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AN INTEGRATIVE NEUROFUNCTIONAL APPROACH FOR ANXIETY DISORDERS: SYMPTOMS, NEUROBIOLOGY AND RDOC

UN ENFOQUE NEUROFUNCIONAL INTEGRADOR PARA LOS TRASTORNOS DE ANSIEDAD: SÍNTOMAS, NEUROBIOLOGÍA Y RDOC

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An Integrative Neurofunctional Approach for Anxiety Disorders: Symptoms, Neurobiology and RDoC

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ABSTRACT

Background: Anxiety disorders are among the most prevalent mental health conditions worldwide. Although the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), provides a reliable symptom-based classification, it offers limited insight into the neurobiological mechanisms underlying symptom expression. Consequently, the integration of neuroscience into psychotherapeutic formulation remains limited. Aims: To develop an Integrative Neurofunctional Approach linking DSM-5 symptom-level criteria, neurobiology, and the Research Domain Criteria (RDoC) framework across Specific Phobia (SP), Panic Disorder (PD), Social Anxiety Disorder (SAD), and Generalized Anxiety Disorder (GAD). Method: Narrative and conceptual review synthesizing empirical evidence and theoretical perspectives from clinical psychopathology, neurobiology, and the RDoC framework. Results: DSM-5 symptom-level criteria were systematically mapped onto neural circuit dysfunctions and corresponding RDoC domains and constructs, demonstrating that anxiety disorders reflect distinct patterns of dysfunction across partially overlapping neurofunctional systems. Conclusions: The proposed Integrative Neurofunctional Approach complements categorical diagnosis by integrating DSM-5 symptomatology with neurobiology and the RDoC framework, providing a conceptual foundation for neuroscience-informed case formulation, personalized psychotherapeutic planning, and future research on the neurofunctional mechanisms underlying anxiety disorders.

***Keywords*:** anxiety disorders; DSM-5; RDoC; neurobiology; psychotherapy

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Un Enfoque Neurofuncional Integrador para los Trastornos de Ansiedad: Síntomas, Neurobiología y RDoC

RESUMEN

Antecedentes: Los trastornos de ansiedad se encuentran entre las afecciones más prevalentes. Aunque el Manual Diagnóstico y Estadístico de los Trastornos Mentales, 5ta-edición (DSM-5), proporciona una clasificación basada en síntomas, ofrece una comprensión limitada de los mecanismos neurobiológicos subyacentes. En consecuencia, la integración de la neurociencia en la formulación psicoterapéutica sigue siendo limitada. Objetivo: Desarrollar un enfoque neurofuncional integrador que vincule los criterios diagnósticos del DSM-5, la neurobiología y los Criterios de Dominio de Investigación (RDoC) en la Fobia Específica (FE), el Trastorno de Pánico (TP), el Trastorno de Ansiedad Social (TAS) y el Trastorno de Ansiedad Generalizada (TAG). Método: Revisión narrativa y conceptual que integra evidencia de la psicopatología clínica, la neurobiología y el marco RDoC. Resultados: Los criterios diagnósticos del DSM-5 se mapearon sistemáticamente con disfunciones de circuitos neuronales y el marco RDoC, demostrando que los trastornos de ansiedad reflejan patrones diferenciados de disfunción en sistemas neurofuncionales superpuestos. Conclusiones: El enfoque neurofuncional integrador complementa el diagnóstico categórico al integrar la sintomatología del DSM-5, la neurobiología y el marco RDoC, proporcionando una base conceptual para la formulación de casos basada en la neurociencia, la psicoterapia personalizada y futuras investigaciones sobre los mecanismos neurofuncionales de los trastornos de ansiedad.

***Palabras clave*:** trastornos de ansiedad; DSM-5; RDoC; neurobiología; psicoterapia

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INTRODUCTION

Anxiety disorders comprise a group of mental disorders that include Separation Anxiety Disorder, Selective Mutism, Specific Phobia (SP), Social Anxiety Disorder (SAD), Panic Disorder (PD), Agoraphobia, and Generalized Anxiety Disorder (GAD). Although clinically distinct, these disorders share core features including excessive fear, physiological hyperarousal, avoidance, and anticipation of threat (American Psychiatric Association, 2013; Craske & Stein, 2016). Anxiety disorders are among the most prevalent mental health conditions worldwide, affecting approximately 4.4 % of global population, considering SP the most common followed by PD, SAD and GAD, with a prevalence of 10.3%, 6%, 2.7% and 2.2% respectively (Bandelow & Michaelis, 2017; Javaid et al., 2023; Mental Health - Our World in Data, 2025).

Despite their clinical heterogeneity, neuroimaging studies consistently demonstrate shared dysfunctions involving the amygdala, prefrontal cortex, anterior cingulate cortex, and insula, supporting common alterations in fear processing, emotional regulation, and threat anticipation (Janiri et al., 2020; Steinhäuser et al., 2023). These findings suggest that, despite diagnostic distinctions, anxiety disorders share common patterns of neural dysregulation, particularly within fear-processing, salience, and stress-response systems (Akiki et al., 2025; Staufenbiel et al., 2013; Zorn et al., 2017).

However, despite these advances, the categorical classifications of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), do not fully capture the underlying neurobiological mechanisms of anxiety disorders. While clinically useful for diagnostic reliability, this symptom-based approach offers limited explanatory power for key phenomena such as comorbidity and clinical heterogeneity, both of which are common across anxiety disorders. (Cuthbert & Insel, 2013; Drzewiecki & Fox, 2024; Sanislow et al., 2010).

