Specific Aims:

Depression is a serious mood disorder, which is quite popular among all age groups, especially for young people. Nearly 8.4% of American adults are suffering from this disease, and the number is 17.0% of people who aged at 18-25, and this number could even be higher in other countries and regions. This disease will severely influence the way you feel, think, and handle daily activities. To reduce the pain of the patients and put their lives back on track, understanding the mechanisms of depression is of vital importance, which makes it possible for us to design an effective treatment.

Depression already has a huge impact on our society. However, current pharmacological treatments have been helpful to some extent, they have several limitations, including a slow onset of action, low efficacy, and side effects. Therefore, it is crucial to explore the underlying mechanisms of depression and develop novel therapeutic approaches that target the root cause of the disorder. Recent evidence suggests that alterations in resting membrane potential may play a critical role in the pathophysiology of depression. However, the underlying mechanisms and their network-level effects remain unclear [1].

Specific Aim 1: The membrane potential is altered by depression

Membrane lipids are fatty molecules that form the outer layer of cells and influence their communication and signaling. They are essential for brain function and mood regulation. Depression may affect membrane lipids by altering their levels, types, or interactions with other molecules in the brain. This may impair neuronal function and mood regulation [1]. And we assume that the membrane potential might be altered as the change of membrane lipids.

Moreover, depression may impair the metabolism of glycerophospholipids, such as phosphatidylinositol (PI) and phosphatidylserine (PS), which are involved in intracellular signaling pathways that regulate neurotransmitter release, synaptic plasticity, and neurogenesis. Additionally, depression may disrupt the balance of sphingolipids, such as ceramide and sphingosine-1-phosphate (S1P), which modulate neuronal survival, inflammation, and stress responses [1].

Specific Aim 2: analyzing the gut microbiome composition

The aim of this project is to investigate the role of gut microbiome in the development of depression and to explore the potential of probiotics as a novel treatment approach. The project will involve analyzing the gut microbiome composition of individuals with and without depression, as well as conducting preclinical trials with probiotics to determine their effects on depressive symptoms.

Significance:

Depression is a serious mood disorder, which is quite popular among all age groups, especially for young people. Nearly 8.4% of American adults are suffering from this disease, and the number is 17.0% of people who aged at 18-25, and this number could even be higher in other countries and regions. This disease will severely influence the way you feel, think, and handle daily activities. To reduce the pain of the patients and put their lives back on track, understanding the mechanisms of depression is of vital importance, which makes it possible for us to design an effective treatment.

This research will fill a significant gap in the current understanding of depression, which currently lacks a clear physiological basis. By elucidating how depression affects the membrane potential, this research could help pave the way for more targeted and effective treatments for depression. Additionally, this research will contribute to the development of new methods for measuring membrane potential, which could have broad applications in the study of neuronal function in both healthy and diseased states. Overall, the proposed research has the potential to make a significant impact on both the field of neuroscience and the treatment of depression.

Background:

Depression can alter the electrical activity of neurons by changing their resting membrane potential. Neurons normally have a negative resting potential due to the concentration of charged ions inside and outside of the cell, which is necessary for their normal functioning. However, in depression, the resting membrane potential of neurons may become more positive or less negative, which can interfere with their normal firing patterns [1].

This aim of this proposal is to measure membrane potential using voltage-sensitive dyes. Voltage-sensitive dyes allow for non-invasive measurements of membrane potential and have been shown to accurately measure changes in membrane potential in a variety of cell types.

For example, depression may reduce the levels of n-3 polyunsaturated fatty acids (PUFAs), which are important for brain development and function. Depression may also change the composition or metabolism of glycerolipids, such as phosphatidylcholine (PC) and phosphatidylethanolamine (PE), which are important for membrane fluidity and signaling.

Depression is a highly prevalent and debilitating mental disorder that affects millions of people worldwide. While traditional treatments such as antidepressants and psychotherapy can be effective, they are not universally successful, and many individuals continue to experience symptoms despite treatment. As a result, there is a growing interest in exploring alternative treatment approaches, including those that focus on the gut-brain axis.

The gut-brain axis is a bidirectional communication pathway between the gastrointestinal tract and the central nervous system. Emerging research has implicated the gut microbiome, the complex community of microorganisms that inhabit the gut, in a variety of neurological and psychiatric disorders, including depression. Studies have shown that alterations in gut microbiome composition can lead to changes in brain function and behavior, including depressive symptoms [2].

