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The effects of major depressive disorder on cognition and the brain

Ashlee Stewart
Purchase College, State University of New York, ashlee.stewart@purchase.edu

Lauren L. Harburger
Purchase College, State University of New York, lauren.harburger@purchase.edu

Abstract

Major depressive disorder is commonly known for its prevalence and impairing effects on the brain and behavior. One such effect is a decrease in processing speed, which leads to slower response times and an increased difficulty performing tasks that require careful attention. Impairments in spatial ability have also been reported in depressed subjects, which may be linked to impairments in executive functioning. GABA is a neurotransmitter that has been shown to play a role in the symptoms of depression. This review will examine the effects of depression on cognitive functioning and the brain, and will suggest that future research examine the link between low concentrations of GABA in the brain and performance on cognitive tasks in depressed patients.

Keywords*: Major Depressive Disorder; Cognitive Functioning; Psychopathology; Neurotransmitters; GABA*

Major depressive disorder has often been referred to as “the common cold” of psychiatric illnesses due to its prevalence. According to the Anxiety and Depression Association of America (ADAA) in 2015 major depressive disorder was noted to be the leading cause of disability in the United States for people aged 15 to 44 (ADAA, 2015). In that same report, major depressive disorder was recorded to have affected more than 16.1 million adults in America alone (ADAA, 2015). The University of Pittsburgh Medical Center estimated that 1 in 10 adults in the United States suffered from some kind of mood disorder with the two most common disorders being depression and bipolar disorder, which also includes a depressed state (UPMC, 2015). Major depressive disorder has many symptoms including diminished interest or pleasure in activities, depressed mood, slowed thought and reduced physical movement, fatigue, feelings of worthlessness, and a diminished ability to think or concentrate (Psycom, 2019). In addition, depressed individuals may experience deficits in memory and attention, psychomotor delays, lack of motivation, and may even lead to suicide in more extreme cases. Thus, the severity of depression is something that is important to study. It is important to observe how the effects of depression go beyond mood and affect the brain as well as the body. This review will explore changes to various cognitive and neurological processes that are observed among those with depression. Understanding the effects of depression is useful for future research that could inevitably advance the treatment of this disorder.

The Effects of Major Depressive Disorder on Cognitive Performance

Speed of Processing

The time taken to complete a task is an important behavioral measure that can affect task performance. Indeed, a study by Favre et al. from 2008 was originally aimed to examine how adolescents with major depressive disorder compared to their healthy counterparts in working memory and academic skills, but they found that the main differences between the groups were caused by a

difference in processing speed. Data from 40 depressed children whose ages ranged from 8 to 17 years of age was compared to 25 non-depressed adolescents in the control group. Researchers found that there were no significant differences in the participants' ability to spell, to read, or their grades in school. The main difference was found in their processing speed. It was observed that those with major depressive disorder processed information more slowly than those without the disorder.

A decrease in processing speed was also observed in a study by Chen et al. (2013) that examined depression in an adult population. Chen and colleagues (2013) instructed participants to observe images of hands in one of 12 different orientations and to determine whether the hand shown belonged to a left arm or a right arm. Participants were also given a letters task. This task involved observing a single letter in one of 12 different orientations. Participants had to determine whether the letter shown was the normal view of the letter or its mirror image. Interestingly, participants in the study who were diagnosed with major depressive disorder were significantly slower at giving their answer than the control group. It was also noted that those with depression were significantly slower at telling the orientation of hands as compared to letters. This difference may be due to differential task demands on the visuospatial sketchpad, which will be discussed later in this review. It may also be inferred that this is due to the relatively heterogeneous nature of letters, while hands are near identical.

Furthermore, Oshiyama et al. (2018) replicated the hand mental rotation task and observed similar results. This study also looked at the response times of depressed and non-depressed adults while they mentally rotated hands and assessed whether they were being shown a right or left hand, similar to the experiment done by Chen and colleagues (2013). The study by Oshiyama and others found that depressed women took significantly longer to give their responses than depressed males, as well as their less-depressed counterparts. Additionally, response time for males was not influenced by the severity of depression. The results from both studies, Chen et al. (2013) and Oshiyama et al. (2018),

demonstrate impaired processing speed as it took significantly longer for depressed adults to give a response compared to their healthy peers.

