Use a Brain-Computer Interface to Treat Depression

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Abstract. Brain-computer interface to treat depression is a very important new therapy that is highly effective without side effects. Depression is an growing mental health problem that affects the quality of life of hundreds of millions of people worldwide. Traditional treatments for depression, such as medication and psychotherapy, although effective to some extent, are accompanied by a range of side effects and limitations. In recent years, the brain-computer interface (BCI), as an emerging treatment method, has brought unprecedented hope for patients with depression. This article will explore in depth the mechanisms and methods of BCI treatment for depression and the advantages over conventional therapies. Compared with traditional depression therapy, treating depression with brain-computer interface has the advantage of noninvasive, painless and no side effects. The three main treatments for depression include transcranial direct current stimulation, transcranial alternating current stimulation, and transcranial magnetic stimulation. This paper explores the therapeutic mechanism and basic treatment of the three methods, comparing their advantages and disadvantages with those of conventional drugs. Overall, transcranial direct current stimulation, rTMS, and transcranial AC stimulation are all highly efficient and non-side-effective BCI treatments for depression.

Keywords: Brain-computer interface, depression, tDCS, tACS, tMS.

1. Introduction

Brain-computer interface to treat depression is a very important new therapy that is highly effective without side effects. According to statistics, there are more than 340million of depression patients in the world, depression has caused serious trouble to the patient's life and work, its four typical symptoms include: 1) Low mood; 2) Slow thinking; 3) reduced volition activity; 4) suicidal thoughts and behavior. Based on incomplete data, approximately 15 percent of individuals with depression die by suicide. A collaborative study involving the World Health Organization, the World Bank, and Harvard University has revealed that depression ranks as the second most significant disease burden in China. Numerous studies suggest that depression is intricately linked to genetic, neurobiological, and psychosocial factors. Investigations into genetic factors have highlighted significantly elevated risks among individuals with a family history of depression, with closer blood relations correlating with higher disease probabilities, typically following a polygenic inheritance pattern. In terms of neurobiological factors, extensive research has established a strong association between depression and neurotransmitters such as serotonin, norepinephrine, dopamine, and γ-aminobutyric acid. Clinical observations, particularly the efficacy of serotonin reuptake inhibitors in medication, underscore the importance of these neurochemical factors in managing depression effectively. Some studies believe that the onset of depression is closely related to the above neurotransmitters. The structure and function of the brain are generally abnormal in depression, usually accompanied by changes in certain cortical activity (especially the prefrontal cortex, which is closely related to emotion and cognition). Glutamatergic and GABA ergic neurotransmission seem to have important effects on the pathogenesis of MDD. Increasing evidence suggests that dysregulation of glutamatergic neurotransmission, especially in neurotransmission through N-methyl-D-aspartate (NMDA) receptors, has some impact on the neurobiology of MDD. Several studies have shown that altered expression of NMDA receptor subtypes in brain circuits of MDD patients and that NMDA receptor-mediated intracellular signaling is impaired [1, 2]. Studies have shown that the left hemisphere of the brain has reduced activity and excessive activity in the right hemisphere of the brain, which may be an important neural basis for depression, including the lack of long-term enhancement (long-term

potentiation) plasticity dysfunction also plays a role (Normann et al., 2007). Therefore, non-invasive brain stimulation techniques for treating depression are focused on enhancing activity in the dorsolateral prefrontal cortex in the left hemisphere, and / or reducing activity in the dorsolateral prefrontal cortex in the right hemisphere. In general, in most studies using tDCS for depression, stimulation current intensity ranged between 1 and 2 mA for 20 min each. However, the number of sessions, the interval between sessions, electrode location, and disease severity vary widely between studies.

2. Related Works

Currently, the main treatment methods for depression using brain-computer interfaces are divided into three categories: transcranial direct current stimulation, transcranial magnetic stimulation and transcranial alternating current stimulation.

