HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 1 (2024)

Using Lithium Based Medications to Increase Gray Matter Volume in Depressed Adolescents

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ABSTRACT

In this paper, the correlation between gray matter and depression will be presented and speculations on the effectiveness of anti-depression treatments will be made. Over time, the gray matter volume in a depressed individual will continue to decrease unless the mental illness is treated. The effectiveness of treatments varies but in terms of halting the decrease of gray matter volume or increasing gray matter volume, medications containing lithium have proven to be the most effective. While an increase in gray matter volume has the potential to increase one's mood some tradeoffs come with taking antidepressants of any sort. Lithium appears to be the most effective component of medications that increase gray matter volume, but it is crucial to examine potential side effects as well as entirely different medications that target different areas of the brain.

Introduction

As mental health continues to become destigmatized the most important step forward is research on effective solutions. Major depressive disorder is one of the most common mental illnesses, and while the disorder can begin at any age, the adolescent and young adult age group is particularly vulnerable. Depression is a complex condition that impacts an individual's ability to experience joy, enthusiasm, and purpose in life. To be diagnosed with depression five or more of the symptoms explained below must be present in the same 2-week time period where a change in functioning has been shown. In order to meet the criteria, at least one symptom must be a depressed mood or loss of interest. The additional criteria are indicators if experienced nearly every day. Depressed mood most of the day, as indicated in the subjective report or in observation made by others. Markedly diminished interest in pleasure in all, or almost all, activities most of the day. Significant weight loss when not dieting or weight gain, for example, more than 5 percent of body weight in a month or changes in appetite. Insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, or loss of energy. Feelings of worthlessness or excessive or inappropriate guilt. Diminished ability to think or concentrate, or indecisiveness, and recurrent thoughts of death (5th ed.; DSM–5; American Psychiatric Association, 2013).

The above symptoms are a result of the changes occurring in an individual's brain, specifically reduced gray matter volume. (Singh, Gotlib. 2015). Gray matter is a specific tissue found in the outer layers of the brain. It is responsible for the processing of sensation and perception, as well as being the location where voluntary movement, learning, speech and cognition take place. The reduction in gray matter volume that depression causes, leads to a reduced ability to complete everyday tasks.

Fortunately, modern medicine has made significant strides in the treatment of depression, and even increasing gray matter volume. Treatment can be approached in a variety of different ways, however, in cases of severe depression, antidepressants are often necessary to alleviate symptoms. These medications work by targeting and ultimately increasing levels of certain neurotransmitters in the brain, such as serotonin, norepinephrine, and dopamine. These chemicals play an important role in regulating mood and emotional well-being. Antidepressants can be an effective form of treatment because of their ability to alter chemical levels in an

individual's brain (Harmer, et al. 2017). Over the years, various types of antidepressants have been developed, each with their own unique mechanism of action. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and atypical antidepressants are some of the commonly prescribed categories. It is important to note that while antidepressants can be effective for many individuals, the right antidepressant may be different for everybody. Each person's response to these medications can vary, and finding the right antidepressant and dosage will require careful consideration and medical supervision.

Treating adolescent depression comes with its own set of difficulties: from deciphering between typical teenage mood swings and mental illness to working with an individual who may need parental consent for many aspects of treatment. The best ways to work through these difficulties is through taking all the necessary precautions and understanding which medications are beneficial for each symptom. An individual will typically begin a medication at a low dosage, if the medication is a good fit and there are no negative side effects, the dosage will continue to be increased until the right dosage is discovered. In more extreme cases, the medication needed will need to be stronger and given at an increased level. Typically, more extreme medications will have more potential to cause changes in an individual's brain. This is the case with lithium medications. Lithium medication is classified as an antimanic medication, meaning that it is helpful in the treatment of mental health disorders such as, mania, hypomania, and bipolar disorder (Bhandari, 2022). These disorders have also shown to lead to a decrease in gray matter volume, and a subsequent increase when lithium is used as a treatment (Lyoo et, al. 2010). Lithium medications have been used in the treatment of depression when in conjunction with a manic disorder. While lithium is not the first choice for psychiatrists looking to get a depressed patient on medication, it presents itself as a good alternative for patients who do not respond well to antidepressants (Bschor, et al. 2014). Even though lithium is not typically used to treat depression, it is the best medication for the increase of gray matter volume.

Why Is the Adolescent Age Important for Further Research?