The Research Domain Criteria (RDoC) emerged as a novel, neurobiologically based dimensional framework for understanding psychopathology—not exclusive to anxiety disorders—. Its domains and constructs are inherently latent and were not designed to function as diagnostic entities, limiting their application in everyday clinical practice. This gap underscores the need for integrative approaches that link RDoC constructs with established diagnostic systems such as the DSM-5 (Cuthbert, 2022; Morris et al., 2022).

Moreover, traditional psychotherapeutic approaches have not yet fully incorporated knowledge of the neurobiology of mental disorders. Consequently, psychotherapeutic interventions remain widely applied, with limited precision regarding the specific neural circuits or processes implicated in specific symptom presentations (Rief et al., 2024; Scangos et al., 2023).

Therefore, the objective of this narrative and conceptual review is to propose an integrative neurofunctional approach that integrates DSM-5 symptomatology, neurobiology, and the RDoC framework by mapping clinical symptoms onto neural circuit dysfunctions and their corresponding RDoC domains and constructs, providing a conceptual foundation for neuroscience-informed psychotherapy.

METHODOLOGY

This study adopts a narrative and conceptual review methodology aimed at developing an translational integrative framework that connects clinical symptomatology, neurobiology and the dimensional perspective of the RDoC framework in the understanding of anxiety disorders. Unlike systematic reviews, which seek to comprehensively identify and synthesize all available evidence using predefined search strategies, this approach emphasizes the conceptual integration of representative empirical findings relevant to the objectives of the study.

The literature was selected based on its scientific relevance, methodological quality, and contribution to three complementary areas: 1) the diagnostic characteristics of anxiety disorders described in the DSM-5; 2) evidence on the neural circuits and neurobiological mechanisms underlying anxiety disorders obtained from neuroimaging, experimental, and clinical research; and 3) the domains and constructs proposed by the RDoC framework. Rather than providing an exhaustive review of the literature, the selected studies were synthesized to establish conceptual relationships between these three perspectives.

The proposed integration focuses on four of the most prevalent anxiety disorders— SP, PD, SAD and GAD—. Through this conceptual synthesis, clinical symptoms were systematically linked to underlying neural circuit dysfunctions and corresponding RDoC domains and constructs, resulting in the development of the proposed Integrative Neurofunctional Approach for anxiety disorders.

RESULTS

Clinical Overview of DSM-5 Anxiety Disorders

A summary of the DSM-5 diagnostic criteria for four of the most common anxiety disorders is presented in Table 1. These include SP, PD, SAD, and GAD.

Although each disorder is characterized by a distinct symptom profile, they differ primarily in the feared stimulus, the pattern of symptom expression, and the diagnostic duration requirements. Nevertheless, these disorders share several core features, including excessive fear or anxiety, (American Psychiatric Association, 2013; Andrews et al., 2018; Craske & Stein, 2016; Kessler et al., 2015; Pellecchia et al., 2018; Saha et al., 2021).

Table 1. DSM-5 symptom for anxiety disorders: SP, PD, SAD and GAD

Disorder	Symptom	Duration Requirement
Specific Phobia	▪ Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, injections). ▪ The phobic object or situation almost always provokes immediate fear or anxiety. ▪ The phobic object or situation is actively avoided or endured with intense fear or anxiety. ▪ The fear or anxiety is out of proportion to the actual danger posed.	≥ 6 months
Panic Disorder	▪ Recurrent unexpected panic attacks, defined as abrupt surges of intense fear or discomfort that reach a peak within minutes and include ≥4 following symptoms: ▪ Palpitations, sweating, trembling, shortness of breath, chest pain, nausea, dizziness, fear of losing control, fear of dying. ▪ At least one attack followed by ≥1 month of persistent concern or behavior change.	≥ 1 month (after at least one panic attack)
Social Anxiety Disorder	▪ Marked fear or anxiety about ≥1 social situations in which the individual is exposed to possible scrutiny by others (e.g., social interactions, being observed, performing in front of others). ▪ The individual fears that they will act in a way or show anxiety symptoms that will be negatively evaluated. ▪ Social situations are avoided or endured with intense fear.	≥ 6 months
Generalized Anxiety Disorder	▪ Excessive anxiety and worry (apprehensive expectation) occurring more days than not for at least 6 months, about a number of events or activities (e.g., work or school performance). ▪ The individual finds it difficult to control the worry. ▪ The anxiety and worry are associated with ≥3 following symptoms: restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbance).	≥ 6 months

Table 1 lists the symptoms and required duration, according to the DSM-5, for the four most prevalent anxiety disorders worldwide—SP, PD, SAD and GAD. Abbreviatures: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; SP, specific phobia; PD, panic disorder; SAD, social anxiety disorder; GAD, generalized anxiety disorder.

Neurobiology in SP, PD, SAD, and GAD

Specific Phobia

Specific phobia (SP) involves dysfunction across prefrontal-limbic circuits that support fear processing, cognitive control, emotional regulation, and salience detection. The prefrontal cortex (PFC) and its subdivisions, including the dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), ventrolateral prefrontal cortex (vlPFC), and ventromedial prefrontal cortex (vmPFC), contribute to executive control, cognitive reappraisal, working memory, emotional regulation, and environmental evaluation. Together, these regions participate in the cognitive regulation of fear and adaptive responses to threatening stimuli (Del Casale et al., 2012; Garcia, 2017; Hilbert et al., 2024; Hinze et al., 2021; Linares et al., 2012).

The orbitofrontal cortex (OFC) is involved in emotional learning, stimulus discrimination, and behavioral adaptation, whereas the insula integrates sensory, interoceptive, and autonomic information associated with fear responses. The anterior cingulate cortex (ACC) and its subdivisions, including the dorsal anterior cingulate cortex (dACC), rostral anterior cingulate cortex (rACC), and posterior cingulate cortex (PCC), contribute to attention, threat monitoring, motivation, emotional regulation, and cognitive control. The thalamus relays sensory information to the amygdala, facilitating the processing of threatening stimuli and the generation of defensive emotional responses (Álvarez-Pérez et al., 2021; Del Casale et al., 2012; Garcia, 2017; Linares et al., 2012; Oar et al., 2019).