Transcranial Direct Current Stimulation (tDCS) is a non-invasive method of electrically stimulating nerves. The application of tDCS for Major Depressive Disorder (MDD) is supported by positive outcomes seen in studies utilizing Transcranial Magnetic Stimulation (TMS) in depressed individuals, along with evidence indicating functional and structural alterations in various cortical regions among those with depression, notably the left dorsolateral prefrontal cortex (DLPFC), ventromedial cortex, amygdala, and hippocampus. Neuroimaging studies have revealed decreased activity in the left DLPFC and increased activity in the right DLPFC in depressed patients, leading to the frontal hypofunction hypothesis and a shift in emotional processing towards negative stimuli. However, the validity of the hypofrontal hypothesis is debated due to conflicting evidence regarding interhemispheric frontal imbalance, taking into consideration potential effects of differences in symptomatology, comorbidities, and subcortical structures (e.g., amygdala, hippocampus, subgenual cortex, and their interactions). Earlier studies proposed that tDCS could normalize cortical activity by stimulating the left DLPFC excitatorily and inhibiting the right orbit, while recent research suggests normalization through inhibitory stimulation of the right DLPFC. In studies involving healthy subjects, tDCS targeting the left DLPFC has been shown to reduce EEG delta activity in the left subgenual prefrontal cortex and alter resting-state network connectivity in functional magnetic resonance imaging (fcMRI), affecting the Frontoparietal Network (FPN) and connectivity within the Default Mode Network. The relationship between changes in resting-state network connectivity post-tDCS intervention and improvements in depression and cognition remains unclear. Additionally, the specific role of anodal/cathodal tDCS in symptom alleviation versus a combined approach involving both polarizations is still a topic of investigation [1, 2]. It uses both positive and negative electrodes to apply a weak current on the scalp, contacting the scalp surface through a conductive medium, and then injecting a stimulating current into a specific scalp area that acts on cortical neurons in the cerebral cortex. According to the input current polarity, LDCS is divided into Yang (polar) (anodal) stimulation and negative (polar) (cathodal) stimulation. Usually, positive stimuli enhance cortical excitability and depolarize the neuronal resting membrane potential; negative stimuli reduce cortical excitability and hyperpolarize the resting membrane potential. In this way, tDCS changes the neural electrical activity state of the cognitive and emotional function areas of the cerebral cortex by promoting or inhibiting the neuronal firing rate, and its stimulation effect is related to various parameters such as electrode location and size, stimulation polarity, injection current intensity, time and number of treatments. Cognitive and affective disorders in depressed patients may be caused by the unbalanced activity in the cognitive and emotional function areas in the prefrontal lobe, mainly reflected in the left dorsolateral prefrontal (DLPFC) hypometabolism and the right DLPFC hypermetabolism. Therefore, enhancing the excitability of the left DLPFC and inhibiting the right DLPFC should achieve the effect of regulating the emotional loop activity of the brain and alleviating the depressive condition. Therefore, the conventional protocol for tDCS in depression treatment is the left dorsolateral prefrontal lobe as the anodal stimulation site and the right dorsolateral prefrontal lobe as the cathodal stimulation site. The sponge electrode is 25~35 cm^2, the stimulation time lasts

20~30 min, and the current intensity is 1 ~ 2 mA. The mood scale was evaluated at 15 and 30 days after tDCS stimulation and found that the efficacy of tDCS lasted for about 1 month, with good time stability and no side effects compared to traditional antidepressants [3, 4]. For instance, in a double-blind controlled study, anodal tDCS demonstrated a significant improvement in clinical symptoms (Fregni et al., 2006). In two other double-blind controlled studies, the stimulation intensity was raised to 2 mA for 15 consecutive days, and the clinical benefits of tDCS persisted for up to one month (Boggio et al., 2008; Loo et al., 2012). The mechanism of action of tDCS is believed to be neuromodulatory. The effects of excitatory tDCS can last from several minutes to an hour and a half, measurable through changes in the amplitude of motor evoked potentials induced by a single TMS pulse in the digital abductor, abductor pollicis, or the primary inter-finger muscle cortex representation area. Modifications in Motor Evoked Potential (MEP) amplitude could serve as a substitute for alterations in neural plasticity, specifically referring to activity-induced changes in neuronal information processing. Initially, many studies viewed transcranial Direct Current Stimulation (tDCS) as either a standalone treatment for medication-free individuals or as an adjunct therapy alongside stable antidepressants over a duration of 3 to 4 weeks. In a double-blind randomized trial, Rigonatti et al. directly compared the effectiveness of tDCS with antidepressants by assessing three treatment groups: active tDCS, sham tDCS, and fluoxetine 20mg. Their findings revealed that the active tDCS group exhibited faster improvement compared to the fluoxetine group. Following the start of the six-week therapy, the groups receiving active tDCS and fluoxetine showed comparable improvements on the Beck Depression Scale (BDI), exceeding the sham tDCS group by a wide margin. The SELECTTDCS research by Brunoni et al., which compared sertraline 50 mg with tDCS in a four-arm factorial experiment, is the biggest study carried out to date. Sertraline + tDCS, placebo-sertraline + tDCS, sertraline + sham tDCS, and placebo-sertraline + sham tDCS were the four groups to which 120 patients were randomly allocated in this study. When compared to the other groups, the sertraline plus tDCS group showed better results.While there was no significant difference between the two groups receiving a single active intervention (sertraline or tDCS), they both outperformed the placebo-sertraline + sham tDCS group. The modification of cortical structures caused by tDCS may be the source of the combined therapy's synergistic impact. Network-related changes in these deeper brain areas, including the thalamus, amygdala, and striatum, have also been identified. Conversely, antidepressants affect the brainstem's noradrenergic and serotonin structures as well as how they project to the lateral striatum and amygdala. Combination treatment may therefore be an effective means of targeting all corticolimbic neural networks that are impacted during depression [1].

