0,698	0,771	0,969	0,727	0,372	0,771
Beta	**0,011***	**0,028***	**0,028***	0,095	**0,006***	**0,020***	0,132	0,727	0,801

Repeated measures ANOVA showed significant EEG band power spectrum changes after rTMS therapy in delta, theta and alpha bands. Significant effect differences for different brain areas were not found. Differences between 10 Hz and 1 Hz rTMS protocols were significant in theta and beta frequency bands (Table 3.1.6).

Table 3.1.6. Analysis of variance for EEG band power spectrum between different rTMS protocols and brain areas (N=50).

Band	Factors	F	p value
Delta	Procedure	9,807	**0,002***
	Procedure*Area	0,255	0,957
	Protocol	3,717	0,055
Theta	Procedure	21,906	**0,000***
	Procedure*Area	1,015	0,415
	Protocol	5,018	**0,026***
Alpha	Procedure	9,517	**0,002***
	Procedure*Area	0,631	0,705
	Protocol	0,177	0,674
Beta	Procedure	2,223	0,137
	Procedure*Area	0,820	0,555
	Protocol	25,901	**0,000***

3.2 Study of neuronavigated TMS therapy effect on EEG band power spectrum.

After 10 Hz neuronavigated rTMS therapy course EEG spectral power of all bands was increased (Fog. 3.2.1). According to Wilcoxon test statistically significant ($p<0,05$) changes were found in all brain areas for delta band power and in the left hemisphere temporal area for alpha band power (Table 3.2.1). Cerebral activity asymmetry in the frontal areas after 10 Hz neuronavigated rTMS course shifted to the right hemisphere side for delta, theta and beta bands. Temporal asymmetry of all EEG bands and frontal asymmetry of alpha band shifted towards the left hemisphere after the therapy (Fig. 3.2.2). However none of these changes were statistically significant according to Wilcoxon test (Table 3.2.2).

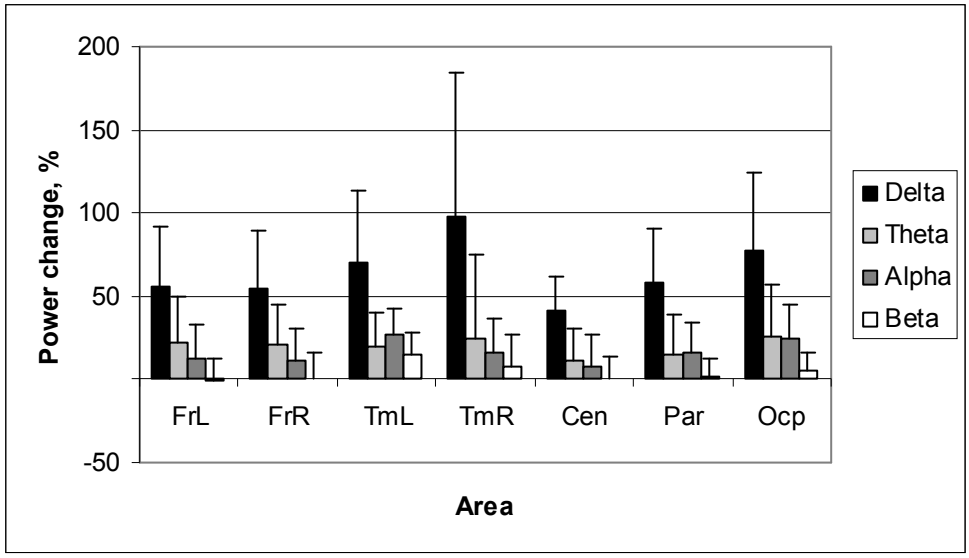

Fig. 3.2.1. Percent changes of EEG band spectrum power after 10 Hz neuronavigated rTMS therapy (N=34).

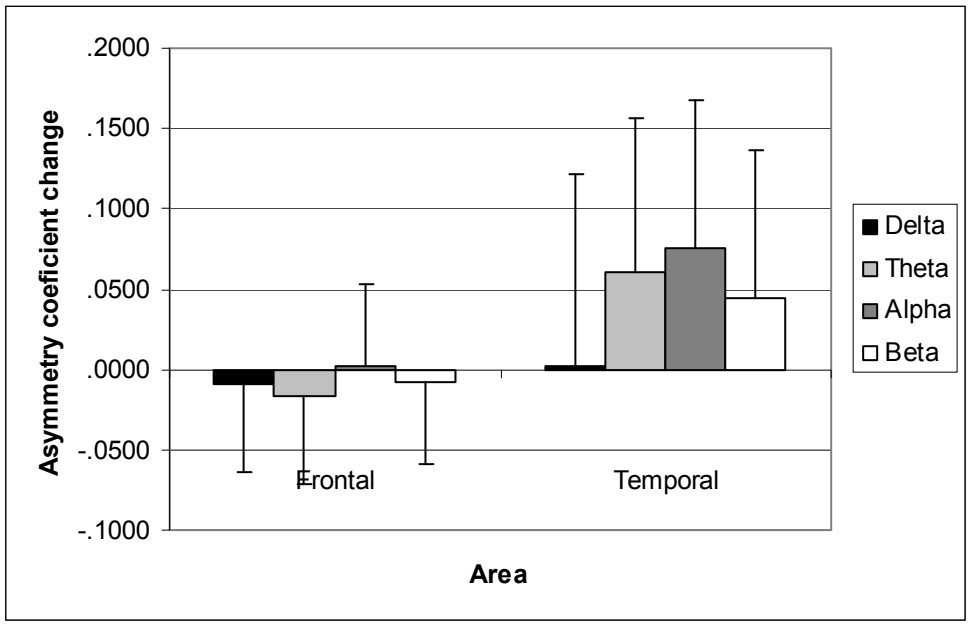

Fig. 3.2.2. Changes of cerebral hemisphere EEG activity asymmetry coefficient after 10 Hz neuronavigated rTMS therapy (N=34).

Table 3.2.1. EEG band spectrum power (μV^2) averages before and after 10 Hz neuronavigated rTMS therapy (N=34; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal left FrL	Before TMS	**7,74±8,18***	8,17±5,00	8,66±7,35	2,57±1,94
	After TMS	**10,49±11,22***	9,87±10,96	8,43±7,35	2,21±1,49
Frontal right FrR	Before TMS	**6,73±5,54***	7,56±4,96	8,61±7,09	2,51±2,00
	After TMS	**10,27±11,23***	9,76±11,39	8,71±7,34	2,27±1,68
Temporal left TmL	Before TMS	**3,48±1,88***	5,43±4,00	**8,31±6,42***	2,14±1,49
	After TMS	**5,27±3,93***	6,12±6,81	**9,74±7,76***	2,21±1,42
Temporal right TmR	Before TMS	**3,12±1,93***	4,95±3,75	7,40±5,21	1,91±1,40
	After TMS	**5,46±6,75***	6,08±8,51	7,67±5,29	1,91±1,54
Central Cen	Before TMS	**5,67±3,43***	11,05±9,08	16,59±14,40	4,02±2,95
	After TMS	**7,69±5,08***	12,69±15,45	16,62±16,90	3,74±2,88
Parietal Par	Before TMS	**5,48±3,48***	10,98±10,73	25,26±24,68	4,12±3,14
	After TMS	**7,95±5,56***	12,45±15,52	26,70±26,42	3,90±2,82
Occipital Ocp	Before TMS	**5,19±3,44***	9,67±10,00	26,59±24,04	3,42±2,29
	After TMS	**7,66±5,08***	10,53±11,03	29,36±27,08	3,53±2,73

Table 3.2.2. Averages of cerebral hemisphere EEG activity asymmetry coefficient before and after 10 Hz neuronavigated rTMS therapy (N=34; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal	Before TMS	0,049±0,139	0,037±0,123	-0,012±0,125	0,008±0,092
	After TMS	0,021±0,175	0,041±0,195	-0,010±0,137	0,000±0,120
Temporal	Before TMS	0,055±0,219	0,057±0,220	0,027±0,220	0,055±0,210
	After TMS	0,117±0,265	0,057±0,265	0,102±0,256	0,099±0,260

After 1 Hz neuronavigated rTMS therapy course EEG spectral power was increased across the brain in all bands (Fig. 3.2.3). According to Wilcoxon test statistically significant (p<0,05) changes were found in right frontal, left temporal, central, parietal and occipital areas for delta and theta bands, delta band power change was also significant in the right temporal area (Table 3.2.3). Cerebral activity asymmetry after 1 Hz neuronavigated rTMS course in the frontal areas shifted to the right

hemisphere for delta band and to the left hemisphere for theta, alpha and beta bands. Temporal asymmetry for delta, theta and alpha bands shifted towards the left hemisphere and towards the right hemisphere for the beta band (Fig. 3.2.4). However none of these changes were statistically significant according to Wilcoxon test (Table 3.2.4).

