Review

A multiscale psychopathological-psychophysiological nexus in anxiety-related pathways

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Abstract

This review explores the intricate psychopathological and psychophysiological connections underlying anxiety-related behavior through a multiscale neuroscience perspective. Anxiety is conceptualized as arising from dynamic interactions among neural circuits, metabolic processes, and neuroendocrine systems that regulate stress and threat responses in both adaptive and maladaptive manners, thereby influencing vulnerability to psychopathology. Central to this framework is the bidirectional coupling of hypothalamic–pituitary–adrenal (HPA) axis activity with amygdala–hippocampal circuitry within forebrain threat-processing pathways, alongside modulation by the behavioral inhibition system. Dysregulation across these interacting systems provides a mechanistic foundation for the cognitive and behavioral manifestations of anxiety-related disorders.

Keywords: psychopathology, psychophysiology, amygdala, anxiety disorder, emotional disorders, regulation, fear responses, stress hormones, motivational system, behavioral inhibition system

1. Introduction

The psychological and behavioral aspects of anxiety arise from the dynamic interplay of multiscale brain interactions that generate emotional experiences while interfacing with cognitive processes. These interactions substantially shape behavioral intentions (Fowles, 1988; Harle et al. 2013) though the latter more directly addresses related affective influences on decision-making. Individual multiscale states are likely to evolve converging on complex neural dynamics of emotions that need to be conceptualized and consciously linked to the multicomponent of cognitive processes from which they emerge as adaptive responses in anticipation of stimuli that threaten to disturb homeostasis (Almada et al., 2013; Edelman et al., 2011; Pape & Pare, 2010; Davidson, 2003). The brain mechanism of affect underlying perception and cognitive appraisal of a situation is likely to activate specific brain circuits that instigate to multiscale experience related to the behavioral responses associated with fear and anxiety (Damasio, 2000; Panksepp 1998). Collectively, these mental representations of the interpreted context on the subjective quality of multiscale states are an essential contributor to future emotional and behavioral tendencies (Heim et al., 2008; Tononi, 2005). This behavioral experience accompanies spontaneous physiological and emotional reactions leading to anxiety psychopathology.

Steimer (2002) identified these reactions associated with emotions ultimately facilitate adaptive responses to environmental challenges and boost memory presentation, to a certain extent enabling the famous "fight or flight" reaction. The human brain and its context-dependent response functions, including cross-level integration of signaling structures and circulating hormones, are sophisticated and flexible. The study of Raz et al. (2012) examines emotions emerging from the neurodynamics of many interacting brain systems, like how neurons behave in relations to emotions can have a substantial influence on cognitive processes and impact different systems that have specialized functions in doing the body works (Pessoa et al., 2012; Cacha & Poznanski, 2011). In this intriguing reciprocal connection underlying a psychophysiological condition, emotional processing in the brain transmits to bodily changes associated with emotion-specific expression,

cognition, and motivated behavior once dysregulated by GABAergic activity implicates neural pathways that appear I to be involved in anxiety psychopathology (Cacha & Poznanski, 2022).

In essence, anxiety reflects an adaptive threat-detection system that turns maladaptive when regulatory mechanisms (e.g., GABAergic modulation, prefrontal control) fail, producing persistent emotional and behavioral patterns. This integrates multiscale neural dynamics, cognitive appraisal, and physiological output, balancing protection, and pathology.

2. Psychophysiological and behavioral responses in anxiety

The limbic system comprises interconnected brain regions that support flexible emotional processing, though the classical model has limitations (LeDoux, 2000). It forms the core "emotional brain," integrating subcortical structures with the cerebral cortex for affective responses (Dalgleish, 2004). The amygdala, adjacent to the hippocampus and linked to other limbic components, is central to emotion. It processes fear-related facial expressions, detects anxiety cues, and forms/consolidates fear- and anxiety-related memories via rapid subcortical pathways for threat detection and hippocampal interactions for contextual learning (Hennion et al., 2015; Monti & Meletti, 2015). In anxiety disorders, dysregulation often manifesting as heightened amygdala reactivity, altered connectivity with the hippocampus and prefrontal regions, and impaired regulation, drives excessive emotional reactivity, persistent fear, and maladaptive threat processing.

