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Abnormal EEG activity in major depressive disorder

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Depression is a common mental disorder that affects 350 million people worldwide. Studies using neuroimaging techniques have shown a number of changes both in the structure and functioning of the brain of individuals suffering from depression, which may contribute to the underpinnings of the disease. This article focuses on disturbed EEG activity in patients with depression, especially in the alpha and theta frequency bands. Research in this area allows us to optimize transcranial magnetic stimulation therapy by normalizing the pathological pattern of EEG activity in individuals for whom pharmacotherapy is ineffective. In addition, many studies point the high predictive power of a specific pattern of cerebral activity in patients to individualize treatment and estimate its effectiveness.

Key words: EEG; theta; alpha; major depressive disorder; drug response predictors; rTMS.

INTRODUCTION

Major depressive disorder has become a serious problem throughout our civilization that affects 350 million people worldwide—roughly 5% of the population. On average, one in 20 people has experienced a depressive episode in the last year. Depression can be fatal. Nearly one million people with mood disorders takes their own lives each year, which means more than 3,000 suicides each day (WHO, 2012). Depression affects both men and women, but the risk is 50% higher in females (WHO, 2008). According to the World Health Organization, depression will become the second most costly disease after cancer in

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the world (WHO, 2010). Symptoms of affective disorders are not limited to the emotional and motivational sphere, but impair cognitive functioning as well (Murrough, Jacoviello, Neumeister, Charney, & Iosifescu, 2011). The most common symptoms of depression include: low mood, anhedonia, ruminations, psychomotor retardation, disturbance of circadian rhythm, lack of motivation, difficulties with concentration and decision-making, and dysfunction of executive functions (APA, 2004; Joormann, Dkane, & Gotlib, 2006). It is a very complex disease and its etiology is still unclear. Among the factors that can lead to affective disorders are severe illnesses, hormonal imbalances, stress, loss of beloved person, addiction to psychoactive substances, and genetic predisposition. A neuroscientific approach provides an opportunity to better understand depression by examining changes in the structure and functioning of the brain in people suffering from mood disorders. The aim of this article is to approximate these changes, especially in the field of abnormal brain bioelectrical activity, and to indicate the practical implications of this knowledge.

Structural and functional brain changes in depression

Structural and functional neuroimaging studies of the brain are usually performed using magnetic resonance imaging (MRI), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). All these methods are characterized by very good spatial resolution. Structural studies show that there are changes in the volume of particular brain structures in people suffering from depression when compared to control groups. Mood disorders are associated with decreased volume of the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), anterior cingulate gyrus, hippocampus, and amygdala associated with the limbic system, which plays a key role in emotional regulation (Konarski et al., 2008; Rajkowska et al., 1999; Cotter, Mackay, Landau, Kerwin, & Everall, 2001; Cotter et al., 2002). While taking into account the functional changes, depression is primarily associated with increased activity of the amygdala and ventral cingulate gyrus. This leads to disturbances in emotional regulation and decreased activity of the hippocampus and DLPFC, which are critical for cognitive functioning (including executive functions) (Phillips, Drevets, Rauch, & Lane, 2003).

In addition, the default mode network (DMN) appears to be overactive in depression, especially in the areas of the ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), and the precuneus and posterior cingulate gyrus. The DMN network is one of the basic functional networks that includes interconnected brain structures that activate primarily in resting situations. This network shows significantly reduced activity during completion of cognitive tasks (Raichle, 2010). DMN activity is related to daydreaming or concentration on one's own mental states. It is suggested that the hyperactivity of this network in depressive individuals may be associated with rumination (automatic, negative thoughts), which in turn may be responsible for poorer cognitive performance.

The fronto-parietal network (FPN), which is active in intellectual effort conditions and particularly related to cognitive functions such as reasoning and working memory, is negatively correlated with DMN activity. Activity within the FPN network is reduced in people suffering from mood disorders (Brzezicka et al., 2011). With regard to reduced activity in the frontal and parietal cortex in depression, it is considered as inhibited brain activity within cortical structures called cortical hypoactivity. The purpose of treating depressed patients with transcranial magnetic stimulation is to modify brain activity towards the correct pattern, in particular to reduce the cortical hypoactivity and modulate neuronal transmission (which will be discussed further in the next sections).

Abnormal brain bioelectrical activity in depression

Depression specific changes also occur in the pattern of brain bioelectrical activity (neural oscillations). EEG oscillations (brainwaves) are rhythmic neuronal activities in the central nervous system that emerge from the interaction of large neuronal populations (Başar, Özgören, Karakaş, & Başar-Eroğlu, 2004). Neural oscillations are traditionally classified in five frequency bands—delta, theta, alpha, beta, gamma—and are generated in different areas of the brain. The time and spatial correlations between them are the basic mechanisms that constitute a record of running cognitive processes (Başar, Başar-Eroğlu, Karakaş, & Schurmann, 1999; Pfurtsheller & da Silva, 1999).

