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In patients suffering from major depressive disorders, quantitative EEG showed favorable changes in left and right prefrontal cortex

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ABSTRACT

Background: Patients suffering from major depressive disorders (MDD) report anhedonia, low concentration and lack of goal-oriented behavior. Data from imaging and quantitative EEG (QEEG) studies show an asymmetry in the prefrontal cortex (PFC), with lower left as compared to right PFC-activity, associated with specific depression-related behavior. Cordance is a QEEG measurement, which combines absolute and relative power of EEG-spectra with strong correlations with regional perfusion. The aim of the present study was to investigate to what extent a four weeks lasting treatment with a standard SSRI had an influence on neuronal activation and MDD-related symptoms.

Method: Twenty patients suffering from severe MDD were treated with citalopram (40 mg) for four consecutive weeks. At baseline and at the end of the treatment, patients underwent QEEG. Experts rated the degree of depression with the Hamilton Depression Rating Scale (HDRS).

Results: Over time, theta cordance increased over right ventromedial and left dorsolateral PFC, whereas alpha cordance decreased over dorsolateral PFC. Improvement in MDD-related symptoms was higher in patients showing decreased EEG theta cordance over right dorsal PFC and increased EEG alpha cordance over left dorsolateral PFC.

Conclusions: In patients suffering from MDD, treatment response was associated with favorable changes in neuronal activity.

1. Introduction

Patients with major depressive disorders (MDD) report to suffer from poor sleep (disrupted sleep, non-restoring sleep), lack of motivation, enjoyments and interests, dysphoric mood, and difficulties in cognitive performance (DSM-IV; American Psychiatric Association, 2000). The 12-months prevalence of MDD is about 7.5% among adolescents (Avenevoli et al., 2015). In this line, Saltiel and Silvershein (2015) estimated that in the USA about 7–9% of the adult population experience a major depressive episode each year. Not surprisingly, low productivity and days missed as indices of indirect workplace costs due to employees with MDD accounted for about two third of the total economic burden of depression (Greenberg et al., 2003).

From a pathophysiologically point of view, patients suffering from MDD show for instance a highly increased cortisol secretion (see Holsboer and Ising, 2010 for an overview), and blunted secretion of growth hormone (GH) during the first half of sleep (Steiger et al., 2013). Moreover, Coffey et al. (1993) observed that relative to healthy controls, in patients with MDD the volume of the prefrontal cortex was smaller by 7%. Similarly, Rajkowska (2000) investigated post-mortem brain volumes of patients with MDD and observed that, relative to healthy controls, the number, density and size of PFC neurons were smaller; the reduced density varied between 17% and 30%, with a reduction of glia cell volume of 19%. Importantly, there is evidence of altered structural brain changes already in children and adolescents with early-onset of bipolar and unipolar disorders (Serafini et al., 2014). A recent review also highlighted that besides alterations of brain

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volume also functional connectivity in the prefrontal cortex were associated with psychiatric disorders such as MDD (Negron-Oyarzo et al., 2016). For short, MDD is associated with a reduced amount and volume of neurons and their activity. In this context, for instance Bruder et al. (2001) were able to show in patients with MDD an asymmetry of PFC activity, with a relative reduced PFC activity on the left side, as compared to a relative increased PFC activity on the right side. If we follow Davidson and colleagues (Davidson, 2003; Davidson et al., 2000, 2002; Davidson and McEwen, 2012; Sutton and Davidson, 2000), activity of the left PFC is more involved in generating goal-oriented behavior and positive emotions, whereas activity of the right PFC is more involved in generating avoidance behavior and negative emotions. Importantly, following Lindquist et al. (2012), several brain regions are commonly involved in processing emotions. Taken together, there is evidence that in patients suffering from MDD the left PFC seems to be hypoactivated (therefore, a successful treatment should lead to an increased activity of the left PFC), relative to a hyperactivated right PFC (therefore, a successful treatment should lead to a decreased activity of the right PFC).

