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Diagnostic and Therapeutic Mechanisms of Depression Based on CRISPR Gene Editing and Brain-Machine Interface Technologies

Yujun Bai[1],

Wenyan Duan[2] **and**

Anqi Nie[3,*]

[1] Xi'an Tie Yi High School, Xi'an, China
[2]Ready Global Academy, Columbus, America
[3]School of Life Health Information Science and Engineering, Chongqing University of Posts and Telecommunications, Chongqing, China
*Corresponding author: 2022212330@stu.cqupt.edu.cn

Abstract:

Depression, particularly treatment-resistant depression (TRD), is characterized by symptoms such as depressed mood, motivation lack, and recurrent relapses. It significantly impacts the normal work and daily life of patients. In the long run, the absence of effective treatment is one of most crucial factors leading to disability among these patients. Traditional therapies such as pharmacotherapy and psychotherapy are ineffective in a substantial number of patients. Therefore, there is an urgent imperative to develop revolutionary diagnostic and therapeutic strategies. This study delves into therapeutic strategies and clinical challenges of treatment of two new technologies for TRD. CRISPR technology identified potential targets and performed target editing of depression related genes such as FZD6, BDNF, LRFN5 and OTX2. Such editing contributes to regulating neural plasticity at the genetic level. BCI technology summarized and analyzed two distinct algorithms that decoded electroencephalogram (EEG) signals to offer objective biomarkers for diagnosis. Additionally, it discussed the use of closed - loop systems to modulate neuromodulation techniques such as deep brain stimulation (DBS) in real time for personalized treatment. This study indicates that both offer highly valuable breakthrough directions for addressing TRD despite the different technical pathways of the two approaches with one focusing on the genetic level and the other on the neural circuit level. These findings contribute to develop diagnostic and therapeutic strategies for TRD.

Keywords: Depression; CRISPR; BCI.

1. Introduction

Major depressive disorder (MDD), is a prevalent mental disorder and primarily characterized by symptoms such as low mood, loss of interest in life, and difficulty falling asleep. In severe cases, patients may even exhibit self - harm behaviors. Based on the latest epidemiological data from the World Health Organization, approximately 3.8% of the global population is affected by depression [1]. It is worthy nothing that the prevalence rate of adolescents is showing a rising trend. In China, the number of major depressive disorder increased from 34.4 million in 1990 to 53.1 million in 2021, manifesting a 54% increase [2]. Based on incomplete statistics, the number of Chinese suffering from major depressive disorder had exceeded 100 million by 2025 [3]. With the increasing number of patients, we can find younger age of onset. The "National Depression Blue Book" reveals that among the Chinese patients with MDD, 30% of them are people under the age of 18. Moreover, the prevalence rate among adolescents has reached 15% - 20%. Among all populations affected by MDD, the proportion of female is higher than that of male. World Health Organization data also indicates that the incidence rate of MDD in females is 6%, but prevalence rate of males is 4% [4]. Currently in the clinical diagnosis and treatment, drug treatment remains the main method. For example, the Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, sertraline, and bupropion. Significant clinical effect are observed 4-6weeks after taking medicine. But, the treatment response rate is only 50 - 60%, and it is possible that 30% of patients form treatment-resistant depression (TRD) [5].To be specific, for patients experiencing their first episode, the recurrence rate within five years is more than 50%, and for patients with multiple episodes, the recurrence rate can reach up 80% [6]. It means that the existing treatment strategies have not solved the fundamental problems of the disorder. Therefore, it is necessary to improve the efficacy of drug treatment.

Taken above, innovating treatment techniques and searching for new therapeutic targets and mechanisms are top priority. For instance, new strategies should be developed from different aspects, such as neurobiology and immunology. Concurrently, researchers need to propel the development of non-pharmacological treatment method, including those based on gene editing, artificial intelligence, and other fields. This paper supports to explore the current status and potential applications of two forefront biotechnologies, CRISPR gene editing and brain computer interface (BCI), in the field of diagnosis and treatment of TDR. Additionally, it outlooks the future development of these technologies.