Innovation:

The proposed research aims to investigate the role of altered resting membrane potential in depression and develop a novel therapeutic approach that targets this mechanism. The current treatments for depression focus on increasing neurotransmitter levels, which have limited efficacy and take time to take effect. The proposed research targets the root cause of the disorder by exploring altered resting membrane potential and developing a novel therapeutic approach that targets this mechanism. This innovative approach may potentially provide a more effective and faster-acting treatment for depression.

This project seeks to investigate the potential of probiotics, beneficial bacteria that can be ingested to promote gut health, as a novel treatment approach for depression. While previous studies have explored the effects of probiotics on gut health and other medical conditions, their potential to improve depressive symptoms is not yet fully understood. This project aims to fill this gap by conducting preclinical trials with probiotics to determine their effects on depressive symptoms.

Approach:

Experimental Plan

For the first aim, the experimental plan could involve the use of voltage-sensitive dyes to measure changes in membrane potential. Voltage-sensitive dyes are fluorescent molecules that can be loaded into cells and emit light in response to changes in membrane potential. The dye molecules change their conformation in response to the electric field across the membrane, resulting in a change in fluorescence intensity. This technique has been used to successfully measure changes in membrane potential in various cell types, including neurons and cardiomyocytes[3].

For the second aim, the experimental plan could involve collecting stool samples from the study participants and performing DNA extraction and sequencing to identify the bacterial species present in the samples. This could be done using techniques such as 16S rRNA sequencing, which allows for the identification of bacterial species based on their genetic sequences [4]. The

resulting sequence data could then be analyzed to determine the relative abundance of different bacterial species and compare the gut microbiome composition between the two groups of participants. Additional analyses such as alpha and beta diversity metrics could be used to gain further insights into the diversity and structure of the gut microbiome [5].

Specific Aim 1: analyze the membrane potential

Recording Membrane Potential

To investigate the role of membrane potential in depression, we will utilize electrophysiological techniques to record the membrane potential of preclinical models of depression and compare it to that of control animals. This will involve inserting microelectrodes into specific brain regions implicated in depression, such as the prefrontal cortex and amygdala, and recording the electrical activity of individual neurons. We will also manipulate the membrane potential using ion channel modulators and measure the resulting changes in neuronal activity [6].

Manipulating Membrane Potential

In addition to recording membrane potential, we will also utilize a variety of techniques to manipulate membrane potential and investigate its effects on depressive behavior. This will include optogenetic stimulation and inhibition of specific neurons involved in depression, as well as pharmacological manipulation of ion channels to alter membrane potential. We will measure changes in behavior using a battery of established tests for depressive-like behavior, such as the forced swim test and sucrose preference test.

Specific Aim 2: analyzing the gut microbiome composition

analyzing the gut microbiome composition of individuals with and without depression

The gut microbiome analysis will involve collecting fecal samples from participants and using next-generation sequencing techniques to identify and quantify the microorganisms present. The probiotics trials will involve administering specific strains of probiotics to preclinical models of depression and measuring their effects on depressive symptoms using a battery of behavioral tests [7].

Expected Results and Future Directions:

For the first aim, the use of voltage-sensitive dyes to measure changes in membrane potential is expected to provide accurate and reliable measurements of membrane potential changes in response to different stimuli. The results obtained from this technique will help to establish a clearer understanding of the relationship between membrane potential and depression, which could potentially lead to the development of novel therapies for depression.

Future studies could build on this work by exploring the effect of different antidepressants on membrane potential changes in the brain. This could help to identify new targets for drug development and provide a more comprehensive understanding of the mechanisms underlying depression [8].

For the specific aim of "gut microbiome composition, the analysis of gut microbiome composition is expected to reveal differences in bacterial species abundance and diversity between individuals with and without depression. These findings could potentially shed light on the underlying mechanisms linking gut microbiota and depression.

Future studies could explore the effect of different interventions such as dietary changes, prebiotic or probiotic supplements, and fecal microbiota transplantation on gut microbiome composition and depressive symptoms. This could help to identify effective interventions for the treatment and prevention of depression, and provide a better understanding of the gut-brain axis. Additionally, further research could focus on the mechanisms underlying the gut-brain axis and the role of specific bacterial species in depression [9].

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