Adolescence is generally regarded as a time filled with confusion, rash decisions, and self-discovery. These stereotypes aren't nonsense, an analysis of the adolescent brain reveals underdeveloped areas that support these behavioral changes. The combination of an underdeveloped brain, changes in hormones, and increased social pressures help to explain why 20% of adolescents report experiencing depression prior to adulthood. The changes experienced during the adolescent age are often used as a way to mitigate the depression these individuals experience. Depression is often amounted to a teenage stage instead of a chemical imbalance. Depression that is untreated and unnoticed often continues to worsen, providing additional reasoning for increased research on depression in young adults.

Examining adolescents is not only important because of how susceptible this population is to depression, gray matter volume begins to decrease after a certain age, so ensuring proper growth is another positive to additional research. The Journal of Psychopharmacology's paper entitled, "Antidepressants and the adolescent brain" discusses the results of a specific longitudinal study that analyzed gray matter volume in different areas of the brain over an extended period. The study concluded that the period gray matter volume can grow is different depending on the area of the brain it is in. Regardless of the age at which gray matter was at its peak, each area all had one thing in common, after adolescence gray matter volume began to decline. Adolescence is a critical time in brain development. If depression is limiting gray matter volume in youth, these individuals will never be able to obtain the projected maximum amount of gray matter volume. While there is no way to tell how much gray matter volume they are missing out on, the mere fact that their brains are losing the ability to fully mature is reason enough for increased research.

Gray matter volume plays a crucial role in the development of the human brain. Throughout adolescence, gray matter volume undergoes changes as the brain goes through a process called synaptic pruning.

Synaptic pruning involves eliminating excess synapses to allow for the efficient processing of necessary information. As individual ages, the volume of gray matter begins to decrease due to this process. The individual's brain matures and becomes more tuned to specific functions necessary for the growth of the person. Gray matter volume is particularly important for cognitive development.

Regions with greater gray matter volume are associated with higher cognitive abilities, such as memory, attention, language processing, and problem-solving. In addition, gray matter volume has been linked to emotional regulation and social cognition, which are crucial skills for a young adult navigating all kinds of change. It is difficult to expect an underdeveloped brain to maneuver through an illness as overwhelming as depression. Proper development and maintenance of gray matter volume is vital for acquiring important cognitive and emotional skills throughout childhood and adolescence. Understanding gray matter volume at an adolescent age allows for insight into gray matter volume at its peak, potentially leading to additional information on the cognitive function lost with rapid decreases in gray matter volume.

The Impact of Depression On the Brain

Depression is diagnosed according to certain criteria that can be examined by observing behavior. Treating depression at times requires looking into the specific brain structures that shift due to a person's mental state. As researchers continue to examine the brain it has become evident that depression is linked with a decrease in gray matter volume. The Journal of Affective Disorders examined 53 depressed adolescents and observed their brain's volume of gray matter by using a high-resolution structural MRI. To analyze the extent of one's depression, researchers tested the individual's ability to link words associated with themselves and words associated with death. After everyone was interviewed and the researchers discovered their level of suicide ideation, the researchers took MRIs. They found that the higher the suicidal ideation, the smaller the caudate gray matter volume. These researchers were not the only ones to find these results. With the help of Mujeeb U. Shad, Srirangam Muddasani, and Uma Rao, the National Institute of Health published a different study with similar results. Using a voxel-based morphometric method the researchers found gray matter deficits in the thalamus, cerebellum, and frontopolar cortex of the depressed group.

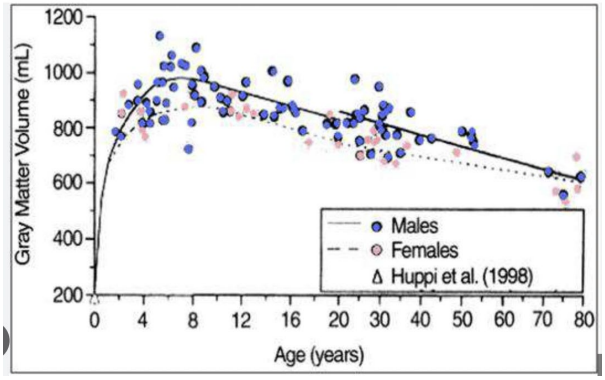

Figure 1. Changes in gray matter volume as age increases. (Courchesne et al. 2000)

To understand the importance of gray matter volume in the brain, it is crucial to understand how it develops throughout an individual's life. Gray matter volume increases until around the age of eight, after this point the volume of gray matter begins to decrease, but the density of the grey matter increases. (Mercadante, Tadi, 2022). Decreasing gray matter volume because of depression leaves individuals living life with gray matter volume levels they shouldn't be at until years in the future.