Alternatively, the amygdala may register emotional stimuli and initiate coordinated physiological and behavioral responses that underlie defensive reactions (Salzman & Fusi, 2010; Delgado et al., 2008). Some studies have shown, using functional magnetic resonance imaging (fMRI), that these brain regions where the amygdala as being directly responsible for immediate reaction associated with conditioned fear, become active when experiencing anxiety (Damsa et al., 2009; Kim et al., 2012) which generally helped to shed light on the underlying neurobiological causes of anxiety (Del Casale et al., 2013; Paulus, 2008).

The limbic system attends a variety of functions. In addition to its involvement in metabolism, it controls the physical and psychological responses to environmental stimuli, especially those with emotional content (Hakamata et al., 2017; Bota et al., 2015). Together with the hypothalamus, the amygdala produces autonomic components of feelings and is responsible for mediating all emotional responses and influence homeostatic mechanisms and neuroendocrine signaling (Tovote et al., 2015).

Conversely, the close association between the amygdala and hippocampus provides complimentary action on emotionally salient stimuli and sub-optimal stress-related information, which generates responses through the hypothalamic-pituitary-adrenal (HPA) and other effectors systems (Lebow & Chen, 2016). In several imaging studies, the amygdala is found to mediate emotional reactions that modulate fear and anxiety behavior (Feinstein et al., 2011; Davis & Whalen, 2001). With its role as center for emotion, the hippocampus likewise plays an essential role in the formation of new memories and expression of adaptive emotional behaviors. The critical function of fear and anxiety acted as a signal of threat or motivational conflict, and thus triggers appropriate adaptive responses. (Sheppes et al., 2015) underscore that anxiety is a generalized response to an unknown threat or internal conflict.

In contrast, fear is focused on known external danger, which implies a different mechanism of the neural circuit (Mobbs et al., 2015). This response is likely to be mediated by a network of subcortical structures centered on the amygdala. To reiterate, the amygdala contributes to emotional arousal processing and is specifically involved in memory processes and motivation. Consistent with this view, some ablation and fear extinction studies showed that the amygdala is directly responsible for responding to threats that contribute to feelings of anxiety (Davis & Whalen, 2001; LeDoux, 2000). By the same intention, they found that patients with diminished feelings following amygdala damage may reflect the elimination of the indirect consequences of amygdala activity on feelings without increasing their negative impact (Buckholtz & Meyer-Lindenberg, 2012; Feinstein et al., 2011).

Another comparable investigation of Feinstein et al. (2013) inferred that a healthy amygdala might well usually serve to inhibit panic. In another empirical observation suggested that hyperactive amygdala can result in dramatic changes in emotional responses such as fear and anxiety responses (Kim et al., 2012). These findings presumably indicate enormous evidence that the amygdala plays an essential role in processing emotions and anxiety states. However, some studies referred to patients with amygdala damage still can feel

fear, panic, and express pain (Anderson & Phelps, 2002; Feinnstein et al. 2016). From the perspective of this empirical result, numerous experimental paradigms put forward the process by which the subjects modify the expression, the experience, and the physiology of their emotions, as a form of cognitive change characterized by adjusting the meaning of an emotional stimulus (Shin et al., 2005; Etkin et al., 2004; Gross, 1998). According to these experimental studies, which endeavored to apply emotion regulation strategies have made explicit that subjects can modify the behavioral expression, experience, and the bodily processes of their emotions (Blalock et al., 2016; Sheppes et al., 2014; Gross et al., 2006).

In another study, LeDoux (2015) stressed, the amygdala is an essential part of the circuit that allows the brain to detect and respond to threats, but it is not necessary to feel fear. He added that once learned, and the emotional and behavioral response occurs unconsciously and automatically. Indeed, embedded within this experience shifts, the emotional value of a stimulus is modified. The subject is expected to more automatic responses to match the newly acquired stimulus value (Kehagia, 2010; Broomfield & Turpin, 2005). In this view, psychophysiological, cognitive, and behavioral responses may simultaneously form the experience of emotion (Kassam & Mendes, 2013). Specific limbic system structures, the hypothalamus, amygdala, and the hippocampus, deals with the basic drives, emotions, motivations, and memory that can have a substantial influence on the cognitive process (Harle et al., 2013; Proudfit et al., 2013). These regions work in concert to both generate and modulate fear responses to imminent and identifiable threats (Shin & Liberson, 2010; Panksepp, 2005), where the amygdala and the hippocampus carry out synergistically to form long-term memories of significant emotional events.

