REVIEW

A relationship between early life stress and depression: the role of the serotonin transporter gene polymorphism (5-HTTLPR)

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Abstract

Early life stress has been associated with many different negative outcomes including adulthood depression. Studies have suggested a role of the serotonin transporter gene polymorphism (5-HTTLPR) in explaining this relationship. However, consistent replication of this gene-environment interaction have proven difficult. This paper will review contrasting evidence assessing this interaction. Previous research has revealed a complex interplay of factors that might explain how certain 5-HTTLPR genotypes interact with early life stress to produce sensitivity to stress and adulthood depression. Maladaptive cognitive and behavioral patterns will be reviewed in light of 5-HTTLPR's impact on brain regions associated with mood regulation. Future research directions and clinical interventions will also be discussed.

Keywords: Early life stress, Childhood abuse, 5-HTTLPR, Depression.

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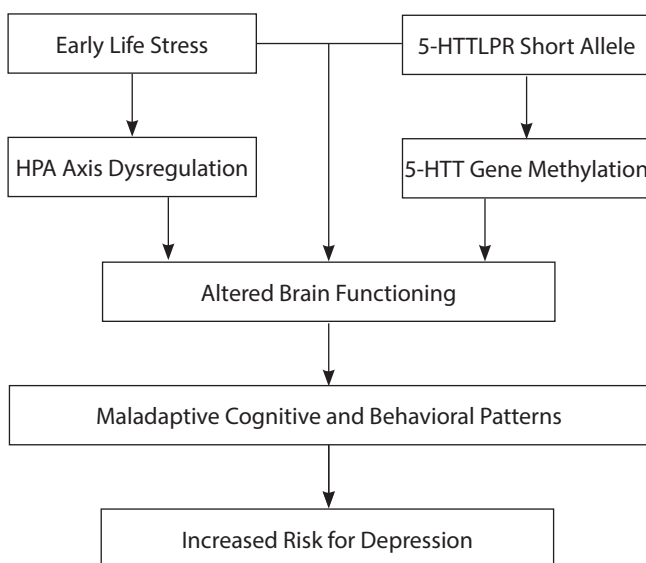Email: jorge.valderrama@downstate.edu

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Introduction

Major depressive disorder is a pervasive psychiatric disorder affecting up to 300 million people across the world [1]. Major depressive disorder is characterized by depressed mood and/or anhedonia alongside a variety of behavioral and cognitive symptoms that might involve fatigue, change in sleep, significant weight change, change in activity, feelings of worthlessness, difficulty concentrating, and suicidality [2]. Ongoing research continues to reveal the complex and multi-dimensional nature of risk factors that contribute to depression. Risk factors such as early life stress and altered serotonergic functioning have been previously linked with depressive symptoms. This paper will review serotonin (5-HT) and the serotonin transporter polymorphism (5-HTTLPR) relationship to mood regulation, how early life stress relates to different disorders, and behaviors that often precede or are co-morbid with depression. This will be followed by an in-depth examination of the relationship between 5-HTTLPR genotypes, early life stress, and depression. Finally, we will discuss different cognitive and affective vulnerabilities to depressive symptoms that might result from an interaction between 5-HTTLPR genotypes, altered neurobiological and neuroendocrinological functioning, and early life stress (**Figure 1**).

The serotonin transporter and depression

Serotonin (5-HT) is a neurotransmitter that is functionally important for various physiological and psychological processes including sleep, emotional processing, and mood regulation [3]. 5-HT is widely found in the upper brain stem with projections terminating throughout the brain including the cerebral cortex, hypothalamus, and amygdala [4]. Abnormal serotonergic functioning has been implicated in depressed mood [5]. Much of the research establishing an association between 5-HT dysfunction and depression has focused on the serotonin transporter (5-HTT).