Recent evidence further supports a circuit-based model of SP. Structural neuroimaging studies have identified accelerated brain aging affecting frontal and temporal regions, whereas functional neuroimaging has demonstrated that successful exposure therapy is associated with reduced activation of the amygdala and anterior insula. Altered functional connectivity within the salience network, particularly involving the amygdala, insula, and ACC, further suggests that abnormalities in fear processing, salience detection, and emotional regulation constitute the principal neurobiological mechanisms underlying SP (Blake et al., 2025; Fumero et al., 2022; Ipser et al., 2013; Staufenbiel et al., 2013).

Panic Disorder

Panic disorder (PD) is characterized by dysfunction across interconnected neural systems involved in threat detection, autonomic regulation, interoceptive processing, and cognitive-emotional integration. Current neurobiological models conceptualize PD as the result of network-level alterations involving prefrontal, limbic, and brainstem structures, providing a systems-level framework for understanding the sudden onset and multisystem nature of panic attacks.

The prefrontal cortex (PFC), particularly the dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC), contributes to cognitive control, emotional regulation, and top-down modulation of fear responses. Reduced activation of the dlPFC, together with structural alterations involving the dorsomedial prefrontal cortex (dmPFC) and orbitofrontal cortex (OFC), suggests impaired executive function and deficient regulation of emotional reactivity (Chen et al., 2022; Kaldewaij et al., 2019; Wang et al., 2018).

The amygdala, a central structure for fear processing, exhibits heightened activation in response to threatening stimuli, whereas the anterior insula contributes to interoceptive awareness and the perception of autonomic sensations that are frequently misinterpreted as signs of imminent danger. The fear network further comprises the hippocampus, thalamus, periaqueductal gray (PAG), and locus coeruleus (LC), which collectively participate in contextual memory, sensory relay, defensive responses, and autonomic arousal. Functional abnormalities within this network, including reduced connectivity between the PFC and amygdala and increased connectivity between the anterior cingulate cortex (ACC) and the precuneus, are associated with impaired cognitive regulation of fear and maladaptive internal monitoring (Kim et al., 2012; Sobanski & Wagner, 2017; Wang et al., 2024; Zhang et al., 2023).

Recent neuroimaging studies further support a circuit-based model of PD. Voxel-based morphometry has demonstrated gray matter reductions in the PFC and amygdala, together with increased insular volume, suggesting structural reorganization associated with chronic hyperactivation of fear-related networks. In addition, alterations in γ-aminobutyric acid (GABA) and serotonergic neurotransmission, including reduced GABA receptor binding within the PFC, may contribute to deficient inhibitory control and heightened anxiety, reinforcing the view that PD arises from dysfunction across

interconnected fear, interoceptive, and autonomic regulatory circuits (Kim et al., 2012; Lai & Wu, 2014; Wang et al., 2024; Zhang et al., 2023).

Social Anxiety Disorder

Social anxiety disorder (SAD) is characterized by dysfunction across large-scale brain networks involved in emotional processing, motivation, cognitive control, attention, and self-referential cognition. These include the emotional network (EN), motivation network (MN), cognitive control network (CCN), dorsal attention network (DAN), and default mode network (DMN), which interact to regulate emotional responses, fear processing, social evaluation, and cognitive functioning (Boehme et al., 2015; Brühl et al., 2014; Cremers & Roelofs, 2016; Marazziti et al., 2015).

Recent resting-state neuroimaging studies have demonstrated altered functional connectivity between frontal and limbic regions, particularly between the prefrontal cortex (PFC) and the amygdala, with reduced connectivity involving the dorsolateral prefrontal cortex (dlPFC) being associated with heightened emotional reactivity and impaired regulation of perceived social threats. These connectivity alterations may serve as potential biomarkers for symptom severity and treatment response in SAD (Blake et al., 2025).

The EN comprises the amygdala, bed nucleus of the stria terminalis (BNST), and insula, which collectively mediate emotion processing, anticipation of social threat, interoception, and fear learning. Alterations in γ-aminobutyric acid (GABA) metabolism, particularly within the anterior cingulate cortex (ACC) and the insula, may further contribute to emotional dysregulation.

The MN includes the ventral tegmental area (VTA), ventral and dorsal striatum, medial prefrontal cortex (mPFC), medial orbitofrontal cortex (mOFC), ACC, and dlPFC, supporting social reward processing, avoidance learning, fear conditioning, motivation, and conflict monitoring. Dysfunction within this network may impair the ability to discriminate between neutral and socially threatening stimuli. The CCN, comprising the ACC, ventromedial prefrontal cortex (vmPFC), and dlPFC, supports cognitive regulation of emotional responses, self-referential processing, and anticipation of social outcomes (Blake et al., 2025; Boehme et al., 2015; Brühl et al., 2014; Coutinho et al., 2016; Cremers & Roelofs, 2016; Kurita et al., 2023; Marazziti et al., 2015).

The DAN, including the inferior prefrontal cortex (iPFC), posterior cingulate cortex (PCC), supramarginal gyrus, and temporo-occipital cortices, mediates attention, alertness, and environmental monitoring, contributing to the hypervigilance characteristic of SAD (Brühl et al., 2014; Majerus et al., 2018; Zhang et al., 2022). Finally, DMN, connecting the mPFC, PCC, and ACC, is associated with self-referential processing and threat-related cognition, promoting the persistent negative self-evaluation and heightened sensitivity to social threat that characterize the disorder (Coutinho et al., 2016; Zidda et al., 2017).