2. The Applications of CRISPR Technology in TRD

Depression is a multi-faceted psychiatric disorder involving multiple genes that affect neurotransmitters, neural plasticity, stress responses, and neurodegeneration. Conventional drugs have only one target which results in limited therapeutic efficacy. CRISPR allows researchers to target and manipulate specific genes or regulatory elements, thus providing a more precise dissection of causal mechanisms. A number of studies in recent times have used CRISPR to edit the various genes present in the nervous system. Some of the experimental findings indicate that there were improvements in behavioral outcomes, suggesting the therapeutic potential of gene therapy for depression.

2.1 The Principles of CRISPR Technology

The CRISPR-Cas9 method comes from the type II system of CRISPR cas. Bacteria acquire adaptive immunity to viruses and plasmids through this system. The principle of CRISPR/Cas9 uses sgRNA to accurately identify the target DNA sequence. After making this search on the target DNA, the sgRNA directs the endonuclease Cas9 protein to cleave the target at the corresponding site, producing double strand breaks (DSB). Cells primarily rely on two pathways to repair DNA breaks. One pathway is non-homologous end joining (NHEJ). NHEJ might result in insertion or deletion (indel) events that cause frameshifts leading to gene knockout. On the other hand, precise sequence insertion or site-specific repair at the target locus may be accomplished by supplying a homologous donor template and inducing homology directed repair (HDR) Such repair mechanism explains the basic fundamental by gene editing.

2.2 The Advantages of CRISPR Technology

CRISPR-Cas9 technology is simple, precisely cleaves DNA, and is capable of multi-target recognition. In addition, in the past 10 years, the development of this system has advanced rapidly because there are many types, predominantly type II natural CRISPR-Cas systems. It is possible to accurately and efficiently target, edit, modify, regulate and label genomic loci within a wide variety of cells and organisms.

Unlike conventional drugs used for the regulation of neurotransmitters, the genes and genetic loci involved in depression can be identified by CRISPR-Cas9 technology. Detailed studies of the functioning of these genes in animal models searches for appropriate therapeutic targets leading to precise targeted therapy. Potential for a genetic

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intervention that can target the disease may be possible.

2.3 The Development and Applications of CRISPR Technology

CRISPR-Cas9 system primarily works by establishing gene specific alterations in vitro cell models and in vivo animal models in the contemporary research on depression The genetic anatomy and genetic map of depression that involve different regions in the brain system can give a clear view of depression. In the last 10 years, there has been rapid development of CRISPR technologies including gene knockout, single base editing, or conditional gene editing. By imitating human depression like phenotypes at molecular, cellular, and neural circuit levels, these technologies open up possibilities for functioning research and therapeutics.

The most classical approach of CRISPR technology is gene knockout, which can completely abrogate the function of genes. For example, in mice with FZD6 (Frizzled Class Receptor 6) edited by CRISPR, depressive behaviors are decreased.

Furthermore, as the demand for precise point mutations has been on the rise, technologies such as base editors (e.g., Adenine Base Editor, ABE; Cytosine Base Editor, CBE) and prime editing (PE) have emerged and evolved. These technologies enable the precise substitution of a single base without cleaving the DNA double strand. The core mechanism of ABE involves fusing an engineered adenine deaminase with a catalytically compromised Cas9, nCas9, which cleaves only one strand of the DNA duplex. This enzyme directly catalyzes the conversion of adenine (A) to hypoxanthine (I). During cellular replication, the cell reads I as guanine (G). In CBE, nCas9 aids in the transformation of cytosine to uracil. Uracil (U) is recognized as thymine (T) during the cell repair process. The core mechanism of PE involves fusing nCas9 with a reverse transcriptase and requires a special pegRNA. The pegRNA not only targets the genomic locus of interest with precision, but it also contains an extended sequence that encodes the desired editing template. Studies show that GABA receptor is invaluable in promoting relaxation in the brain and preventing the deregulation of excitatory inputs into the brain. When the δ subunit of the GABA receptor undergoes a point mutation, mice show higher stress sensitivity and increased susceptibility to depressive-like behaviors.

Furthermore, by integrating and engineering the Cas9 protein with transcription factors, epigenetic modifying enzymes, and other functional proteins, it becomes feasible to achieve gene activation/inhibition (Activation/Interference) and epigenetic editing (Epigenetic Editing). This allows for the reversible and meticulous regulation of gene expression levels. Additionally, it enables the addition or removal of epigenetic marks (e.g., methylation) within the regulatory regions of specific genes, such as promoters.