It is possible that deficits in processing speed could affect other cognitive functions. It has been proposed that processing speed is a resource for cognitive functioning as a whole and not a byproduct of cognitive functions (Kail & Salthouse, 1994). As such, slower processing speeds may indicate a lack of cognitive resources needed to achieve higher cognitive functioning. If processing speed is impaired in depressed subjects, then performance on tasks that require attention and deliberation may also be impaired.

Automatic vs. Effortful Processing

Automatic processing has been defined as processes or behaviors that take place without requiring attentional resources (Hartlage et al., 1993). Automatic processing does not require conscious awareness. On the other hand, effortful processing requires conscious awareness and is directly influenced by attentional resources. Tasks that require more effortful processing require conscious strategies that often interfere with other mental processes (Hartlage et al., 1993). Two articles by Hasher and Zacks (1979, 1984) suggest that effortful processes are done with great difficulty during times of stress, as stress is known to decrease cognitive capacity. Depression can act as a stressor for many individuals, and therefore can affect effortful processing. In fact, the authors of these studies concluded that the level of interference brought on by depression depends on the severity of the disorder itself, subjective valence of the task, and how much effort the task requires.

Hammar (2003) examined differences in performance on effortful and automatic cognitive tasks in depressed and non-depressed participants. They found that depressed participants were impaired on tasks that required more effortful processing. It was also noted that the more effort the task required, the more impaired performance became. On the other hand, results from a study by Hartog et al. (2003) directly contradict these findings. Hartog and colleagues (2003) found that participants with major

depressive disorder showed impairments in their performance on automatic processing tasks, and no impairments on effortful processing tasks. The automatic processing tasks included response inhibition, verbal memory, and searching through one's working memory, which could be argued as being an effortful processing task. Indeed, one could easily consider tasks such as verbal memory and memory searching to be more effortful than automatic, which may account for the contradictions between the study by Hartog and colleagues (2003) and Hammar's (2003).

A study by Nilsson et al. (2016) offers another possible explanation for these conflicting results. Nilsson and colleagues (2016) propose that all cognitive deficits within depressed individuals are a direct result of a primary deficit in attention. Therefore, it is possible that the conflicting findings of Hammar (2003) and Hartog and colleagues (2003) may be the result of differences in the attentional demands of the different tasks used in each study. Another, and possibly more likely, reason for the discrepancy between the studies could emerge from differences in definition for automatic and effortful processing. Neither Hammar (2003) nor Hartog and colleagues (2003) specified how they determined which tasks were deemed effortful and which were deemed automatic.

Spatial Ability

Depression is often accompanied by deficits in spatial memory and spatial ability. Indeed, studies by both Oshiyama et al. (2018) and Chen et al. (2013) found that depressed participants were worse at recognizing the rotation of hands in a mental rotation task compared to controls. Differences in mental rotation task performance between depressed and control participants may be due to differences in processing speed, as mental rotation tasks require one to mentally manipulate an object in a short amount of time. Another possible explanation as to why depressed participants experience impaired mental rotation task performance may be the result of deficits in the visuospatial sketchpad. The visuospatial sketchpad allows one to memorize an object or setting and manipulate it in their mind (Shan et al., 2018). Interestingly, a study by Shan et al. (2018) found that participants with major

depressive disorder had noticeably worse performance than controls on the Visual Reproduction Subtest (VRS), a test of visual working memory. The authors suggest that deficits on the VRS are the result of deficits of the visuospatial sketchpad in depressed participants (Shan et al., 2018). In addition to the visuospatial deficits reported in this study, the results of Shan and colleagues (2018) also suggest that there are deficits in working memory capacity in depressed individuals.