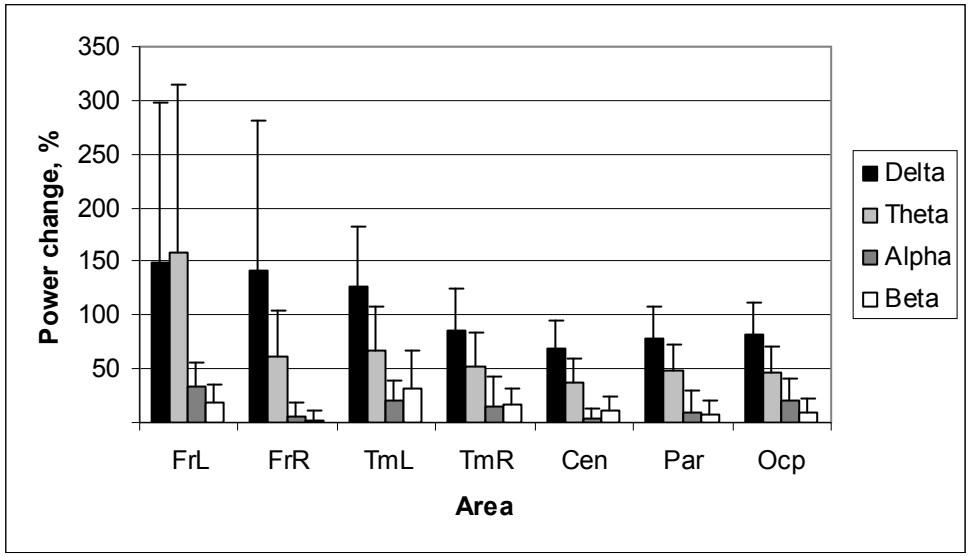

Fig. 3.2.3. Percent changes of EEG band spectrum power after 1 Hz neuronavigated rTMS therapy (N=21).

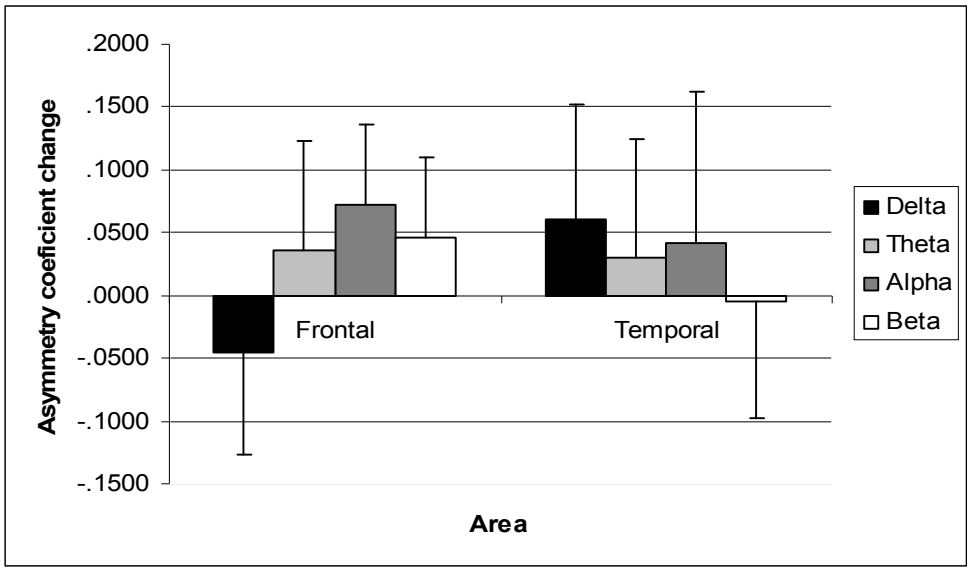

Fig. 3.2.4. Changes of cerebral hemisphere EEG activity asymmetry coefficient after 1 Hz neuronavigated rTMS therapy (N=21).

Table 3.2.3. EEG band spectrum power (μV^2) averages before and after 1 Hz neuronavigated rTMS therapy (N=21; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal left FrL	Before TMS	6,01±3,61	4,84±2,96	5,94±3,35	1,81±1,05
	After TMS	10,14±10,59	10,30±17,10	6,98±4,14	1,96±1,11
Frontal right FrR	Before TMS	**5,20±3,07***	**4,87±3,51***	6,26±3,50	1,86±1,15
	After TMS	**8,38±6,29***	**7,24±6,93***	6,31±3,96	1,80±1,13
Temporal left TmL	Before TMS	**2,39±1,35***	**2,98±2,47***	5,86±3,87	1,68±1,27
	After TMS	**5,19±4,56***	**4,34±4,32***	5,66±3,06	1,68±,92
Temporal right TmR	Before TMS	**2,29±1,16***	2,83±2,25	5,90±4,08	1,59±1,08
	After TMS	**3,77±2,38***	3,96±3,51	5,76±4,14	1,75±1,19
Central Cen	Before TMS	**4,03±2,04***	**5,11±3,54***	9,25±5,19	2,72±1,84
	After TMS	**6,21±3,59***	**6,70±5,45***	8,75±4,47	2,60±1,56
Parietal Par	Before TMS	**3,70±2,06***	**4,74±3,76***	15,59±11,56	2,95±2,38
	After TMS	**6,03±4,38***	**6,54±5,56***	15,42±11,27	2,93±2,30
Occipital Ocp	Before TMS	**3,17±1,73***	**4,25±3,27***	23,55±31,30	2,60±1,77
	After TMS	**5,18±3,22***	**5,80±4,71***	22,67±23,53	2,69±1,79

Table 3.2.4. Averages of cerebral hemisphere EEG activity asymmetry coefficient before and after 1 Hz neuronavigated rTMS therapy (N=21; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal	Before TMS	0,061±0,169	0,000±0,136	-0,028±0,094	0,006±0,139
	After TMS	0,015±0,153	0,035±0,194	0,045±0,205	0,051±0,207
Temporal	Before TMS	0,007±0,158	0,005±0,220	-0,009±0,285	0,019±0,193
	After TMS	0,067±0,252	0,036±0,220	0,033±0,216	0,015±0,229

Mann-Whitney U test showed that when using neuronavigational system 10 Hz and 1 Hz rTMS groups before the therapy were homogeneous in alpha and beta bands for EEG spectral power and in all bands for asymmetry coefficient (Table 3.2.5). Significant differences were found in the delta band spectral power in left temporal and central, parietal and ocipital areas and in the theta band spectral power in all brain areas (Table 3.2.5). In both cases initial spectral power was greater in 10 Hz rTMS group,

compared to 1 Hz rTMS patients (Table 3.2.1; Table 3.2.3). When 10 Hz rTMS groups using neuronavigation system and standard coil positioning were compared physiological differences before the treatment were not found (Table 3.2.6). However, in the 1 Hz rTMS protocol case different coil positioning groups before the treatment were homogeneous only in the theta and alpha bands for spectral power and in all bands for asymmetry coefficient (Table 3.2.7). Significant differences were found in the delta band spectral power, evident in right temporal and central areas and in the beta band spectral power, evident in frontal, temporal, central and parietal areas (Table 3.2.7). In both cases initial spectral power was larger in the standard coil positioning group compared to neuronavigational positioning group (Table 3.1.3; Table 3.2.3).