Delta oscillations are very slow waves with high amplitude in the frequency range of 0.5–4 Hz; they are associated with sleep and their prevalence is in the spectrum in children and newborns (De Gennaro, Ferrara, & Bertini, 2000). Delta oscillations also play a role in the processing of emotional stimuli (Bhattacharya & Petsche, 2002), motivational processes (Knyazev, 2012), attention and behavioral inhibition (Putman, 2011). The theta band is characterized by a slow, regular and high amplitude oscillation between 4 and 7 Hz, and mainly is associated with working memory and cognitive effort. In addition, theta oscillations play a very important role in attentional processes, sensorimotor information integration, and volitional movement control (Bland, 1986; Bland & Colom, 1993; Vinogradova, 1995). Alpha oscillations are characterized by variable amplitudes in the frequency range of 7-13 Hz, and are negatively correlated with the metabolism of nerve cells. They occur mainly in states of relaxation, but are associated with perceptual and attention processes as well. The alpha rhythm is related to working memory and long-term memory (Sauseng, Klimesch, Schabus, & Doppelmayr, 2005), visual imagination, and mental calculations (Palva, Linkenkaer-Hansen, Naatanen, & Palva, 2005; Palva & Palva, 2007). Some studies also suggest a link between alpha oscillation and inhibition processes (Handel, Haarmeier, & Jensen 2011). Beta band oscillations are characterized by a frequency of 13–30 Hz and are associated with cognitive activity, in particular concentration of attention, memory, and visual attention. Beta waves also play an important role in motor activity, particularly in motor control (Salenius & Hari, 2003) and

movement preparation (Sanes & Donoghue, 1993). Gamma oscillations are very high frequencies above 30 Hz and are associated with higher cognitive processes, especially integration of information among different sensory modalities (Gray, 1994), memory (Fell et al., 2001), the focus of attention (Fries, Reynolds, Rorie, & Desimone, 2001), and "conscious" experience (Llinás, Ribary, Contreras, & Pedroarena, 1998; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Gamma waves also play an important role in encoding and retrieving engrams (Bragin et al., 1995; Lisman & Idiart, 1995).

The oscillations of nerve cells coordinate the activity of different brain regions. Specific oscillation frequencies dominate in certain cortical areas (Buzsaki & Draguhn, 2004), which act as communication networks between large neuronal populations (Hoppensteadt & Izhikevich, 1997). One of the basic methods of analyzing EEG data is frequency analysis, which separates the individual components of the full EEG signal and analyzes their characteristics, such as power (amplitude). The oscillation amplitude reflects the distance between the maximum positive and negative points of the oscillation cycle (phase). Another very popular method is the event related potentials (ERP) analysis, which is interpreted as correlates of cognitive processes. Its background exceeds the scope of this article, although it is worthwhile to mention that it is also used in research on depression (e.g., Bruder et al., 2002). An electroencephalograph is used to measure brain bioelectrical activity, which has a very good time resolution. This method is relatively inexpensive, which greatly increases its attractiveness and accessibility.

Depression is a mental disorder that greatly modifies the pattern of EEG oscillations over a wide frequency range (Fingelkurts et al., 2007). This specific, altered pattern may reflect the involvement of specific mental functions in the pathological process (Başar et al., 2004). Because oscillations are homeostatically regulated and are generated by postsynaptic potentials, they exhibit high sensitivity to changes in the functioning of individual neural circuits and to modifications in neurotransmission in states of altered brain functioning (Lopes da Silva, 1991; Başar & Guntekin, 2008). Studies on disturbed EEG activity in depression were started in the 1930s by Lemere, who pointed out the differences in alpha band activity between depressive and healthy individuals. In the following section, we will focus on changes in the different EEG oscillations bands associated with mood disorders.