There are many processes associated with the limbic system. Still, the system is most frequently linked to emotion, believed to involve such cognitive processes which in turn has to do with the role of a conscious effort to control innate behavior thought and feeling (Ochsner & Gross, 2005; Proverbio et al., 2011; Harle et al., 2013). The essence of this point suggests anxiety response starts in the amygdala (Stein et al., 2007) and dorsal anterior cingulate cortex (dACC) process aversive signals and send output to the hypothalamus, basal ganglia, and brainstem to produce defensive behaviors (Buckholtz & Meyer-Lindenberg, 2012; Lee, et al., 2013). Supplementary to this study are the inquiries making impressive claims that, although it is held that the limbic system and in particular the amygdala because they have been identified with the highest density of neuropeptides that influence the activity of the brain and the body in specific ways (Pape, 2010; Dong et al., 2001). The investigation addressed that this mixture of neurotransmitters called neuropeptides travels throughout the body and the brain to support the experience of emotion through body-brain interactions (Ludwig & Leng, 2006). Neuropeptides presumably enhance the perception of multisensory signals, and in the case of threats, the signals are suggested to reach a threshold that triggers a fear response.

3. The hypothalamic-pituitary-adrenal axis and cortisol connection

The amygdala's reciprocal connections with multiple cortical and subcortical regions exhibit high levels of neural activity associated with emotion generation and regulation. These interconnected networks contribute to psychophysiological responses and may underlie various forms of anxiety-related psychopathology (Buckholtz & Meyer-Lindenberg, 2012). The amygdala responds to a wide range of emotionally salient stimuli and plays a central role in emotional memory, appraisal of mental states, and automatic processes such as threat detection (Tovote et al., 2015; Damasio et al., 2000). Given its involvement in processing emotionally charged information, fear responses are closely linked to amygdala functioning (Van den Stock et al., 2011). Evidence further suggests that damage to or dysfunction of the amygdala disrupts the brain's alarm system, impairing the ability to recognize and respond appropriately to danger (Feinstein et al., 2011).

The brain serves as the central organ of the anxiety response, as it evaluates environmental stimuli to determine what is potentially threatening and therefore stressful (McEwen, 2007). It coordinates both behavioral and physiological reactions to perceived stressors and shapes emotional responses based on stored knowledge and prior experience. The hippocampus and amygdala play key regulatory roles in modulating the hypothalamic–pituitary–adrenal (HPA) axis, which mediates the fight-or-flight response (Heim et al., 2008). The hypothalamus, in turn, communicates with the rest of the body through the autonomic nervous system, reallocating energy resources to support adaptive survival responses (Godoy et al., 2018). Stress activation triggers the HPA axis, a major neuroendocrine system responsible for regulating central and peripheral homeostatic

adaptations to anxiety (Freberg, 2015; Bale & Vale, 2004). Through its regulation of hormonal secretion and physiological arousal, the HPA axis plays a critical role in coordinating neuroendocrine and behavioral processes involved in fear and anxiety (Gray & Bingaman, 1996).

When a threat is perceived, the body initiates a coordinated stress response by releasing hormones into the bloodstream. These biochemical messengers circulate systemically and activate physiological processes associated with anxiety. The response begins in the hypothalamus, which secretes corticotropin-releasing hormone (CRH). The CRH stimulates the anterior pituitary gland to synthesize and release adrenocorticotropic hormone (ACTH), thereby sustaining the body's capacity to cope with the stressor until homeostasis is restored (Aguilera, 2011; Shin & Liberzon, 2010). The ACTH enters the bloodstream and targets receptors in the adrenal cortex, prompting the secretion of cortisol. Often referred to as the primary "stress hormone," cortisol mobilizes energy by increasing blood glucose availability, directing metabolic resources to essential tissues and muscles, and modulating inflammatory responses (Cook, 2002). Circulating cortisol levels serve as a key biomarker of stress reactivity. Importantly, the hypothalamic–pituitary–adrenal (HPA) axis operates through a negative feedback mechanism. Elevated cortisol concentrations inhibit further release of CRH from the hypothalamus and ACTH from the pituitary gland, thereby preventing excessive hormonal activation. As part of this adaptive process, hormonal levels fluctuate in proportion to perceived threat intensity; higher stress exposure is generally associated with increased cortisol secretion (Ebrecht et al., 2004; Mavoungou et al., 2005).