Table 3.2.5. 10 Hz and 1 Hz rTMS patient group comparison before therapy using Mann-Whitney U test p values (N=55).

Band	FrL	FrR	TmL	TmR	Cen	Par	Ocp	AsF	AsT
Delta	0,467	0,425	**0,020***	0,061	**0,027***	**0,032***	**0,025***	0,876	0,556
Theta	**0,013***	**0,020***	**0,003***	**0,011***	**0,001***	**0,001***	**0,001***	0,115	0,446
Alpha	0,341	0,303	0,212	0,299	0,069	0,275	0,359	0,782	0,544
Beta	0,215	0,271	0,143	0,401	0,103	0,148	0,303	0,862	0,659

Table 3.2.6. 10 Hz standard and neuronavigated positioning group comparison before therapy using Mann-Whitney U test p values (N=60).

Band	FrL	FrR	TmL	TmR	Cen	Par	Ocp	AsF	AsT
Delta	0,460	0,210	0,970	0,266	0,551	0,864	0,098	0,602	0,293
Theta	0,483	0,693	0,693	0,817	0,293	0,146	0,051	0,623	0,864
Alpha	0,720	0,958	0,905	0,343	0,531	0,460	0,061	0,958	0,367
Beta	0,260	0,408	0,420	0,644	0,116	0,130	0,068	0,230	0,383

Table 3.2.7. 1 Hz standard and neuronavigated positioning group comparison before therapy using Mann-Whitney U test p values (N=45).

Band	FrL	FrR	TmL	TmR	Cen	Par	Ocp	AsF	AsT
Delta	0,172	0,062	0,069	**0,012***	**0,041***	0,149	0,509	0,802	0,666
Theta	0,750	0,891	0,275	0,381	0,357	0,524	0,937	0,211	0,328
Alpha	0,699	0,946	0,228	0,195	0,539	0,733	0,453	0,237	0,873
Beta	**0,010***	**0,014***	**0,007***	**0,012***	**0,016***	**0,031***	0,351	0,873	0,909

Repeated measures ANOVA together with standard coil positioning rTMS data showed significant EEG band power spectrum changes after rTMS therapy in delta,

theta and alpha bands. Significant effect differences for different brain areas were not found. Coil positioning method had significant influence on beta band power change. Both coil positioning and rTMS protocol factors combined produced significant differences in theta, alpha and beta band power change (Table 3.2.8).

Table 3.2.8. Analysis of variance for EEG band power spectrum between different TMS coil positioning (standard vs. neuronavigated), rTMS protocols and brain areas (N=105).

Band	Factors	F	p value
Delta	Procedure	82,924	**0,000***
	Procedure*Area	0,326	0,923
	Positioning	0,089	0,766
	Positioning*Protocol	0,415	0,520
Theta	Procedure	31,611	**0,000***
	Procedure*Area	0,593	0,736
	Positioning	0,457	0,499
	Positioning*Protocol	4,492	**0,034***
Alpha	Procedure	8,897	**0,003***
	Procedure*Area	0,446	0,848
	Positioning	2,537	0,112
	Positioning*Protocol	6,158	**0,013***
Beta	Procedure	0,296	0,587
	Procedure*Area	0,144	0,990
	Positioning	5,610	**0,018***
	Positioning*Protocol	37,967	**0,000***

3.3 Study of ECT effect on EEG band power spectrum.

After ECT course there was an increase in delta, theta and alpha band power across the brain, whereas beta band power was decreased in parietal and occipital areas (Fig. 3.3.1). According to Wilcoxon test delta band power increase was statistically significant ($p<0,05$) in all brain areas, theta band power increase – in frontal, left temporal, central and parietal areas (Table 3.3.1). Cerebral activity asymmetry after ECT course in the frontal area shifted towards the right hemisphere for delta, theta and alpha bands and for theta, alpha and beta bands in the temporal area. Frontal beta band asymmetry and temporal delta band asymmetry shifted to the left hemisphere side (Fig. 3.3.2). However none of these changes were statistically significant (Table 3.3.2).

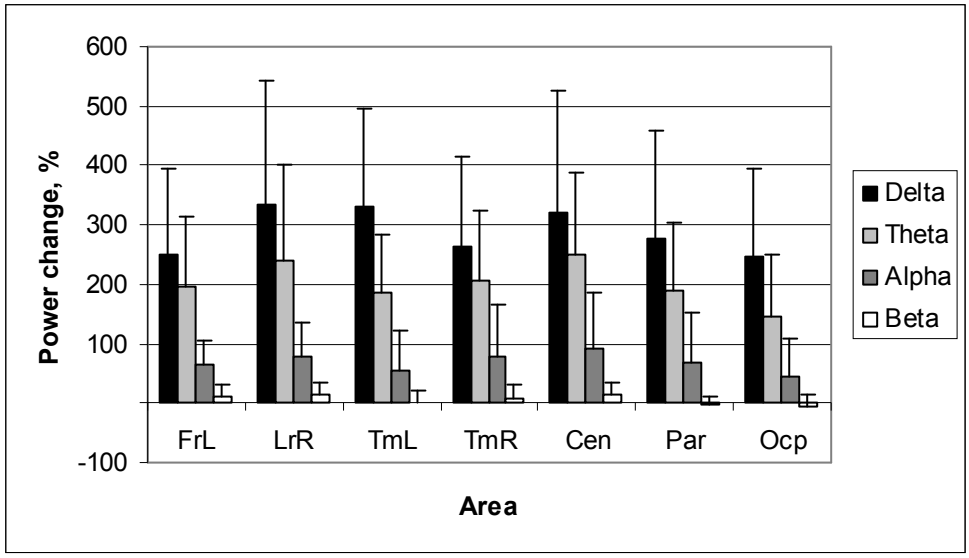

Fig 3.3.1. Percent changes of EEG band spectrum power after ECT course (N=15).

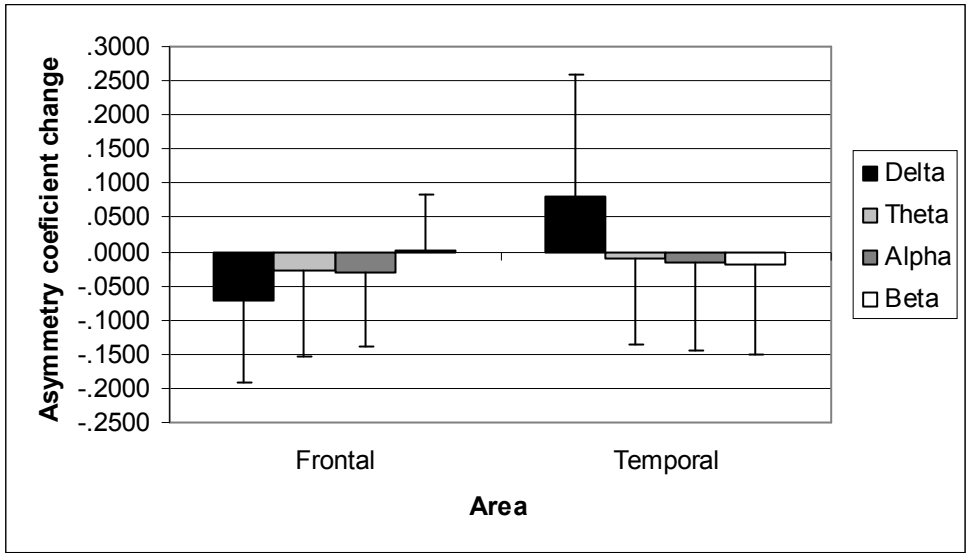

Fig. 3.3.2. Changes of cerebral hemisphere EEG activity asymmetry coefficient after ECT course (N=15).

