Environmental & Genetic Factors and Depression

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ABSTRACT

As reported by the World Health Organization (WHO) in 2021, depression is prevalent among ~3.8% of the world population, and it is impacting people's life in many negative ways including effects such as lack of motivation, low mood, suicidal thoughts and acts, etc. Such extensive influence involves various triggers and causes --- environmental factors like childhood trauma, early-life experience, diet, etc. --- which could also lead to malfunction and structural change in certain brain areas like ACC and amygdala; Genetic factor is linked with the inherited genes with specific SNPs of individuals, in which the sequencing associated with depression is noticed by GWAS study. Common intervention strategies include taking antidepressants and doing mindfulness-based interventions to treat depressions are also being looked at in this paper.

Introduction

Depression or depressive symptoms are very common mental states that develops in individuals. The World Health Organization (WHO) reported that depression occurs among ~3.8% of the world population and is closely linked to the neurobiological malfunction and cognitive bias of individuals (Depression, 2021). More specifically, lack of production of certain happiness-related neurotransmitters (e.g. Dopamine, serotonin) and regulation failure of the regions in the subcortical brain higher up in the cognitive hierarchy to the activity in those lower regions lead to the inability for an individual to disengage from negative thoughts (Disner et al, 2011). In addition, it is observed that individuals with depression generally have increased level of amygdala reactivity, the ability to detect emotion, when exposed to negative stimuli, whereas healthy individuals have increased reactivity when exposed to positive stimuli. This means that individuals with depression are able to detect negative emotions faster and more easily than heathy individuals, and thus they experience low mood a lot more frequently (Disner et al, 2011).

The cause of depression varies, but they could be generally categorized into environmental and genetic factors, and will be discussed further in this paper. Environmental factors may include childhood trauma, life experience, and even dietary habits. The genetic factor involves certain types of depression-related common SNPs (Single Nucleotide Polymorphisms) variations that are associated with depression and are more frequently found in depressive individuals. These SNPs are detected through a method called GWAS (Genome-wide Association Study) testing, which will be further explained later in this paper (Mullins & Lewis, 2017). It is important to keep in mind that there's no single variation in gene that can directly lead to depression, instead, depression is induced by combined effect of multiple genetic variation, early-life experience, or many more other factors.

Understanding the mechanics and causes of depression, scientists and therapists have came up with strategies to treat depression. Medical and environmental interventions are the two main categories, which are going to be introduced at the last section of the paper.

Discussion

Environmental Factors

To begin with, early life stress (ELS), including childhood trauma and adverse early-life experiences can be the main contributors of depression and many other mental disorders. Common ELS may include sexual abuse, physical abuse, death of a family member, domestic violence, emotional abuse, poverty, and illness/injury (LeMoult et al., 2020). Studies shows that these ELS can alter the structure and function of certain areas of the brain in a way that is consistent with depression. For example, the heightened attention towards negative stimuli, a common characteristic of individuals with depressions, is found to be associated with ELS.

As brain is a complex structure, many parts of it are involved in the development of depression and have different mechanisms. Two main regions of the brain that are hypothesized to be responsible for this are amygdala and anterior cingulate cortex (ACC) (Herzog & Schmahl, 2018). Though there's not a clear reason, a relationship between the amygdala volume and exposure to adverse childhood experiences, as well as the length of time after the experience, is discussed in many scientific studies. Studies have reported an increased amygdala volume among children with experiences of material depressive symptomatology and institutional-ized children. (Lupien et al., 2011). On the other hand, several other studies reported a decreased amygdala volume among adults who once had adverse childhood experiences and later diagnosed with personality disor-der and dissociative identity disorder (Schulze et al., 2016; Vermetten et al., 2006). The initial volume increase could be explained by the increased level of amygdala reactivity due to exposure to negative stimuli in the moment, while the decrease of volume may suggest the adverse child experiences might have a suppressive effect over the amygdala volume over time (Whittle et al., 2013). Since amygdala is responsible for the detection of emotions as it has densed receptors on its stress-susceptible cells, and as mentioned above, increased level of amygdala reactivity is correlated with depressive symptoms, the volume change of amygdala due to ELS and adverse childhood experience is strongly correlated with the development of depression.