2.4 The Important Targets of CRISPR Technology for Depression Treatment

The following introduces several target points closely related to depression research. These target points correspond to key factors in different signaling pathways, such as FZD6, the signal receptor of the Wnt/β-catenin signaling pathway, and BDNF, the brain-derived neurotrophic factor that binds to the TrkB receptor. Among them, BDNF is an active protein in antidepressants and has been clinically verified to be related to depression. There is also OTX2, which is located upstream of the depression pathogenic pathway and can be regulated by controlling the downstream gene network. This gene can also reduce the expression of BDNF and decrease the activity of the TrkB signaling pathway. Notably, it increases the anxiety level of mice, indicating its role in mood disorders. These target points provide new targets for depression intervention.

FZD6 is a signal receptor of the classic pathway Wnt/β-catenin related to cell proliferation and differentiation activities. Studies have shown that it regulates neural development and emotions. Han used CRISPR/Cas9 to create Fzd6-Δ5 (5 nt deletion) or Q152E point mutations in mice. It revealed that the mutant mice showed reduced activity, increased immobility time, and exhibited depressive/anxiety-like behaviors, indicating that FZD6 is related to emotion regulation [7]. Further research can reveal that FZD6 participates in emotion regulation through the Wnt signaling pathway.

BDNF (brain-derived neurotrophic factor) binds to the TrkB receptor and promotes the formation of new synapses and neurogenesis in the hippocampus. Chronic stress and depression can lead to atrophy of the hippocampus, so many antidepressants ultimately aim to increase the expression of BDNF. Converting the 66th valine (Val) of the BDNF gene to methionine (Met) or deleting the upstream enhancer BE5.1 will reduce BDNF secretion and decrease the activity of the TrkB signaling pathway using CRISPR single-base editing technology. It is worth noting that it increases the anxiety level of mice, indicating the role of this gene in mood disorders. These target points provide new targets for depression intervention.

OTX2 (Orthodenticle homeobox 2) is located upstream of the depression pathogenic pathway and can control a series of other depression-related genes in the downstream network. This provides ideas for developing treatment strategies that target the entire gene network rather than individual genes. Overexpress OTX2 in human neural

progenitor cells promotes hippocampal neurogenesis and alleviates stress-induced depressive-like behaviors via CRISPRa (CRISPR activation).

LRFN5 (Leucine Rich Repeat and Fibronectin Type III Domain Containing 5) encodes a protein (SALM5). It is highly expressed in the nucleus accumbens, which is the core area of the "reward center" in brain and the core symptom of depression is anhedonia (inability to feel pleasure). Therefore, the dysfunction of this brain region is directly related to depression. The latest research found that editing a specific SNP in the promoter region of its gene using CRISPR technology will reduce the expression of LRFN5, and mice show obvious anhedonia and despair behaviors, thus indicating that this gene is related to depression. These target points are effective targets and provide ideas for future treatment strategies.

2.5 Challenges in Clinical Translation

Notwithstanding its extensive potential for application, the clinical translation of CRISPR technology continues to encounter numerous hurdles. Firstly, the issue of delivery efficiency remains a significant concern. Secondly, the problem of off-target effects persists. Thirdly, immunogenicity is a notable concern. Exogenous Cas proteins have the potential to elicit an immune response in the host organism, thereby diminishing their efficacy. Moreover, ethical considerations come into play. Clinically, there is a dearth of long-term safety data regarding somatic cell editing.

3. Application of Brain-Computer Interface Technology in TRD

3.1 The Principles of BCI

A Brain-Computer Interface (BCI) is a communication system that combines both hardware and software. It allows humans to interact with the surrounding without the involvement of peripheral nerves and muscles by using signals generated from electroencephalographic (EEG) activity. BCI shows potential value in the diagnosis and treatment of mental disorders such as depression. The closed-loop neuromodulation strategy based on brain-computer intelligence is expected to be an effective way for patients with treatment-resistant depression. In the future, by real-time monitoring of neural activity in specific brain regions and delivering individualized and precise stimulation to target brain regions, it may be possible to efficiently alleviate depressive symptoms.