Table 3.3.1. EEG band spectrum power (μV^2) averages before and after ECT course (N=15; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal left FrL	Before ECT	**12,95±18,78***	**8,54±8,27***	6,25±6,58	1,62±,54
	After ECT	**24,09±18,38***	**14,92±8,99***	7,35±5,25	1,70±,61
Frontal right FrR	Before ECT	**11,83±15,71***	**8,15±7,87***	6,03±5,96	1,63±,59
	After ECT	**23,32±15,60***	**15,04±8,12***	7,88±6,21	1,69±,61
Temporal left TmL	Before ECT	**4,60±4,88***	**6,06±7,10***	5,94±5,38	1,64±,71
	After ECT	**12,10±8,80***	**10,12±8,21***	6,49±4,88	1,48±,60
Temporal right TmR	Before ECT	**6,55±7,72***	6,68±7,70	6,15±4,80	1,72±,75
	After ECT	**13,05±8,02***	10,62±6,40	7,30±5,61	1,60±,65
Central Cen	Before ECT	**7,31±8,20***	**9,89±12,25***	7,77±6,20	2,11±,91
	After ECT	**17,10±12,70***	**16,26±8,51***	9,46±6,72	2,23±1,14
Parietal Par	Before ECT	**7,24±8,72***	**9,63±12,18***	10,83±9,16	2,38±,97
	After ECT	**16,89±14,31***	**14,19±7,83***	11,53±8,77	2,11±,71
Occipital Ocp	Before ECT	**6,49±6,57***	9,59±10,72	15,38±16,66	3,01±1,46
	After ECT	**16,47±11,92***	13,90±9,36	15,99±17,66	2,53±1,22

Table 3.3.2. Averages of cerebral hemisphere EEG activity asymmetry coefficient before and after ECT course (N=15; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal	Before ECT	0,067±0,180	0,020±0,194	0,000±0,149	0,003±0,107
	After ECT	-0,005±0,176	-0,006±0,131	-0,032±0,140	0,005±0,103
Temporal	Before ECT	-0,109±0,295	-0,032±0,203	-0,025±0,186	-0,018±0,233
	After ECT	-0,027±0,246	-0,043±0,172	-0,042±0,213	-0,036±0,198

Mann-Whitney U test showed that ECT patient group and rTMS groups combined before the treatment were homogeneous in the delta, theta and beta bands for EEG spectral power and in all frequency bands for asymmetry coefficient (Table 3.3.3). Significant differences were found in the alpha band, evident in central and parietal areas (Table 3.3.3), where initial spectral power was lesser in the ECT group compared to rTMS patient groups (Table 3.3.1; Table 3.1.1; Table 3.1.3; Table 3.2.1; Table 3.2.3).

Table 3.3.3. ECT and rTMS patient group comparison before therapy using Mann-Whitney U test p values (N=120).

Band	FrL	FrR	TmL	TmR	Cen	Par	Ocp	AsF	AsT
Delta	0,325	0,821	0,815	0,164	0,803	0,815	0,214	0,706	0,113
Theta	0,959	0,893	0,934	0,562	0,614	0,890	0,277	0,355	0,113
Alpha	0,148	0,125	0,189	0,291	**0,038***	**0,042***	0,258	0,821	0,576
Beta	0,331	0,239	0,434	0,968	0,039	0,243	0,427	0,978	0,331

Repeated measures analysis of variance (ANOVA) carried out together with the rTMS data showed significant EEG spectral power changes after the treatment in the delta, theta and alpha frequency bands. Statistically significant EEG band spectral power change differences between different brain areas were not found. Significant differences between different treatment methods were found in all EEG frequency bands (Table 3.3.4). Bonferroni post hoc test showed that statistically significant ($p<0,05$) differences in physiological treatment method influence are evident between ECT and rTMS in the delta and theta bands, in the effect to the alpha frequency band ECT does not differ from 1 Hz neuronavigated rTMS, whereas in the effect to the beta frequency band 1 Hz standard positioning rTMS tends to differ from the rest of therapeutic methods.

Table 3.3.4. Analysis of variance for EEG band power spectrum between different therapeutic methods (ECT vs 10 Hz or 1 Hz standard or neuronavigated rTMS) and brain areas (N=120).

Band	Factor	F	p value
Delta	Procedure	198,230	0,000*
	Procedure*Area	17,182	0,511
	Method	33,922	0,000*
Theta	Procedure	69,087	0,000*
	Procedure*Area	0,851	0,530
	Method	14,591	0,000*
Alpha	Procedure	10,462	0,001*
	Procedure*Area	0,322	0,926
	Method	5,833	0,000*
Beta	Procedure	0,000	0,996
	Procedure*Area	0,364	0,902
	Method	15,919	0,000*

3.4 Study of EEG band power spectrum long term dynamics for rTMS patients

EEG recording of returning patients several months after rTMS therapy course showed delta band power decrease in frontal, temporal, central and parietal areas.

Delta power was increased in occipital area. In other frequency bands power increase was observed, excluding alpha and beta band power decrease in the left temporal area and alpha band power decrease in the parietal area (Fig. 3.4.1). According to Wilcoxon test statistically significant ($p<0,05$) changes were found for delta band in frontal and right temporal areas and for alpha band in left temporal area (Table 3.4.1).

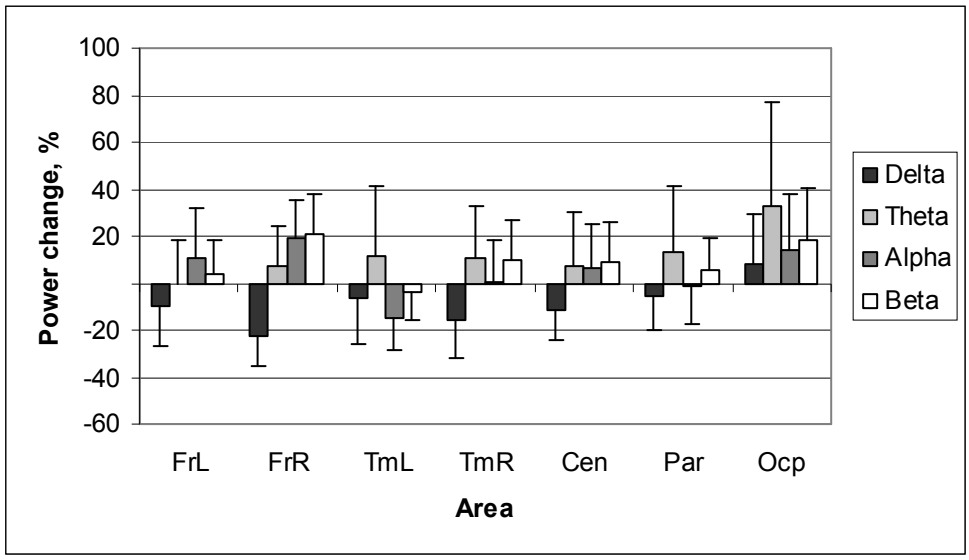

Fig. 3.4.1. Percent changes of EEG band spectrum power in patients returning after rTMS course (N=20).

Table 3.4.1. EEG band spectrum power (μV^2) averages after rTMS course and upon return (N=20; * p<0,05 according to Wilcoxon test).