Working Memory

The various cognitive deficits discussed thus far make it clear that working memory deficits are a part of the cognitive effects of depression. Depressed patients have difficulty storing and updating previously gathered information. They may also have trouble sorting through their memory to find relevant information (Hartog et al., 2003). In one study, depressed and control participants completed a 2-back test, which required participants to observe a sequence of stimuli and to judge whether the current stimulus on the screen was same as what was observed 2 steps back in the sequence (Shan et al., 2018). The 2-back task is a working memory task that requires subjects to repeatedly update information of stimuli. Depressed participants performed significantly worse than control participants on the 2-back test, indicating impaired working memory.

Impairments in the ability to update information may be a contributing factor to deficits in emotional regulation observed in depressed individuals. These impairments may especially affect negative self-rumination, which refers to the excessive focusing on one's negative thoughts and emotions. A study by Şimşek (2013) examined how self-reflection and self-rumination affects college students. They found that self-rumination was positively correlated with depression. The more the depressed individual focused on themselves the more they began to ruminate, and the less they were able to accurately update information about reality. This may touch upon one of the symptoms of

depression as listed by the DSM-V as “feelings of worthlessness, or excessive or inappropriate guilt nearly every day” (Psycom, 2019).

Language

The tendency to get stuck in self-centered rumination is often demonstrated in the word choice of those who suffer from depression. One study conducted by Rude et al. in 2004 examined depression in college students. The experiment assigned participants to one of three categories: Currently-Depressed, Formerly-Depressed, and Never-Depressed, and each participant had to complete a short essay about themselves. Researchers later examined their writing to look for major differences in language. They noticed that the Currently-Depressed group used the word “I” significantly more than those in the Non-Depressed group. Currently-Depressed subjects also used more negative words than the other groups. Interestingly, the more participants wrote in the Formerly-Depressed group, the more they used the word “I” in their writing. Fineberg and colleagues (2016) also found that participants with psychosis and depression tended to use more first-person pronouns and negative emotion words.

The Effects of Major Depressive Disorder on the Brain

Epigenetics

A person’s environment can influence whether or not genetic risk factors linked to depression affect an individual. This is an example of epigenetics. Epigenetics is the study of environmental factors that influence or change gene expression (Breedlove & Watson 2018).

Tozzi et al. (2018) examined how stress, particularly childhood trauma, influences the FKBP5 gene. The FKBP5 gene is responsible for regulating the sensitivity of various steroid receptors. The specific steroids the study focused on were glucocorticoids. The study found that a subgroup of participants diagnosed with major depressive disorder had a high-risk T allele called rs1360780. Those

with the T allele had lower levels of methylation of the FKBP5 gene and that was correlated with higher levels of chronic stress during their early childhood years. It is thought that this high-risk allele helps influence the structure of certain brain areas depending on methylation of the FKBP5 gene. When examining all participants, those with lower FKBP5 methylation levels had lower concentrations of grey matter in the inferior orbital gyrus- a region associated with response inhibition (Chikazoe et al., 2007) and emotional regulation (Goldin et al, 2008). These results also suggest that methylation of the FKBP5 gene may be influenced by the function of glucocorticoid receptors and how they react to chronic stress. This, in turn, could influence the size and shape of the inferior frontal orbital gyrus, as well as many other structures.

The HPA Axis

The HPA (Hypothalamic-Pituitary-Adrenal) axis is part of the endocrine system that responds to stress. The HPA axis is overactive in those with major depressive disorder (Pariante & Miller, 2001). This hyperactivity is attributed to the low number of glucocorticoid receptors in those with the disorder. High levels of the stress hormone cortisol in depressed individuals may negatively affect several cognitive processes such as attention, working memory, executive functioning, and verbal memory (Keller et al., 2016).

Wang et al. (2018) examined fMRI scans and resting-state blood cortisol levels of depressed patients who had been unmedicated for at least 6 months. They found that cortisol levels were positively correlated with the functional connectivity of the orbital frontal cortex and cerebellum. The orbital frontal cortex is a brain structure involved with processing emotion, recognizing rewards, decision-making, and social cognition (Fettes et al., 2017); while the cerebellum is involved with motor control and, to a lesser extent, learning (Glickstein, 2007). Therefore, these brain areas may be sensitive to changes in cortisol levels.