Alpha oscillations

Many studies have shown frontal alpha asymmetry in people with depression (Henriques & Davidson, 1991; Deldin & Chiu, 2005; Kemp et al., 2010; Allen, Urrry, Hitt, & Coan, 2004; Gotlib, Ranganath, & Rosenfeld, 1998). Alpha band asymmetry is associated with an increase in the amplitude of alpha frequency in the left frontal region comparing to the right. This means left frontal hypoactivity, because the amplitude of this rhythm is inversely proportional to the activity of the brain. The asymmetry is related to the different involvement of the right and left prefrontal cortex in emotional and motivational processes. It is assumed that the left prefrontal cortex is associated

with positive emotions and approach, while the right is linked to negative affective states and avoidance processes (Davidson, 1998). Alpha asymmetry is not exclusively specific to depression, as it was also found in healthy adults with high Beck Depression Inventory scores (Jacobs & Snyder, 1996), children and adults with low scores on social skills scales (Schmidt, 1999), infants of mothers suffering from depression (Field, Fox, Pickens, & Nawrocki, 1995), timid people (Schmidt, 1999), and individuals with high cortisol levels (Kalin, Larson, Shelton, & Davidson, 1998). It allows for the conclusion that people with frontal alpha asymmetry exhibit a psychophysical profile that is more susceptible to experiencing negative emotions (e.g. avoidance emotions) (Davidson, 1995).

Research also shows that the left prefrontal cortex is involved in meta-cognitive processes—creating strategies, initiating and correcting action in response to changing environmental conditions. It seems that the difficulties with action initiation and strategic use of information in depressive individuals may be due to reduced activity in the left prefrontal cortex (Banich, 2004; Heller & Nitschke, 1997; Levin, Heller, Mohanty, Herrington, & Miller, 2007). In addition, parietal asymmetry—the greater activity in right parietotemporal region in the alpha band, which means the area of the left hemisphere is relatively more active—has been noticed in depression (Bruder et al., 2005; Reid, Duke, & Allen, 1998; Henriques & Davidson, 1990; Kentgen et al., 2010). Parieto-temporal activity may play an important role in the arousal dimension of emotions (Heller, Etienne, & Miller, 1995) and may be associated with the blunted affect that accompanies depression. The right posterior hemisphere is also associated with facial information processing, and its functioning is often disturbed in depressive individuals and can be the cause of co-occurring problems in social skills (Deveney & Deldin, 2004; Levin et al., 2007).

Mood disorders are therefore associated with disturbed interhemispheric balance, where the right frontal and left parieto-temporal regions are hyperactive (Hecht, 2010). Interestingly, anxiety—a frequent depressive symptom —reflects an asymmetric pattern of brain activity: relatively greater left frontal and right parieto-temporal hemispheric activity (Nitschke, Heller, Palmieri, & Miller, 1999). On the other hand, the anxiety symptoms co-occurring with depression show another pattern of EEG activity: increased right frontal and parietal regions activity (Bruder et al., 1997; Mathersul, Williams, Hopkinson, & Kemp, 2008; Manna et al., 2010), which may alter frontal alpha band activity.

A study conducted by Jaworska and collaborators (2012) showed higher frontal and parietal alpha amplitude in a depressed group compared to a control group, while the effect was particularly noticeable in the male group. These results are consistent with the cortical hypoactivity theory occurring in depression. Importantly, the amplitude of alpha oscillation and its asymmetry has a high predictive value for choosing the pharmacological treatment for depressed patients (Bruder et al., 2008; Ulrich, Renfordt, & Frick, 1986; Knott, Telner, Lapierre, Browne, & Horn, 1996).

In a study conducted by Tenke and collaborators (2011), 41 patients with diagnosed depression and 41 healthy subjects underwent measurement of resting state EEG activity before treatment onset. Depressive individuals received one of three types of medicine: SSRIs (selective serotonin reuptake inhibitors), NDRIs (noradrenaline—dopamine reuptake inhibitors), and SNRIs (selective serotonin and noradrenaline reuptake inhibitors) for 8 to 12 weeks. A significantly lower power in posterior alpha was observed in those who did not respond to therapy compared to those who responded to the treatment and control group. There were no differences between the individual drug classes. Research has shown a very high rate of predictive power for amplitude in the alpha frequency band, with 93.3% accuracy in predicting positive responders and 92.3% accuracy in predicting non-responders. In addition to changes in alpha band, a large number of studies also indicate a different pattern of oscillatory activity in the theta frequency band.

Theta oscillations

The theta waves—especially those recorded from the medial prefrontal cortex (mPFC)—are important for information coding, memory retrieval (Klimesch, 1999), and emotional information processing (Vinogradova, 1995). Studies show that depressive individuals evinced altered theta oscillations compared to healthy people, which may constitute the basis of the negative impact of depression on coding and retrieving information in memory (Zakzanis, Leach, & Kaplan, 1998). Moreover, it is typical for depressive individuals to remember negative information better than positive (Blaney, 1986).