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD), like specific phobia (SP) and social anxiety disorder (SAD), is characterized by dysfunction across prefrontal-limbic circuits involved in emotional regulation, fear processing, cognitive control, and self-referential cognition. Although these disorders share several neurobiological substrates, GAD exhibits distinctive abnormalities in functional connectivity within the prefrontal-limbic network that are associated with excessive worry and persistent anxiety.

The prefrontal cortex (PFC) and its subdivisions, including the dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), ventromedial prefrontal cortex (vmPFC), and ventrolateral prefrontal cortex (vlPFC), play complementary roles in executive control, emotional regulation, and cognitive appraisal of threat. Functional neuroimaging studies have demonstrated hypoactivation of the dlPFC and dmPFC together with hyperactivation of the vlPFC during emotional regulation tasks involving threatening stimuli. These alterations are accompanied by increased activation of the amygdala and insula, reflecting enhanced emotional reactivity and interoceptive processing (Fonzo & Etkin, 2016; Madonna et al., 2019; Michopoulos et al., 2017; Santos et al., 2019).

The ventromedial anterior cingulate cortex (vmACC) exhibits reduced functional connectivity with the vmPFC and dmPFC during amygdala hyperactivation, suggesting impaired regulation of fear inhibition, fear extinction, and avoidant behaviors. In addition, connectivity between the amygdala and the PFC, particularly involving the vlPFC and vmPFC, has been associated with excessive worry, rumination, and maladaptive mentalization in threatening contexts.

Alterations within the default mode network (DMN), especially its connectivity with prefrontal regions, further promote excessive self-referential processing and the persistence of internally generated anxious thoughts, reinforcing the chronic nature of GAD (Maron & Nutt, 2017; Yuan et al., 2023).

Research Domain Criteria

The Research Domain Criteria (RDoC), developed by the National Institute of Mental Health (NIMH), is a dimensional, transdiagnostic, and neurobiologically grounded framework for understanding psychopathology. It is organized into six functional domains comprising 25 constructs. These domains and constructs are investigated across multiple units of analysis, including genes, molecules, cells, neural circuits, physiology, behavior, self-reports, and environmental factors, providing a multidimensional approach to the study of psychopathology (About RDoC - National Institute of Mental Health (NIMH), 2025; Cuthbert & Insel, 2013; Insel et al., 2010; Kozak & Cuthbert, 2016).

By providing a dimensional and systems-based perspective, the RDoC framework facilitates the identification of core psychological and neurobiological processes that transcend traditional diagnostic categories, offering a transdiagnostic approach to understanding psychopathology.

Table 2 summarizes the principal RDoC domains, their corresponding constructs, and the brain regions most consistently associated with each functional system. Together, these functional systems provide the conceptual foundation for the integrative neurofunctional approach proposed in this review, mapping DSM-5 symptomatology, neurobiology, and RDoC domains.

Table 2. RDoC Domains, Constructs and Implicated Brain Regions

Domain	Construct	Implicated Brain Regions
Negative Valence Systems	▪ Acute Threat (“Fear”)	Amygdala (central, basolateral, lateral), periaqueductal gray, vmPFC, dACC, insula, hypothalamus, hippocampus, locus coeruleus.
	▪ Potential Threat (“Anxiety”)	Bed nucleus of the stria terminalis, hippocampus, amygdala, insula, mPFC, hypothalamus.
	▪ Sustained Threat	Amygdala, hippocampus, PFC, cingulate cortex, hypothalamus, striatum, visual cortex.
	▪ Loss	vmPFC, OFC, amygdala, ACC, insula.
	▪ Frustrative Nonreward	OFC, amygdala, striatum, hypothalamus, periaqueductal gray, septum.

Positive Valence Systems	▪ Reward Responsiveness	Ventral striatum (nucleus accumbens), OFC, vmPFC, ACC, amygdala.
	▪ Reward Learning	Ventral tegmental area, nucleus accumbens, dorsal striatum, OFC, dlPFC, ACC.
	▪ Reward Valuation	OFC, vmPFC, ACC, dorsal striatum.
Cognitive Systems	▪ Attention	Dorsal attention network (e.g., intraparietal sulcus, frontal eye fields), ACC, dlPFC.
	▪ Perception	Primary sensory cortices (visual, auditory, somatosensory), association cortices.
	▪ Declarative Memory	Hippocampus, medial temporal lobe, PFC.
	▪ Language	Broca's area, Wernicke's area, angular gyrus, superior temporal gyrus.
	▪ Cognitive Control	dlPFC, ACC, parietal cortex.
	▪ Working Memory	dlPFC, parietal cortex, hippocampus.
Social Processes	▪ Affiliation and Attachment	Ventral striatum, amygdala, OFC, vmPFC, hypothalamus.
	▪ Social Communication	Fusiform face area, superior temporal sulcus, inferior frontal gyrus, amygdala, insula, ACC.
	▪ Perception and Understanding of Self	mPFC, posterior cingulate cortex, precuneus.
	▪ Perception and Understanding of Others	Temporoparietal junction, mPFC, superior temporal sulcus, amygdala.
Arousal & Regulatory Systems	▪ Arousal	Locus coeruleus, thalamus, hypothalamus, brainstem reticular formation.
	▪ Circadian Rhythms	Suprachiasmatic nucleus, pineal gland, hypothalamus.
	▪ Sleep-Wakefulness	Brainstem (reticular activating system), thalamus, hypothalamus.
Sensorimotor Systems	▪ Motor Actions	Primary motor cortex, supplementary motor area, premotor cortex, basal ganglia, cerebellum.
	▪ Agency and Ownership	Inferior parietal lobule, temporoparietal junction, supplementary motor area, cerebellum.
	▪ Sensorimotor Habits	Sensorimotor cortex, basal ganglia (putamen, caudate), cerebellum.
	▪ Innate Motor Patterns	Brainstem nuclei, spinal cord circuits, cerebellum.

