

Enhancing neuroplasticity and mood in patients with major depressive disorder by inducing BDNF expression^{*}

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With 210 million people diagnosed with major depressive disorder (MDD) worldwide, antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are widely used. SSRIs stop or delay the body from reabsorbing serotonin, leaving more of it available for the body to use. This regulates mood, but patients don't see results for up to six weeks. However, research found that depression is the failure of neuroplasticity (the brain's ability to change and adapt), and that SSRIs work partly due to their ability to boost this. Studies found that synaptic density and plasticity were improved with prolonged use of SSRIs. However, this improvement often takes weeks, likely explaining the delay in mood enhancement. SSRIs enhance brain-derived neurotrophic factor (BDNF) gene expression, which encodes the BDNF protein. BDNF regulates synapse functions through its TrkB receptors. The BDNF-TrkB pathway is key in supporting neuroplasticity. The objective of this research is to enhance BDNF expression and therefore accelerate neuroplasticity which will allow patients to experience the effects of SSRI treatment faster. Epigenetic changes are observed in depressed patients; methyl groups attach to BDNF histones, inhibiting the gene expression, and there are not enough acetyl groups on its promoters to counteract this. The method of increasing BDNF transcription is through administering autologous mesenchymal stem cells (MSCs) that contain BDNF protein in secretory vesicles via intrastriatal injection. These MSCs deliver BDNF protein to neurons, promoting the activation of the BDNF-TrkB pathway and ultimately improving neuroplasticity. Activating the transcription factor cAMP-response element binding protein (CREB) induces BDNF expression by increasing acetylation. With the increase of BDNF expression, it is expected that neuroplasticity will improve. Complemented with SSRIs, the improvements in neuroplasticity would hopefully decrease the time it takes to relieve depression symptoms. However, this research is not limited to only complementing SSRIs. Theoretically, just by improving neuroplasticity patients' MDD will be improved. The possible applications of enhancing BDNF can be applied to other ongoing research and can spark new medications regarding the treatment of MDD.

Keywords: neuroplasticity, depression, BDNF, antidepressants, SSRI



The need for fast-acting medicine to treat patients with major depressive disorder (MDD) is ever more pressing with mental health disorders becoming more

prevalent. The delay in selective serotonin reuptake inhibitors' (SSRI) effectiveness can be detrimental towards patients' cooperation with taking medicine and consequently may

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lead patients to suicide. Enhancing patients' neuroplasticity can accelerate the benefits of SSRIs and improve the lives of patients suffering from MDD.

Around the globe, countries are grappling with mental health crises. According to the 2021 National Survey on Drug Use and Health (NIMH, 2023), 8.3% of adults in the United States have been diagnosed with MDD. From the 12 leading causes of deaths from the CDC WISQARS of 2022, suicide accounts for over 49,000 deaths a year in the United States. Suicide is the third leading cause of death among 15–29-year-olds globally. It is now more important than ever to effectively treat depression. Antidepressants are the most frequently prescribed MDD medication, with SSRIs being the most common. (Chu & Wadhwa, 2023). However, up to two-thirds of patients don't get better with their first antidepressant (Bruce and Cameron, 2024), which can often be discouraging and leads patients to stop taking them altogether.

Serotonin is a neurotransmitter that can help regulate mood, sleep, and many other bodily functions (*Serotonin, What is It*, 2022). Lack of serotonin is associated with depression, anxiety, and other health conditions (*Serotonin, What is It*, 2022). Typically, nerve cells in the brain reabsorb the serotonin (reuptake) after it has carried its message. Figure 1 demonstrates how SSRIs will block or delay the body from reuptake, which leaves more serotonin available for the

body to use (Chu & Wadhwa, 2023). SSRIs on average can take up to six weeks to work (Chu & Wadhwa, 2023) the reason for which was unclear for a long time. We now know that SSRI response is polygenic, which means genetic variation in patients contributes to their response to the medication (Pain et al., 2021). Recent breakthroughs have led researchers to believe that the delay is partly due to the effects that SSRIs have on neuroplasticity, which is a process of neural remodeling that can take weeks (Johansen et al., 2023). Following the use of SSRIs, patients' brains show an increase in serotonin within a day or two, but the effects on mood are unnoticeable (Levy, 2023). As SSRI treatment continues it takes weeks for synaptic density to "accumulate", which correlates to the six week period that patients often see before "receiving" effects. Therefore, it is believed that it is actually the patients' neuroplasticity that is essential to the effectiveness of antidepressants, and that lack of neuroplasticity is associated with chronic depression and other neurological conditions (Price & Duman, 2019).

