Brain Changes and Related Environmental Factors in Depression of Adolescents

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Abstract: Depression is one of the most common mental health problems in adolescents, which can lead to serious negative influence on school maladaptation, social adaptation, healthy development, even increase the risk of self-injury and suicide. Increasing number of studies demonstrate that both brain changes and environmental factors are relevant to depressive symptoms and disorder in adolescents. The present study is interested in the brain changes related to adolescent depression and how the environmental factors interact with the brain under the depression. Specifically, this study reviewed the influence of the alter in brain structure (e.g., white matter abnormality) and large-scale brain functional networks (e.g., default mode network) of adolescent depression. Moreover, the present review also introduced some environmental factors (e.g., parenting style) and how they can predict adolescent depression by affecting related brain structure and function. Finally, the limitations of the present study and suggestions for future studies are also conducted.

1. Introduction

According to the official website of the *World Health Organization* (WHO), as of 2017, the number of people suffering from depression has reached 322 million, and adolescents are among the most at risk. Empirical studies have pointed out that adolescence is a critical period for depression susceptibility. At this period, the risk of depression increases rapidly [1][2]. Adolescence is a transitional period from the childish childhood to the mature adulthood and also a period when the body and mind experience great changes and confront various growth crises, which leads to the increasing risk of depressive symptoms in adolescents [3]. Depression will negatively influence adolescents in many respects, such as school maladaptation [4], social adaptation [5], healthy development [6], even self-injury [7] and suicide [8].

On the influence factors of depression, researchers in different fields have different hypothesis, which includes genetic (e.g., the accentuation hypothesis), physical development (e.g., the hormonal influence hypothesis), and environmental factors (e.g., the contextual amplification hypothesis) [9]. Early empirical studies focused on the impact of environmental factors on adolescent depression. For example, according to ecological model, family factors (e.g., parental rearing behaviors) have an

important influence on the occurrence of depression in adolescence [10]. As technology advances in recent years, increasing studies have begun to explore the underlying brain mechanism on adolescent depression, which indicated that adolescent depression and the brain can interact [11]. In addition, there are a number of environmental factors that may protect against changes in the brain caused by depression. In the present study, we summarize and discuss the brain changes related to adolescent depression and how the environmental factors protect the brain under the depression.

2. Brain Changes Correlate with Adolescent Depression

Adolescent depression occurs in the context of the brain's ongoing maturation [12]. Major depressive disorder (MDD) is one of the most common Mood Disorder (MD) among adolescents. Extensive evidence from neuroimaging techniques revealed that white matter (WM) abnormality is a factor of the neuronal circuit dysfunction [13], which is related to depression [14]. WM abnormalities result in damaged connection between the brain regions related to emotional and cognitive regulation, which contribute to the pathogenesis of major depression. Diffusion tensor imaging (DTI) is an advanced imaging technique commonly used to detect the microstructure of white matter, which can evaluate the integrity of cerebral nerve fibers [15]. The evaluation parameters of DTI include fractional anisotropy (FA), relative anisotropy (RA), and mean diffusivity (MD). Currently, there are three common approaches to analyze the anisotropy of brain white matter: region-of-interest (ROI), voxel-based morphometry (VBM) and tract-based spatial-statistics (TBSS).

The parahippocampus is an important structure located on the medial side below the occipital and temporal lobes. Damage to the parahippocampus may lead to abnormal emotional and cognitive behaviors. Researchers have found that the decrease of FA values in WM in the parahippocampal gyrus is associated with the pathophysiological mechanism of depression in adolescents [16]. The posterior cingulate cortex (PCC) is also an important part of the emotional circuit, involved in emotional and self-evaluation processes that may associated with depression [17]. Evidences from TBSS studies have indicated that decreased FA value of white matter cellulose in the PCC is associated with first-episode depression in adolescents [18]. In addition to aforementioned structures, researchers have found other structures with white matter abnormalities that are predictors of adolescent depression, such as the bilateral anterior/posterior limbs of the internal capsule, tracts through the midbrain, left external capsule, right thalamic radiation and left inferior longitudinal fasciculus [19]. In addition, the subgenual anterior cingulate cortex (ACC) has been thought to be related to MDD in adolescents [20]. Adolescents with MDD were observed lower FA in the WM tract connecting subgenual ACC to amygdala [21].