Table 2 links the brain regions implicated in each construct within the six RDoC domains. RDoC propose a dimensional, transdiagnostic, and neurobiologically grounded framework for understanding psychopathology, organized into six major functional domains, each composed of specific constructs. Each of these constructs is studied across multiple units of analysis, including neural circuits.
Abbreviatures: RDoC, Research Domains Criteria; vmPFC, Ventromedial Prefrontal Cortex; dACC, Dorsal Anterior Cingulate Cortex; mPFC, Medial Prefrontal Cortex; PFC, Prefrontal Cortex; OFC, Orbitofrontal Cortex; ACC, Anterior Cingulate Cortex; dlPFC, Dorsolateral Prefrontal Cortex.

Integrative Neurofunctional Approach for Anxiety Disorders

The Integrative Neurofunctional Approach links DSM-5 diagnostic criteria with their underlying neurobiological mechanisms and corresponding RDoC domains and constructs, bridging descriptive psychopathology with the functional organization of the brain. This framework provides a dimensional

understanding of anxiety disorders. The proposed mappings for SP, PD, SAD, and GAD are described below, summarized in table 3 and visually complementing figure 1.

SP

Specific Phobia is characterized by the convergence of neural circuits involved in rapid threat detection, emotional regulation, and cognitive control. Marked fear or anxiety toward a specific object or situation is supported by hyperactivation of the amygdala, ACC, insula, OFC, and thalamus. Within the RDoC framework, these regions primarily correspond to the Acute Threat (Fear) construct of the Negative Valence Systems domain, responsible for the rapid detection of aversive stimuli. The immediate fear response elicited by the phobic stimulus additionally recruits higher-order cortical regions—including the dACC and rACC, PCC, and dlPFC, vmPFC, vlPFC, and dmPFC—reflecting the interaction between Acute Threat (Fear), Attention, and Cognitive Control across the Negative Valence Systems and Cognitive Systems domains.

Likewise, persistent avoidance behavior and the disproportionate perception of danger are better understood as behavioral consequences of impaired top–down regulation over hyperresponsive limbic circuits. This neurofunctional profile reflects the convergence of dysfunctional Acute Threat (Fear) and Cognitive Control constructs, providing a biological explanation for exaggerated threat perception, deficient emotional regulation, and the maintenance of phobic behavior (About RDoC - National Institute of Mental Health (NIMH), 2025; American Psychiatric Association, 2013; Del Casale et al., 2012; Garcia, 2017; Linares et al., 2012; Oar et al., 2019).

PD

Panic Disorder is characterized by the convergence of neural circuits involved in threat detection, autonomic arousal, interoceptive processing, and cognitive regulation. Recurrent unexpected panic attacks are supported by hyperactivation of the amygdala, periaqueductal gray, anterior insula, thalamus, locus coeruleus, and hippocampus. Within the RDoC framework, these regions primarily correspond to the Acute Threat (Fear) and Potential Threat (Anxiety) constructs of the Negative Valence Systems domain, together with the Arousal construct of the Arousal and Regulatory Systems domain. This neurofunctional organization reflects the interaction between rapid threat detection, anticipatory anxiety, and autonomic activation underlying the physiological alarm response.

Likewise, persistent concern about additional attacks and the characteristic physiological and cognitive symptoms of panic—including palpitations, sweating, trembling, dyspnea, chest pain, dizziness, fear of losing control, and fear of dying—are better understood as clinical consequences of impaired prefrontal regulation over hyperresponsive limbic and autonomic circuits. Dysfunction involving the dorsolateral, ventromedial, dlPFC, vmPFC, and dmPFC, OFC, ACC, and precuneus reflects the convergence of the Potential Threat (Anxiety), Sustained Threat, Attention, and Cognitive Control constructs across the Negative Valence Systems and Cognitive Systems domains. This integrated neurofunctional profile provides a biological explanation for anticipatory anxiety, heightened interoceptive vigilance, autonomic hyperarousal, and the catastrophic interpretation of bodily sensations that characterize PD (About RDoC - National Institute of Mental Health (NIMH), 2025; American Psychiatric Association, 2013; Kaldewaij et al., 2019; Kim et al., 2012; Lai & Wu, 2014; Sobanski & Wagner, 2017; Wang et al., 2024; Wang et al., 2018; Zhang et al., 2023).

Table 3. Mapping DSM-5 symptoms to neurobiology and RDoC in Anxiety Disorders

DSM-5 diagnostic criteria		**Neurobiology**	**RDoC**	
Disorder	**Symptom**	**Brain Region(s)**	**Construct**	**Domain**
Specific Phobia	Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, injections).	Amygdala, ACC, Insula, OFC, Thalamus	Acute Threat (Fear)	Negative Valence Systems
	The phobic object or situation almost always provokes immediate fear or anxiety.	dACC, rACC, PCC, dlPFC, vmPFC, vlPFC, dmPFC	Acute Threat (Fear) Attention Cognitive Control	Negative Valence Systems Cognitive Systems
	The phobic object or situation is actively avoided or endured with intense fear or anxiety.	dlPFC, vmPFC, dmPFC, OFC	Cognitive Control Attention	Cognitive Systems
	The fear or anxiety is out of proportion to the actual danger posed.	Amygdala, Insula (anterior), dlPFC, vmPFC, dmPFC, dACC.	Acute Threat (Fear) Cognitive Control	Negative Valence Systems Cognitive Systems
Panic Disorder	Recurrent unexpected panic attacks	Amygdala, Periaqueductal Gray, Insula (anterior), Thalamus, Locus Coeruleus, Hippocampus	Acute Threat (Fear) Potential Threat (“Anxiety”) Arousal	Negative Valence Systems Arousal and Regulatory Systems
	Persistent worry about future attacks	dlPFC, vmPFC, dmPFC, OFC	Potential Threat (“Anxiety”) Attention Cognitive Control	Negative Valence Systems Cognitive Systems