During 5-HT neural transmission, serotonergic neurons release 5-HT onto receptors of the postsynaptic neuron. 5-HTT is responsible for reuptaking 5-HT from the synaptic cleft back to the presynaptic neuron, thus, terminating the action of 5-HT and recycling it for future neural transmission [6]. The class of anti-depressant medications known as selective serotonin reuptake inhibitors (SSRI's) block the action of 5-HTT, thereby increasing the amount of 5-HT in extracellular space. The increased 5-HT initially results in an inhibition of 5-HT release from the presynaptic cell due to a negative feedback loop caused by increased autoreceptor activation. Over time (several weeks), continual administration of SSRI's downregulates the autoreceptors and a diminished negative feedback loop results in an increase in 5-HT release [7]. The greater availability of 5-HT is believed to influence mood regulation [8].

The relationship between the 5-HTT gene (SLC6A4) and depression has been extensively investigated. The promoter region of 5-HTT is a 43 base pair insertion/deletion polymorphism named the 5-HTT gene-linked polymorphic region (5-HTTLPR). Variants of 5-HTTLPR include short and long allele forms which are associated with different 5-HTT expression [9]. Importantly, two different types of long alleles (La and Lg) are yielded by genotyping 5-HTTLPR and the single nucleotide polymorphism (SNP) rs25531 [10]. The Lg allele results in similar 5-HTT expression as the short allele. For the purpose of clarity, the Lg allele will be referenced as a short allele in this paper. For example, individuals that carry two short alleles can include persons carrying the following allele pairs: S/S, S/Lg, Lg/Lg. Long allele carriers can be homozygous and have two La alleles (La/La) or heterozygous with a long and short allele (La/S or La/Lg).

Possessing two long alleles result in higher 5-HTT expression than the other allele pairs [10]. The short allele has been associated with lower 5-HTT transcriptional efficiency and abnormal serotonergic functioning [11]. Moreover, possessing the short allele may be associated with altered amygdala, hippocampal, and Hypothalamic Pituitary Axis (HPA) functioning [12-14]. Whether or not the short allele confers risk for these abnormalities and depression may be dependent on a number of factors including an individual's exposure to early life stress.

The relationship between early life stress and depression

Early life stress has been assessed via a variety of instruments, some examine stressors experienced before the onset of adolescence, while others examine stressors expe-

Figure 1. Possible pathways toward depression. The interaction between early life stress and the 5-HTTLPR short allele is associated with HPA Axis dysregulation, 5-HTT gene methylation, and altered functioning in brain regions important for mood and emotion regulation. Such dysfunction is associated with increased risk of maladaptive cognitive and behavioral patterns that can precede depressive symptoms.

rienced anytime before the age of 18 [15, 16]. How early life stress impacts an individual may depend on the type, frequency, severity, and timing of the stressor. Early life stress has been examined via a variety of dimensions, including but not limited to sexual abuse (unwanted sexual contact), physical abuse (physical contact with the intent to harm or injure), emotional abuse (verbal communication that humiliates or degrades the victim), emotional neglect (i.e., emotional deprivation or lack of emotional nurturing environment), and familial disruption (i.e., family conflict, parental divorce/separation, death in family, etc.) [16-19]. Each of these dimensions have been associated with many different negative outcomes, including depression [20]. Moreover, abuse type might relate to specific consequences that create a pathway toward depressive symptoms in adulthood. Childhood physical abuse has been linked to increased anger, aggressiveness, poor physical health, PTSD symptoms, impulsivity, and problems with drugs and alcohol later in life when other types of abuse have been controlled for [21-25]. Evidence also suggests that early life emotional abuse is specifically linked to poor physical health, PTSD symptoms, and drug use in adulthood as well as other predictors and correlates of depression including increased stress reactivity, rumination, social phobia and anxiety [19, 24-29]. Early life sexual abuse has been linked to PTSD symptoms and drug use later in life along with a variety of disorders that are often co-morbid with depression including panic disorder and obsessive-compulsive disorder [30-32].