Other than the increase reactivity of amygdala and variation in amygdala volume, ACC activity can also be affected by the exposures to childhood trauma and ELS. ACC is associated with attention inhibitory process towards stimulus, and the increased activity of which indicates successful inhibition. For healthy indi-viduals, higher ACC activity is needed to inhibit attentions to positive stimuli, but for people with depression, more ACC activity is required when inhibiting attention to negative stimuli. What this relationship suggests is that while healthy individuals require more cognitive effort to move away from positive stimuli than negative stimuli, depressive individuals experience the opposite, meaning that depressive individuals' attention is more prone to be attracted to negative stimuli than positive stimuli (Disner et al., 2011). Study shows that ELS and childhood trauma can result in the attenuation of ACC development and reduction in volume and thickness (Heim et al., 2013). This will subsequently result in alteration of ACC function, and thus contribute to biased attention towards negative information and disrupt effective inhibition, which are all symptoms of depression (Disner et al., 2011).

Amygdala and ACC are two common examples of how ELS are highly relevant to depression. More in-depth information in regards to brain structure and function and depression can be found in other studies and researches.

Besides ELS and childhood trauma, daily diet is another factor that could contribute to depressive symptoms. Diet may seem to have very little to do with mental disorder, but it is found that the abnormal level certain nutrients and chemicals, such as phytochemicals, vitamins and minerals, omega-3 fatty acid, poly- and mono- unsaturated fat, and fiber, can lead to depressive symptoms by causing various types of body dysfunc-tions (Marx et al., 2020).

About 25% patients with neuropsychiatric conditions experiences inflammation of different extent. Three parts are necessary in triggering inflammatory responses --- inducers which are often pathogen relate

molecular pattern, sensors that detect the inducers which are often immune cells, and most importantly, inflammation mediators –cytokines. Cytokines are proteins produced by our body that can significantly influence cell communication and interaction. The pro-inflammatory cytokines are the ones that promote inflammation. They do this by directing the immune cells to sites of infection or where the inflammatory inducers present. When facing a stressor, the inflammatory inducers appear most likely in the brain; in the process of fighting inducers, the immune activities might disturb the functions of neurotransmitters metabolism, neuroendocrine activity, brain activity, etc., which can subsequently cause depressive symptoms like low mood, anxiety, cognitive dysfunction, and etc. (Marx et al., 2020).

Furthermore, observation study done by Joseph Firth et al. found that people with depression have a considerably higher level of dietary inflammation than the control group (Firth et al., 2018). Dietary inflammation is mainly caused by the excess intake of pro-inflammatory foods (e.g. trans-fat and refined carbohydrates) and the deficient intake of anti-inflammatory ones (e.g. whole fruits and vegetables) (Marx et al., 2020). Therefore, to reduce the risk of dietary inflammation, consuming more anti-inflammatory foods would be helpful.

As mentioned in other studies, phytochemicals are one type of substance that has strong anti-inflammatory function, and they are abundant in cocoa, blue berries, etc. (Yahfoufi et al., 2018). Another study mentioned omega-3 fatty acid as another highly effective anti-inflammatory chemical, which are plentiful in marine foods (Liao et al., 2021). Regularly consuming both anti-inflammatory chemicals mentioned above can to a large extent lower the level of dietary inflammation, and thus, mitigates and prevent depressive symptoms.

Another environmental factor that is also worth to mentions and has effect on mood is the function of HPA (Hypothalamic – Pituitary – Adrenal) axis. As can be seen from the name, the HPA axis involves function of the hypothalamus part of the brain, pituitary, and adrenal glands. The HPA axis is involved in the individuals' reaction to stress, as its capacity of regulating the glucocorticoid, a type of hormones that fights inflammations, is closely related to the individual's mental behavior (Marx et al., 2020). However, study shows that around 60% of the people with depression have excessive production of cortisol, which is a factor that could disturb the function of HPA, indicating a correlation between excessive cortisol production and depressive symptoms (Marx et al., 2020). Moreover, intervention studies using omega-3 fatty acid and polyphenol-rich food (e.g. dark chocolate, berries, nuts, etc.) have suggested that intake of these chemicals could significantly reduce the cortisol level in human body (Marx et al., 2020). The mechanics of how the dietary intake impact the cortisol level or HPA axis function still remain unclear, but the correlation that those dietary intakes of omega-3 fatty acid and polyphenol might be able to regulate the pro-inflammatory responses to hypothalamic activation to a normal level when facing a stressor is seen (Marx et al., 2020).