	Palpitations, sweating, trembling, shortness of breath, chest pain, nausea, dizziness, fear of losing control, fear of dying.	ACC, Precuneus, PFC	Sustained Threat Cognitive Control	Negative Valence Systems Cognitive Systems
Social Anxiety Disorder	Marked fear or anxiety about ≥1 social situations in which the individual is exposed to possible scrutiny by others (e.g., social interactions, being observed, performing in front of others).	Amygdala, BNST, Insula (anterior), dlPFC, vmPFC	Acute Threat ("Fear") Potential Threat ("Anxiety") Affiliation and Attachment Perception and Understanding of Self	Negative Valence Systems Social Processes
	Social situations are avoided or endured with intense fear	DMN: mPFC, PCC, ACC; CCN: dlPFC, ACC, vmPFC; MN: VTA, Striatum, mOFC	Potential Threat ("Anxiety") Social Communication Reward Learning	Negative Valence Systems Social Processes Positive Valence Systems
	The individual fears that they will act in a way or show anxiety symptoms that will be negatively evaluated	DAN: PFC, PCC, supramarginal gyrus; Amygdala–PFC connectivity, ACC/Insula	Cognitive Control Affiliation and Attachment Social Communication Perception and Understanding of Others	Cognitive Systems Social Processes
Generalized Anxiety Disorder	Excessive uncontrollable worry	Amygdala, vlPFC, vmPFC, Insula, dmPFC	Sustained Threat Potential Threat ("Anxiety")	Negative Valence Systems
	The individual finds it difficult to control the worry.	dlPFC, vmACC, dmPFC	Cognitive Control	Cognitive Systems
	Restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbance.	dlPFC, vmACC, dmPFC, Amygdala–PFC connectivity, DMN, PFC–DMN, Thalamus,	Arousal Cognitive Control	Arousal and Regulatory Systems Cognitive Systems

Table 3 maps DSM-5 diagnostic criteria onto the neurobiology and RDoC framework of the most prevalent anxiety disorders—Specific Phobia, Panic Disorder, Social Anxiety Disorder and, Generalized Anxiety Disorder— linking each symptom with the corresponding brain regions previously identified, as well as the specific RDoC constructs and domains involved. Brain regions involved in anxiety-related processes that currently lack sufficient evidence to support a direct symptom–construct integration within the RDoC framework were not included in the table. These regions are therefore considered important targets for future research aimed at complementing neurofunctional mappings across anxiety disorders.

Abbreviatures: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; RDoC, Research Domains Criteria; ACC, Anterior Cingulate Cortex; OFC, Orbitofrontal Cortex; dACC, Dorsal Anterior Cingulate Cortex; rACC, Rostral Anterior Cingulate; PCC, Posterior Cingulate Cortex; dlPFC, Dorsolateral Prefrontal Cortex; vmPFC, Ventromedial Prefrontal Cortex; vlPFC, Ventrolateral Prefrontal Cortex; dmPFC, Dorsomedial Prefrontal Cortex; PFC, Prefrontal Cortex; BNST, Bed Nucleus of the Stria Terminalis; CCN, Cognitive Control Network; MN, Motivation Network; VTA, Ventral Tegmental Area; mOFC, Medial Orbitofrontal Cortex; DAN, Dorsal Attention Network; vmACC, Ventromedial Anterior Cingulate Cortex; DMN, Default Mode Network.

SAD

SAD is characterized by the convergence of neural circuits involved in threat detection, self-referential processing, social cognition, and reward processing. Hyperactivation of the amygdala, bed nucleus of the stria terminalis (BNST), anterior insula, and prefrontal regions—including dlPFC and vmPFC—primarily corresponds to the Acute Threat (Fear) and Potential Threat (Anxiety) constructs of the Negative Valence Systems domain, together with the Affiliation and Attachment, Perception and Understanding of Self, and Social Communication constructs of the Social Processes domain. Dysfunction within the Default Mode Network (DMN), Cognitive Control Network (CCN), Motivational Network (MN), and Dorsal Attention Network (DAN) further reflects the interaction between social cognition, attentional regulation, and reward processing.

From this perspective, the DSM-5 criteria—including fear of social situations, avoidance or endurance with intense anxiety, and fear of negative evaluation—represent different clinical manifestations of a shared neurofunctional dysfunction involving heightened sensitivity to social threat, impaired cognitive regulation, altered self-referential processing, and reduced processing of social reward. This integrated neurofunctional profile reflects the convergence of the Negative Valence Systems, Social Processes, Cognitive Systems, and Positive Valence Systems domains, providing a biological explanation for persistent social avoidance, hypervigilance toward external evaluation, and the perception of social interaction as threatening rather than rewarding (About RDoC - National Institute of Mental Health (NIMH), 2025.; American Psychiatric Association, 2013; Blake et al., 2025; Boehme et al., 2015; Brühl et al., 2014; Coutinho et al., 2016; Cremers & Roelofs, 2016; Marazziti et al., 2015; Zidda et al., 2017).