Researchers have already begun to explore how to accelerate neuroplasticity with treatments involving the drug ketamine. ketamine is able to rapidly enhance neuroplasticity, and promotes the growth of new synapses which are able to combat those lost from depression (Wu et al., 2021). However, it is an illegal drug and highly dangerous in an uncontrolled setting due to its addictiveness and intense effects. Our research focuses on brain-derived neurotrophic factor (*BDNF*), a gene already enhanced by SSRIs that regulates neuroplasticity (Martinowich, Lu, 2008). Levels of *BDNF* decrease naturally with age, and low levels are associated with chronic neurological conditions like depression (Head, 2022). Increasing levels of *BDNF* promotes dendritic growth which improves synaptic plasticity and therefore neuroplasticity (Martinowich & Lu, 2008). This would not directly increase the "effectiveness of SSRIs" but would increase the adaptability of the brain so it can adapt to use SSRIs at faster rates. This will in turn reduce the time delay that many patients experience when taking SSRIs. Although

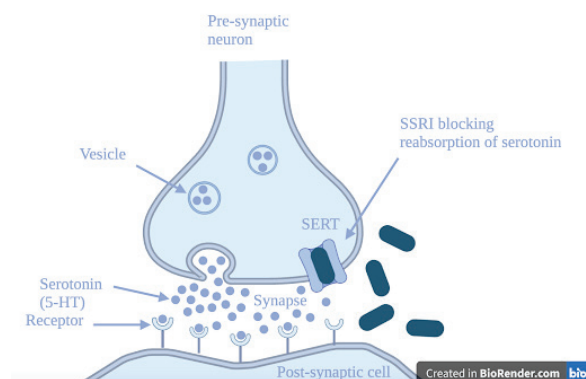


Figure 1. Diagram of SSRI action at a synapse. SSRIs prevent reuptake of serotonin, which increases the amount present in the synapse and magnifies its effects. Created in <https://BioRender.com>.

neuroplasticity is known to influence depression symptoms, the applications of how to use this breakthrough in treatment has not been widely discussed; research pertaining to BDNF is also not as vast as studies that focus on serotonin. The possible implications of studying BDNF can spur new debate in terms of how MDD is traditionally treated and the results could be essential to furthering research on how to effectively treat MDD.

Systems level

The slow response time of SSRIs in some patients creates the need for accelerating antidepressant effects. Increased *BDNF* expression may increase neuroplasticity (Yang et al., 2020), and neuroplasticity may speed up the response time to SSRIs. Figure 2 displays that targeting the underlying mechanisms responsible for neuroplasticity and inducing the perceptible effects of SSRIs quicker can potentially reduce patient discouragement and improve treatment reliability.



Figure 2. Systems Level Input and Output.

Device level

To address the delayed therapeutic response of SSRIs in treating MDD, targeting the epigenetic regulation of *BDNF* expression is crucial. Previous research has shown that the imbalance between histone acetylation and DNA methylation suppresses neuroplasticity in depressed patients (Shirata et al., 2020). In histone acetylation, acetyl groups are attached to amino acids in histone tails (Urry et al., 2019). This generally loosens chromatin structure, promoting the initiation of transcription, as seen in Figure 3 (Urry et al., 2019). In contrast, DNA methylation is the addition of methyl groups to certain bases in DNA, which can condense chromatin and inhibit transcription (Urry et al., 2019). In patients with MDD, the *BDNF* gene is more

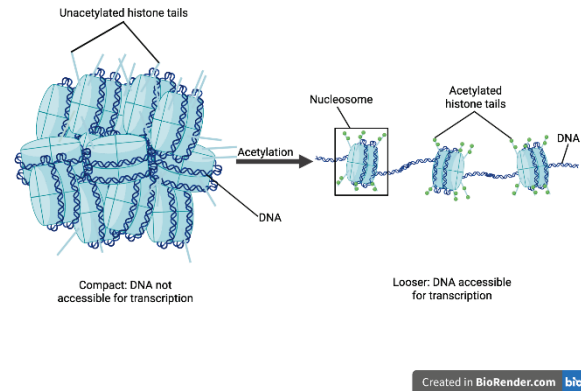


Figure 3. A Model of the Effect of Histone Acetylation. Created in <https://BioRender.com>.

