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Review Article

Unveiling the Neuroscientific Underpinnings of Mood and Anxiety Disorders

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Abstract

Depression, anxiety and stress-related disorders are the most prevalent mental health disorders worldwide, affecting millions of individuals across various age groups, and social categories. While the origins of these disorders are complex and multifaceted, recent advancements in Neuroscience provide valuable insights into the underlying mechanisms that contribute to the development and maintenance of mood and anxiety disorders. This review delves into the intricate interplay of neurobiological factors involved in these mental disorders, shedding light on the neural pathways, neurotransmitters, and structural/functional circuit changes that contribute to their manifestations. A special focus is given here on new and upcoming insights in Neuroscience that emerge from a deeper understanding of the complex interplay of biological and environmental factors that takes place at a multi-scale level, from genes to behaviors, and from external exposome to the internal state factors.

Keywords: Mood disorders; Stress; Interoception; Emotions; Biomarkers; Homeostasis

Introduction

Recently, it was estimated that 970 million people worldwide are living with a mental health disorder [1]. Among these people, the World Health Organization estimates that depressive disorders are the most common form of mental disorder, therefore with the greatest impact worldwide [2]. Mood, anxiety and stress-related disorders are categories of mental health conditions that involve disturbances in a person's emotional and psychological well-being [3]. These disorders impact an individual's mood, emotions, thoughts, and behaviors, leading to significant distress and impairment in daily functioning. This family of illnesses encompasses a range of specific disorders, each characterized by distinct symptoms and diagnostic criteria [4]. For instance, mood disorders, also known as affective disorders, involve persistent changes in mood or emotional states that go beyond typical fluctuations. The primary mood disorders include Major Depressive Disorder (MDD) characterized by persistent feelings of sadness or hopelessness, along with a loss of interest or pleasure in activities that were once enjoyable. Other symptoms accompanying the disease may include changes in appetite and sleep patterns, fatigue, difficulty concentrating, and thoughts of death or suicide. But mood disorders also encompass bipolar disorder that involves cycles of depressive episodes and periods of mania or hypomania. In this case, depressive episodes resemble those in MDD (with some a typicity nevertheless), while manic or hypomanic episodes involve elevated mood, increased energy, faster speech and thoughts, distractibility, decreased need for sleep and sometimes risky behavior.

On the other hand, anxiety and stress-related disorders are marked by excessive and persistent feelings of fear, worry, or apprehension that can interfere with an individual's daily life. Anxiety disorders are mainly divided into five entities:

- **Generalized Anxiety Disorder (GAD):** GAD involves chronic and excessive worry which is not focused on a specific area but concern a variety of aspects of everyday life (health, financial resources, etc.). This often leads to disturbance of sleep, difficulty concentrating and physical symptoms like restlessness, muscle tension and fatigue.

- **Panic Disorder:** People with panic disorder experience sudden and intense episodes of fear known as panic attacks appearing either with a stress trigger or apparently with no reason. These attacks are accompanied by various physical symptoms like rapid heartbeat, sweating, trembling, nausea, with the feeling of shortness of breath, fainting or choking, and a sense of impending doom.

- **Social Anxiety Disorder (Social Phobia):** This disorder is characterized by an intense fear of social situations and interactions due to the fear of being judged, rejected, or embarrassed. Individuals may go to great lengths to avoid such situations, then impacting daily life and often school or professional career.

- **Specific Phobias:** These phobias involve an irrational fear of a particular non-harmful object or situation, such as

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heights, spiders, or flying. The fear is excessive and often leads to avoidance behavior.

- **Obsessive-Compulsive Disorder (OCD):** OCD is marked by unwanted persistent thoughts (obsessions) and repetitive behaviors or mental acts (compulsions) performed to alleviate the distress caused by these thoughts. These obsessions and compulsions are time consuming and impact the daily life of people with OCD. Common obsessions include fears of contamination or harm.

Recently, trauma and stressor-related disorders have been moved from the category of anxiety disorders to a specific category of mental illnesses including two main entities:

- **Post-Traumatic Stress Disorder (PTSD):** PTSD occurs following direct exposure to a traumatic event, which corresponds to a severe stressor (personal death threat, actual or threatened serious injury, actual or threatened sexual violence) or indirect exposure (witnessing the trauma, learning that a relative was exposed to a trauma, indirect exposure to aversive details of the trauma). It involves symptoms such as intrusive memories, nightmares, flashbacks associated with emotional distress; avoidance of stimuli constituting trauma-reminders; heightened arousal with irritability and hypervigilance; negative alterations in cognition and mood.

- **Acute Stress Disorder (ASD):** ASD has the same diagnostic criteria as PTSD but occurs within a month of exposure to the stressor. It may, or may not, lead to PTSD.

