Research Progress on Non-Biological Mechanisms of Depression

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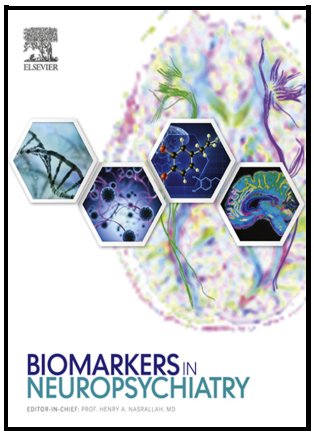

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Research Progress on Non-Biological Mechanisms of Depression

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Abstract

Background: Progress has been achieved in many fields in understanding the biological mechanisms of depression, including genome-wide association analysis, neurotransmitter system function, brain regions and neural networks, inflammatory response, neuroplasticity, neuroimaging, and neuro electrophysiology. These progresses provide a reliable basis for developing the medical and physical therapies for depression. However, the current treatments developed from biological mechanisms can only address less than 60% of depressive symptoms and have limited efficacy in improving social functioning and reducing recurrence. Studies have explored the non-biological mechanisms of depression in mental fields. These progresses are helpful to develop more interventions that could alleviate depressive symptoms, improve functional impairments, and reduce recurrence, thereby promoting a more comprehensive recovery in depressed patients. However, there is not a systematic and deep review to highlight the non-biological mechanisms of depression.
Methods: This study summarizes the recent progress in the non-biological fields of depression by searching publications on human studies in PubMed, PMC, and Google Schooler with exclusion of animal studies.
Results: This study reviews the intergenerational transmission characteristics, the relationship between depression and emotional trauma, cognitive deficit, relationship impairment, self-function, sense of the meaning of life, motivation deficit, and psycho-rationality of depression.
Conclusions: This study was clarified the non-biological mechanisms and characteristics of depression and provided a theoretical basis for the development of non-drug interventions.

Keywords: Depression；Inter-generational transmission；Emotional trauma；Cognitive impairment; Self-functioning； Motivation

1. Introduction

To date, studies on the pathogenesis of depression are mainly focus on its biological mechanisms (Miao & Chang, 2021), including studies on epigenetic alterations, genome-wide association, neurotransmitter system, brain regions and neural networks, inflammatory responses, neuroplasticity, neuroimaging, and neuro electrophysiological changes (Li et al., 2021). The outstanding contributions of these studies provide a theoretical basis for pharmacotherapy and physical therapy of depression (Li et al., 2019). However, the current treatments developed from biological mechanisms can only relieve 58% of depressive symptoms (Ormel et al., 2019). Moreover, these current pharmacotherapy and physical therapy have limited efficacy in improving prognosis and social function, as well as reducing relapse rates (Cieślik et al., 2020). The cognitive behavioral therapy has been shown to be highly effective in treating depression but has limited impact on generational deficits and trauma-related emotional responses in the symptomatic components of depressive symptoms (Johnsen, T. J., & Friborg, O. 2015). The eye movement desensitization and reprocessing therapy has shown some positive outcomes in helping individuals to reprocess traumatic memories of some emotional traumas, but it is not appropriate for traumatized populations of all backgrounds and can exacerbate symptoms in some populations. Therefore, its limitations and side effects need to be considered (Shapiro, F. 2014). Thus, exploration of new mechanisms and subsequent development of new treatments is an urgent need for patients with depression.

In the past decade, many studies on the non-biological mechanisms of depression have been reported, such as studies on the correlations between depression and childhood trauma, cognitive deficits, self-consciousness deficits, impairments in the meaning of life, lack of motivation, and other psychiatric activities (Taylor et al., 2019). However, these studies are relatively fragmented and lack systematicity, and ignore important mechanisms of psychopathology such as intergenerational transmission. Therefore, they cannot provide a sufficient and accurate basis for the development of more effective treatments. Thus, there is a deficiency of the non-drug treatment on depression currently. This study summarizes the recent progress in the non-biological fields of depression. The aim is to explore the pathogenesis of depression from a non-biological perspective and provide evidence and ideas for the development of non-drug treatments.