As cortisol levels rise, circulating ACTH concentrations decline due to the negative feedback regulation of the HPA axis. Cortisol represents the primary end product of HPA axis activation, alongside other stress-related mediators such as norepinephrine and epinephrine, which collectively contribute to the body's inflammatory and autonomic responses. Cortisol, a major glucocorticoid hormone, performs essential physiological functions, including the regulation of metabolism, immune activity, and overall homeostasis (Peters et al., 2017). Elevated cortisol levels place the body in a heightened state of arousal, which may intensify affective experiences and contribute to feelings of hyperactivation or overwhelm (Knezevic et al., 2023). To sustain the psychophysiological stress response, cortisol mobilizes energy reserves by stimulating gluconeogenesis in the liver, thereby increasing glucose availability in the bloodstream. It also enhances the brain's utilization of glucose and promotes the availability of substrates involved in tissue repair, while modulating inflammatory processes (Otmishi et al., 2008; Gunnar & Quevedo, 2007; McEwen, 2007).

4. The behavioral inhibitory system in anxiety-related behavior

Appetitive motivational system is a reward seeking behavior that avoids situations where emotional responses are expected to be painful. The inhibition of appetitive motivational behavior produces anxiety which is referred to as the activity of the behavioral inhibition system (BIS) (Gray & McNaughton 2003). Neuropsychology of anxiety in which individuals with a more reactive behavioral inhibitory system are prone to the effects of aversive stimuli leading to anxiety (Gray, 1982). Moreover, should the BIS malfunction to the degree that it is activated in the absence of external stimuli, the emotional disturbance is implicated in anxiety psychopathy without any environmental explanation. A Proposed metacognitive mechanism of the BIS is shown in **Fig. 1**.

The CNS coordinates the functions of all body systems and organs, extending to its fundamental functional unit, the neuron. Behavior, emotion, and other essential features of human functioning arise from complex interactions across distributed neural networks. Patterns of neuronal activity associated with emotional processing contribute to central affective states such as fear and anxiety. The HPA axis integrates neuroendocrine processes and regulates the release of hormones and neurotransmitters, including γ-aminobutyric acid (GABA), within stress- and anxiety-related brain circuits (Crestani et al., 1999; Bowery, 2010; Roman et al., 2017). Neurotransmitters released from presynaptic axon terminals into the synaptic cleft bind to specific receptors and may exert either excitatory or inhibitory effects. Within the CNS, glutamate serves as the principal excitatory neurotransmitter, whereas GABA functions as the primary inhibitory neurotransmitter (Pasani et al., 2014; Compagnone & Mellon, 2002). GABA, a naturally occurring amino acid in the brain, reduces neuronal excitability by inhibiting synaptic transmission and slowing the flow of neural information, thereby dampening overall nervous system activity (Compagnone & Mellon, 2002). In

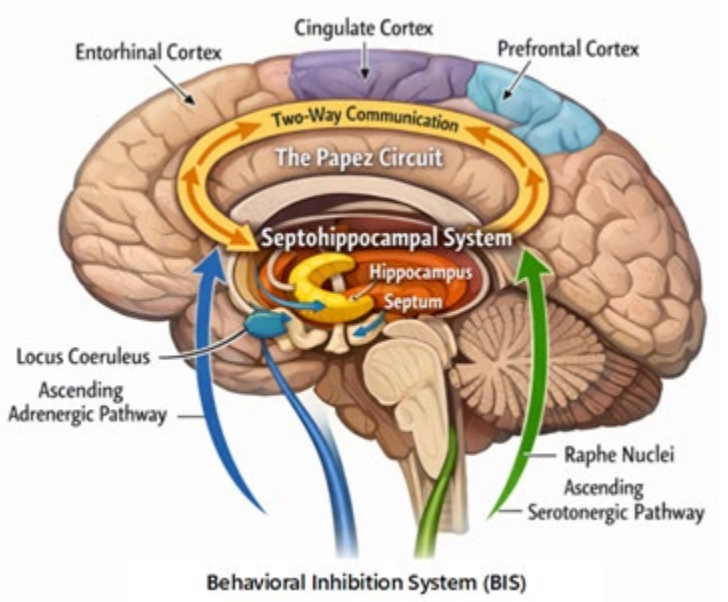

Figure 1 Illustrates the proposed mechanism of the Behavioral Inhibition System (BIS) as a septo-hippocampal–centered network responsible for detecting conflict, novelty, and potential threat and initiating behavioral inhibition. This core system is closely interconnected with the Papez-loop, supporting the integration of emotional processing and memory. Ascending noradrenergic pathways from the locus coeruleus and serotonergic pathways from the raphe nuclei modulate arousal, attention, and behavioral restraint. Bidirectional connections with the entorhinal, prefrontal, and cingulate cortices enable cognitive appraisal, emotional regulation, and executive control to shape inhibitory responses. Collectively, these interactions support adaptive behavior under conditions of uncertainty and risk.

states of anxiety, hyperactivation of fear-related circuits—particularly those involving the lateral and central nuclei of the amygdala—contributes to heightened emotional and physiological reactivity.