Mood and anxiety disorders are prevalent and can have a profound impact on an individual's quality of life. They often co-occur or share similar underlying mechanisms [5]. In Western countries during the 20th century, public awareness and policy towards mental illnesses have improved. Although social acceptance of these illnesses is still difficult, with a significant stigma attached to those affected, there is simultaneously a raising greater expectation for discovering of new effective therapeutics. Treatment against these disorders typically involves medication [6] and psychotherapy such as cognitive-behavioral therapy [7] or Eye-Movement Desensitization Reprocessing therapy [8]. Yet, despite all efforts, the reported benefits from psychological treatments remain rather small [9,10,11]. In addition, as the diagnostic criteria for mood and anxiety disorders are numerous, each clinical entity is heterogeneous and brings together different clinical situations. The general lack of an actionable understanding of disease pathophysiology together with the scarcity of reliable biomarkers limits clinical interventions and prevents a personalized therapeutic approach. Early intervention and a comprehensive approach that considers together biological and psychological factors are essential for future effective management and better success in recovery. Let us now describe where interactions between biological and psychological factors take place.

Neurotransmitter Imbalance

Our understanding of the neurobiology of mood and anxiety disorders was greatly exacerbated by the serendipitous discovery of the antidepressant effects of some drugs that were not initially designed to enhance the levels of brain monoamines [for a review see 12]. A link between lowered serotonin's level and depression was first suggested by the English psychiatrist Alec Coppen in the late 1960s [13] and then widely publicized with the advent of the Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants [14]. However, one should keep in mind the fact that depression results from abnormalities in brain level of serotonin (the so-called serotonin hypothesis) is essentially due to the effectiveness of these drugs which increase the synaptic level of serotonin and not by direct evidence of low serotonin levels in the brain [15]. Since then, the neurotransmitter systems of serotonin, dopamine, and norepinephrine have been implicated in depression and anxiety. Dopamine and norepinephrine are known to be involved in certain dimensions of depression that are poorly targeted by SSRIs: dopamine dysregulation contributes to anhedonia, a reduced ability to experience pleasure, and implicates dysfunction within the corticostriatal circuits, a core feature of depression [16], while norepinephrine irregularities underlie the hyperarousal seen in anxiety disorders [17].

More recently, the imbalance between GABA, the brain's primary inhibitory neurotransmitter in mature neural circuits, and glutamate, the major excitatory neurotransmitter of the brain, has been highlighted by the launch of new antidepressants targeting these neurotransmissions (brexanolone for GABA and esketamine for glutamate) [18,19].

In addition, there is abundant evidence that patients suffering from depression display a chronic low-grade inflammatory state, evidenced by elevated pro-inflammatory blood markers [20]. It has been shown in animals that the neuroinflammatory state can interfere with glutamatergic signaling via the secretion of pro-inflammatory molecules by immune cells in the brain [21]. However, the use of new therapeutics [22] such as immunotherapeutics (*e.g.*, anti-inflammatory properties including inhibitors of cyclo-oxygenase 2, minocycline, omega-3 fatty acids and cytokine-targeted brain-sensitive therapies) are promising but are not yet currently used in routine care.

Finally, a major site for production of brain-sensitive molecules is the gastrointestinal tract in which dietary components are chemically transformed by the microbiota and gut-derived metabolites. These compounds are disseminated to all organs, including the brain [23]. At least in rodents, the gut microbiota has been clearly described to impact various behaviors [24], but the gut microbiome seems also capable to act on human brain functioning [25], where it modulates neurotransmitter production [26,27]. Similarly, although very promising, this approach has not yet led to recommendations for routine care in the treatment of affective disorders.

Neural Pathways and Related Brain Regions

Traditionally, the common 'biological' foresight of psychiatric illness has highlighted cellular and molecular mechanisms that were considered to be putative therapeutic targets. However, the numerous advances in Neuroscience and rapid technological progresses have challenged this traditional concept leading to a new emerging vision that considers the need of multi-scale approaches (overlapping cell types, circuits, and brain areas). Moreover, understanding brain circuit dysfunctions can only be achieved in interaction with environmental cues and their interplay with internal state leading to a multi-space dimension for comprehensive understanding and treatment of mental disorders. Only then will it be possible to unify the symptoms and perhaps to redefine the mental disorder affecting the patient (based on potential biomarkers). The intricate interplay between various brain cell types, neural circuits and brain regions plays a pivotal role in the etiology of depression, mania and anxiety [28]. The dysfunction might originate across multiple brain areas, circuits and/or cell types as described below. Yet, the most

concerned brain areas include the medial prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala that are key players in the emotional processing [22,29]. Overactivity of the amygdala, responsible for processing threat-related stimuli, has been linked to heightened anxiety responses. Conversely, alterations in the prefrontal cortex's functioning disrupt emotion regulation, potentially leading to depressive symptoms [5]. Moreover, areas such as the dorsal raphe nucleus, ventral tegmental area, ventral striatum, and locus coeruleus which are at the origin of monoaminergic projections in the brain complete the circuitry involved in affective disorders.