2. Methods

Literature on the progress in the non-biological mechanisms of depression was searched on human studies in PubMed, PMC, and Google Schooler with exclusion of animal studies using ‘Depression’, ‘inter-generational transmission’, ‘emotional trauma’, ‘cognitive impairment’, ‘relational damage’, ‘Self-functioning’, ‘meaning of life’, ‘motivation’ from January 2013 to July 2023. A total of 189 articles were retrieved, and 91 articles were included in this review.

3. Results

3.1. Non-biological transgenerational transmission of depression

Intergenerational transmission of pathological psychology refers to the phenomenon that psychological disorders or problems presented in the previous generation can reappear in the next generation, or that the behavior or psychological trauma of the previous generation causes mental and psychological problems in the next generation. These problems may span generations and manifest in different ways and degrees (Cooke et al., 2019). In recent years, evidence on the intergenerational transmission of depression has been accumulated. In the biomedical field, family and twin studies have repeatedly validated that the intergenerational transmission of depression is often a result of gene-mediated genetic disorders or epigenetic inheritance (Goodman, 2020; Park et al., 2019). However, the non-biological transgenerational mechanisms of depression have also attracted attention recently (Gotlib et al., 2020).

More and more non-biological transmissions have been observed, while the intergenerational phenomenon of depression and its transmission ways have different explanations (Hentges et al., 2021). For example, parental depression may be transmitted to the next generation through multiple pathways: intergenerational transmission of trauma (Hankerson et al., 2022); intergenerational damage to emotions, self-esteem, and cognition; family culture; parenting style; and behavioral consequences etc. (Kang et al., 2021; Risi et al., 2021; Kujawa et al., 2020; Johnco et al., 2021). These transgenerational mechanisms may indirectly influence the biological changes that evolve into the symptoms of depression (Allison et al., 2023). In the intergenerational transmission of depression, offspring may not inherit the symptoms of depression, but instead display a variety of psychological dysfunctions a variety of psychological dysfunctions, including a tendency to react negatively to emotions (Israel & Gibb, 2024), a state of self-esteem hypersensitivity, cognitive biases, and excessive self-focus (Woody et al., 2022). In addition, offspring may also display relationships with alienation, control, and unclear boundaries (Wei et al., 2023), and even the characteristics of illness that appear in early adulthood or suicidal tendencies (Gijzen et al., 2021).

The study on different modes of transgenerational transmission is important because current biological treatments have little effect on intergenerational transmission (Nedic Erjavec et al., 2021). In contrast, exploration of the non-biological mechanisms of intergenerational transmission of depression, allows for the development of effective methods to terminate intergenerational transmissions, such as extended and modified family therapy, family therapy, and cognitive-behavioral therapy (Wei et al., 2023). Therefore, the study of intergenerational transmission of depression will provide new perspectives for a deep understanding of its transmission mechanisms, as well as new directions for developing more effective interventions.

3.2. Emotional trauma and depression

The negative emotion in depressed patients contains many different components, mainly consisting of fear, feelings of guilt, anger, shame, rejection, and sense of negation (Martins-Monteverde et al., 2019; Leonardi et al., 2020; Zhou et al., 2020). Most of these emotions come from emotional trauma caused by previous negative experiences (including neglect, loss of loved ones, violent experiences, abuse, bullying, etc. (MacMillan et al., 2021). The relationship between emotional trauma and depression is the most studied phenomenon among the non-biological mechanisms of depression (Sengutta et al., 2019). Traumatic experiences in childhood are thought the most potent contributing risk factors for depression in adulthood (Nikkheslat et al., 2020). For example, data from the World Health Organization's Global Mental Health Survey confirmed that childhood traumatic experiences can form lasting fear, shame, rejection, feelings of guilt, and other negative emotional experiences; the data also confirmed the relationship between these psychological effects and adult depression (Nikkheslat et al., 2020).