In addition to studies of structural changes in the brain, there are increasing research explore functional connectivity (FC) in the brain, which hopes to understand the relationship between the neural networks of functional connectivity and cognitive function of MDD [22-24]. Resting-state functional magnetic resonance imaging (rfMRI) is an emerging brain imaging technology that can be used to probe the changes in network connectivity while the individual is "at rest" in an fMRI scanner. Functional connectivity analysis based on temporal coupling of brain regions generates an interconnected neural map that can be used to assess the changes of multiple brain regions over time [25].

The default mode network (DMN) is a network of functionally connected brain regions, including the medial prefrontal cortex (mPFC), posterior cingulate cortex/precuneus (PCC/PCu), inferior parietal cortex, medial parietal cortex, and lateral parietal cortex; these regions are related to undirected or internally directed mental states, such as thinking back the past, imagining the future, and passively resting [26][27]. Studies demonstrated that the DMN is a common brain region

associated with depression in adolescents [28][29], especially the two regions from DMN: the mPFC and the PCC; mPFC is regarded as a role of supporting self-referential mentation [30], and the PCC is considered as a region that implicated in consciousness, awareness, and memory-related processes [31]. Recent years, increasing resting state rfMRI studies verified the correlation between DMN and depression. For example, a functional connectivity dynamics study of the DMN indicated that inflexibly elevated DMN functional connections may strongly related to adolescent depression, manifested as compared with healthy control adolescents, MDD group showed the PCC–subcallosal cingulate connections remained inflexibly elevated in two groups (MDD adolescents versus healthy control adolescents) during the resting state fMRI [28]. Besides, a novel method named network homogeneity (NH), which is a voxel-wise measure conducted to value the associations of a voxel with other voxels in a particular network, was used to resting state fMRI study and claimed that an abnormal DMN homogeneity could be found among MDD adolescents, specifically, NH in the left dorsolateral medial prefrontal cortex (mPFC) was observed a significantly increased and NH in the right inferior temporal gyrus (ITG) was observed a significantly decreased in depressed adolescents than in healthy control adolescents [32].

The cognitive control network (CCN) is a network as well as a frontoparietal system that is considered to be crucial to executive functioning, problem-solving, and the flexibility to changes in situation [22]. Increasing studies explored the relationships between mental illness and the CCN, and the disruption in the CCN is considered as underlie psychopathology of MDD [33]. A study of MDD in adolescents demonstrated that the attenuation in intrinsic connectivity within the CCN is related to adolescent depression. The attenuating effects were observed within the entire CCN, specifically, in the right dorsolateral prefrontal cortex and right inferior parietal lobule, as well as in the left dorsolateral prefrontal cortex and bilateral anterior inferior frontal gyrus/insula [33].

In addition to DMN and CCN, limbic system, which includes cingulate, hypothalamus, hippocampus, amygdala, is considered as an emotional regulation as well as an important role in depression [34], especially the amygdala networks [35]. Amygdala networks include emotion regulation, sensory information adjustment, and the process of visceral information in response to emotional stimuli, which involved in crucial functions associated with depression [36]. Several studies found that amygdala functional connectivity abnormalities may be related to MDD in adolescents [37]. For instance, Luking et al found that depressive adolescents had lower negative amygdala functional connectivity as well as lower positive functional connectivity with inferior limbic network [38]. Some studies claimed that adolescents with MDD were observed lower positive functional connectivity between amygdala and hippocampus [39]. In addition, decreasing connectivity between ACC and amygdala may be a trend in MMD patients [40].

3. Environmental Factors of Adolescent Depression

Substantial empirical studies have shown that environmental factors such as parental aggressive behaviors and low family socio-economic status can strongly predict adolescent depression [41], while some positive environmental factors can protect adolescents from depression. Moreover, in recent years, more and more studies have begun to explore the mechanism of environmental factors correlated with adolescent depression by means of MRI technique.