GAD

Generalized Anxiety Disorder is characterized by the convergence of neural circuits involved in sustained threat processing, cognitive regulation, and physiological arousal. GAD is characterized by persistent activation of neural circuits involved in sustained threat processing, cognitive regulation, and physiological arousal. Hyperactivation of the amygdala, insula, ventrolateral, ventromedial, and dorsomedial prefrontal cortices (vlPFC, vmPFC, and dmPFC) primarily corresponds to the Sustained Threat and Potential Threat (Anxiety) constructs of the Negative Valence Systems domain. Dysfunction of the dorsolateral prefrontal cortex (dlPFC), ventromedial anterior cingulate cortex (vmACC), Default

Mode Network (DMN), PFC–DMN connectivity, and thalamic circuits further reflects alterations in the Cognitive Control and Arousal constructs within the Cognitive Systems and Arousal and Regulatory Systems domains.

From this perspective, the DSM-5 criteria—including excessive and uncontrollable worry, difficulty controlling worry, and the associated physiological symptoms of restlessness, fatigue, impaired concentration, irritability, muscle tension, and sleep disturbances—represent different clinical manifestations of a shared neurofunctional dysfunction characterized by persistent threat anticipation, deficient cognitive regulation, and dysregulated arousal. This integrated neurofunctional profile provides a biological expla ation for the coexistence of chronic worry, physiological hyperarousal, sleep disruption, and cognitive fatigue that characterize GAD (About RDoC - National Institute of Mental Health (NIMH), 2025; American Psychiatric Association, 2013; Fonzo & Etkin, 2016; Madonna et al., 2019; Maron & Nutt, 2017; Michopoulos et al., 2017; Santos et al., 2019).

Collectively, these findings reinforce the proposed integrative neurofunctional approach for anxiety disorders, which views anxiety symptoms as circuit-level expressions of dysregulated RDoC domains and constructs. This framework advances a systems-oriented perspective that bridges categorical diagnosis and neurobiological function, providing a conceptual foundation for the development of neuroscience-informed psychotherapy and precision mental health approach.

DISCUSSION

This narrative and conceptual review represents a novel contribution by bridging DSM-5 diagnosis, neurobiology, and the dimensional perspective of the RDoC framework for anxiety disorders. Unlike previous descriptive reviews, the proposed Integrative Neurofunctional Approach systematically maps DSM-5 symptom-level criteria onto specific neural circuit dysfunctions and corresponding RDoC domains and constructs, providing a conceptual foundation for neuroscience-informed psychotherapeutic formulation.

Diagnostic Criteria and RDoC

Although SP, PD, SAD, and GAD are traditionally conceptualized as distinct diagnostic categories, the present framework suggests that their clinical manifestations are better understood as expressions of dysfunction within shared neurofunctional systems.

This dimensional perspective complements symptom-based classification by providing a more comprehensive understanding of the mechanisms underlying anxiety disorders.

While DSM-5 remains indispensable for clinical diagnosis and treatment planning, it offers limited insight into the neural circuits underlying symptom expression. The RDoC framework complements categorical diagnosis by organizing psychopathology according to functional neurobiological systems, supporting a more mechanistic interpretation of anxiety disorders (Cuthbert, 2014; Regier et al., 2013; Sanislow et al., 2019).