The regulation of GABA neurotransmission within the central nucleus of the amygdala plays a critical role in synaptic inhibition (Jie et al., 2018). GABAergic interneurons modulate neuronal excitability by influencing synaptic positioning and inhibitory signaling. Upon activation, these interneurons transmit inhibitory signals that are strongly implicated in the regulation of anxiety (Nuss, 2015). When GABA binds to GABAA_AA receptors—ligand-gated chloride ion channels—it typically results in chloride influx into the neuron. This influx leads to hyperpolarization of the postsynaptic membrane, thereby decreasing neuronal excitability and inhibiting nerve transmission. Notably, GABA is not the only modulator of these receptor channels; other endogenous and pharmacological agents can also influence their opening and conductance. The underlying mechanism involves dampening excessive neural signaling within the amygdala, particularly in circuits associated with fear and anxiety (Löw et al., 2000). By reducing neuronal hyperactivity, GABA helps prevent the generation of inappropriate or exaggerated emotional responses. Empirical studies consistently indicate that increased GABA release is associated with reduced anxiety, reflecting its fundamental inhibitory function.

Endogenous GABA contributes to the regulation of fear responses, particularly when excitatory neuronal activity becomes excessive. Given its central role in modulating behavior, cognition, and emotional regulation, GABAergic inhibitory interneurons represent a significant therapeutic target in the treatment of anxiety disorders.

5. A dysfunction of the motivational system leading to anxiety psychopathology

The motivational system connects psychophysiology (how the body and brain function) with psychopathology (mental disorders). In anxiety, problems in the motivational system may occur when it is repeatedly activated by environmental stressors (Vaidyanathan et al., 2009). This suggests that anxiety disorders are not caused only by psychological factors but also by biological processes. The development of anxiety can be understood as a chain of influences. It

begins with genes and enzymes, which affect neurotransmitters in the brain. These neurochemical processes shape how the brain responds to stress and environmental cues. Over time, the interaction between biological factors and environmental experiences leads to observable emotional and behavioral symptoms (Ochsner & Gross, 2005). Therefore, anxiety reflects the combined effects of genetic, neurochemical, environmental, and psychological processes.

The amygdala plays a crucial role in emotional responses to perceived danger by sending a distress signal to the hypothalamus. This, in turn, activates the sympathetic nervous system and initiates a hormonal cascade, culminating in the release of cortisol from the adrenal cortex located atop the kidneys (Hakamata et al., 2017). Abnormal release of stress hormones by the HPA axis is associated with various risks (Dai et al., 2002), contributing not only to anxiety and depression but also affecting digestion, the immune system, mood, emotions, and energy storage and utilization, due to the complex functions of the HPA axis. Cortisol receptors are present in most body cells, influencing numerous tissues (Yaribeygi et al., 2017). The interplay between the HPA axis and anxiety disorders is evident, as tension and anxiety can disrupt healthy body functioning. Excessive cortisol release, resulting from prolonged stress response activation, can impair bodily functions. When elevated cortisol levels interact with the hypothalamus, the HPA axis reduces its activity to maintain hormonal balance (McLaughlin, 2009). In the presence of circulating hormonal factors, cortisol and other stress hormones mobilize the body's resources by increasing energy availability and reducing inflammation, particularly in response to injuries.

At the systems-level, psychophysiological changes suggest that CRH plays an important role both in the development of a functional HPA axis and is a major integrator of adaptive responses in mediating anxiety-related behavioral consequences (Sapolsky, 2000). However, the high levels of cortisol due to unrelenting anxiety can wear down the brain's ability to function appropriately, including metabolism. Cortisol has been considered one of the main culprits in the stress-anxiety connection, although it plays a fundamental role in helping one cope with threats (Stein et al., 2007). It can be enlightening to consider that anxiety disorders involve prominent disturbances of both cognitive and emotional regions deeply interwoven in the fabric of the brain that can be conceptualized as disorders of the emotional-cognitive brain (Lindquist & Barrett, 2012; Panksepp, 2005). Disturbances in how fear-inducing information is perceived and processed surges a defective pattern of thinking and leading to different psychological vulnerabilities and the emotional risks that go with it (Gray, 1982; Ledoux, 2000; Amir et al., 2003).