heavily methylated than normal, shown in Figure 4 (Shirata et al., 2020), causing levels too low for optimal neuroplasticity. We propose to specifically targeting increased acetylation to counteract excessive methylation (*Acetylation and Methylation*, , 2024), thereby overcoming the negative impact on *BDNF* expression. The restoration of adequate *BDNF* expression would accelerate the neuroplasticity changes that typically take SSRIs weeks to achieve. Once methylated, genes usually remain so (Urry et al., 2019); however, the effects of these epigenetic modifications can be reversed. Chromatin-modifying enzymes provide control of gene expression by making a region of DNA either more or less able to bind the transcription machinery (Urry et al., 2019). The proposed device for this project aims to increase acetylation enough to outweigh the methylation, therefore causing *BDNF* expression to reach sufficient levels and promote healthy neuroplasticity (Figure

Methyl group

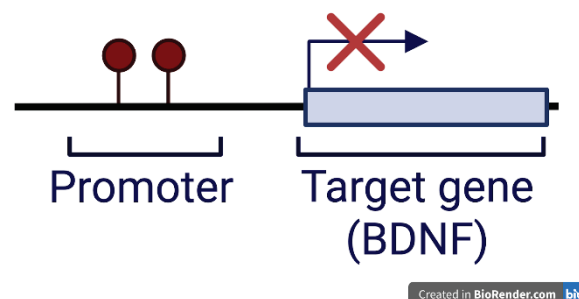


Figure 4. DNA Methylation in *BDNF*'s Promoter Region. Created in <https://BioRender.com>.

5), and ultimately enabling SSRIs to alleviate MDD symptoms more rapidly.

Parts level

SSRIs enhance *BDNF* gene expression (Martinowich & Lu, 2008), which encodes the BDNF protein. BDNF regulates synapse functions by binding to its TrkB receptors (Deng et al., 2016). The BDNF-TrkB pathway (Figure 6) is key in supporting neuroplasticity (Jin, 2020). When methyl groups attach to *BDNF* promoters and there

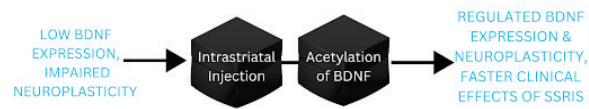
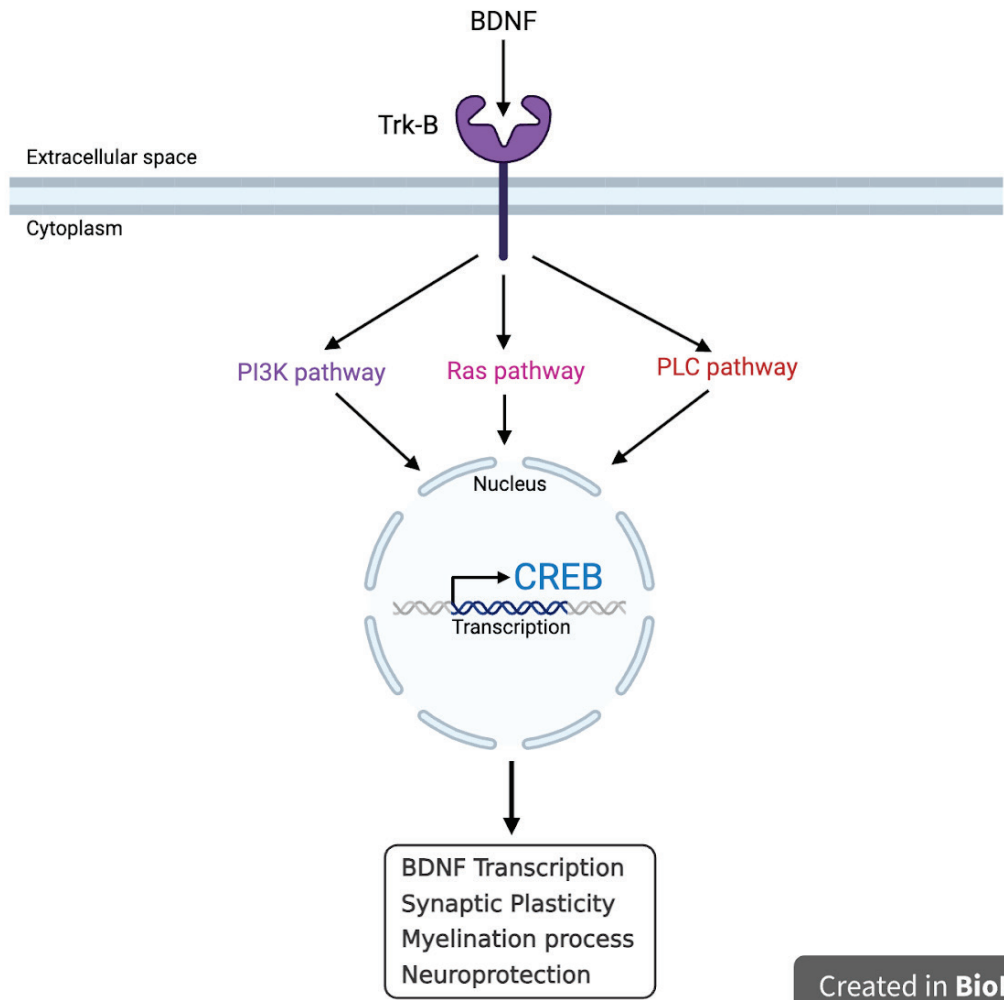