How Depression Can Lead to A Decrease in Gray Matter Volume

While it is relatively simple to wrap one's mind around the fact that depression can cause a decrease in gray matter volume, it is difficult to understand how exactly this happens. Often a decrease in gray matter volume is a direct result of an increase in plaque. The plaque occupies the space that the gray matter volume used to occupy, causing a decrease in gray matter. Studies have shown that both plaques and tangles accumulate in higher numbers in the hippocampus of patients with depression than in patients without depression. Plaque is not the only way for a loss of gray matter to come about. Sometimes a loss in gray matter is a result of degenerative changes such as a loss of neurons or dendritic arborization. Other times the loss is a result of brain maturation, including events such as synaptic pruning. Both events can result in the decline of gray matter volume so observed decreases are often attributed to both degenerative and maturational change. Grey matter decreases can also be a result of a lack of blood flow to the cells. These cells rely on oxygen from the blood to function efficiently. Without oxygen the cells die and gray matter volume decreases. Recent studies have linked depression to reduced oxygen in the body. Depression can often coincide with other mental illnesses such as anxiety, depression, or a combination of these two illnesses can lead to changes in breathing. When the brain doesn't get enough oxygen, the body produces a protein called HIF-1. A 2013 study called "the alteration of hypoxia-inducible factor-1 (HIF-1) and its target genes in mood disorder patients" found that HIF-1 is elevated in specific immune cells found in people with MDD. The lack of oxygen may be the reason for the decrease in gray matter volume found in patients with depression. Another explanation for how depression causes a decrease in gray matter volume may be linked back to stress. As previously mentioned, depression often comes along with other mental illnesses indicated by high stress levels. Chronic stress has been found by a recent study entitled "Dendritic Spines in Depression: What We Learned from Animal Models" to increase the levels of the stress hormone glucocorticoid and suppress the production of new neurons in the hippocampus.

Depression can impact the choices one makes, sometimes resulting in less physical activity and diminished motivation to learn. These two activities are crucial for the brain and especially for gray matter volume. A 2020 study done by the Mayo Clinic explains the correlation between increased gray matter and increased cognitive abilities, as well as demonstrating the clear benefits of physical activity. Using MRI brain data researchers found results that suggest cardiorespiratory exercise may contribute to improved brain health and decelerate a decline in gray matter. Erickson, Leckie, and Weinstein corroborate this claim with a similar study showing how higher fitness levels minimized the age-related loss in gray matter. The researchers utilized 165 individuals and obtained MRI imaging prior to the instruction to exercise. Their summary suggests that higher fitness levels are associated with greater volume. However, the effects are not evenly spread throughout all areas of the cortex. When breaking down the specific areas it was found that areas that tend to shrink the most, such as the frontal lobe and hippocampus, were impacted most by the increase in exercise. An analysis of these results raises the question of whether physical activity could be used as a tool to increase gray matter volume. Additionally, it gives a possible explanation for the decreased levels of gray matter volume in depressed individuals. If these people have difficulty finding the motivation to learn and exercise, their brains will continue to decrease quickly.

Using Antidepressants as A Means of Protecting the Brain from Decreasing Levels of Gray Matter Volume

Understanding the relationship between depression and a decrease in gray matter volume, logically introduces the following question: what can be done to stop depression from continuing to decrease gray matter volume? A recent study titled, "Gray matter reorganization underpinnings of antidepressant treatment of persistent depressive disorder" from European Neuropsychopharmacology, discussed the impact of a specific antidepressant

on depression and suicidal ideation. The study found evidence supporting the notion that gray matter volume can be reconfigured using antidepressants: as depression increases, gray matter volume decreases.

Additional studies corroborate these results. In just ten short days of taking an SSRI, whole-brain connectivity density, a measure of the brain's functional network hubs, was recorded to have increased. (Kraus et al., 2014). The increase of gray matter volume allows for increased functional connectivity in one of the brain's most active regions. This impact will inevitably lead to different changes in the brain, reinforcing the fact that gray matter volume is not the only area impacted by the SSRIs. A third study taking place over twelve weeks revealed similar data: SSRI-treated patients showed a region of significantly increasing gray matter volume over time within the left dorsolateral prefrontal cortex (DLPFC) that specifically correlated with decreases in self-reported depression levels. (Smith et al., 2012).