Area	Measures	Delta	Theta	Alpha	Beta
Frontal left FrL	After therapy	**8,29±5,73***	7,61±8,64	7,04±4,59	2,30±1,77
	Upon return	**6,36±4,04***	5,72±3,78	7,23±5,65	2,24±1,98
Frontal right FrR	After therapy	**9,26±8,16***	6,33±5,26	6,48±4,21	2,10±1,44
	Upon return	**6,17±4,29***	5,79±4,34	7,41±6,65	2,44±2,31
Temporal left TmL	After therapy	4,13±3,21	5,07±4,81	**11,53±9,98***	2,26±1,42
	Upon return	3,03±1,89	4,73±4,22	**8,45±6,33***	2,12±1,49
Temporal right TmR	After therapy	**3,77±2,18***	4,55±3,64	8,54±7,05	1,85±1,18
	Upon return	**2,85±2,21***	4,24±4,22	7,50±6,23	1,91±1,62
Central Cen	After therapy	6,83±4,85	9,61±11,01	15,42±12,26	3,71±3,32
	Upon return	5,44±4,04	8,47±7,41	14,64±12,36	3,79±3,29
Parietal Par	After therapy	6,16±3,95	8,34±7,41	29,49±29,07	3,62±2,59
	Upon return	5,31±4,07	9,10±10,57	24,41±23,39	3,80±3,15
Occipital Ocp	After therapy	5,44±3,96	6,90±5,18	29,84±33,27	2,95±1,75
	Upon return	4,85±3,68	8,87±11,24	31,80±37,04	3,12±2,01

3.5 Study of rTMS therapy effect on evoked potential P300.

After 10 Hz standard coil placement and neuronavigated rTMS as well as 1 Hz standard rTMS therapy decrease in P300 latency was found, gaining statistical significance (p<0,05) in 1 Hz standard coil placement rTMS therapy case. Decrease in P300 amplitude was statistically significant in all three mentioned cases. After 1 Hz neuronavigated rTMS course statistically insignificant increase in P300 latency and amplitude was found (Table 3.5.1).

Table 3.5.1. P300 potential parameters before and after rTMS therapy (N=82).

Parameter	Method	Before TMS		After TMS		p value
		Mean	SD	Mean	SD	
Latency	10 Hz standard	354,97	21,69	353,50	25,05	0,604
	1 Hz standard	356,77	32,16	347,00	30,83	**0,014***
	10 Hz navigated	352,75	19,74	347,57	26,68	0,074
	1 Hz navigated	346,17	27,29	346,48	23,78	0,909
Amplitude	10 Hz standard	13,15	4,88	11,77	5,08	**0,039***
	1 Hz standard	14,52	7,78	12,93	7,63	**0,026***
	10 Hz navigated	13,98	6,47	12,66	6,84	**0,038***
	1 Hz navigated	11,83	6,33	12,23	6,39	0,515

Repeated measures ANOVA showed significant changes in P300 latency and amplitude after the therapy, however no statistically significant differences between brain areas or rTMS methods were found (Table 3.5.2).

Table 3.5.2. Analysis of variance for P300 parameters between different TMS methods (standard vs. neuronavigated) and brain areas (Fz, Cz, Pz electrodes)(N=82).

Parameter	Factor	F	p value
Latency	Procedure	6,514	**0,011***
	Procedure*Area	0,144	0,866
	Method	1,290	0,278
Amplitude	Procedure	8,663	**0,004***
	Procedure*Area	0,405	0,668
	Method	1,077	0,359

3.6 Study of relationship between bioelectrical brain activity and depression symptoms.

Application of neuronavigated system led to a larger decrease in MADRS and HAM-D clinical test scores and a smaller decrease in BDI test scores for both rTMS protocols without statistical significance (Table 3.6.1).

Table 3.6.1. Percent decrease in clinical test scores after different method rTMS therapy (N=82).

Test	Method	Score decrease, %	SD	F	p value
MADRS	10 Hz stand	47,63	27,48	0,336	0,799
	1 Hz stand	48,08	24,45		
	10 Hz navi	53,33	16,65		
	1 Hz navi	53,65	23,08		
BDI	10 Hz stand	47,95	22,91	0,371	0,774
	1 Hz stand	42,23	31,55		
	10 Hz navi	44,00	26,53		
	1 Hz navi	38,47	26,94		
HAM-D	10 Hz stand	56,31	23,79	0,553	0,648
	1 Hz stand	47,98	28,59		
	10 Hz navi	57,14	17,31		
	1 Hz navi	54,06	23,69		

When neuronavigation system was applied in rTMS therapy proportion of patients, achieving considerable clinical effect (MADRS test score drop >50%) increased by 17,5%, whereas the fraction of patients to whom clinical effect was weak (MADRS test score drop <10%) decreased by 9,7%. However, when using the standard coil placement rTMS therapy 4,3% more patients achieved remission. None of these differences were statistically significant (Table 3.6.2).

Table 3.6.2. Comparison of standard coil placement and neuronavigated rTMS therapy clinical effect (N=82).

Method	Effect	Patients	p value
Standard	Weak	12,8%	0,099
	Significant	35,9%	
	Considerable	51,3%	
	Remission	23,1%	0,659
Neuronavigated	Weak	3,1%	0,099
	Significant	28,1%	
	Considerable	68,8%	
	Remission	18,8%	0,659

In most of brain areas negative correlation between the increase of delta and theta band power and clinical test score change and positive correlation between increase of alpha and beta band power and clinical test score change was found. Statistically significant negative correlation was found between MADRS test score changes and delta band power increase in left temporal, central and parietal areas as well as theta band power increase in parietal and occipital areas. BDI test score change showed significant negative correlation with delta band power increase in the central brain area, HAM-D test score change correlated negatively and statistically significant with delta band power

increase in the central area and theta band power increase in the occipital area. Correlation between clinical test score changes and changes in cerebral activity asymmetry was inconsistent and statistically insignificant (Table 3.6.3).

Table 3.6.3. Correlations between EEG changes and clinical test scores (N=82; * - p<0,05).

Band	Test	FrL	FrR	TmL	TmR	Cen	Par	Ocp	AsF	AsT
Delta	MADRS	-0,014	-0,007	**-0,308****	-0,059	**-0,290***	**-0,303***	-0,207	0,017	-0,097
	BDI	-0,087	-0,114	-0,223	-0,052	**-0,279***	-0,236	-0,177	0,130	0,005
	HAM-D	0,011	0,031	-0,230	-0,052	**-0,256***	-0,232	-0,157	0,024	0,002
Theta	MADRS	-0,008	-0,193	-0,232	-0,034	-0,199	**-0,256***	**-0,278***	0,173	-0,120
	BDI	-0,078	-0,109	-0,081	0,007	-0,007	-0,078	-0,072	0,216	-0,045
	HAM-D	-0,018	-0,105	-0,087	0,032	-0,193	-0,200	**-0,243***	0,146	-0,069
Alpha	MADRS	0,081	0,116	0,036	0,155	0,109	0,041	0,035	0,032	-0,032
	BDI	0,083	0,085	0,084	0,038	0,073	0,009	0,093	0,096	0,110
	HAM-D	0,149	0,151	0,144	0,144	0,132	0,105	0,097	0,046	0,059
Beta	MADRS	-0,071	0,114	-0,054	0,095	0,102	0,108	0,053	-0,172	-0,072
	BDI	-0,001	0,058	0,041	0,022	0,178	0,199	0,189	-0,053	0,086
	HAM-D	0,069	0,160	0,052	0,075	0,175	0,172	0,104	-0,066	0,069

Statistically significant negative correlation between P300 latency change and changes of all clinical tests was found. Correlation between P300 amplitude and clinical test scores was inconsistent and statistically insignificant (Table 3.6.4).

Table 3.6.4. Correlations between P300 parameter changes and changes in clinical test scores (N=82; * - p<0,05).

P300 parameters	MADRS	BDI	HAM-D
Latency	**-0,331****	**-0,189***	**-0,271****
Amplitude	0,005	-0,105	-0,002

After the comparison of different clinical efficacy patients P300 parameters before rTMS therapy, statistically significant prolongation of P300 latency for patients of considerable (MADRS test score drop >50%) clinical response was found (Table 3.6.5).