Several studies have found a significant association between adverse experiences in childhood and an increased risk of depression in adulthood (Vieira et al., 2020; Klumparendt et al., 2019). Hamilton et al. (2018) found that childhood trauma increases the risk of depression in adulthood through changing the neuroendocrine functions of the hypothalamic-pituitary-adrenal axis. Thus, understanding the effects of emotional trauma on the onset of depression is an important basis for the development of more effective treatments. Currently, many treatments for emotional trauma have been developed, such as EMDR, cognitive behavioral therapy for trauma, etc. (Shapiro & Brown, 2019). However, the overall efficacy is not satisfactory. These findings may help the trauma treatments become more effective (Lewis et al., 2020).

3.3. The impact of early cognitive deficits on the onset of depression

The cognitive deficits commonly include poor memory, attention deficits, attentional bias, working memory disorders, excessive self-attention, low executive functioning, intrusive thinking, negative automaticity, rumination, cognitive bias, cognitive vulnerability, and rigidity of thought (Liu et al., 2019; Mao et al., 2020; Zhang et al., 2023). Studies have observed cognitive impairments in early adulthood in some patients with depression (Sumiyoshi et al., 2021), while early cognitive deficits are revealed to be a risk factor for the development of depression (Zhang et al., 2023). Hards et al. (2020) study confirmed the relationship between cognitive deficits and increased risk of depression, including attentional bias, working memory, self-attention, and cognitive brittleness. Wahl et al. (2020) study found that intrusive thinking, rumination, and negative automatic thinking have a negative impact on emotion regulation in depression. Sierra-Aparicio et al. (2019) explored the specific deficits of executive functioning in depression and confirmed the role of cognitive deficits in the pathogenesis of depression). The study has demonstrated that cognitive vulnerability and cognitive rigidity are predictors of depressed mood (Camuso & Rohan, 2020). The above studies all support the role of cognitive deficits in the onset of depression.

Studies on the impact of early cognitive deficits in depression have demonstrated that early cognitive functions have plasticity, can be altered, and their improvements can prevent the occurrence of depression and promote prognosis (Grist et al., 2019). Early cognitive deficits may be caused by different causes, such as intergenerational trauma and deficits in parenting styles (Basanovic et al., 2020). Early identification and accurate assessment of cognitive deficits, full understanding of their pathogenicity, and timely and effective intervention are all important for the prevention and treatment of depression.

3.4. Impairment of relational functions and depression

Relational function is an important psychological function. Impairment of relational function means deficits of interpersonal abilities in establishing, maintaining, and developing relationships with others, as well as handling conflicts and maintaining boundaries (Chen et al., 2023). Impairment of relational function also implies that the ways to obtain understanding, approval, support, emotional adjustment, and cognitive building from others are blocked. The relationship status and functioning have greater impact on relational function in younger people (Hopwood & Good, 2019). It has been found that patients with depression often exhibit poor relational functions in a variety of interpersonal relationships (including with parents, peers, partners, or other social beings); this is evidenced by difficulties in establishing and maintaining close relationships, apathy, difficulty in expressing and responding to emotions, negative interactions, vulnerability to conflict, and difficulty coping with it (Black et al., 2019), social avoidance, excessive self-focus, poor interpersonal attraction, social skill deficits, and doubts about the support and care of others (Day et al., 2020; Sahin &Usta, 2020).

Several studies have demonstrated that impairment of relational function is one of the risk factors for the onset of depression (Collazzoni et al., 2020). The younger the person who is neglected, alienated, rejected, denied, humiliated, and other relationship-injured, the more likely he or she is to develop depression (Wilde & Dozois, 2019). Forbes et al. (2020) study found that social avoidance, poor interpersonal attraction, and a lack of social skills greatly increased the risk of depression. Mavrandrea & Giovazolias (2022) revealed that relationship disfunction such as dysgraphia, negative interactions, apathy, and difficulty maintaining relationships are associated with the worsening of depression symptoms and disease recurrence. Bifulco et al. (2019) pointed out that impairments in relational function can be used as a predictor of depression.

Several studies have further explored the mechanisms how impairment of relational function leads to depression. For example, Christensen et al study demonstrated that low relational function is associated with diminished person's ability to cope with stress and tolerate frustration (Christensen et al., 2022); The reduced emotional interactions can cause a person to feel isolated and excluded from a variety of important relationships, greatly affecting the acquisition of interpersonal support (Barros et al.,

2022); and Impairment in relational function can also reduce self-identity and create a sense of worthlessness (Collins et al., 2022). All the above symptoms are important components of the depressive symptoms.