3.2 The Types of BCI

There are mainly two types of BCI applications in depression: one focuses on the diagnosis and identification of depression, which is called recognition based BCI; the other focuses on the treatment of depression by regulating depressive emotions, which is called regulation based BCI.

3.3 Principle and Application of Recognition-Based BCI in TDR

The core of Recognition Based Brain Computer Interface (BCI) lies in machine learning (ML) and deep learning (DL) algorithms to decode the characteristic biomarkers of depression from EEG signals, thereby assisting in clinical diagnosis.

3.3.1 Machine learning

The machine learning (ML) method this study refer to here is the traditional one. Typically, experts first manually extract EEG features such as resting-state signals, event-related potentials from EEG data. This process converts the lengthy raw EEG signals into a series of fixed length numerical vectors that can represent their essential characteristics. Subsequently, the extracted vectors are input into a trained classification model, which ultimately outputs a "risk probability" or "severity index". This result that can be used to assist in evaluating and quantifying the severity of a patient's depression. Studies have shown that when a well-trained classification model is input with signals from specific brain regions, its accuracy in identifying depression can reach as high as 91.74% [8], which indicates that characteristic EEG signals have the potential to serve as biomarkers for depression. Although ML methods feature simple models, strong interpretability, and low requirements for data volume, they heavily rely on expert experience, involve time-consuming processes, and have limited model generalization ability.

3.3.2 Deep learning

Deep learning (DL) algorithms are different from traditional ML methods. Traditional ML needs manual feature extraction, but DL algorithms-like convolutional neural networks (CNNs) and long short-term memory (LSTM) networks-can automatically learn features from raw data or slightly processed data. When data moves forward through the network, it automatically goes through multi-level feature transformations. Finally, it outputs a probability vector, which is used to accurately identify patients with depression. Studies have shown that DL models achieve higher classification accuracy. Among these models, the approach that separately constructs CNNs and LSTM networks based on EEG signals from the left and

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right cerebral hemispheres and then fuses these networks delivers the optimal performance, with a recognition accuracy exceeding 98% [9]. Its advantages may stem from the full exploitation of the spatiotemporal features of EEG signals. DL algorithms eliminate the need for complex manual feature extraction and can detect intricate features that are difficult for humans to perceive. However, they suffer from several drawbacks: the requirement for large volumes of data, long training times, a tendency to overfit, and poor model interpretability. Enhancing the interpretability of algorithms will be a crucial direction for future research, so as to promote the practical application of DL in the diagnosis and treatment of depression.

3.4 Principle and Application of Regulation-Based BCI in TDR

In the treatment of Treatment-Resistant Depression (TRD), regulatory BCIs mainly rely on technologies such as Deep Brain Stimulation (DBS). Based on the identification of emotion-related neural representations, they deliver targeted stimulation to achieve symptom relief and regulation of neural circit function.

3.4.1 Technical principle and current status of clinical research on deep brain stimulation

DBS is a neurosurgical therapeutic approach that delivers electrical pulses to regulate abnormal neural circuit activity via electrodes implanted in specific target areas of the brain. Its exact mechanism has not yet been fully clarified, but the mainstream theory holds that it works through neuromodulation. It may inhibit the abnormal activity of the target area or "normalize" the activity of neural networks, rather than simply exciting or inhibiting them.

In the early stage of DBS treatment, the open-loop stimulation mode was mostly adopted, which means the parameters were preset and could not be dynamically adjusted according to the neural state. As a result, there were significant differences in therapeutic effects among different clinical studies [10, 11]. To address this issue, the closed-loop control strategy has emerged as a solution. Its core lies in dynamically adjusting based on the patient's real-time physiological status or clinical symptoms. For instance, implantable electrodes are used to read real-time neural signals such as local field potentials (LFP). ML algorithms then decode emotional states, such as the severity of depression or anxiety and based on this, stimulation parameters are automatically adjusted to form an individualized and precise treatment closed loop [12, 13]. The study by Scangos was the first to verify the feasibility of this strategy at the individual level [13]. Through multi-target intracranial recording and stimulation-response mapping, they found that the gamma oscillatory activity of the amygdala is associated with the severity of depression, and that stimulating the ventral capsule/ventral striatum can effectively regulate this activity and alleviate symptoms.