Symptoms such as inflammation and HPA axis dysregulation are not the only factors that are related to depressive symptoms; other causes may include oxidative stress, unhealthy gut microbiota, mitochondrial dysfunction, etc., their specific mechanisms are elaborated in detail in other researches and studies.

The relationship between diet and depression might seems to be clear and easy to manipulate, but the fact that cannot be undermined is that in most of the cases, people who are experiencing depression are unlikely to have the power and determination to strive and get better by themselves; therefore, instead of cooking and eating healthy food, they are more likely to continue with unhealthy fast foods which could even aggravate their depression. Then, this positive feedback loop of aggravating the symptoms cycle and behaving more unhealthily may continue. Despite the potential obstacles of carrying out a plan of eating healthy diet but to talk about the relationship of dietary pattern and depression in general, existing study has suggested the Mediterranean diet, which includes a lot of fruits, vegetables, and sea food, as they contain a higher concentration of various chemicals that could result in the mitigation of not only depression, but many other mental disorders, anxiety, for example (Marx et al., 2020). Of course, it is impractical for everyone with depression to have Mediterranean diet daily, so keep in mind of eating food with high phytochemicals, vitamins, minerals, Omega-3 fatty acid, mono- and poly- unsaturated fat, and fiber could also be helpful for depressive symptoms and depression (Marx et al., 2020).

Genetic Factors

Genetic sequences of individuals, though do not have a direct cause-and-effect relationship with depression, it is associated with depression in comparison to other causes of depression with heritability of 37%, according to twin studies (Mullins & Lewis, 2017). Other than causing depression directly, depression-related genetic sequences can also make individuals more vulnerable in getting depression under the effect of environmental or other depression-causing triggers. Depression is discovered to be a polygenic disorder, meaning that it is not induced by any single gene variant but multiple gene variants, each contribute a small effort to the symptoms of depression. These genetic variations are referred to as common Single Nucleotide Polymorphism (SNPs). One of the established methods to depict those SNPs is the Genome-wide Association Study (GWAS), which examines the frequency of alleles between massive MDD (Major Depression Disorder) patients and healthy people at their common SNPs across a genome and look for inconformity between the two groups (Mullins & Lewis, 2017). Multiple trials of GWAS are done by different groups of people and complementary results have shown up, and this paper is going to introduce a few of the top SNPs that are discovered to be correlated with depression. However, it is important to note that GWAS is a very recent study, so there might not be much known for the genes and depression.

To begin with, the CONVERGE (China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology) Consortium had carried out an experiment using low-converge sequencing, an effective approach for doing genome studies for a large group of people, with 5303 Han Chinese with MDD and 5337 controlled Han Chinese with no depression ((N et al., 2017). Two discrepancies of SNPs on chromosome 10 are observed through the study, which are found near the SIRT1 gene and the intron of LHPP gene. To analyze the SIRT1 gene as an example, the SIRT1 gene is associated with the biogenesis of mitochondria, and it has been observed that there's more mitochondrial DNA (energy) in individuals with depression than in the control groups and the amount of which have a positive correlation with the stressors of the depression individuals (Mullins & Lewis, 2017). Hence, excessive SIRT1 gene could be related to the genetic cause of depression for Chinese people. However, it is important to note that the correlation of SIRT1 gene variation and depression can only be representative for Chinese people but not for people from other parts of the world, because SNPs might have different effects on different groups of people due to the physiology of people of different races.

Additionally, another organization, SSGAC (Social Science Genetic Association Consortium), has proposed a strategy to increase the sample size by using the data collected from heterogenous measures of depression from pre-existing studies. The two studies that were incorporated are PGC GWAS and GERA study, which have 16,471 MDD cases and 58,835 control individuals in total (Ripke et al., 2013). This sample was again analyzed with GWAS on their depressive symptom. This is done by inquiring them questions about feelings of unenthusiasm or disinterest and depression or hopelessness in the past 2 week. Through this study, two other depression–related SNPs are noticed, which are KSR2 and DCC gene, and both of which are related to the neuron reception and processing of signals (Ripke et al., 2013). Thus, it is reasonable that the SNPs on KSR2 and DCC genes are correlated with depression, as depression involves cognitive abnormality and sensitivity to various negative stimuli that can be impacted by neural functions.