Improvements in relational function can significantly improve the treatment response in depressed patients reported in Blanchard et al. (2021). Although impairments in relational function can be the result from very different causes, a method of "rebuilding attachment and repairing relational capacity" has been developed to treat depression (Waraan et al., 2021). Therefore, assessment and relationship-focused treatment are valuable interventions to improve the prognosis of depression.

3.5. Ego dysfunction and depression

Self-functioning consists of multiple dimensions, including self-esteem (corresponding to feelings of inferiority), self-worth (corresponding to feelings of guilt), self-identity (corresponding to feelings of self-denial and unworthiness), self-efficacy (corresponding to feelings of powerlessness), and self-mastery (corresponding to feelings of helplessness) (Clark et al., 2021; Clucas, 2020; Hellmann, 2023; LeMoult & Gotlib, 2019). Most depressed patients have self-dysfunction, just in different manifestations (Knight et al., 2019).

Traumatic experiences such as being ignored, denied, rejected, abandoned, abused, isolated, bullied, humiliated, and controlled can cause serious damage to psychological functioning and psychological resilience, but even more so to self-functions (Killian-Farrell et al., 2020). These traumas caused injuries usually persist and have widespread and long-lasting effects (Yuan et al., 2022).

Several studies have shown that self-dysfunction is an important etiologic factor in depression. For example, a study found that the lower the self-identity in a person, the more likely the person suffers from depression (Sowislo & Orth, 2013); A long-term follow-up study found that low self-esteem is a significant risk factor for depression and that low self-esteem could be a predictor of the onset of depression (Wang et al., 2022). Veale et al study found a significantly negative correlation between self-mastery and depression, self-compassion, self-criticism, and a low sense of self-worth are all risk factors for the onset of depression (Veale et al., 2023). Zhang et al. (2021) also found that low self-efficacy is one of the important factors leading to depression.

Self-function is a complex set of mental activities, and it is difficult to clearly explain and comprehensively treat the impairment of self-function based on the currently available biological mechanisms (Saeedi et al., 2020). Changing emotions cannot significantly improve the damaged self-function, indicating that self-function is a relatively independent mental activity (Howard, 2022). A systematic review found that targeted improvements in self-function can effectively relieve symptoms of depression, improve quality of life, as well as reduce relapse rates in depressed patients (Zhang &

Jia, 2021). Therefore, treating the impairment of self-function might be an important intervention for depression therapy.

3.6. Impairment of "sense of meaning in life" and the onset of depression

The "sense of meaning in life" is an important spiritual activity. Depressed patients often have a "sense of meaninglessness" (Monroe & Harkness, 2022). This symptom is attracted attention because "meaninglessness" is one of the main drivers of suicidal behavior in depression (Ribeiro et al., 2018), and it is also a main component of the "residual symptoms" of depression (Mikulincer et al., 2020). Usually, psychiatric clinicians believe that "meaninglessness" in depressed patients is caused by negative emotions or is the result of cognitive biases (Levin & Vasenina, 2019). However, a sense of meaninglessness has been found in some patients before the onset of depression (Hammen, 2018). When other symptoms of depression, especially mood symptoms, are relieved, the sense of meaninglessness remains in many patients. This implies that the symptomatic component of "meaninglessness" has a relatively independent mechanism (Chang et al., 2019).

Anhedonia is a composite symptom, including loss of pleasure, loss of interest, lack of motivation, impairment of the sense of meaning in life, etc. Thus, depression with the symptom of "meaninglessness" is classified as "anhedonia-type depression" (De Fruyt et al., 2020; Laird et al., 2019). The “sense of meaninglessness” is thought to be an early psychiatric impairment in depression caused by intergenerational trauma, emotional trauma, and self-esteem trauma, etc. (Olstad et al., 2022). Impairment of the "sense of meaning in life" is even thought to be the etiology of some patients with depression; Lee et al study found that the lower the "sense of meaning in life is", the more severe the degree of depression will be (Lee et al., 2022). However, if there is still a "residue" of "sense of meaninglessness" even after significant improvement in depressive mood, or some patients have a "sense of meaninglessness" in early adulthood (before illness), it is necessary to consider "meaninglessness" as an independent symptom (Zeng et al., 2021).