Categorical examination of early life stress has allowed for a greater understanding of specific vulnerabilities to depression. However, importantly, individuals that experience early life stress are often exposed to multiple types of adverse events in their childhood [33]. Increased number of such experiences relate to greater likelihood of depressive symptoms later in life and overall increased intensity of depression as well as shorter life expectancy [34, 35]. High frequency of stressful events early in life positively relate to increased prevalence of impaired memory, substance abuse, depression, suicidal behavior and other negative outcomes related to disordered brain function in adulthood [34, 36, 37].

Brain regions important for emotional and mood regulation may be particularly vulnerable to the negative impact of early life stress during specific periods of development. [38, 39]. Such time windows are considered to be critical periods where experiences can have everlasting effects on various neurobiological and neuroendocrinological systems [39]. Moreover, the timing of critical periods appear to differ between brain regions. Andersen et al. found that reduced hippocampal volume was associated with childhood sexual abuse experienced during the specific age ranges of 3-5 and 11-13 years [40]. By contrast, reduced prefrontal cortex volume was associated with experiencing childhood sexual abuse between the ages 14 and 16. In addition, increased right amygdala volume has been linked to experi-

encing physical and emotional abuse during the ages 10 and 11 [41]. Importantly, 5-HTTLPR might influence how early life stress impacts these brain regions and subsequent risk for depression.

5-HTTLPR, early life stress, and depression

A direct association between the 5-HTTLPR polymorphism and depression has not been established (Anguelova et al., 2003) [42]. However, Caspi et al. examined early life stress and recent life stress as environmental factors that might interact with 5-HTTLPR to predict the likelihood of depressive symptoms in a sample of 847 young adults [15]. A significant and positive association between early life stress and current or recent depression amongst individuals possessing one or two copies of the short allele was found. However, no such association was found in individuals possessing two copies of the long allele. Numerous studies and several meta-analyses have sought to replicate Caspi et al's seminal findings.

The first such meta-analysis examined 14 studies and found no evidence of an interactive relationship between 5-HTTLPR and life stress in the development of depression [43]. However, this meta-analysis did not include studies that examined early life stress as an environmental factor. Karg et al.'s meta-analysis of 54 studies included 10 studies (Total N = 6936) that examined early life stress, 5-HTTLPR, and depression [11]. The results indicated that exposure to early life stress in individuals possessing the short allele increased their sensitivity to stress and increased the risk of developing depression. Additionally, another meta-analysis contributed further evidence of the link between life stress, 5-HTTLPR, and depression [44]. Of the 81 studies analyzed, 20 specifically examined early life stress (this analysis included the 10 studies indicated above examined by Karg and colleagues). These studies revealed a strong relationship between the short allele, early life stress, and depression (p = 0.00026011).

More recently, a collaborative meta-analysis examined 31 data sets and found no evidence of an interaction between 5-HTTLPR, early life stress, and depression [45]. Contrary to the recommendation of Moffitt and Caspi, this meta-analysis did not include studies with sample sizes under 300 participants [46]. Moffitt and Caspi argued that smaller sample sizes are more likely to have higher quality measures (e.g., face to face interviews versus surveys) that yield better information about temporal order and such data is necessary when establishing whether or not a stressor preceded depression. In response, the authors of the meta-analysis expressed concerns for the increased likelihood of statistical errors in small studies. They further noted that publication bias for small studies with positive findings exaggerate the influence of 5-HTTLPR in the relationship between early life stress and depression. Indeed, de Vries et al. [47] found citation bias for such positive findings in an examination of 73 studies. The authors concluded that more

positive findings are cited than negative findings and that negative findings are viewed with a positive focus in article abstracts. These conclusions have been disputed on the basis of concerns with de Vries and colleagues methodological approach (e.g., coding method that differentiated positive and negative results, how article abstracts were evaluated) [48]. There continues to be an ongoing debate regarding the impact, if any, of 5-HTTLPR in the relationship between early life stress and depression. Importantly, mechanisms by which the interaction of early life stress and 5-HTTLPR variants might produce depression are being examined. Such investigations are necessary in light of the contentious results discussed above.