Interventions

Two main types of interventions that could be used to mitigate or even treat depression are medical interventions and cognitive interventions, which are going to be briefly introduced.

Starting with medical interventions, because depression is usually associated with reduction or functional deficiency of noradrenaline, serotonin and dopamine, antidepressants are developed to increase or regulate their functions (Agius & Bonnici, 2017). Antidepressants are separated into 3 major types, monoamine

uptake inhibitor, monoamine oxidase inhibitor, and atypical antidepressants. Monoamine uptake inhibitors are the most used one in treating depression, and some examples of this type of antidepressant includes: Selective Serotonin Reuptake Inhibitors (SSRIs), Noradrenaline Reuptake Inhibitors (NARIs), Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs), Noradrenaline – Dopamine Reuptake Inhibitors (NRDIs), etc. As can be seen from their names, different types of monoamine uptake inhibitors are able to regulate different neurotransmitters. The mechanism for the function of all monoamine uptake inhibitors is basically that they stop the process of certain helpful neurotransmitters from going back to the axon (a pathway in the neuron in which neurotransmitters have to pass through) from the synapses (area of the neurons connecting to each other) of the next neuron. This increases the concentration of those neurotransmitters in the synapses and thus enhance neurotransmission of the specific neurotransmitters that the patient is lack of, thereby controls depressive symptoms (Agius & Bonnici, 2017).

The pros of antidepressants are that they are convenient to use and have very high effectiveness in treating depression if taken correctly, which are why antidepressants are the main way used to fight depression. Several limitations are the inevitable side-effects, the danger of overdoses, and unsuitable prescriptions. Side effects of antidepressants may include drowsiness, weight gain, dry mouths, dry eyes, headache, fatigue, anxiety, etc. Overdoses of antidepressants may lead to irreversible damages to the body or even death, and since patients themselves are prone to suicidal acts, antidepressants are especially dangerous for them to keep for themselves. It is also worth mentioning that as depression patients might have different yet complex dysregulation in neurotransmitter production but the specific dysregulated neurotransmitter is usually not identified before giving the prescription, the prescription and its effect on the patient is like a test and trial, which may be a waste of time and aggravate the symptoms of the patients. To solve this problem, GWAS study mentioned above could be a useful way to determine specific dysregulated part of the patients and thus, personalized the prescription to treat their depressions.

Moreover, cognitive based treatments can provide an effective assistant tool for antidepressants. Mindfulness Based Intervention (MBIs) is a type of cognitive behavioral therapy aiming to help individuals to be less sensitive to negative emotions and thoughts through practicing mindfulness. Mindfulness is practice but also a mental state that withdraw one's attention to sensations, consciousness, and the environment but encourages openness, curiosity, and acceptance (Hofmann & Gómez, 2018).

The good things about MBIs are that it can be done in anywhere and has immediate effect of enhancing one's mood. Study also pointed out that a specific type of mindfulness called MBCT, which is a combination of mindfulness and cognitive treatment, is found to be an effective method in preventing relapses of depression; however, MBCT is not found to be exceedingly effective for depression remissions (Hofmann & Gómez, 2018). A challenge with the practical use of MBI is that it requires persistent and long-term practices to have a prominent and long-lasting effect on patients.

MBI is not the only cognitive based interventions, other includes retreats and residential programs, brief mindfulness interventions, and internet and smartphone MBIs (Hofmann & Gómez, 2018). These might not be as professional and reliable as MBI mentioned above, but they are also ways to mitigate depression when MBI can't be done.

Conclusion

Genetic and environmental factors all play a role in the causes and development of depression, but the environmental factors, especially childhood trauma and ELS, are to have greater effects. The depression symptoms that could be triggered by genetic factors could also be avoided or remitted through a positive and healthy living environment, as environmental factors are the decisive major factors in causing depression. For genetic factors, no single gene could lead to depression alone, and even for the ones that are associated with depressive symptoms, the correlation is not so strong in comparison to environmental factors that could directly and severely

effect one's mental health. Therefore, having a healthy lifestyle and living environment is the most crucial step in avoiding depression and even other mental illnesses.

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