Hippocampal Volume

The hippocampus is a brain structure that plays an important role in memory and navigation. It is specifically involved in encoding and consolidating memory (Dutta, 2019). A study by Schmall et al. (2016) found that the volume of the hippocampus was significantly reduced in those with major depressive disorder when compared to healthy controls. This reduction was observed most in those who experienced an early onset of depression, meaning they started showing symptoms at 21 years of age or younger. Those with a later age of onset (22 and older) experienced a less pronounced reduction in the volume of their hippocampus. The reduced hippocampal volume in depressed patients is likely involved in the working memory and spatial ability deficits observed in depressed individuals and discussed previously in this review.

Another study by MacQueen et al. (2003) also examined hippocampal volume in depressed patients and healthy controls. Healthy controls were compared to first episode depressed patients (FEs) and to patients who experienced multiple episodes (MEs). It was found that ME patients had significantly smaller hippocampal volumes in both the right and left hemispheres when compared to healthy controls and FE patients. FE patients had no significant differences in hippocampal volume compared to controls.

Neurotransmitters

In addition to the differences in hippocampal volume observed in depressed patients and healthy controls, there are also differences in the concentration of neurotransmitters in the brain. Two neurotransmitters that have been examined in depressed patients are GABA and glutamate. GABA and glutamate are the primary inhibitory and excitatory neurotransmitters, respectively, in the mammalian brain (Hampe et al., 2017; Samardzic, 2018). They are responsible for mediating the brain's level of excitement. Depressed patients have lower concentrations of GABA within the occipital cortex (Godfrey

et al., 2018; Luscher et al., 2010), despite glutamate levels being like healthy controls (Godfrey et al., 2018). The occipital cortex is involved in visual processing, and as such it may be that low levels of GABA can influence a depressed patient's perception of their environment.

There is support for this idea, as a study by Bubl et al. (2010) found that that depressed and non-depressed individuals may see visual contrast differently. In this study, researchers placed electrodes near the eyes of participants while they viewed 5 checkerboards, each with varying levels of contrast. Results indicated that depressed participants were not as sensitive to contrasts on a checkerboard when compared to the healthy controls. A study by Golomb et al. (2009) reported a similar change in contract perception in depressed participants when compared to healthy controls. A possible explanation for these findings is that the low levels of GABA in the occipital cortex of depressed patients affect visual perception of contrasting colors.

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are a type of antidepressant meant to treat depression and other comorbid disorders such as anxiety. It is one of the more popular antidepressants. Serotonin is a neurotransmitter that is believed to influence emotions, mood, and sleep patterns (National Health Service, 2018) and can act as an inhibitory neurotransmitter like GABA. SSRIs work by blocking the reabsorption of serotonin by the sending neuron; by doing so more serotonin is available in the synapse which facilitates better communication between neurons (MayoClinic, 2019). Some of the most common SSRIs are Prozac, Zoloft, and Lexapro (MayoClinic, 2019).

In one study, Sanacora et al. (2002) examined the occipital cortex to determine if SSRI treatment would alter GABA concentrations. After depressed participants were treated with SSRIs and therapy, researchers observed a significant increase in GABA concentrations in the occipital cortex. Further, Bhagwagar et al. (2004) found a 35% increase in GABA production in those treated with an SSRI

medication called citalopram- more commonly known as Celexa. These findings suggest that SSRI treatment can increase GABA concentrations in depressed patients. Perhaps this increase in GABA may be involved in relieving some of the negative symptoms of depression.

Directions for Future Research

The research discussed herein suggest that low levels of GABA may be responsible for some of the many symptoms of depression. To our knowledge, no study has examined the direct link between concentrations of GABA in the brain and performance on cognitive tasks in depressed patients and healthy controls. As such it would prove beneficial for a future study to examine this link. If low levels of GABA are linked to disturbances in cognitive functions, such as visual processing, then future treatments may be developed to specifically promote higher concentrations of GABA in the brain.

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