How Do Antidepressants Increase Gray Matter Volume?

There are a variety of different antidepressants available to choose from, however, one of the most prescribed medications are SSRI's. SSRI's are able to increase gray matter volume through increasing rates of functioning serotonin receptors and as a result, regulating gray matter volume development. When dealing with depression, serotonin is one of the most discussed chemicals. There are 16 identified serotonin receptors, and three of them (5-HT1A, 5-HT1B, and 5-HT2A) have been found to be involved in the neuroplasticity processes(Kraus et al., 2014). This means that certain receptors can reorganize areas of the brain, a lack of serotonin directly leads to potentially detrimental brain changes. SSRIs function by binding to a site and blocking the reuptake of 5-HT. This leads to an increase in 5HT ultimately leads to an increase in binding, which alters neuron firing rates and allows for the desensitization of 5-HT1A receptors. The desensitized receptors lead to a lack of autoinhibition and trigger 5-HT release at axon terminals (Kraus et al., 2014.) This release allows for 5-HT to carry out its function as a component of the development and regulation of gray matter morphology. Using an SSRI consistently will allow the brain to build and maintain gray matter volume.

Antidepressants are also capable of increasing gray matter volume through promoting neurogenesis. The impact of antidepressant on neurogenesis is mediated by a brain derived neurotrophic factor. It is an important molecule involved in neuroplasticity changes related to learning and memory (Miranda, et al. 2019). Antidepressant treatments can increase the level of expression of BDNF in an individual's brain, and BDNF has an antidepressant effect (Chen et al. 2001). This antidepressant-like effect occurs when the signaling in nucleus accumbens is blocked (Björkholm, et al. 2015). This effect as well as the fact that the administration of BDNF increases adult neurogenesis, points to the fact that the ability for antidepressants to increase the number of neurons in the brain is mediated by BDNF (Taupin 2006; Scharfman et al. 2005). This happens through a signaling pathway called the mitogen-activated protein (MAP) kinase pathway (Duman et al. 2006).

This pathway is a BDNF signaling cascade and is mediated by the activation of MAP kinase. The MAP kinase phosphorylates and activates the extracellular signal-regulated kinase (ERK) pathway (Taupin 2006). Through this process antidepressants can promote neurogenesis and increase important parts of the adolescent brain such as gray matter volume.

Which Antidepressants Are the Most Effective in Increasing Gray Matter Volume?

Understanding that antidepressants can be used to increase gray matter volume is just the first step. It is now important to wonder which antidepressant is the most effective at doing so. Depending on which antidepressant an individual chooses to take, the parts of their brain will be targeted in different ways. To increase gray matter volume, the most effective antidepressant is lithium. While many medications have been shown to increase

gray matter volume in depressed individuals, lithium has been thoroughly tested and has consistently shown to be efficient in increasing gray matter. Around 50 individuals with bipolar disorder were examined in The University of Washington's research study. The university conducted two cross-sectional brain magnetic resonance imaging studies and reported that patients with bipolar disorder on lithium treatment had greater gray matter volumes compared to patients with bipolar disorder who were not on lithium medication. Their results suggest that lithium exerts neurotrophic effects that can rework pathological processes and ultimately lead to an increase in gray matter volume. (Lyoo, et al. 2010).

The study moved on to explain in further depth that in just a short 4-week period the gray matter volume increased by about 3% in patients suffering from bipolar disorder. This study has proved to be replicable as a similar trial was done and the same results were found.