Table 3.6.5. Differences in P300 latency before rTMS therapy for patients of different clinical efficacy result (N=82).

Effect	P300 latency	SD	F	p value
Weak	343,49	21,83	10,16	**0,000***
Significant	339,08	20,31		
Considerable	360,23	29,64		

4. DISCUSSION

4.1. Effect of high and low frequency rTMS therapy on EEG band power spectrum.

After 10 Hz rTMS therapy there was a considerable increase in delta, theta and alpha band power, most prominent changes being located at central, parietal and occipital areas. Changes in delta and theta band power was to be expected, because wave parameters of these bands display a low level of heredity and a strong susceptibilty to outside factors (Anokhin et al, 2006). Delta power increase also corresponded to Griškova and co-workers (2006) as well as Spronk and colleagues (2008) study results. However, theta and alpha power increase, taking into account that 10 Hz rTMS protocol tends to locally boast cerebral cortex activity (George and Belmaker, 2007), came as a surprise, because greater power of these bands are related to a reduction of brain activity and sometimes are observed in the initial depression stages (Grin-Yatsenko et al, 2009). Physiological marker, related to an increase in cerebral activity – the beta band power, after 10 Hz rTMS course increased minutely and statistically insignificantly.

High frequency rTMS therapy caused frontal EEG activity asymmetry to insignificantly shift towards the right hemisphere in all frequency bands. It could be postulated, that proportional reduction of slow waves (delta, theta and alpha) in the left hemisphere frontal area does indicate an increase of neuronal activity in this particular area. It is also worth mentioning that before rTMS therapy delta and theta band power was larger on the left hemisphere frontal area, whereas alpha and beta power was larger on the right hemisphere. Therefore, excluding the alpha band power, EEG band power asymmetry before the therapy coincided with depression physiology theory, claiming the reduction of neuronal activity over the left hemisphere PFDLC (Henriques and Davidson, 1991) and an increase of activity over the right hemisphere PFDLC (Cook et al, 2005). The fact, that despite initially larger alpha band power in the right hemisphere frontal area, frontal alpha asymmetry after 10 Hz rTMS course tended to shift further to the right, does support the notion of therapeutically standard and purposeful alpha asymmetry change and contradicts Price and colleagues (2008) study results.

After 1 Hz rTMS therapy an increase of power was observed in all EEG frequency bands, however, compared to 10 Hz rTMS course, these changes were smaller and statistically insignificant in all brain areas. It is an adequate result, because the scope

of neurophysiological changes in the brain does depend on the number of impulses in the rTMS procedure (Thut and Pascual-Leone, 2010), of which in the session of 1 Hz rTMS protocol there are more than 13 times fewer, when compared to the 10 Hz rTMS procedure.

Frontal and temporal area EEG asymmetry after 1 Hz rTMS therapy course moved towards the right hemisphere side in all frequency bands, reaching statistical significance for frontal alpha band shift. Higher beta band power on the right hemisphere after 1 Hz rTMS therapy did came as a surprise, because this EEG frequency is related to cerebral cortex activation, which should have been suppressed in the right frontal area after the local application of low frequency rTMS (Klein et al, 1999). In the case of slow waves (delta, theta and alpha) frontal asymmetry purposefully shifted from higher power on the left hemisphere to higher power on the right side of the brain, which does coincide with both the hemisphere frontal activity imbalance depression theory (Henriques and Davidson, 1991; Cook et al, 2005) and the expected local effect of low frequency rTMS on the cerebral cortex (Klein et al, 1999; George and Belmaker, 2007). The dynamics of frontal alpha asymmetry, observed when using both mentioned rTMS therapy protocols does support the rTMS theory of standard brain „fixing“, described by Ridding and Rothwell (2007), manifesting itself by universal alpha band power increase in the right frontal area after the rTMS course, despite the differences in initial conditions.

Before the therapy course 10 Hz and 1 Hz rTMS protocol groups were homogeneous in the delta, theta and alpha frequency bands, however there was a significant difference in beta band power, which initially tended to be higher in 1 Hz rTMS patient group. It is worth noticing that an increase of beta power in depressive patients already has been observed in the previous studies (Gin-Yatsenko et al, 2009; Kemp et al, 2010). Because this trait was more apparent in the low frequency rTMS group, which has been compiled by a psychiatrist based on prevalence of anxiety symptoms, it can be concluded that the rise of beta power in depression must be caused by the presence of anxiety in disorder manifestation.

Comparison between 10 Hz and 1 Hz rTMS protocol physiology showed that both of these therapies produce the most notable changes in delta, theta and alpha frequency bands. For all frequency bands observed changes were greater when using 10 Hz rTMS therapy, however statistically significant differences between the two protocols

were proved for only theta and beta frequency bands. Delta band power change differences, although being rather considerable (20-50% increase when using 10 Hz rTMS therapy; 5-20% increase when using 1 Hz rTMS therapy) did not reach the level of statistical significance (p=0,055). However, taking into account the significant effect difference on the theta band power, while keeping in mind the initial homogeneity of delta, theta and alpha band power of both study groups, results yielded are sufficient to state that low frequency rTMS does produce lesser electrophysiological changes in the brain than a high frequency protocol.

4.2 Effect of neuronavigated rTMS therapy on EEG band power spectrum.

When using neuronavigation system after 10 Hz rTMS therapy the largest EEG power increase was observed in delta frequency band, which was statistically significant in all the brain areas. Theta and alpha band power also increased across the brain, however for theta band the change was utterly statistically insignificant, whereas for alpha band power the only significant change was observed in the left temporal area. Beta band power increase was minute and insignificant, in the left frontal area even slight decrease in beta band power was observed, which contradicts the notion that 10 Hz rTMS should necessarily increase the stimulated cerebral cortex activity (George and Belmaker, 2007).

EEG activity asymmetry change after 10 Hz neuronavigated rTMS therapy was tiny, statistically insignificant and controversial between different areas. In the frontal cortex delta, theta and beta band power, initially larger on the left hemisphere after was therapy increased on the right, however the change was insufficient to shift the EEG asymmetry balance towards the right hemisphere. Alpha band power, more pronounced in the right hemisphere before the therapy after the treatment slightly moved to the left hemisphere side thus, although weakly, but still contradicting the purposeful frontal alpha asymmetry change theory (Ridding and Rothwell, 2007) after rTMS and matched Price and co-workers (2008) study results. It seems that despite rather uniform results, observed in the standard coil placement study, changes in frontal EEG asymmetry after 10 Hz rTMS therapy are not always universal and purposeful and can be influenced by initial variables in asymmetry as well as by unknown outside factors. Temporal EEG asymmetry changes after 10 Hz rTMS therapy also did not meet the

expectations, because initial power imbalance towards the left hemisphere in all frequency band only grew larger after the treatment.

After neuronavigated 1 Hz rTMS therapy increments in all EEG band power were found, however, unlike in the standard coil positioning 1 Hz rTMS case, statistically significant changes in delta band power were found in all brain areas except the left frontal cortex. Theta band power increase was significant in right frontal, left temporal, central, parietal and occipital areas. Although theta band increase after 1 Hz rTMS procedure was also observed in Schutter et al (2003) study, these results do not match the expectations, based on the fact that the use of a more precise neuronavigational coil positioning should yield lesser variability of physiological changes (Rusjan et al, 2010). This study, contradictory to 10 Hz rTMS case which proved the use neuronavigation to be effective in diminishing theta and alpha band power changes, led to completely opposite reaction. Neuronavigated coil positioning in 1 Hz rTMS therapy actually amplified an increase of delta and theta band power to the point where it became close to the standard coil positioning 10 Hz rTMS therapy changes.