Figure 1

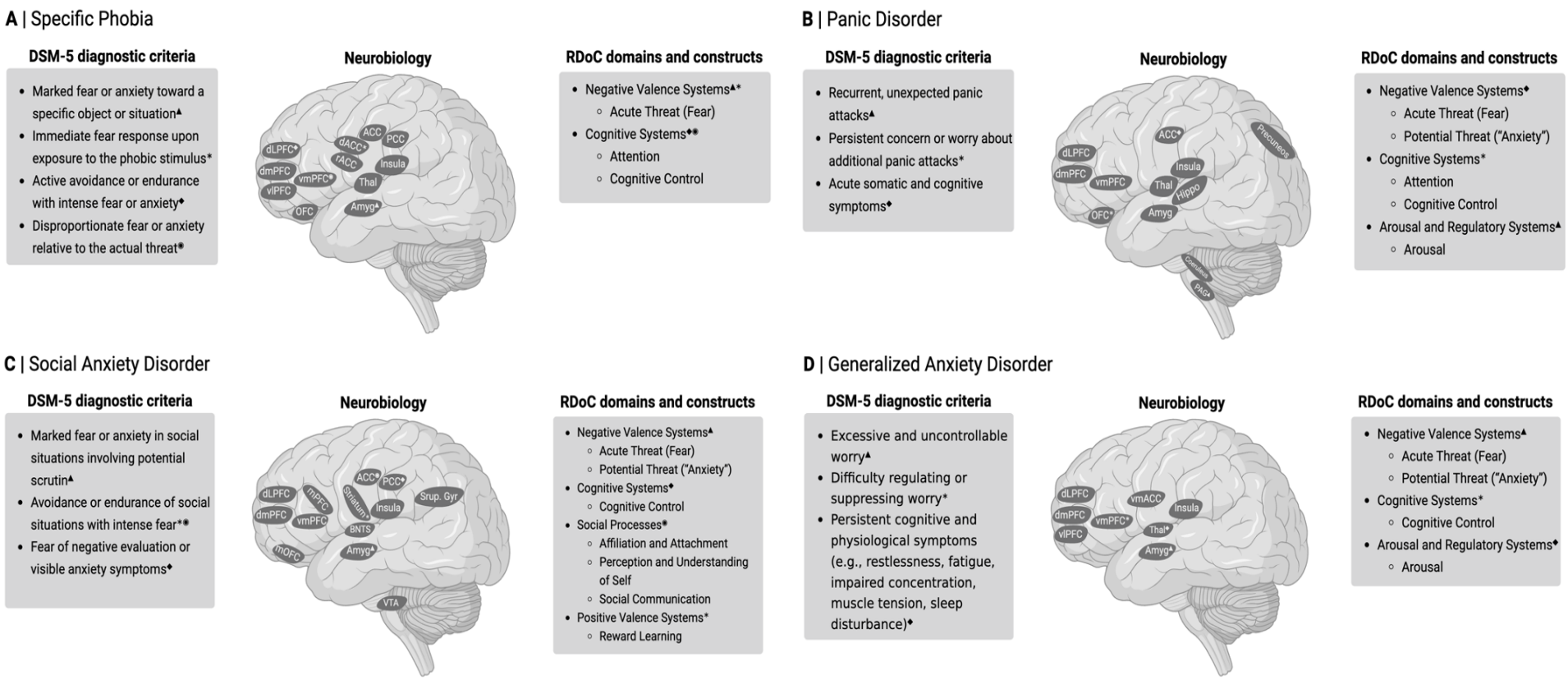


Figure 1 illustrates the integrative neurofunctional approach to anxiety disorders—A) Specific Phobia, B) Panic Disorder, C) Social Anxiety Disorder, and D) Generalized Anxiety Disorder—by linking (▲ ∗ ◆ ◉) DSM-5 diagnostic criteria with the underlying neurobiology and the corresponding RDoC domains and constructs for each disorder. The figure highlights shared and disorder-specific patterns of neural dysfunction, providing a visual synthesis that complements Table 3 and facilitates conceptual integration.
Abbreviatures: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; RDoC, Research Domains Criteria; ACC, Anterior Cingulate Cortex; OFC, Orbitofrontal Cortex; dACC, Dorsal Anterior Cingulate Cortex; rACC, Rostral Anterior Cingulate; PCC, Posterior Cingulate Cortex; dlPFC, Dorsolateral Prefrontal Cortex; vmPFC, Ventromedial Prefrontal Cortex; vlPFC, Ventrolateral Prefrontal Cortex; dmPFC, Dorsomedial Prefrontal Cortex; BNST, Bed Nucleus of the Stria Terminalis; VTA, Ventral Tegmental Area; mOFC, Medial Orbitofrontal Cortex; vmACC, Ventromedial Anterior Cingulate Cortex; Thal, Thalamus; Hippo, Hippocampus; Amyg, Amygdale.

Neurobiology and RDoC

Across anxiety disorders, common clinical manifestations—including excessive worry, anticipatory fear, physiological hyperarousal, and avoidance—emerge from dysfunctions within overlapping neurofunctional systems rather than entirely distinct pathophysiological processes. Consistent alterations involving the amygdala, prefrontal cortex, anterior cingulate cortex, insula, thalamus, and related regulatory systems support the existence of shared neural substrates across anxiety disorders (McTeague et al., 2016).

Within this context, the RDoC framework provides a dimensional organization of these neurobiological systems, whereas the proposed Integrative Neurofunctional Approach links these systems directly to DSM-5 symptom-level criteria. This integration offers a mechanistic interpretation of anxiety disorders, suggesting that their clinical manifestations reflect distinct patterns of dysfunction across partially overlapping neurofunctional systems and providing a conceptual basis for neuroscience-informed clinical formulation and personalized intervention strategies (Cuthbert & Insel, 2013; Hawn et al., 2022; Kozak & Cuthbert, 2016; Musser & Raiker, 2019).

Integrative Neurofunctional Approach

The principal contribution of the Integrative Neurofunctional Approach lies in neuroscience-informed clinical case formulation. By linking symptom expression to specific neurofunctional systems, the framework extends conventional diagnostic classification toward a translational perspective that may facilitate more precise case conceptualization and individualized treatment planning.

Importantly, this framework should not be interpreted as a new psychotherapeutic model. Instead, it provides a neurobiological rationale for organizing existing evidence-based psychotherapeutic interventions according to the predominant neurofunctional mechanisms underlying symptom expression, thereby offering a bridge between advances in neuroscience and routine clinical practice.

The translational relevance of this perspective is illustrated by emerging mechanism-based interventions derived from the RDoC framework. ENGAGE therapy, for example, represents an early effort to target dysfunctions in positive valence and reward-related neural systems in late-life depression, demonstrating how RDoC constructs can inform psychotherapeutic development (Alexopoulos et al., 2016, 2021; Pasion et al., 2019).

Although comparable applications in anxiety disorders remain limited, the proposed framework provides a conceptual basis for the future development of neuroscience-informed psychotherapeutic interventions grounded in neurofunctional mechanisms.

CONCLUSION

This narrative and conceptual review proposes an integrative neurofunctional approach that unifies DSM-5 symptomatology, neurobiology, and the RDoC into a conceptual approach for understanding anxiety disorders. Beyond integrating existing knowledge, this proposal systematically links clinical symptoms, underlying neural circuit dysfunctions, and corresponding RDoC domains and constructs into a coherent neurofunctional perspective, providing a more comprehensive understanding of anxiety disorders and a conceptual foundation for neuroscience-informed case formulation and personalized psychotherapeutic interventions.

By systematically mapping DSM-5 symptom-level criteria onto specific neural circuit dysfunctions and corresponding RDoC domains and constructs, the proposed framework complements traditional categorical diagnosis with a translational perspective that connects clinical psychopathology to its underlying neurobiological mechanisms. Rather than replacing current diagnostic systems or proposing a new psychotherapeutic model, the Integrative Neurofunctional Approach provides a conceptual framework for neuroscience-informed clinical formulation, facilitating a more precise understanding of symptom expression and supporting the personalization of evidence-based psychotherapeutic interventions.

Furthermore, this framework establishes a conceptual basis for future research aimed at developing mechanism-based models of psychopathology and evaluating neuroscience-informed psychotherapeutic interventions across psychiatric disorders. By bridging clinical psychopathology and neuroscience within a unified conceptual framework, the proposed Integrative Neurofunctional Approach represents a step toward translating advances in neuroscience into clinical practice.

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