Figure 5. Device Level Input and Output.

autologous mesenchymal stem cells (MSCs) to enhance BDNF expression. The circuits in the striatum are what are disrupted in depression, leading to changes in connectivity and activity in this region (Pandya, 2012). Thus, the MSCs will be injected into the patient’s striatum via intrastriatal injection. MSCs can be



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Figure 6. BDNF-TrkB Signaling. Created in <https://BioRender.com>.

are not enough acetyl groups on the histones to counteract this, gene expression is inhibited (*Acetylation and Methylation*, 2024). Our system targets neuroplasticity insufficiency in MDD by using engineered

engineered to deliver therapeutic agents, such as proteins and drugs, directly to the striatum microenvironment (Shi et al., 2025). They are autologous so that foreign cells are not introduced into patients. These autologous MSCs would have secretory vesicles that

contain BDNF, and this vesicular transport of BDNF would occur along microtubules in neurons (Deng et al., 2016). Neurotrophins like BDNF cannot cross the blood-brain barrier (BBB) directly as they are large and polarized proteins (Deng et al., 2016), which is why intrastriatal injection is the channel of delivery.

Once injected into the striata, the MSCs will migrate into the brain (Tashima, 2024). In this way, the BDNF protein will be able to access neurons in the striatum, which are otherwise inaccessible. MSCs also migrate into areas of tissue damage which may prevent degenerative atrophy and apoptosis of neurons, unlike direct BDNF delivery via viral vector injection or recombinant protein administration into the brain (Deng et al., 2016). The injection would allow MSCs to cross into the striatum (Kitic et al., 2013) through fenestrated capillary endothelial cells (Miyata, 2015). Once alone in the brain tissue, MSCs release the therapeutic cargo (BDNF protein) they're engineered to express to the surrounding brain cells, supplementing the slow induction of increased *BDNF* expression that occurs with SSRIs. At the molecular level, our system activates the transcription factor CREB through the exposure of neurons to BDNF (Finkbeiner et al., 1997), which increases the acetylation of *BDNF* promoters and counteracts the excessive methylation observed in depressed patients. The engineered MSCs create a self-reinforcing cycle of *BDNF* expression.

The upregulated BDNF binds to TrkB receptors on neurons, activating signaling cascades including the Ras-mitogen-activated protein kinase (Ras-MAPK), phosphoinositide 3-kinases (PI3K)-AKT (PI3K-AKT), and phospholipase C γ 1 (PLC- γ 1)-protein kinase C (PKC) pathways that phosphorylate CREB (Sen & Snyder, 2011). These are generally known to promote synaptic plasticity, dendritic growth, and neuronal survival (Jin, 2020). Phosphorylated CREB recruits coactivators like CREB-binding protein, which is a histone acetyltransferase, to *BDNF* promoters (Caccamo et al., 2010). This acetylation disrupts the gene silencing of *BDNF* that occurs from methylation in MDD and allows for increased transcription (Kim et al., 2021). The resulting *BDNF*

transcription produces BDNF protein that further amplifies the TrkB signaling (Jin, 2020), creating a positive feedback loop that accelerates neuroplasticity. As a result, neuron strength and connectivity improve, directly impacting patients' response