Pizzagalli and collaborators (2003) conducted a study on the relationship between theta rhythm and metabolism in the anterior cingulate cortex (ACC) during the resting state condition, as well as the relationship between theta band activity in the ACC and frontal area. In addition, the researchers were interested if the neural paths connecting the frontal region and cingulate cortex are disturbed in depressive individuals. The study was conducted on people suffering from depression and a healthy control group. Both groups underwent PET and EEG in a resting state condition. Researchers expected a positive relationship between theta activity and metabolism level in the ACC in both groups, and indeed this correlation was confirmed. In addition, a strong positive correlation between the theta wave amplitude in the ACC, PFC, and OFC was observed in healthy individuals, especially in the right hemisphere. On the other hand, a completely different pattern was noticed in people suffering from depression. A significantly lower correlation between the theta amplitude recorded in the ACC and the right PFC and OFC was observed compared to the control group. This confirms the assumption of functional connection abnormalities between frontal regions and the ACC (mediating emotional regulation) in depression. Altered oscillation in the theta band may be a reflection of this. Many studies also suggest greater power in the theta (and alpha) band in the parietal and occipital regions in depression, suggesting reduced cortical activity in these brain regions (Roemer, Shagass, Du-

bin, Jaffe, & Siegal, 1992; Volf & Passynkova, 2002; Grin-Yatsenko, Baas, Ponomarev, & Kropotov, 2010).

Korb and collaborators (2009) demonstrated that theta activity in the rostral anterior cingulate cortex (rACC) and medial orbitofrontal cortex (mOFC) helps predict the body's response to antidepressant therapy. Individuals suffering from depression were randomly assigned to two conditions where they received antidepressants or a placebo for a period of eight weeks. Everyone underwent EEG before the onset of the therapy, and the study design was double-blind. The researchers found that increased theta amplitude in the rACC and mOFC in the drug users predicted a positive response to antidepressant treatment. There were no significant relationships for the placebo condition. Several prognostic studies also indicated that substantially lower theta power in the frontal region in depressed patients is associated with a positive response to antidepressant therapy and transcranial magnetic stimulation (Iosifescu et al., 2009; Knott et al., 1996; Arns, Drinkenburg, Fitzgerald, & Kenemans, 2012).

Abnormal theta oscillations may also be associated with changes in the hippocampus in patients suffering from depression. Sheline and collaborators (1999) have shown that depressive patients have reduced hippocampal volume, and this effect is proportional to the duration of life-long depression. In addition, people with a history of depression underperform on verbal memory tests—a neuropsychological measure of the functioning of the hippocampus—and indicates that reduction in the volume of this structure is related to cognitive functioning. There was no significant correlation between hippocampal size and age in any of the groups. These results suggest that repeated exposure to stress during depressive episodes successively leads to greater damage to the hippocampus. The basis for these changes is the hypothalamic-pituitary adrenal axis dysfunction in depression, which results in an excess of glucocorticosteroids (cortisol) responsible for the destruction of hippocampal cells (Sapolsky, 2000).

Analysis of the reference literature indicates that frontal and parietal alpha asymmetry, higher alpha activity in frontal and parietal regions, higher power in theta band in parietal and occipital areas, and a significantly lower correlation between the dominance of theta waves in the ACC and right PFC and OFC can all be characterized as the electrophysiological biomarkers of depression, which may help to diagnose and understand the mechanisms of this disease. In addition, the positive response to the pharmacological treatment of depressed patients can be deduced from higher alpha power in the posterior brain regions, theta dominance in the rACC and mOFC, and significantly lower theta power in frontal brain regions. The whole body of studies on altered patterns of EEG activity in major depressive disorder has become an incentive to look for ways to restore normal brain bioelectric activity to eliminate the symptoms of the disease.

Table 1.