During periods of mood or anxiety disorders, the brain affects many systems of the organism to increase survival and ensure homeostasis, especially of the immune system. Experimental research has revealed the complex network of neurons, neurotransmitters, and hormonal signals by which the brain sends command to the whole body to adaptively respond to perceived threats or stressors. One of the most important results showed that patients with depression had dysfunction of the hypothalamic-pituitary-adrenal axis (HPA axis), with an increase in salivary and serum cortisol [30].

But the brain-body communication is not unidirectional starting from the brain and ending to the body. The actual processes are much more intricate and involve a bidirectional pathway with a route from the body to the brain as well, as initially conceptualized a century ago by Lange and James [31]. According to the existence of such feedback loop, a natural response to stress or perceived threats by the body would be detected by the brain. The existence of such bottom-up pathway named interoception, *i.e.,* the continuous perception by the brain of internal body signals, was recently demonstrated experimentally by showing how a worried body - induced by modifications of the heart rate - communicates to the brain, and how this communication in turn, controls emotional behaviors [32]. This study demonstrates the power of interoception in triggering or alleviating anxiety according to the nature of the internal signals perceive by the brain. To achieve this effect, interoception send cues first to the brainstem and then to the posterior insular cortex known to trigger anxiety-related behaviors [32].

Moreover, in the last decade, the vagus nerve was revealed as a key player in this bidirectional pathway: it is responsible of an immune reflex [33] by receiving inflammatory signals, such as an elevated blood level of pro-inflammatory cytokine IL1b via afferent fibres and in return modulates the function of immune organs such as the spleen via parasympathetic efferent fibres. Collectively, the recent studies bring insights into the notion of the embodied brain and raise new questions and open up new areas for research and clinical treatment which, in order to act on the brain, decide first to influence the body.

Hormonal Factors

The HPA axis and its release of cortisol are intimately connected to the stress response and subsequent development of depression and anxiety [34]. Thus, prolonged exposure to stressors or the accumulation of different stress factors can dysregulate the HPA axis. This dysregulation leads to cortisol hypersecretion and alterations in its negative feedback loop [35]: some patients suffering from depression have persistently high levels of cortisol throughout the day (whereas this level falls after a morning peak under normal conditions) and their HPA axis no longer responds to the usual stimuli, with no inhibition of this axis following exposure to glucocorticoids [36]. Excessive cortisol release, in turn, influences neurotransmitter systems, reduces the degree of adult neurogenesis in the dentate gyrus of the hippocampus [37], and contributes to the persistent mood disturbances seen in these disorders. Moreover, since the glucocorticoid immunomodulatory effects are widespread, complex, and multifaceted, they target nearly all cell types and functions of immune systems [38]. In the context of chronic stress and depression, the pro-inflammatory effects of glucocorticoids may surpass their anti-inflammatory effects [39].

Today, mounting clinical and preclinical evidence support the assumption that the main players in brain immunity, as well as blood-borne inflammatory cues, play major role in the pathophysiological cascade leading to mood disorders [40]. This strong involvement of immune dysregulation in affective disorders could partly explain the predominance of depressive and anxiety disorders among women. Female sex hormones, in particular 17b-estradiol, have a direct effect on immune responses and inflammation, which could explain the greater vulnerability of women [41].

Genetic and Epigenetic Influences

As described above, mood and anxiety disorders result from a complex interplay (*i.e.*, maladaptation) between an individual and his environment. Genetic factors contribute to a person's susceptibility to developing a mood disorder, while epigenetic factors refer to changes in gene expression in response to environmental influences, but that do not involve alterations to the underlying DNA sequence. Certain gene variants related to neurotransmitter metabolism, stress response, and neural plasticity have been associated with increased vulnerability [42]. However, the heritability of mood and anxiety disorders – that is the part due to genetic variation in developing these diseases- is relatively low and is estimated around 40% [43].