Parenting style (i.e., autocratic parenting, authoritative parenting, permissive parenting, and unengaged parenting) is correlated to the higher likelihood of adolescent depression. Parenting style is mainly reflected in the form of interaction between parents and children. Positive parenting can be warm, usually respond to their children's thoughts and behaviors in a gentle and supportive way. In contrast, for some negative parenting styles, the parents show a tendency to be “aggressive” in the

interaction with their children. The aggressive usually refers to the dismissive, angry or threatening words and behaviors of the mother during the interaction with their children. The parenting behaviors can not only influence the development of the adolescent brain, but also play a moderate role between the changes of the brain morphology and the adolescent depression. In other words, the development and changes in the brain of adolescent may provide a predisposing environment for depression, but parenting behavior may play a role in determining whether or not adolescents actually exhibit depressive symptoms.

A longitudinal study certified that that the more positive parenting behavior, the slower amygdala volume development in adolescence, as well as the accelerated thinning of orbitofrontal cortex (OFC) [42]. In adolescents, a smaller amygdala may indicate better emotional regulation ability. The accelerated thinning of the OFC may account for increased control ability. In other words, maternal positive parenting behavior can be a protective factor for depression in adolescents. Bedsides, a recent study showed that parental warmth can protect adolescent from depression by decreasing the activation of areas of the brain, including the left amygdala, ACC, and the right dorsolateral prefrontal cortex, in the face of negative emotional events [43].

In addition to the study of positive parenting behavior, some researchers have also focused on the possible negative effects of negative parental aggressive behavior on adolescents. A resting-state MRI study found that the frequency of maternal aggressive behaviors played a moderate role in the relationships between both ACC and the amygdala, and adolescent depressive symptoms [44]. Another MRI research suggested that the larger the bilateral hippocampal volume, the more sensitive to the maternal aggressive behavior, and the more the depressive symptoms of adolescents [45]. Moreover, a recent longitudinal study certified that the higher level of the sensitivity to maternal aggressive behavior, the thinner the frontal cortex in adolescents, which can further affect depressive symptoms [46]. Besides, a seven-year longitudinal study demonstrated that maternal aggressive behaviors influence the functional connectivity in the brain (the amygdala, right superior temporal-posterior insula-Heschl gyri, bilateral visual cortex, left temporal and insula cortices) and is highly associated with depression in adolescents [47].

Family socio-economic status (SES), which includes financial, educational, and occupational influences, is also considered as a crucial predictive factor to the maturation of the brain and adolescent depression [48]. Recent research demonstrated that SES play an important role in brain function and further adolescent depression. Specifically, lower family SES related to an increase in amygdala reactivity when feeling threatened in adolescent, and the abnormal activity in the amygdala is strongly associated with depression [49]. Besides, the mPFC that extending to the ACC may mediate the relationships between family SES and depressive symptoms in adolescents [50].

Childhood maltreatment, which includes physical, emotional, and sexual abuse/neglect, have a long-term negative effect, and such effect may accelerate the development of adolescent depression [51]. Some researchers explored the brain mechanisms of childhood maltreatment and adolescent depression, and the results shown that adolescents who experience childhood maltreatment showed reduced hippocampal volumes and elevated amygdala activity, which hinting at the occurrence of depression [52][53].

4. Conclusion

To sum up, adolescent depression is associated with the brain changes in both morphological structure and functional connectivity. However, the causality underlying these relations are unclear, and researchers did not come to a very consistent conclusion about these brain changes in depressive adolescents. Thereby, more research on the brain changes in adolescent depression needs to be carried

out. Specifically, more longitudinal studies are required in the future, which can demonstrate the causality of brain changes and adolescent depression. In addition, the importance of environmental predictors of adolescent depression should be given greater prominence. However, previous studies pay more attention to the influence of single environmental factor or the interaction of several different factors to adolescent depression, whereas environmental factors may influence the brain of adolescents in many cases, which may make adolescents more sensitive to depression. Therefore, more research on the interaction between environmental factors and brain mechanism should be carried out in the future. Exploring the relationships between the environment factors, the brain changes, and adolescent depression is a study-worthy topic and also have practical implications. For example, studies of the impact of environmental factors on depression provided advice on parenting that parents should avoid aggressive behaviors and abuse toward their children and need to improve family functioning and parental warmth. Research on the interaction between these three can help clarify the mechanism of adolescent depression and provide more targeted and effective interventions.

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