Examples of research on changes in EEG activity in depression

Study	Test Group/ Type of disorder	Changes in EEG Activity
Henriques & Davidson, 1991; Deldin & Chiu, 2005; Kemp et al., 2010; Allen et al., 2004; Stewart, Coan, Towers, & Allen, 2011; Gotlib et al., 1998; Cantisani, Koenig, Horn, Müller, Strik, & Walther, 2015	Patients with depression, patients in remission	Frontal alpha asymmetry
Bruder et al., 2005; Reid et al., 1998; Henriques & Davidson, 1990; Kentgen et al., 2000; Volf & Passynkova, 2002; Kaiser, Doppelmayr & Iglseder, 2016	Descendants of people with depression, depressed women, patients in remission, depressive patients taking mood stabilizing drugs, seasonal affective disorder patients	Parietal alpha asymmetry
Bruder et al., 1997; Mathersul et al., 2008; Manna et al., 2010; Kentgen et al., 2000; Metzger et al., 2004; Jaworska, Blier, Fusee, & Knott, 2012; Kemp et al., 2010; Ricardo-Garcell et al., 2009; Bauer & Hesselbrock, 2002; Roemer et al., 1992; Stewart, Coan, Towers, & Allen, 2014	People suffering from depression, depressive patients with anxiety disorders, depressive patients with PTSD, depressed women, depressed elderly	Higher frontal and parietal activity in alpha band
Roemer et al., 1992; Volf & Passynkova, 2002; Grin-Yatsenko et al., 2010; Arns et al., 2015	Depression beginning, older people with depression, patients suffering from seasonal affective disorder	Higher parietal and occipital theta power
Pizzagalli, Oakes, & Davidson, 2003; Li, Kang, Qu, Zhou, Wang, & Hu, 2016	Depressive patients	Significantly lower correlation between the dominance of theta waves in the ACC and right PFC and OFC
Tenke et al., 2011; Bruder et al., 2008; Ulrich et al., 1986; Knott et al., 1996;	Depressive patients—response to treatment	Significantly lower power in posterior alpha observed in those who did not respond to pharmacotherapy
Korb, Hunter, Cook, & Leuchter, 2009; Mulert et al., 2007; Pizzagalli et al., 2001	Depressive patients—response to treatment	Theta dominance in the rACC and mOFC predicts positive response to antidepressant treatment
Iosifescu et al., 2009; Knott et al., 1996; Arns et al., 2012	Depressive patients—response to treatment	Significantly lower frontal theta power in positive treatment responders

Transcranial magnetic stimulation (TMS)

The rTMS (repetitive transcranial magnetic stimulation) changes the course of current cortical activity. rTMS induces long-lasting changes in brain activity that are based on neuroplasticity mechanisms, and are a result of synaptic long-term potentiation or long-term depression. Studies using this method provide evidence for the functional significance of altered oscillatory patterns in depression and to draw causal conclusions about their role in pathogenesis.

Of particular importance is the study conducted by O'Reardon and colleagues (2007) on a large group of 300 depressed patients who did not take medication but had a history of ineffective pharmacotherapy with at least one group of antidepressants. Participants were assigned to one of two conditions, real or sham stimulation, in a double-blind study. The experiment was conducted in several research centers in the USA, Australia, and Canada. The area of stimulation was the DLPFC and the duration of therapy was 4 to 6 weeks. Questionnaires based on interviews were used to assess health status at the end of the treatment. It was found that significantly more patients (25%) showed remission after 6 weeks of treatment compared to the control group (16%). This study prompted the introduction of rTMS by the American Food and Drug Administration in 2008 in the case of specific depressive disorders, including those resistant to pharmacotherapy.

Carpenter and collaborators (2012) showed very high rates of remission and reaction to rTMS treatment, ranging between 37% and 58%. Fitzgerald et al. (2013) investigated how long the effects of TMS persist, considering the fact that depression is a disease with a high-risk of relapse. 35 patients with depressive disorders who did not respond to pharmacological treatment participated in the study. Subjects performed 5 sessions with rTMS in a four-week study. Three months before they started, they introduced a one-session introductory course. In general, patients participated in about 20 sessions with rTMS. The results showed that 71% of patients who had previously responded to rTMS did not experience recurrence for more than 10 months. According to the authors, this indicates the long-term effects of this method in depressive disorders and the appropriateness of supporting treatment.

SUMMARY

Depression is a very hard illness to treat; less than half of patients treated with 8 weeks of pharmacotherapy respond positively to it (Papakostas, Thase, Fava, Nelson, & Shelton, 2007; Quitkin, Rabkin, Gerald, Davis, & Klein, 2000). This demonstrates the insufficient effectiveness of current treatments. Neuroimaging studies using EEG in depression patients provide new possibilities for adapting pharmacological treatment to an individual patient and estimating its effectiveness. The review of this article focuses on changes in the alpha and theta frequency bands, as most of the available research concerns them. In addition, it is becoming increasingly popular to treat depression with TMS. This method is already used routinely in the USA (FDA, 2011), and a growing interest in it can be observed in the European Union.

It is very likely that the effectiveness of the rTMS method could increase if the pacing area was differentiated and adapted to individual patients. DLPFC stimulation is currently the most common way to normalize the activity of the prefrontal and limbic regions involved in mood regulation, but this is considered to be a significant simplification. Hence, there is a need for further studies on EEG activity in people suffering from depression to optimize rTMS and to increase the effectiveness of treatment with this method. What is more, TMS is an alternative for depressed patients who do not respond to pharmacological treatment and do not tolerate drugs.

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