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APPLICATION OF BDNF DYNAMICS TO STUDY BRAIN STIMULATION THERAPIES OF TREATMENT RESISTANT DEPRESSION AND SCHIZOPHRENIA

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1. Introduction

Objectives. In the clinical psychiatric practice approximately 20% of depression and 20-30 % of schizophrenia patients develop pharmacological treatment resistance (TR). Such cases are usually treated with brain stimulation therapies, including transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) (Pantelis & Lambert, 2003; Cusin & Dougherty, 2012). However, the biodynamics of TR psychiatric disorders, as well as the mechanism of brain stimulation therapies, still remains elusive.

Brain derived neurotrophic factor (BDNF) is a protein crucial for neural growth and plasticity (Gersner et al., 2011). Therefore it has been proposed as an important and universal biomarker in the formation and treatment of various psychiatric illnesses. Decreased quantity of BDNF has been observed in the blood samples of both depressive (Karege et al., 2005) and schizophrenic patients (Jindal et al., 2010; Cui et al., 2012). Lowered BDNF was also observed in the post mortem studies of psychiatric patient's brain (Perlman et al., 2004; Lee & Kim, 2010).

BDNF level has been shown to increase after a successful pharmacological therapy, suggesting it's use as a potential biomarker for treatment outcomes (Shimizu et al., 2003; Bocchio-Chiavetto et al., 2006; Chen & Huang, 2011). BDNF studies of TR patients, undergoing brain stimulation therapy, on the other hand, have produced controversial results so far (Zanardini et al., 2006; Gedge et al., 2012; Favalli et al., 2012; Brunoni et al., 2015).

Background and aims. Since BDNF can be regarded as a marker for brain plasticity potential, it is important to evaluate its initial level and dynamic changes during treatment-resistant psychiatric disorder therapy. Also it is important to try and understand the role BDNF plays in the brain stimulation based treatment. Therefore we aim to measure the initial differences and dynamics of BDNF levels in TR depression and schizophrenia patients, subjected to TMS and ECT.

2. Methods

Subjects. 20 treatment resistant depressive patients (8 male, 12 female, age 45.2±13.1 years), subjected to TMS, 17 treatment resistant schizophrenia patients (11 male, 6 female, mean age 37.7±12.8 years), subjected to ECT, and 20 healthy control subjects (5 male, 15 female, mean age 45±14.8 years) participated in this study. For psychiatric patients, blood serum derived BDNF levels were measured before the treatment course, after 5 procedures and after 10 procedures. BDNF was measured once for the healthy control group. Additional psychiatric tests (MADRS and HAM-D for depressive patients and PANSS for schizophrenic patients) were used to evaluate the change of clinical symptoms.

TMS application. Overall TMS treatment course ranged from 15 to 30 procedures depending on the clinical outcome. Procedures were carried out using MagVenture Magpro X100 TMS stimulator with MagVenture Cool Coil B65 figure eight liquid cooled coil. During the stimulation procedure biphasic 280 µs impulses were used. Localite TMS Navigator MR-less system was utilized for neuronavigated coil placement. This system uses MNI ICBM152 non-linear symmetric T1 Average Brain map. Left dorsolateral prefrontal cortex (DLPFC) target was set to coordinates (-38.0; 44.0; 26.0) (Fox et al, 2012)(Fig. 1). 10 Hz or intermittent theta burst (iTBS) TMS protocols were utilized at 100% and 80% motor threshold value.

Fig. 1. TMS target in the MNI Brain map.

ECT application. ECT procedures, depending on clinical progress, ranged from 10 to 20. For ECT Somatics Inc. Thymatron DGx apparatus with DualGraph EEG recorder were used. Before ECT procedure patients underwent anesthesia using IV thiopental solution 2-5 mg/kg body mass, seizures were controlled using neuromuscular-blocker suxamethonium chloride (Lysthenon) 0.5-1 mg/kg body mass. Stimulation electrodes were placed using bipolar setup on the temporal areas (Fig. 2). During the stimulation 0.5 ms duration biphasic square impulses were applied. Impulse current strength was constant at 0.9 A. During the procedure stimulation was applied from 0.47 to 4 seconds at 70 Hz frequency.

Fig. 2. Position of ECT electrodes.

Blood sampling and testing. Blood (6 ml) was gathered into 2 ACD test-tube 3 ml each, kept at room temperature for 30 min, then centrifuged for 15 min at 1000xg. Serum produced was transefed into 3 Eppendorf type test tubes 1 ml each and kept at ≤ -20 oC temperature until the ELISA test. ELISA test was performed using Human Free BDNF Quantikine ELISA set (R&D Systems), according to the protocol of the manufacturer. BDNF concentration measurements were using ELx808 apparatus (BioTek Instruments, Inc.).