To investigate the neuronal activity, beside (f)MRIs, quantitative EEG analysis turned out to be a reliable mean to delineate regional brain activity (Steiger and Kimura, 2010). More specifically, cordance is a quantitative EEG measure, which combines complementary information from absolute and relative power EEG spectra. Following Leuchter et al. (1999), these combined variables have stronger correlations with regional perfusion than either measured alone. Following Leuchter et al. (1994a, 1994b), cordance is a measure of cortical deafferences: positive values denote “concordance”, an indicator associated normally brain functioning brain tissue; negative values denote “discordance”, an indicator associated with low perfusion and low metabolism. Most importantly, Leuchter et al. (1994a, 1994b, 1999) and Leuchter and Jacobson (1991) showed that data derived from cordance do highly match data from PET and f(MRI), suggesting therefore strong associations between cordance and other measures of brain structure and function. To illustrate, Leuchter et al. (2002) investigated differences between medication and placebo responders in depressed patients treated for nine weeks with either placebo, fluoxetine or venlafaxine. In the placebo condition, responders showed a significant increase in prefrontal cordance as compared to medication non-responders. Leuchter et al. (2002) summarized that ‘effective’ placebo treatment induces changes in brain function that are different from those associated with antidepressants. Similarly, Cook et al. (2005) observed that decreases in prefrontal cordance differentiated responders from non-responders in patients treated with SSRI monotherapy. Bares et al. (2007, 2015a, 2015b) could show that changes in QEEG prefrontal cordance was a predictor of response to antidepressants in patients with treatment-resistant depressive disorder. Likewise, Hunter et al. (2010) could show in a sample of 49 inpatients suffering from MDD that cordance decreased in responders as compared to non-responders, suggesting therefore that changes in cordance and its underlying strong relationship with perfusion mirrors possible improvements in MDD.

To summarize, decrease in cordance QEEG activity has proved to mirror favorable changes in neuronal activity over time in patients suffering from MDD. The aim of the present study was therefore to compare changes in neuronal activity and symptoms in patients suffering from MDD. Accordingly, we hypothesized that pharmacological treatment decreases MDD-related symptoms and induces a normalization of prefrontal neuronal activity (Bares et al., 2007, 2015a, 2015b; Cook et al., 2005, Hunter et al., 2010), as indexed by increased frontal concordance.

2. Method

2.1. Study design

Inpatients suffering from MDD at the psychiatric ward of the Research Center for Behavioral Disorders and Substances Abuse (Frashchian Hospital; Hamadan University of Medical Sciences, Hamadan Iran) were approached. At baseline and four weeks later resting state QEEGs were performed and experts assessed patients’ depressive symptoms (see below). All patients were treated with citalopram (40 mg) for four consecutive weeks. All patients were fully informed about the aim and procedure of the study and written informed consent was requested. The local ethics committee approved the study, and the entire study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.[1]

2.2. Sample

A total of 20 inpatients (3 males: age: M=28.67, SD=11.93; 17 females age: M=39.53, SD=9.36; t(18)=1.49, p=0.25) diagnosed as suffering from MDD were recruited. Trained professional psychiatrists performed interviews based on the structured clinical interview for psychiatric disorders (M.I.N.I., Mini International Neuropsychiatric Interview; (Sheehan et al., 1998) to diagnose patients according to the DSM-IV (American Psychiatric Association, 2000). All patients were exclusively treated with citalopram (40 mg) for four consecutive weeks. Inclusion criteria were: 1. Diagnose of unipolar major depressive disorder according to the DSM-IV; 2. age 18–60; 3. Right handed. 4. Hamilton Depression Rating Scale score of 18 or higher. Exclusion criteria were: 1. Not meeting the inclusion criteria; 2. comorbidity; 3. physical diseases; 4. intake of further medicaments or drugs, including tranquilizers and sleep supporting drugs; 5. Women being pregnant or intended to getting pregnant; 6. breastfeeding mothers; 7. ECT within the last 3 months. not. but; 8. history of epilepsy. not. but; 9. acute suicidal ideations or suicidal intensions.

2.3. Quantitative EEG

All participants underwent conventional EEG. Recordings were performed in morning hours between 10 and 11 a.m. Patients were in a semi recumbent position with eye closed. A Mitsar 21-channel amplifier system was used (distributed by Ariafanvarzan Co. Ltd, Tehran, Iran). Electrodes were placed according to the international “10–20” system using linked-ears as a reference. The sampling rate was set to 256 Hz and electrode impedance level was kept below 5 kOhm. The data were collected with a computer in 20 min duration for each EEG. All data was filtered offline, so that a frequency range from 5 to 30 Hz remained for analysis. The 20 min recordings were then divided into 60 s epochs, which were visually inspected for artifacts (eye blinks, movement, muscle artifact and similar). Artifact free periods were then averaged and subjected to Fast Fourier Transformation (FFT), using the Hanning Window (20%) algorithm. The frequency bands were theta (4–8 Hz), alpha (8–12 Hz), and beta (12–20 Hz) and the regions included Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz. Absolute and relative powers were calculated.

2.4. Cordance procedure

Cordance is a quantitative EEG measure combining complementary information from absolute and relative power spectra. Following Leuchter et al. (1999), these combined variables have stronger correlations with regional cerebral perfusion, and following Cook et al. (2002) this correlation provides a physiological basis for inter-

[1] Trial registration number: IRCT: IRCT201203049202N1.