Therefore, assessment and conceptualization of the symptom of "meaninglessness" in depression are necessary to determine whether independent treatment is needed. Zeng et al. (2021) explored the possibility to ameliorate depressive symptoms through the reconstruction and search for meaning in life. Current psychotherapies rarely contribute significantly to improvements in the meaning of life, and more effective treatments are needed.

3.7. Motivation/drive impairment and depression

Most depressive symptoms are characterized by a lack of motivation and a lack of drive to do things (Grahek et al., 2019). Studies have found that 44% of depressed patients be motivated impairment and drive impairment before the onset of a significant

depressive mood (Steinberger & Barch, 2023), suggesting that motivation impairment and drive impairment may be the causes of depression, or they may reflect the damage caused by diseases. In addition, motivational damage is often a dysfunction that easily remains after depression is treated (Booth et al., 2019) [91]. In symptomatologic studies, impairment of motivation/drive has been recognized as a manifestation of " anhedonia " and a consequence of depressed mood, diminished interest, negative cognitions, or injured self-esteem (Barch et al., 2016). However, it has been observed that many patients remain unmotivated even after significant improvement in depressed mood and related cognitions (Growney et al., 2020). These observations suggest deficits in the understanding of mood, cognition, and self-esteem sources of motivational injury. The symptoms of motivational impairment/lack of motivation need to be further explored.

Research has confirmed that lack of motivation and drive is not only a symptom of depression, but also an important etiologic structure of depression, a risk factor for the development of depression, and an important player in the onset of depression and the persistence of the illness (Fervaha et al., 2016).

A growing body of studies has found that lack of motivation and motivational deficits are influenced by multiple factors, which vary from patient to patient. Only some of the patient's motivational impairment is the result of emotional, cognitive, and self-esteem disorders (Frey & McCabe, 2020). In addition, motivational impairment may also be related to intergenerational, relational dilemmas, and self-functioning (Barch et al., 2019) Fortunately, there are relatively effective treatments for motivational impairment. Therefore, it is valuable to accurately assess the mechanism, treat the causes, and promote the recovery of motivation to improve the symptoms and prognosis of depression (Fervaha et al., 2016).

4. Discussion

Recent studies demonstrated that depression is characterized with more complex and multidimensional psychopathological mechanisms. This study for non-biological pathogenesis of depression leads to the following conclusions:

4.1. Non-biological mechanisms are involved in the pathogenesis of any type of depressive disorder; therefore, the non-biological etiology should be given sufficient attention. Many symptoms of depression that cannot be effectively relieved by medications may be relieved by non-pharmacologic treatments.

4.2. Depression is a disorder with multiple etiologies. Thus, almost every patient with depression has a multifaceted etiology. Both biological and non-biological mechanisms are involved in the development of depression, but the etiologic structure of each patient varies greatly, with different structural compositions and weights of etiologic factors; the non-biological mechanisms are even the dominant components in the etiologic structure of certain subtypes.

4.3. Beside the biological mechanisms, non-biological mechanisms may be mutually consistent components and independent mechanisms. Ignoring either one does not

provide an accurate and complete understanding of depression. However, a combined biological and non-biological approaches and treatments may be most effective in the clinical practice. Especially, the non-biological treatment may be effective on the depressed patients with the non-biological etiology.

4.4 Functional impairment, residual symptoms, and easy recurrence of depression are related to non-biological mechanisms; therefore, the development of non-pharmacological treatment based on non-biological mechanisms is an important way to improve the prognosis in patients with depression.

4.5. The non-biological mechanisms mentioned in this study can also be helpful for the early diagnosis of depression and following the process of illness and treatments.

Declaration of Competing Interest

We confirm that there are no known conflicts of interest associated with this paper, and there has been no significant financial support or personal relationships that could have appeared to influence the work reported in this paper.

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