Anxiety is a subjective experience of discomfort in response to an actual or perceived threat via projections to the hypothalamus, visual cortex, and prefrontal cortex (Davis, 2006). The perception of the threat depends upon the anxious, as one perceives threats about self, the world, or related to the future. This threat perception elicits a psychophysiological reaction associated with rapid heartbeat, blood pressure, sweating, and an overall sense of vigilance, exacerbating the activation of the primal response of flight or fight (Cacha et al., 2019; Goldstein, 2010). In some cases, anxiety symptoms may persist even after the threat is gone. Yet, alterations in the HPA axis suggest the neurobiological basis of anxiety disorders with reported structural and functional differences that can manifest dispositional negativity across disparate psychopathologies (Cavanagh & Shackman, 2015).

Anxiety is not the same as fear, which is a response to a real or immediate threat (Davis et al., 2010; Gaynes et al., 1999). Anxiety involves the expectation of future threats, is fear-based, and may occur unexpectedly, even in the absence of real danger. Craske & Stein (2016) indicated that those with heightened sensitivity to anxiety respond to those sensations with dread and pressing urge to escape a dangerous situation. Hence, anxiety can only be understood by considering some of its cognitive traits because a primary aspect of anxiety appears to be uncertainty, which is a negative effect on self-esteem leading to insecurity (Bach & Dolan, 2012). Thus, anxiety and insecurity are both fears for abstract threats that impede the ability to mitigate its adverse impact resulting in helplessness and isolation (Paulus & Yu, 2012). A moderate amount of anxiety helps subjects think and act more effectively and is a normal emotion under stressful circumstances of threat. Thus, mild anxiety is adaptive and sustains motivation for survival. It is characterized by adaptive emotion that prepares one both physically and psychologically for coping with an adverse event that could be dangerous (Steimer, 2002).

Adapting to anxiety as the activity of the aversive system. A ‘panic attack’ reflects on the breakdown of regulation, in which there is activation of behavioral inhibitory system in the absence of environmental cues (Fowles, 1988). Although adapting is not easy, there

must be conscious efforts in part of the executive control system necessary to bring the body and mind in tune and coherence about executing a behavior—the anxious feel vulnerable and weak between threat perceptions over psychopathy. Thus, the anxious often feel a sense of uncertainty and helplessness, becoming withdrawn with a distinct need for solitude (Alexander et al., 2007; Cacha et al., 2019). It is important to note that the entire process begins with negative thoughts due to stressful events and constant threats that intensified over an extended period, escalating through, until panic attacks set in (Lazarus,1982). Intrusive thoughts build-up recurring concerns of risky situations involving threats and bring about the onset of anxiety and panic disorder. Symptoms are caused by feelings of extreme apprehension of impending doom that occur even in the absence of actual danger. Thus, it is always future-oriented, fear-based, and focused on worrying over what is about to come, and conceivably one may become excessively anxious about the need for reasonable safety precautions (Cacha et al., 2019; Wittchen et al., 2002; Brown et al., 2001). Therefore, that leads to the thinking part of anxiety, which brings dominant symptoms of worry, which suggests always planning, looking ahead, trying to control circumstances, and a stressful urge to defeat a threat (Gu et al., 2010; Kendler, 2004). In other words, when anxiety extends beyond legitimate worry in an unreasonable and disproportionate to the actual threat and this according to Fowles (1988) entails a multiscale psychopathological–psychophysiological nexus in anxiety-related pathways.

6. Conclusion

Anxiety-related behavior exists on a continuum from a natural temporary reaction to stress as a normal psychological star in psychophysiology to an abnormal state when the aversive motivational system inhibits motivated behavior to the extent of neurochemical changes resulting in psychopathology. The crux of this review was to decipher the middle ground of this continuum or the psychopathological-psychophysiological nexus. This review has focused on understanding how the HPA stress and anxiety-response pathway, and the amygdala activation contribute to the circuitry underlying adaptive or defensive and psychopathological anxiety behaviors in the amygdala that serves as the interface between emotion and cognition, and with the help of the HPA axis. In this respect, much remains to be discovered on the neurochemical mechanism attributed to GABAergic systems in brain circuits associated with to anxiety-related pathways. This could provide valuable information regarding the nexus between psychopathology and psychophysiology in multiscale neuroscience.

Conflict of Interest Statement

The author declares no conflict of interest.

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