References

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3. Results

Clinical tests. Results have showed a varying response of TR depression patients to TMS treatment, averaging around of 30 percent decrease for both MADRS and HAM-D clinical test scores (Table 1). For TR schizophrenia patients, undergoing ECT treatment, biggest improvement has been observed in the positive symptom scale of the PANSS test (average decrease of 56.85 percent) while negative symptom scale has produced the smallest decrease (22.63 percent), sum decrement of the PANSS test averaging around 40 percent (Table 2).

Table 1. Clinical changes observed in TMS patients.

Clinical test	Mean Change %	Std. Dev. %
MADRS	-29.7730	24.69976
HAM-D	-36.7658	26.50461

Table 2. Clinical changes observed in ECT patients.

PANSS scale	Mean Change %	Std. Dev. %
Positive	-56.8502	13.04161
Negative	-22.6311	14.64187
General	-41.2639	16.10499
Sum	-39.8565	13.23062

BDNF measurement. BDNF change dynamic revealed an observable difference between TMS and ECT patient groups. While TMS produced a steady increase of BDNF concentration during the treatment course, ECT has resulted in a slight dip of BDNF concentration after 5 procedures, followed by a steep rise after 10 procedures (Fig. 3). Although initial TR patient BDNF concentration averages were smaller than that of healthy control group (25.38 ng/ml and 26.95 ng/ml vs 29.94 ng/ml) ANOVA has failed to detect significant differences of BDNF concentrations between all three study groups (Table 3). Paired sample t test on the other hand has revealed overall increase of BDNF during the whole measured TMS and ECT course span (10 procedures) to be statistically significant (Table 4). However, in ECT treatment case, this change occurred during a shorter period, preceded by an initial latency period (Fig. 3. Table 4).

Fig. 3. BDNF chanhge dynamics in all study groups.

Table 3. BDNF concentration comparison between study groups using ANOVA.

	Group	Mean (ng/ml)	Std. Dev. (ng/ml)	F	Sig.
Measure 1	ECT	26.9495	6.96958	2.009	.144
	TMS	25.3753	8.33027		
	Control	29.9350	6.40060		
Measure 2	ECT	24.8278	6.31213	2.824	.068
	TMS	27.6117	6.79001		
	Control	29.9350	6.40060		
Measure 3	ECT	32.3923	8.90330	.627	.538
	TMS	29.6312	8.78680		
	Control	29.9350	6.40060		

Table 4. BDNF concentration comparison during different stages of ECT and TMS treatment using paired sample t test.

Group	Samples	t	Sig. (2-tailed)
ECT	Measure 1 - Measure 2	1.659	.116
	Measure 1 - Measure 3	-2.545	.022*
	Measure 2 - Measure 3	-4.845	.000*
	Measure 1 - Measure 2	-1.474	.157
TMS	Measure 1 - Measure 3	-2.923	.009*
	Measure 2 - Measure 3	-1.583	.131

Correlations between BDNF measurements and clinical tests. For TMS group significant negative correlations have been found between BDNF increase percentage during the treatment and initial measurements of MADRS (r=-0.781; p=0.000) and HAM-D (r=-0.616; p=0.005) clinical tests. No significant correlation between BDNF and the improvement of clinical syntoms has been found in this group. For ECT group the overal proportion of BDNF increase also has held a significant negative correlation with initial clinical test score, in this case being PANSS test positive symptom scale (r=-0.637; p=0.019). This scale in turn has held a significant positive correlation to the PANSS test negative symptom scale result both before (r=0.671; p=0.012) and after (r=0.685; p=0.01) treatment. Overall PANSS positive symptom scale change percent also has correlated with the third measurement of BDNF (r=0.557; p=0.048). These results imply that initial clinical syntom severity relates to limited BDNF increase potential.

Conclusions

No significant differences in BDNF concentrations between treatment resistant patients and healthy control group were found. However, TR depression and schizophrenia patients, undergoing TMS and ECT treatments accordingly, display different patterns of BDNF change dynamics. While TMS treatment of depressed TR patients results in a steady increase of BDNF over time, schizophrenic TR patients, undergoing ECT, display an initial BDNF latency, followed by a swift increase. In both cases of TR pathology at least some of the initial clinical symptom severity seems to be a limiting factor on BDNF growth, which suggests widening the search of possible biomarkers to encompass the full therapeutic mechanism of treatment resistant psychiatric disorders.