In a double-blind control study of dorsolateral prefrontal cortex, the efficacy of the tDCS method, sertraline (sertraline) method were compared in dorsolateral depression (uniploar depression).In this investigation, a daily 30 minute application of a 2 mA current was made for 10 days, and then it was repeated every other week. We discovered that tDCS by itself greatly reduced depression symptoms, almost as well as antidepressants. Additionally, tDCS and sertraline medications together can result in increased effectiveness (Brunoni et al., 2013). Furthermore, a few open-label (open-label) trials utilising bifrontal tDCS have demonstrated the therapeutic efficacy of this method (e.g., Brunoni et al., 2013). Patients who have resisted bilateral prefrontal stimulation respond better to therapy when the right frontal return is moved back to the brain (e.g., neck); and an additional "booster session" showed that an additional week or two weeks after the initial daily tDCS had an 80% response rate after 3 months and a 50% response rate after 6 months (Martin et al., 2013).

With transcranial magnetic stimulation (TMS), depression can be treated by stimulating magnetic impulses directly to brain nerves via the skull without any attenuation. The TMS stimulation pulse may be used to categorise TMS into three different stimulation modes: repeated TMS (rTMS), double pulse TMS (pTMS), and single pulse TMS (sTMS). The sTMS is output by manual control and can also stimulate multiple stimuli, but has long stimulus intervals (e. g. 10 seconds) and is used for routine electrophysiological examinations. The pTMS application of two different stimuli at the same stimulation site at very short intervals, or two stimulators (also known as double-coil TMS, dTMS) at two different sites, is mostly used to study the facilitation and inhibitory effect of nerves. When