Despite the similarities in EEG band power spectrum changes with the standard coil positioning 10 Hz rTMS therapy, changes to the frontal alpha asymmetry when using neuronavigated 1 Hz rTMS therapy did not match previous results and depression physiology theories. Initially larger in the right hemisphere alpha power after 1 Hz neuronavigated rTMS course insignificantly shifted balance to the left hemisphere side. Other EEG band asymmetries, except for frontal delta and temporal beta, after the therapy tended to increase in the left hemisphere side.

Comparison of before treatment EEG power spectrum between 1 Hz neuronavigated rTMS patients and remaining rTMS groups revealed significant heterogeneity of the former group. Compared to 10 Hz neuronavigated rTMS group low frequency neuronavigated rTMS patients displayed lower delta and theta band power. Lesser delta band power in 1 Hz neuronavigated group was also observed when compared to 1 Hz standard coil positioning rTMS group, which exceeded in initial beta band power as well. The causes of differences described remain unclear. Based on a relatively low beta band power in the 1 Hz neuronavigated group before the treatment, more common for high frequency rTMS patients, a different group symptomatic and an

error in patient selection could be suspected, however it does not explain an initial decrease in delta and theta band power. The possibility of screening mistake for 1 Hz neuronavigated rTMS group by psychiatrist is also lessened by the fact that for high frequency rTMS both standard coil positioning and neuronavigated groups were absolutely homogeneous.

Because of previously described 1 Hz neuronavigated rTMS group heterogeneity and larger changes in EEG band power after the treatment, compared to 1 Hz standard coil positioning group, considerable physiological differences between standard coil positioning and neuronavigated rTMS therapies overall were not found. Taking into account both coil positioning and rTMS protocol factors statistically significant changes were found for theta and alpha frequency band power. In both cases the largest increase in power was observed in the standard coil positioning 10 Hz rTMS protocol group, the smallest – in the neuronavigated 10 Hz rTMS protocol group. 1 Hz neuronavigated and standard coil positioning groups were in the middle of EEG band power change spectrum. The fact that after the use of neuronavigation system theta and alpha power changes were milder for 10 Hz rTMS protocol, however did cause significantly larger theta band power increase in 1 Hz rTMS therapy case, does show that higher accuracy of stimulation target does not always yield milder and more purposeful physiological changes. Significantly larger physiological effect of rTMS therapy might also depend on the differences of initial EEG band power.

Summing up all the rTMS data in this study, it is apparent that the most universal and pervasive changes of EEG band power spectrum do appear in the delta frequency power increase, which remains rather stable when using different rTMS therapy methods. The intensity of theta and in part alpha band power can be influenced by TMS coil and target positioning, whereas hemispherical asymmetry of alpha band power is an unstable parameter, strongly influenced by various outside factors. These results match the observations of other authors, considering apparent changes in delta power after rTMS (Griškova et al, 2006; Spronk et al, 2008) and support the general confusion about the frontal alpha asymmetry (Pozzi et al, 1995; Reid et al, 1998; Kemp et al, 2010; Funk and George, 2008; Moratti et al, 2008; Price et al, 2008).

4.3 Effect of ECT on EEG band power spectrum.

After ECT course, similarly to the rTMS therapy case, delta, theta and alpha band power increased across the brain. The rise in delta and theta band power was particularly sound (250-350% increase in delta power and 150-250% increase in theta power). Delta band power change was statistically significant in all brain areas, theta band power change was statistically insignificant only in right temporal and occipital cortex. Notable and consistent delta band power increase after the ECT course corresponded to the data of previous studies (Narayana Dutt et al, 1997; Fosse and Read, 2013).

Although bipolar ECT electrode placement, generating equal electrical charge in both cerebral hemispheres, was used in this study, after the therapy course insignificant EEG asymmetry change, matching Henriques and Davidson (1991) depression theory was observed when slow wave (delta, theta and alpha) power asymmetry shifted from the left cerebral hemisphere to the right. However, this observation should receive additional scrutiny, because ECT study group was considerably smaller (15 patients) and more heterogeneous (involving patients with paranoid schizophrenia) than groups of rTMS studies.

Initial EEG band power spectrum comparison between ECT and rTMS patients revealed that despite the apparent diagnostic heterogeneity these groups were physiologically homogeneous in delta, theta and beta band frequencies.

Comparison of electrophysiological changes between rTMS and ECT methods showed that ECT results in significantly larger effect on delta and theta band power compared to rTMS. Whereas in effect to alpha band power, despite the lower initial value, ECT remains inactive and does produce only minor changes, equal to 1 Hz neuronavigated rTMS treatment. Summing up it can be stated that ECT is considerably more active in enhancing low frequency EEG band power than rTMS.

4.4 Long term dynamics of EEG band power spectrum for rTMS patients.

Mean time interval, after which rTMS patients returned for additional therapy course (14 months) slightly exceeded the result (10 months) of Fitzgerald and colleagues (2006b) study. After the measurement of returning patients EEG band power spectrum, it was found out that during the months without active rTMS treatment delta

band power decreases in all brain areas except for occipital cortex. The most notable and statistically significant delta band power decrease is observed frontal and right temporal areas. In the left hemisphere temporal area alpha and beta band power also decreased slight reduction in alpha band power was also observed in the parietal cortex. These results prove that the most pervasive, notable and potentially pathologic electrophysiological effect of rTMS therapy – the delta band power increase, is a dynamic trait with a tendency of decrease and normalisation after the rTMS therapy course. Potential hazards of blood flow and metabolism reduction (Perera et al, 2004) or deaferentization (Moretti et al, 2012) does not seem to be apparent or permanent in this case. Theta band power increase, on the other hand, proved to be much more rigid, without the tendency of decrease after the therapy course, averaged even displaying a slight continuous rise after the treatment. Fosse and Read (2013) had noticed that EEG power changes in delta and theta bands could remain rigid for several weeks or months. Our study showed the difference between the two, delta band power being more dynamic than theta band power. Under the influence of rTMS delta band power tends to rise instantly and notably, subsidence occurs after the cessation of treatment. Theta band power is more variable, less apparent and much slower to change during the treatment or after it. Having these traits in mind it does not surprise that most of rTMS studies, exploring the effect of single rTMS procedure on EEG band power spectrum does indicate delta, but not theta changes (Griškova et al, 2006; Spronk et al., 2008). Theta band power changes are usually observed only with the EEG registration time delayed (Schutter et al, 2003).

4.5 Effect of rTMS therapy on evoked potential P300.

In the study of rTMS therapy effect on auditory evoked potential P300 decrease in latency was found using all different parameter stimulation except for 1 Hz neuronavigated rTMS therapy, when a fractional increase in P300 latency was found. Although analysis of variance did not show statistically significant differences between different rTMS methods, most notable and significant shortening of P300 latency was observed when using 1 Hz standard coil positioning rTMS therapy. Purposeful decrease in P300 latency is a positive and expected change, because an increase in P300 latency

does relate to the occurrence of depressive symptoms (Xu et al, 2010, Isintas et al, 2012), whereas it‘s shortening indicates an improvement of cognitive functions.

The effect of rTMS therapy on P300 potential amplitude was surprising and contradictory to other researcher data (Moller et al, 2006). After rTMS therapy of most parameters P300 significantly decreased with the exception of 1 Hz neuronavigated TMS when once again a fractional change in opposite direction was found. Despite that analysis of variance once again failed to prove the differences between various parameter rTMS therapies to be statistically significant. Pervasive reduction of P300 potential amplitude after rTMS course cannot be described as a positive change, because it does relate to the smaller number of neurons responding (Dapšys, 2011) as well as occurrence of psychotic and affective symptoms (Salisbury, 1999). On the other hand this change can help to explain why rTMS therapy is usually less effective for patients with initial psychotic symptoms (Fitzgerald, 2004).

The fact that although slightly, 1 Hz neuronavigated rTMS therapy continually separated itself from other rTMS methods (including the same rTMS protocol using standard coil positioning) in terms of electrophysiological effect, does prove the vast influence of variation in stimulation target choice on brain physiology.