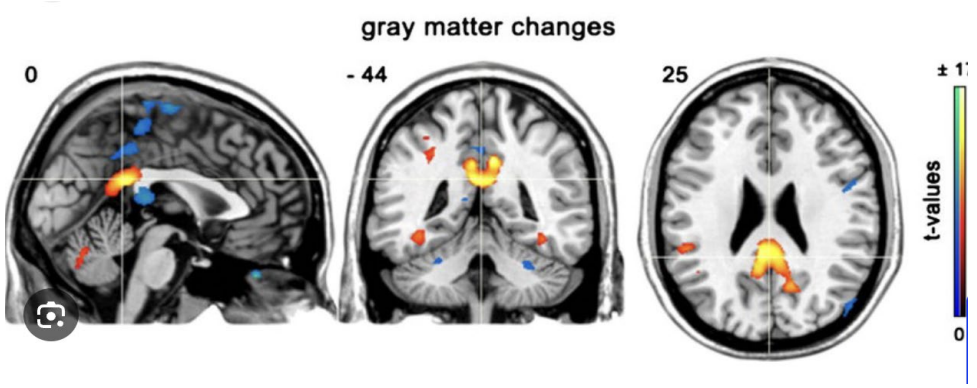

Figure 2. Changes in gray matter volume as a result of antidepressants. (Kraus, 2022).

How Does Lithium-Based Medication Work?

Lithium based medication functions in a different manner than antidepressants because of its different classification. Lithium works by reducing At a neuronal level, lithium reduces excitatory neurotransmission (dopamine and glutamate) while increasing inhibitory (GABA) neurotransmission (Malhi, et al. 2013). While these transmissions are occurring, neurotransmitter systems are attempting to achieve homeostasis through compensatory changes. At a molecular level, lithium is targeting second-messenger systems in order to further modulate neurotransmission (Quiroz, et al. 2010). For example, the effects of lithium on the adenylyl cyclase, phosphoinositide pathways, and protein kinase C, serves to lessen excessive excitatory neurotransmission. In addition to the mechanisms explained above, the strong effect of lithium is also a result of its neuroprotective effects. (Knapp, Mandell, 1973). The effects include lithium's ability to lessen the oxidative stress that comes along with episodes of mania and depression. Also, it increases protective proteins, like brain-derived neurotrophic factor and B-cell lymphoma 2 and reduces apoptotic processes by not allowing the functioning of the glycogen synthase kinase, and autophagy (Malhi, et al. 2013). The different functioning of lithium medication is the secret behind why it is so effective and useful in certain situations.

Risks of Lithium-Based Medicine

The effectiveness of lithium at increasing gray matter volume begs the question: why isn't lithium used as treatment for depression more frequently? As previously stated, lithium is an antimanic, and because of this lithium is not an FDA approved indication for the treatment of major depressive disorder (Geier, 2012). Lithium

is still prescribed and is still approved when a patient suffers from both depression and bipolar disorder, however, more research needs to be done on the impact of lithium on just depression.

Especially when dealing with adolescents, ensuring that the patient's medication is the right fit is crucial. Lithium medications often come with much more risks than other kinds of treatments. Lithium is classified as a high-risk medication, and when used improperly there can be severe consequences (Chokhawala, et al. 2023). If an improper dosage is taken, lithium toxicity is a possibility. Symptoms of lithium toxicity include severe nausea and vomiting, severe hand tremors, and confusion, but severe cases can lead to kidney troubles and loss of consciousness.

Counter Argument

As with most medications, lithium comes with its downsides. When making the decision to take an antidepressant it is important to weigh the risk versus the benefit. Lithium is incredibly powerful, and many people argue that it isn't the right choice for adolescents or young adults. Oftentimes these individuals are taking an antidepressant for the first time, and lithium may not seem to be the right choice. Taking medication at such a young age can lead to a mental dependence. If an individual has taken this medication throughout their adolescence, they may believe that they will not be the same person without it. It is difficult to feel as if a medication has control, and in this instance a strong medication like lithium may not be the correct choice. Lithium is not the right medication for everybody, it has its benefits and can be useful in some instances, but it is not a medication that should be taken lightly.

While there is legitimacy behind the argument that strong medications should not be taken at a young age, it is important to consider the benefits. Among people ages 15 to 24 in the U.S., suicide is the second-leading cause of death. Statistics show that nearly 20% of high school students have had serious thoughts of suicide and 9% have acted on these thoughts (Cohen, 2022). While lithium comes with its risks, the risks do not include death. Mental illness in teens needs to be taken seriously and medication needs to be considered a viable option.

Conclusion

Gray matter volume has a very strong correlation with depression, and not enough research has been done on how to specifically target it. Depression takes away the parts of life that make the world worthwhile. It eats away at the brain and can create a lifeless individual, but there are solutions. Antidepressants have been proven to help, and lithium has been proven to be a great way to increase gray matter volume. To help more research must be done on the effectiveness of this medicine, and potential better alternatives.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

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