5-HTT gene methylation

Gene expression can change via epigenetic mechanisms that are induced by environmental circumstances such as early life stress. DNA methylation is an epigenetic mechanism that occurs by the addition of a methyl group to DNA which can change the function and expression of a gene. Increased 5-HTT gene methylation has been associated with lower 5-HTT expression as well as depression. [49-51]. Thus, short allele carriers that also exhibit 5-HTT gene methylation may be at greater risk of experiencing negative outcomes associated with lower 5-HTT expression. Accordingly, recent research has examined how 5-HTT gene methylation interacts with 5-HTTLPR to confer risk for a variety of psychiatric disorders, including major depressive disorder.

There have been conflicting findings regarding the association between early life stress, 5-HTTLPR, and 5-HTT gene methylation, where methylation levels vary in its association to early life stress exposure. Short allele carriers exposed to early life stress were more likely to display increased 5-HTT gene methylation than homozygous long allele carriers in a sample of 105 young adults [52]. Consistent with this finding, short allele carriers that have grown up in dangerous neighborhoods show greater methylation than long allele carriers [53]. This association conferred a significant risk for depressive symptoms in this sample. By contrast, Booij and colleagues found that long allele homozygotes exposed to early life stress had significantly greater 5-HTT gene methylation than short allele carriers [54]. Notably, only early life physical abuse, not sexual or emotional abuse, was positively correlated with increased 5-HTT gene methylation in this sample. Moreover, in contrast to other studies, there was no significant link between major depressive disorder diagnosis and 5-HTT gene methylation. However, lower hippocampal volume was associated with increased methylation.

Accounting for brain function is important when examining the dynamic interactions between the serotonergic system and early life stress. As such, Swartz et al. [55] investigated the relationship between adversity early in life, 5-HTT gene methylation, amygdala reactivity, and risk for depression. Early life adversity was significantly associated with increased 5-HTT gene methylation and increased threat- related amygdala reactivity. Interestingly, this association only predicted depressive symptoms in individuals with a family history of depression. The role of brain areas and their function in the relationship between early life stress, 5-HTTLPR, and depression will be discussed in the next section.

The role of affective functioning

Early life stress has been linked to long term functional and structural changes to the amygdala, hippocampus, and the Hypothalamic-Pituitary-Adrenal axis [14, 56, 57]. The amygdala processes emotional stimuli and dysfunction in this brain region is associated with deficits in emotion regulation, anxiety and depression. Neuroimaging studies have revealed decreased availability of 5-HTT in the amygdala of individuals diagnosed with major depressive disorder [58].

Previous research has indicated that depressed short allele carriers have lower remission and response rates when treated with SSRIs than long allele carriers [59]. Importantly, SSRI effectiveness may depend on the differential impact, moderated by differences in 5-HTTLPR, of the drug on emotion regulatory circuits connecting the left amygdala and right interior frontal gyrus (IFG) in the prefrontal cortex [60]. An important emotion regulation strategy is the reappraisal of an event or events an individual experiences. Depressed individuals are less likely to reframe negative events into circumstances that might lend opportunities for personal growth. Indeed, depressed individuals often engage in perseverative thinking in the form of brooding rumination [61]. Brooding is characterized by passively dwelling on the reasons for one's negative mood. Recent findings indicate that the interaction of early life emotional abuse and short alleles increases the likelihood of both brooding and impulsive behavior in the face of stress [29]. Such maladaptive cognitive and behavioral patterns may result from biased information processing. Critically, attending toward negative information has long been associated with the onset and maintenance of depressive symptoms [62, 63].

Brain imaging has revealed that effective reappraisal of negative emotional stimuli is associated with decreased connectivity between the left amygdala and right IFG [64]. Homozygous and heterozygous long allele carriers have decreased left amygdala and right IFG connectivity during reappraisal of negative emotional stimuli after 5-HTT blockade from a single dose of an SSRI (escitalopram). By contrast, homozygous short allele carriers have increased left amygdala and right IFG coupling during reappraisal of negative emotional stimuli after a single dose of escitalopram [60]. The SSRI increased 5-HT in both short and long allele carriers, however, increased 5-HT caused increased dysregulation in neural activity associated with dysfunctional emotional regulation in short allele carriers. These

findings might explain why short allele carriers have less of an effective response from SSRI treatment than long allele carriers. Though SSRIs therapeutic effects are not seen for weeks after initial treatment, the acute effects of SSRIs on emotional regulation may provide a base in which depressive symptoms start to improve in individuals with one or two long alleles.