4.6 Relationship between bioelectrical brain activity and depression symptoms.

After the measurement of clinical test score changes it was found out that there were now differences in high and low frequency rTMS protocol clinical effectiveness. These results coincide with other researcher study data (Fitzgerald et al, 2003; Hoppner et al, 2003; Isenberg et al, 2005; Fitzgerald et al, 2009). Application of neuronavigation system in rTMS therapy caused greater, however statistically insignificant changes in MADRS and HAM-D test scores. BDI test, based on patient‘s subjective answers, score decrease was insignificantly smaller after the use of neuronavigation. Neuronavigated 1 Hz rTMS therapy, separated from other methods by unusual and unexpected electrophysiological changes, in terms of clinical score change did not set itself apart. Comparison between standard and neuronavigated coil positioning rTMS by overall clinical effect categories showed that the use of neuronavigation system led to a larger number of patients achieving considerable clinical effect and a smaller part of patients to whom clinical effect was weak.

Study of relationship between EEG band power spectrum and clinical test score changes showed that delta and theta band power increase correlate negatively with the clinical improvement. In the central, parietal and occipital areas, where EEG band power changes were the most apparent, mentioned correlations were statistically significant. This proves that considerable and typical electrophysiological changes described do not „fix“ the brain or indicate the clinical improvement, like it was postulated by several previous authors (Ridding and Rothwell, 2007; Fosse and Read, 2013). It seems that an intense increase in delta and theta band can even diminish the positive clinical effect. Therefore for the future improvement of rTMS method it is especially important to thoroughly observe and try to manipulate the theta band power changes, because their arousal tends to be influenced by stimulation factors, however once caused, they seem to last for a long time. One should bear in mind that long term theta band power increase is not only a non beneficent physiological side effect, but also can be rated as a depressive symptoms (Pozzi et al, 1993; Kwon et al, 1996) or negative rTMS therapy prognosis (Arns et al, 2012) marker.

Frontal and temporal area EEG band power asymmetry changes after rTMS course did not produce consistent results when using different rTMS parameters and did not correlate significantly or purposefully with the clinical test score changes. This confusion matched Gotlib (1998) and Allen et al (2004) study results.

Study of relationship between auditory evoked potential P300 parameters and clinical test score change showed a statistically significant correlation between the decrease of P300 latency and improvement of clinical symptoms. Moreover, comparison of different clinical effectiveness patient groups proved considerable clinical effect achieving patients to have longer P300 potential latencies before the treatment. This is contradictory to Isintas and colleagues (2012) study results. It seems that initially prolonged P300 latency does not necessarily mean negative treatment prognosis. On the contrary it can serve a purpose as an important and observable parameter, dynamics of which during the rTMS therapy course can indicate a positive reaction of the brain to stimulation and prognosticate a positive clinical result.

4.7. Recommendations for future studies.

Concluding the results and shortcomings of this study, for research and clinical practice of the future it is recommended to try and achieve a higher homogeneity of patients according to disorder diagnosis in the study groups. A new larger and more homogeneous to standard coil positioning 1 Hz rTMS group in terms of EEG band spectral power 1 Hz neuronavigated rTMS patient group should be compiled. At the possibility given, larger and more homogeneous group of ECT patients should be gathered for a more objective comparison. Study of rTMS therapy induced electrophysiological change long term dynamics would benefit from standardized EEG recording time after the end of the treatment (i.e. after three months), which would also provide additional data for long term physiological comparison of faster and slower returning patients. Same rule applies to the evoked potential P300 study. A more numerous group of returning patients would enable an additional comparison of rTMS protocols and coil positioning effect on long term EEG dynamics. In case of patients with prolonged P300 latencies before the treatment, measurement of this parameter not only before and after but also during the therapy is highly recommended. For the future studies possible correlations between EEG band spectrum power changes and P300 potential dynamics might also prove to be beneficial.

CONCLUSIONS

1. When using the standard coil positioning, 10 Hz rTMS therapy causes more substantial changes in EEG band power spectrum than 1 Hz rTMS therapy.
2. Application of neuronavigation system in the rTMS therapy causes milder changes of theta and alpha band power spectrum for 10 Hz rTMS protocol, but not the 1 Hz rTMS protocol case.
3. ECT produces a larger increase of delta and theta band power than rTMS therapy.
4. In the long run, rTMS therapy induced delta band power rise decreases significantly, whereas theta band power remains unchanged.
5. rTMS therapy decreases latency and amplitude of auditory evoked potential P300.
6. Decrease in P300 potential latency correlates to an improvement of depression clinical symptoms and could be used as a therapy efficacy marker.

SANTRAUKA (Summary in Lithuanian)

Transkranijinė magnetinė stimuliacija (TMS) – tai modernus neinvazinis vaistams rezistentiškų psichiatrinių sutrikimų gydymo būdas. Didžioji dalis tyrimų pagrindžia TMS terapijos efektvumą depresijos gydyme, tačiau klinikiniai rezultatai atskirais atvejais skiriasi, o tikslus neurofiziologinis šios metodikos mechanizmas iki šiol nėra žinomas. Fiziologiniai TMS tyrimai pasižymi įvairiais, dažnai prieštaringais rezultatais, daugeliu atvejų didžiausias dėmesys skiriamas betarpiškiems poveikiams po vienos TMS procedūros, bet ne po pilno terapinio kurso. Manoma, kad rezultatų įvairovę TMS praktikoje taip pat įtakoja skirtingi stimuliacijos parametrai ir netikslumai parenkant stimuliuojamą zoną smegenyse. Šios problemos bandomos spręsti standartizuojant TMS protokolus ir naudojant neuronavigacinę sistemą stimuliacijos taikinio pozicionavimui. Nors TMS terapija dažnai traktuojama kaip švelnesnė alternatyva labiau įprastai elektros impulsų terapijai (EIT), palyginamųjų fiziologinių šių metodikų tyrimų labai trūksta.

Pagrindinis darbo tikslas buvo įvertinti TMS terapijos kurso poveikį bioelektriniam galvos smegenų aktyvumui ir palyginti jį su kitų vaistams rezistentiškų psichiatinių sutrikimų terapijos metodų (EIT) poveikiu. Buvo tirta kaip dviejų depresinių nuotaikos sutrikimų gydyme dažniausiai naudojamų TMS protokolų (10 Hz ir 1 Hz) terapija įtakoja EEG dažnių galios spektrą bei sukeltinį klausos potencialą P300, naudojant standartinį ir neuronavigacinį taikinio pozicionavimą. TMS terapijos sukelti fiziologiniai pokyčiai palyginti su EIT terapijos sukeltais fiziologiniais pokyčiais, išmatuota TMS terapijos sąlygotų pokyčių dinamika kelių mėnesių bėgyje. Darbo rezultatai parodė, kad TMS terapijos pasekoje smegenyse ryškiausiai padidėja delta dažnio galia. Naudojant standartinį pozicionavimą 10 Hz TMS protokolas sukėlė įvairesnius ir intensyvesnius EEG galios spektro pokyčius nei 1 Hz protokolas. Pritaikius neuronavigacinę sistemą sumažėjo teta ir alfa dažnių galios pokyčių 10 Hz TMS protokolo atveju. Pamatavus EEG po kelių mėnesių nuo TMS terapijos pabaigos paaiškėjo, kad delta galios išaugimas bėgant laikui slopsta ryškiau nei teta galios išaugimas, kuris po terapijos pabaigos išlieka iš esmės nepakitęs. EIT metodika taip pat sukėlė delta ir teta galios išaugimą, tačiau pastaruoju atveju jis buvo kelis kartus didesnis nei taikant TMS terapiją. Po TMS terapijos sumažėjo P300 potencialo latencija ir

amplitudė. P300 latencijos sutrumpėjimas koreliavo su klinikinių depresijo simptomų gerėjimų kas įrodo galimybę naudoti šį parametrą kaip terepinio efektyvumo žymeklį.

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