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**Review**

# Impact of early-life stress on the medial prefrontal cortex functions – a search for the pathomechanisms of anxiety and mood disorders

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**Abstract:**
Although anxiety and mood disorders (MDs) are the most common mental diseases, the etiologies and mechanisms of these psychopathologies are still a matter of debate. The medial prefrontal cortex (mPFC) is a brain structure that is strongly implicated in the pathophysiology of these disorders. A growing number of epidemiological and clinical studies show that early-life stress (ELS) during the critical period of brain development may increase the risk for anxiety and MDs. Neuroimaging analyses in humans and numerous reports from animal models clearly demonstrate that ELS affects behaviors that are dependent on the mPFC, as well as neuronal activity and synaptic plasticity within the mPFC. The mechanisms engaged in ELS-induced changes in mPFC function involve alterations in the developmental trajectory of the mPFC and may be responsible for the emergence of both early-onset (during childhood and adolescence) and adulthood-onset anxiety and MDs. ELS-evoked changes in mPFC synaptic plasticity may constitute an example of metaplasticity. ELS may program brain functions by affecting glucocorticoid levels. On the molecular level, ELS-induced programming is registered by epigenetic mechanisms, such as changes in DNA methylation pattern, histone acetylation and microRNA expression. Vulnerability and resilience to ELS-related anxiety and MDs depend on the interaction between individual genetic predispositions, early-life experiences and later-life environment. In conclusion, ELS may constitute a significant etiological factor for anxiety and MDs, whereas animal models of ELS are helpful tools for understanding the pathomechanisms of these disorders.

**Key words:**
early-life stress, maternal separation, prenatal stress, medial prefrontal cortex, synaptic plasticity, anxiety, mood disorders, epigenetics

**Abbreviations:** 11B-HSD2 – 11β-hydroxysteroid dehydrogenase type 2, BDNF – brain-derived neurotrophic factor, ELS – early-life stress, GDNF – glial cell-derived neurotrophic factor, GFAP – glial fibrillary acidic protein, GR – glucocorticoid receptor, ILC – infralimbic cortex, LTD – long-term depression, LTP – long-term potentiation, MDs – mood disorders, miRNA – microRNA, mPFC – medial prefrontal cortex, MS – maternal separation, NCAM – neural cell adhesion molecules, PLC – prelimbic cortex, PTSD – post-traumatic stress disorder, SHRP – stress hyporesponsive period, vmPFC – ventromedial prefrontal cortex

## Introduction

Anxiety and mood disorders (MDs) are the most prevalent mental disorders and the leading causes of years lived with disability all over the world [68]. They affect all age groups, from children and adolescents to adults [27]. Despite numerous research attempts and existing theories, the pathogenesis of anxiety and MDs is still poorly understood.

Clinical and epidemiological data from the past decade markedly point toward early-life stress (ELS) as a relevant risk factor for the development of anxiety and MDs. Early-life adversity in the maladaptive family functioning cluster (family violence, physical abuse, sexual abuse, neglect, parental mental illness and substance abuse) is most strongly correlated with mental disorder onset [30]. A recent World Mental Health Survey revealed that ELS is associated with 59.5% of childhood-onset MDs and 32.6% and 13.6% of adolescence- and later adulthood- (age 30+) onset MDs, respectively. In the case of anxiety disorders, ELS is generally responsible for approx. 30% of onsets, regardless of age group [30]. The neurobiological substratum for associations between ELS and the development of anxiety and MDs is widely studied with advanced *in vivo* neuroimaging technologies and preclinical studies, which apply various animal models [20, 56].

## The medial prefrontal cortex as the key brain structure implicated in the pathophysiology of anxiety and mood disorders

The medial prefrontal cortex (mPFC) is a forebrain structure known to regulate a variety of cognitive and emotional processes. Specifically, the ventral part of the mPFC (vmPFC) has been shown to be involved in such processes as (1) fear and anxiety, (2) risk taking, (3) decision making, and (4) attentional processes [25]. On the basis of evidence from neuroimaging, lesion analyses and *post-mortem* studies, the mPFC was recognized as a key brain structure, along with the amygdala, hippocampus and ventromedial parts of the basal ganglia, that is affected by anxiety and MDs [20, 44]. It was shown that patients suffering from MDs and anxiety disorder, e.g., post-traumatic stress disorder (PTSD), had reduced gray matter volume of the mPFC [20, 67]. Moreover, histopathological examinations showed several morphological abnormalities, such as reductions in synapses and synaptic proteins and elimination of glial cells in the mPFC of MD subjects [20]. Changes in neural and metabolic activities of the mPFC were also reported in patients with anxiety and MDs. In this respect, most neuroimaging studies demonstrated a decrease in neural activity of the vmPFC in PTSD patients [24]. In the case of MD patients, several reports showed elevated vmPFC activity and its modification during antidepressant medication [44].

As a frontal lobe structure, the mPFC exhibits a prolonged developmental trajectory. It is one of the last brain regions to mature during development [10]. Thus, it is not surprising that the mPFC is especially vulnerable to early-life insults (e.g., ELS). Several neuroimaging studies in humans revealed reduced mPFC volume in children, adolescents and adults with a history of ELS [23, 53, 63]. Moreover, a loss of sustained activity in the vmPFC in response to stress has recently been found in individuals who experienced early-life emotional abuse [65]. Therefore, it is postulated that adverse early-life experiences may constitute a significant etiological factor for anxiety and MDs. Despite the numerous advantages of advanced neuroimaging technologies applied to humans, the search for the specific pathomechanisms of the abovementioned disorders within the mPFC is possible only in preclinical studies that use (1) animal models of ELS, (2) behavioral tests reflecting some symptoms of anxiety and MDs and (3) a variety of biochemical and electrophysiological techniques [56].

## ELS-induced dysfunction of the mPFC – implications from the behavioral studies in animal models

There are many different experimental procedures that model ELS in animals (mostly in rodents). They can be divided simply into prenatal and early postnatal procedures, according to the developmental time when the stressful event is applied (for review, see: [38, 51]). Prenatal stress can be evoked in pregnant dams by various stressors, such as (1) lipopolysaccharide injection and viral infection (both cause maternal immune activation), (2) unpredictable psychological stress (restraint stress) or (3) malnutrition [38]. Early postnatal procedures are strongly represented by maternal separation (MS) paradigms, which are usually conducted during the first three weeks of rodent life. MS procedures are applied in many ways, such as a single 24-h-long MS or a prolonged repeated everyday MS (e.g., 3 h /day, on postnatal days 1–14) [51].