Importantly, a recent meta analysis revealed a small but significant relationship between 5-HTTLPR genotypes and amygdala activity, whereby the short allele was associated with increased amygdala activity in response to aversive stimuli (e.g., presentation of negative words, negative pictures, pictures depicting sad, fearful, or angry faces, etc.) [12]. Possessing the short allele has been previously associated with greater likelihood to attend toward negative stimuli. [65, 66]. Early life stress might strengthen this association. Williams et al. [67] studied the association between early life stress, 5-HTTLPR, limbic activity, and biased attention. Individuals biased toward negative information were more likely to experience heightened amygdala activity as a response to fearful stimuli than individuals biased toward positive information. Moreover, the interaction between high early life stress exposure and the short allele conferred the greatest risk for attending to negative information and increased amygdala activity.

Other research has also indicated a relationship between possessing 5-HTT low expressing genotypes, exposure to early life stress, and a bias toward recalling negative memories over positive memories [68]. Such memory deficits may be a result of altered hippocampal functioning. The hippocampus is functionally important for long-term memory storage of episodic events as well as emotion and mood regulation [69]. A number of studies have linked hippocampal abnormalities with early life stress and depression [70-73]. Evidence suggests 5-HTTLPR may play an important role in explaining this relationship.

Frodl and colleagues reported smaller hippocampal volumes in short allele carriers versus long allele carriers that experienced early life emotional neglect [71]. More recently, a prospective longitudinal study of 174 participants revealed an association between short alleles and smaller right hippocampal volume (Little et al., 2015) [13]. This relationship was significantly stronger in individuals with major depressive disorder that experienced less positive parenting versus those that experienced more positive parenting. Of note, short alleles were associated with smaller hippocampal volumes before the onset of major depressive disorder. This suggests that caregiving environment moderates the impact of 5-HTTLPR on depression via hippocampal volume. Thus, carrying a short allele and having a smaller hippocampus increases vulnerability to depression. These findings further establish the complexity in which 5-HTTLPR might interact with the environment and brain regions to produce certain outcomes. Importantly, these relationships might further depend on how 5-HTTLPR interacts with stress responses governed by the HPA Axis.

The role of the HPA axis

In response to stress, the brain activates neuroendocrine systems, including the HPA Axis, that promote physiological adaptation in a process called allostasis [74]. However, repeated exposure to stress can lead to allostatic load, characterized by a dysregulated stress response [74]. Various hormones are secreted along the HPA axis when stress is encountered. Ultimately, cortisol, a glucocorticoid, is released throughout the bloodstream and will act upon the HPA Axis in a negative feedback loop fashion while also affecting different tissues in the human body, including the prefrontal cortex, amygdala, and hippocampal brain regions [75-78]. Increased cortisol levels as a result of persistent HPA axis hyperactivity can cause structural damage to these brain regions via disruption of neuronal communication, cell atrophy, and suppression of neurogenesis [79, 80]. HPA axis hyperactivity has been linked to early life adversity and depression [39, 81, 82]. Importantly, serotonergic pathways interact with the HPA axis and plays a role in its regulation [83]. Thus, 5-HTTLPR might be involved in differential HPA axis functioning.