rTMS is divided into high frequency and low frequency, the device needs to give slow rhythm low frequency or fast rhythm high frequency rTMS at the same stimulation site. There are two main methods of rTMS: one is high frequency (>5Hz) stimulation of the left dorsolateral area, and the other is low frequency (5Hz) stimulation of the right dorsolateral area. In recent years, some researchers have also explored other treatment methods, such as: bilateral high frequency and low frequency combination therapy, high frequency initiation therapy, θ burst stimulation (TBS), etc. OReardon et al., 301 patients with non-medicated major depression were treated with high frequency left rTMS and sham stimulation, which also had the advantage of no side effects compared with traditional drugs [5]. Depression can be treated using transcranial magnetic stimulation (TMS), which stimulates magnetic impulses directly and without attenuation to brain nerves via the skull. Three distinct stimulation modes—repeated TMS (rTMS), double pulse TMS (pTMS), and single pulse TMS (sTMS)—can be distinguished using the TMS stimulation pulse. Through the establishment of excitatory windows, synchronized gating facilitates information transmission by coordinating local neuronal spikes within and across spatially distinct brain regions. By temporally matching pre- and postsynaptic potentials, this synchronisation also promotes spike timing-dependent plasticity, increasing the possibility of eliciting synaptic plasticity over time. Consequently, it is thought that synchronisation plays a key role in determining the plasticity and communication of whole-brain networks that underpin human cognition [6]. Cross-frequency phase-amplitude coupling (PAC), in which the amplitude of low frequency rhythm (which regulates neuronal excitability) is linked or synchronised with the amplitude of high frequency brain rhythm (which indicates local neuronal spiking), is one of the most researched. Phase-Amplitude Coupling (PAC) is a flexible method for incorporating dynamic data between spatiotemporal scales in networks of linked cortical areas. PAC has been found in the temporal lobe, basal ganglia, frontal medial lobe, frontal motor areas, medial-lateral prefrontal regions, and frontoparietal regions in human cognition and goal-directed behaviour. Magnetoencephalography (MEG), extracranial Electroencephalography (EEG), and intracranial EEG recordings show the presence of PAC, which is associated with a number of cognitive functions, including working memory, reward processing, maintenance of abstract targets, selective attention, and feedback encoding for decision-making. Within-frequency phase synchronisation, which comprises several rhythmic neural impulses oscillating at constant relative phase angles within the same frequency range, is another important factor in the coordination of spatiotemporal neuronal activity connected to cognition. It is believed to help the brain integrate long-distance information as it is frequently seen in geographically distant brain regions. Phase synchronisation has been found in a variety of brain regions, including frontoparietal, frontal temporal, medial frontal, and thalamus; in a range of frequency bands, including θ (4-8Hz), α (8-12Hz), β (12-30Hz), and γ (>30Hz); and in a variety of cognitive processes, including working memory, selective attention, memory retrieval, and adaptive or executive control. Two key methods for coordinating cross-brain communication are thought to be brain-interval phase synchronisation and cross-frequency PAC (phase-amplitude coupling). In certain scenarios, lesions affecting one mechanism can lead to cascading effects on another mechanism, potentially serving as the underlying cause for various cognitive impairments seen in numerous neuropsychiatric disorders. Apart from disruptions in cortical network synchrony linked to working memory functions, atypical synchronization between task-independent networks in the beta frequency band has been documented in Major Depressive Disorder (MDD), indicating a significant alteration in the overall synchronous organization of the brain. A specific transcranial Alternating Current Stimulation (tACS) protocol has shown promise in alleviating depression by modulating brain phase synchronization and cross-frequency coupling known as Phase-Amplitude Coupling (PAC). Through the delivery of low-intensity sinusoidal currents to the scalp to influence activity in cortical brain regions, neuronal populations in the targeted brain areas are entrained to the frequency of the applied alternating current. To enhance efficacy, High-Definition tACS (HD-tACS) is utilized to optimize stimulation site and current intensity for increased focus on the target brain region. Minimal side effects, such as transient itching, tingling, and warmth, are typically experienced during the onset and offset of tACS stimulation. These effects can be managed through sham

stimulation, mimicking the initial and final phases of current delivery without transmitting current for the remainder of the stimulation period (usually lasting 20 to 30 minutes). Increasingly, authentic sham protocols are being employed to assess the frequency and site specificity of effects, excluding potential influences from peripheral concurrent stimuli like transretinal or transcortical effects.Gamma-band power (30-100Hz) and increased local neural activity are closely associated. Recent research shows that MDD patients have lower gamma power in the frontal lobe, which controls emotions, than healthy individuals do under resting conditions and when performing tasks linked to mood (Fitzgerald and Watson, 2018). Furthermore, there is a lot of data supporting the tight correlation between MDD and lower gamma power. For example, ketamine-treated MDD patients showed enhanced gamma power across a wide area of the brain.Repetitive Transcranial Magnetic Stimulation (rTMS) studies have also shown that activating the left DLPFC increases gamma power at rest; better depression symptoms are correlated with higher gamma power. Nonetheless, some research on animals indicates that gamma power may indicate ideal gamma power levels that sustain regular brain activity by reflecting a balance between excitement and inhibition. However, at present, there is no empirical data to support this viewpoint. In MDD, anomalies in theta band (4–7Hz) power have also been noted. Previous research has shown that people with MDD had higher midline theta-wave power in the anterior cingulate cortex (ACC) at rest, which may be a sign of impaired mood regulation. Subsequent research, however, has shown contradictory findings; some have even failed to uncover similar patterns of anomalies. Furthermore, although its functional importance is yet unknown, recent study indicates that alterations in frontal theta asymmetry may be a biomarker for identifying MDD patients from healthy individuals. There are two notable recent observations in terms of theta-wave power. First off, current research indicates that theta-band power anomalies are more strongly linked to anxiety than to depression, which calls for greater research to determine the precise relationship between theta-wave power anomalies and major depressive disorder. Second, long-distance information interchange is made possible by inter-regional theta power synchronisation..According to a recent study, people with depression exhibit abnormally higher total theta synchronisation during resting state and emotion management activities than healthy controls (Xing et al., 2017, 2019). Moreover, anomalies in the beta-band (14–30Hz) associated with serious depression are receiving increased attention. According to some research using classifier techniques, the best technique to distinguish between MDD patients and healthy people is to look for the frontal lobe's beta-band signature . However, there is still more research to be done to determine the exact cause of frontal beta oscillations and MDD symptoms. Notably, current studies regularly demonstrate that individuals with MDD have an aberrant rise in parietal beta power. For example, a research found that the degree of anxiety symptoms in MDD patients was correlated with increased parietal beta activity . Significantly, recent research on neurofeedback training has supported a causal relationship between major depression and parietal beta power. It has shown that downregulating parietal beta power can alleviate anxiety and depressive symptoms, and that an improvement in depressive symptoms is correlated with a decrease in parietal beta power . However, it is still unclear what role parietal beta power oscillations serve functionally [7].