Safety

Any future experiments will be conducted in a sterile controlled Biosafety Level 1 laboratory environment. This experiment will potentially be tested on rat MSCs and evaluated on the effectiveness, potential consequences, and viability before any consideration of human application. The lab will follow biosafety protocols to prevent contamination and unexpected cell behavior. This includes daily decontamination, use of personal protective equipment (PPE), regular hand washing, and other standard microbial practices (*Biosafety Levels and Lab Guidelines*, 2024). All studies will follow the the National Research Council's Guide for the Care of Laboratory Animals (*Guide* 2011). The IACUC guidelines require training for anyone that will work with live, vertebrate animals. This will ensure the wellbeing of animals and the quality of the research. All potential research proposals must first be approved by the IACUC and are reviewed on the following: the transportation, care and use of animals must adhere to the Animal Welfare Act (AWA) and other federal laws. Research involving animals must be evaluated on the scientific relevance to human or animal health, the advancement of knowledge, and/or the good of society. The species of animals should be "appropriate" and researchers should avoid distress and/or discomfort among animals. Should animals be in pain or distress from the procedure, they should be given the appropriate anesthesia/sedation. Animals in chronic pain or distress that cannot be treated following the procedure should be painlessly killed (IACUC, 2002). To prevent harm to researchers or the environment, all waste will be disposed of following biohazard regulations.

Discussion

There are many perspectives on how exactly depression works and the most effective way to carry out treatment. Neuroplasticity, while associated with depression, is not as widely investigated as serotonin is. However the direct tie that neuroplasticity has on depression is essential for researchers to explore and can lead to developing new medicine that could be essential to fighting MDD.

If our proposed injection into the striata of the brain using MSCs to increase *BDNF* expression is successful, then theoretically the neuroplasticity should be improved at rates much faster than SSRIs alone. This will be integral towards patients' treatment of MDD and can decrease the delayed benefit of SSRIs that is often very discouraging. It will encourage more patients to keep using their medicine which is essential to fighting MDD. However, our experiment is hard to carry out with the limited resources available. The BBB makes it impossible to directly administer BDNF. To counter this obstacle, MSCs will be used to pass through the BBB. However, MSC therapy has many potential complications, and clinical trials show that thromboembolism and fibrosis are some of the severe side effects. Some of the minor side effects included fever and local pain. (Baranovskii, et. al., 2022).

Although this research focuses on intrastriatal injection of MSCs to deliver BDNF, researchers can explore different ways to increase BDNF that can be integrated into already existing medicinal practices. Researchers may want to consider a new approach to treating MDD, (as opposed to just increasing serotonin) which will involve neuroplasticity. Whether it be with BDNF or another gene, the possible implications that neuroplasticity has on MDD and treating patients with MDD is essential for researchers to investigate and may serve to be pivotal for new advancements in medicine.

Next steps

To advance research on BDNF delivery for accelerating neuroplasticity in MDD

treatment, there are several potential courses of action to take. First, gaining a better understanding of the components of MSCS and how to engineer them is crucial. Next, reaching out to researchers who have been working on related projects, or have published papers with similar objectives regarding the improvement of MDD medication, may give us access to collaborators with resources that are unavailable in a high school setting. If possible, designing and conducting experiments using rodents may serve as an indicator of the effectiveness of engineered MSCs in enhancing *BDNF* expression. This method builds off of the strategies used in past proposed MSC treatments of both depression (Deltheil et al., 2008) and Parkinson's Disease (Ekran et al., 2024). Additionally, there is the potential for harmful side effects due to too much BDNF which include seizures and epileptiform activities (Xu et al., 2004). The likelihood of these side effects is dependent on how much higher the BDNF levels are than normal. However, this can be suppressed with inhibitors for protein kinase A (PKA). Cyclic adenosine 3', 5' monophosphate (cAMP)-dependent protein kinase A (PKA) regulates gene transcription and synaptic plasticity (Glebov-McCloud et al. 2024). PKA impacts gene expression through phosphorylation of transcription factors, affecting their ability to bind to DNA. To prevent excessive *BDNF* expression which could lead to adverse health effects, updates to our system could incorporate PKA inhibitors like Rp-8-Br-cAMPS that can downregulate CREB activation when BDNF levels reach standard thresholds (Karege et al., 2004). Ultimately, the goal is to open up discussion on new treatments for MDD, specifically by proposing a combined therapy of BDNF and SSRIs that could improve current therapies. However, this treatment may be able to be accomplished in a less invasive way in the future.

Author contributions

M.A. and S.M. created the idea for this project through their passion and personal experience with mental health and more

specifically, with depression. Both authors contributed equally to research; however, M., with a deeper biology background, wrote the Device, Parts, System, and Next Steps sections, while S.M. focused on the Background, Safety, and Discussion sections. Both, however, collaborated to write the abstract and create the diagrams.

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