Epigenetic changes can affect how genes related to mood regulation are turned ‘on’ or ‘off’, potentially leading to long-lasting effects on brain function [44,45]. Chronic stress or trauma, for instance, may induce epigenetic changes that disrupt the balance of mood-related neurotransmitters and increase the risk of mood disorders [46] or stressor-related disorders such as PTSD [47]. In particular, many translational data exist on the impact of early-life trauma on epigenetic changes in genes involved in the HPA axis and neuroplasticity [48]. Interestingly, epigenetic factors also provide a potential bridge between genetic predisposition and environmental influences. A subject with a genetic vulnerability to a mood disorder might be more likely to develop the disorder if they experience epigenetic changes triggered by stressful life events [49]. Therefore, understanding the interactions between genetic and epigenetic factors is critical for gaining new insights into the underlying mechanisms of mood and anxiety disorders. It can guide the development of treatment approaches that target specific genetic and epigenetic vulnerabilities, thus opening a new era of personalized treatment for mood and anxiety disorders. However, the field of epigenetics and its role in mental disorders is still evolving, and more research is needed to fully comprehend these intricate relationships.

According to the current state of evidence-based knowledge, let us describe now how mood and anxiety disorders, considered as a dysbalanced dynamic system involving genetic, epigenetic, environmental and stress vulnerabilities, initiate a cascade of neurobiological events that lead ultimately to functional and structural plasticity, for better or worse.

Neuroplasticity and Structural Changes

Functional and structural plasticity (collectively known as neuroplasticity) are concepts related to the brain's ability to adapt and reorganize in response to experiences and environmental factors. More precisely, functional plasticity refers to the brain's ability to reconfiguring its neural circuits to compensate for damage or changes in function. This feature can be implicated in the pathophysiology of mood and anxiety disorders since it might involve the strengthening or weakening of existing connections between neurons or between neurons and non-neuronal brain cells. In line with this, one of the most intriguing questions nowadays consists in deciphering whether mood and anxiety-related behaviors rely on common or distinct neural circuits and if peculiar neural activity patterns could predict future behavior and/or vulnerability to mood and anxiety disorders.

Recently, the use of rapidly (within few hours) acting antidepressant therapeutics, that either encompass anesthetics (*e.g.*, ketamine, esketamine) and hallucinogens (*e.g.*, psilocybin, LSD or MDMA) have brought about a paradigm shift. These molecules have highlighted the central role of neuroplasticity and neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) in the recovery of patients suffering from affective disorders, as their therapeutic effect is linked to rapid stimulation of neuroplasticity phenomena [50,51]. In rodents, anxio-depressive symptoms induced by chronic stress are correlated with a reduction in synaptic connections and dendrite branching in the prefrontal cortex and this phenomenon is rescued by antidepressant drugs [52]. In humans, the most robust parameter associated with the diagnosis of affective or anxiety and stressor-related disorders is currently the decrease in hippocampal volume estimated by Magnetic Resonance Imaging (MRI). Hippocampal volume has been shown to be decreased in patients with depression [53,54], PTSD [55], panic disorder [56] and social phobia [57]. In depression, this decrease correlates with the duration of untreated illness [58].

Although neuroplasticity and restoring the functionality of certain circuits is essential, maintaining the therapeutic effects of the fast-acting antidepressants probably relies on additional mechanisms for remodeling brain circuitry, with stimulation of adult neurogenesis [59], particularly in the hippocampus [60, 61], as classical antidepressant drugs do [62].

Research into understanding the mechanisms involved in disrupting the neuroplasticity, leading to altered neural circuitry and emotional dysregulation and their relationships to mood and anxiety disorders is ongoing and holds promise for the development of more effective and personalized treatments.

Conclusions

Mood, anxiety and stressor-related disorders are the very expression of the human condition, as philosophy teaches us. Are they resulting from a ‘sad passion’ in the ethical way of Spinoza? The product of a concept in the way of Kierkegaard with his notion of ‘anguish’? Or just the expression of an existentialist symptom following Sartre's ideas expressed in ‘Nausea’? The elucidation of the neuroscientific underpinnings of depression and anxiety disorders has provided a deeper understanding of the complex interplay between neural circuits, neurotransmitters, structural/functional changes, hormones, and genetic/epigenetic influences. While this review provides a rather limited overview, it is crucial to note that these mental disorders are inherently multifactorial, and individual variability in their manifestations persists. The combination of genetic predisposition, biological processes such as adult neurogenesis, cognitive patterns, and environmental influences all contribute to an individual's risk of developing affective disorders.

The insights gleaned from Neuroscience not only enhance our comprehension of these disorders but also pave the way for the development of more targeted and effective interventions, offering hope for improved treatment strategies and a brighter future for those who suffer from such disabling conditions. After all, let us not forget that Sisyphus never showed signs of despair thought Hades punished him by forcing him to roll an immense boulder up a hill only for it to roll back down every time. Current data shows that the determinants of an individual's stress response are complex and that resilience mechanisms exist, enabling us to explore new therapeutic avenues. As Albert Camus said, "one must imagine Sisyphus happy".

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