3. Discussion

In the therapy involving transcranial direct current stimulation (tDCS), the considerable distance between electrodes, such as an extracranial reference, can result in what is known as current drifting. This phenomenon has the potential to impact regions of the brain that are deeper and farther away, albeit with a risk of losing precision. The current placement parameters in use, notably with the cathode electrode positioned on the skull's surface, are believed to induce notable alterations in deeper brain structures like the subpalm cortex and anterior palate, potentially influencing the cortical resting-state network. Furthermore, anatomical factors such as skull size, shape, and brain morphology (including abnormalities, tissue scarring, hematomas, etc.) are considered to play a role in regulating the direction, sector, and depth of penetration. Computational models of intracranial

currents are seen as a valuable tool for assessing optimal electrode positioning and current intensity in future applications. Additionally, combining tDCS with psychotropic drugs like citalopram, amphetamines, and d-cycloserine has been shown to extend or enhance the effects of neutral tDCS, while drugs such as carbamazepine, lamotrigine, pregabalin, acetylcholine, supiride, and nicotine may counteract these effects. Drugs like levodopa, ropinero, and livastin could also modulate the effects of anodal or cathodal tDCS depending on dosage. This experimental approach holds promise for tailored treatment of neuropsychiatric disorders by combining tDCS with drugs, offering a unique potential for precise modulation of local and interregional abnormal brain rhythms that has emerged over the past decade of tACS research. Hence, the increasing body of research is significantly enhancing our comprehension of abnormal brain oscillations in Major Depressive Disorder (MDD) from these dual standpoints, offering a range of transcranial Alternating Current Stimulation (tACS) intervention protocols for treating MDD. Moreover, groundbreaking clinical trials have demonstrated preliminary therapeutic benefits of tACS, underscoring its promise as a feasible treatment avenue for MDD. Nonetheless, additional investigations into the causal link between neurological irregularities and MDD, exploration of standardized tACS intervention protocols, and conducting more randomized controlled trials are imperative to facilitate the potential clinical application of tACS [8-10].

4. Conclusion

These BCI treatments for depression offer a promising alternative to traditional antidepressant medications. With their non-invasive nature and lack of side effects, they provide a safe and effective option for those seeking relief from depression symptoms. However, it is important to note that while these treatments have shown promise in research studies, they may not be suitable for everyone. It is essential to consult with a healthcare professional to determine the best treatment option for each individual case. In conclusion, transcranial direct current stimulation, rTMS, and transcranial AC stimulation are all highly efficient and non-side-effective BCI treatments for depression. These non-invasive techniques offer an alternative to traditional antidepressant medications, with the potential to improve mood and reduce depressive symptoms without the need for surgery or long-term drug therapy. As research in this area continues to advance, it is likely that these treatments will become increasingly common in the treatment of depression and other mental health conditions.

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