The design concept of closed-loop BCI systems has attracted widespread attention due to their success in the treatment of movement disorders, such as Parkinson's disease and epilepsy. Researchers are attempting to apply this successful paradigm to the field of mood disorders. Unlike strategies targeting the motor cortex, the goal of mood BCIs is to regulate limbic system circuits involved in emotional processing such as the amygdala, anterior cingulate cortex. The core of its technology lies in real-time decoding of neural activity features associated with pathological emotions, and using this feedback to dynamically adjust the parameters of DBS, thereby forming an adaptive and individualized treatment closed loop [14]. This precise regulation strategy based on neural feedback is expected to open up new avenues for the treatment of TRD.

3.4.2 Key target regions and neural mechanisms

A certain consensus has been reached regarding the selection of target brain regions for DBS in the treatment of TRD. It mainly includes regions such as the subgenual anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), nucleus accumbens (NAc), ventral capsule/ventral striatum , and bilateral locus coeruleus (LC).

These brain regions play a core role in emotional processing, reward, and motivation regulation. For example, studies have shown that the high-frequency oscillatory activity of the locus coeruleus in patients with TRD is closely associated with the severity of depression and anxiety, and stimulating this target can effectively improve clinical symptoms [15]. These findings not only provide a target basis for DBS treatment but also suggest that specific neuroelectric activity characteristics can serve as biomarkers for efficacy evaluation.

3.5 Limitations and Challenges

Although BCI has demonstrated enormous potential in the diagnosis and treatment of neurological diseases as well as functional enhancement, it still faces several key technical challenges.

3.5.1 Limitations in signal acquisition and quality

Current BCI systems have a major limitation: the accuracy and stability of neural signal acquisition are insufficient. Non-invasive BCI has low spatial resolution and poor signal-to-noise ratio. It is also easily affected by motion artifacts and environmental interference. Invasive BCI, by contrast, can collect high-quality signals. But it faces

significant constraints: there are surgical risks, and long-term implantation triggers biological tissue reactions that cause signal attenuation. These issues prevent its large-scale clinical application.

3.5.2 Insufficient generalization and adaptability of decoding algorithms

Most decoding models rely on training data from specific individuals and specific task scenarios, lack of the ability to generalize across subjects, time, and environments. Neural non-stationarity further increases the risk of model performance degradation in practical use. Additionally, the adaptive capacity of current algorithms for explaining changes in brain plasticity remains limited, making it difficult to achieve long-term stable interaction performance.

3.5.3 Bottlenecks in system closed-loop functionality and real-time performance

A truly closed-loop BCI requires the system to have real-time decoding and feedback capabilities with millisecond-level latency. However, existing systems still have significant delays in links such as data processing, feature extraction, and stimulation decision-making, making it difficult to achieve truly "online" adaptive regulation.

3.5.4 Lack of clinical verification and ethical norms

At present, most BCI studies are still in the laboratory stage or small-scale clinical exploration stage, lacking validity verification through large-scale, multi-center, randomized controlled trials (RCTs). Meanwhile, BCI technology involves the in-depth integration of the human brain and machines. There is still no broad consensus or standardized framework regarding ethical and social issues such as its long-term safety, privacy protection, identity recognition, and agency.

4. Conclusion

CRISPR gene-editing technology and brain-computer interface technology have opened up new breakthroughs for the diagnosis and treatment of depression. CRISPR technology reveals the mechanisms of the disease at the genetic level and provides new ideas for targeted therapy; BCI technology, on the other hand, achieves real-time intervention of symptoms through neural circuit regulation. These two technologies complement each other in advantages and jointly promote the development of depression diagnosis and treatment towards precision and individualization.

However, these new technologies still face numerous challenges in terms of science, technology, and ethical norms. In future, strengthening fundamental research, optimizing technology platforms, improving regulatory system and enhancing clinical translation is essential. Through communication across different disciplines, the aim is for the diagnosis and treatment of depression to ultimately achieve breakthroughs in practice that will provide better treatment options for patients.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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