Miller and colleagues meta analysis of eleven studies revealed a significant and positive association between possessing short alleles and exhibiting HPA Axis hyperactivity in response to acute stress [84]. The nature of this relationship has yet to be fully elucidated. However, given the interaction between stressful life events and 5-HTTLPR, possessing short alleles might increase the likelihood that stressful life events would induce HPA axis hyperactivity. Indeed, the association between 5-HTTLPR and HPA axis activity appears to be dependent on history of life stress in young adults [85]. Individuals possessing two copies of the long allele with a low incidence of stressful life events (e.g., familial disruptions, health problems, interpersonal difficulties, etc.) had significantly greater cortisol output in response to stress than individuals with similar histories of stress with one or two copies of the short allele in a sample of 106 young adults [85]. However, for individuals that experienced high life stress, cortisol output was significantly higher in individuals possessing one or two copies of the short allele than homozygous long allele carriers. Thus, HPA axis activity in response to stress may depend on which 5-HTTLPR polymorphism an individual possesses and whether or not a history of life stress is present. Additionally, homozygous short allele carriers that experienced life stress also exhibited heightened activity in the amygdala in response to fearful stimuli in a subgroup of this study's sample [86]. Importantly, HPA axis hyperactivity has been associated with decreased hippocampal volume in individuals with a history of early life stress [87]. Taken together, these studies reveal that short allele carriers that experienced early life stress might be at greater risk of having an overactive stress response. Such HPA axis hyperactivity can contribute to the development of depression via a variety of mechanisms including altered hippocampal and amygdala functioning.

Conclusions and clinical relevance

The present review examines how early life stress might increase risk for depression via its interaction with serotonin transporter genotypes. Observations of the relationship between allelic variation, gene methylation, brain areas with serotonergic pathways, and stress response systems suggest complex and dynamic interactions influence the development of negative mental health outcomes after the experience of early life stress (**Figure 1**). Further, the timing of the stress, whether or not the stress was chronic, and the type of stress an individual experiences play a role in the likelihood of future depressive symptoms developing. Understanding the antecedents of depressive symptoms and major depressive disorder is important in light of developing targeted therapeutic interventions. SSRIs have proved to be an effective option for some individuals suffering from depression. However, experiencing early life stress and/or possessing the 5-HTTLPR short allele might limit the efficacy of SSRI treatment. Potential harmful side effects can also restrict the use of SSRIs as a primary means of symptom relief. Importantly, treatments focusing on emotion regulation strategies may address the impact early life stress has on information processing in adulthood. Negative attributional bias, greater recall of negative events, and increased sensitivity to stressors are a few of the vulnerabilities to depression that can be targeted by clinical interventions.

Many cognitive behavioral therapies attempt to teach individuals to reappraise stressful events by producing positive or neutral appraisals of such events [88]. These interventions can increase positive attribution bias while also decreasing negative attributional bias. Further, mindfulness-based cognitive therapies focuses on strengthening a person's ability to live in the present moment without judging their current mental content. Such strategies can decrease the likelihood of recalling negative events in the face of stress [89]. Accordingly, dialectical behavior therapy focuses on increasing mindfulness, one's distress tolerance threshold, relaxation skills, acceptance skills and letting go of emotional suffering along with other approaches to improve emotion regulation [90]. These techniques may be particularly helpful to individuals with maladaptive emotion regulation strategies caused by early life stress.

Examining the role of 5-HTTLPR in its relationship to depression has greatly increased our understanding of how the environment and genes might interact to produce altered biological and cognitive processes in an individual. However, contradictory findings, differing sample sizes, and inconsistent methodological approaches demonstrate the challenges of studying the etiology of depression from gene-environment perspective. The interplay of risk factors for depression is complex. Greater understanding of the dynamic interactions between the early life stress, genes, and neural processes is necessary in developing targeted treatments that can complement established therapeutic methods.

Abbreviations

5-HT: Serotonin; 5-HTT: Serotonin Transporter; 5-HTTLPR: Serotonin Transporter Gene Polymorphism; HPA axis: Hypothalamic Pituitary Adrenal Axis; IFG: Interior Frontal Gyrus; SLC6A4: Serotonin Transporter Gene; SNP: Single Nucleotide Polymorphism; SSRI: Selective Serotonin Reuptake Inhibitors

Competing interests

The authors declare no conflict of interest.

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