Neuroscience and Biobehavioral Reviews 152 (2023) 105305

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Understanding anxiety symptoms as aberrant defensive responding along the threat imminence continuum

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ARTICLE INFO

Keywords:
Anxiety
Fear
Defensive response
Threat imminence
Avoidance
Physiological responses
Worry
Anxiety disorders

ABSTRACT

Threat-anticipatory defensive responses have evolved to promote survival in a dynamic world. While inherently adaptive, aberrant expression of defensive responses to potential threat could manifest as pathological anxiety, which is prevalent, impairing, and associated with adverse outcomes. Extensive translational neuroscience research indicates that normative defensive responses are organized by *threat imminence*, such that distinct response patterns are observed in each phase of threat encounter and orchestrated by partially conserved neural circuitry. Anxiety symptoms, such as excessive and pervasive worry, physiological arousal, and avoidance behavior, may reflect aberrant expression of otherwise normative defensive responses, and therefore follow the same imminence-based organization. Here, empirical evidence linking aberrant expression of specific, imminence-dependent defensive responding to distinct anxiety symptoms is reviewed, and plausible contributing neural circuitry is highlighted. Drawing from translational and clinical research, the proposed framework informs our understanding of pathological anxiety by grounding anxiety symptoms in conserved psychobiological mechanisms. Potential implications for research and treatment are discussed.

Through the course of evolution, dedicated systems have emerged to support motivational behaviors, including defensive responding for coping with potential threats (Dranias et al., 2008; LeDoux, 2012; Cisek, 2019; Blanchard et al., 2011; Fox and Shackman, 2019). As species evolved, these systems became increasingly complex, allowing for more nuanced threat detection and assessment and mobilization of behaviors to promote survival when faced with a larger variety of threats (LeDoux, 2012; Cisek, 2019; Adolphs, 2009). While threat-anticipatory defensive responses have evolved to favor a low threshold for initiation (Nesse, 2005), a high rate of false alarms confers the risk for excessive and persistent execution of responses that can lead to pathological anxiety (Nesse, 2005; Grupe and Nitschke, 2013; Kenwood et al., 2022). Anxiety symptoms may therefore reflect aberrant expression of otherwise normative defensive responses.

The goal of the present review is to link specific anxiety symptoms to the aberrant expression of distinct defensive responses. Through this work, an organizing framework for anxiety symptoms emerges, describing when different symptoms, such as excessive vigilance, worry, physiological arousal, or avoidance behavior, should arise. While all are prominently featured in pathological anxiety (APA, 2013), contextualizing these symptoms within the repertoire of normative defensive responses (Krakauer et al., 2017) could guide our expectations as to *which symptoms* to expect in *which situations*. Specifically, the proposed framework extends influential conceptualizations rooted in translational neuroscience research that highlight the role of *threat imminence* in determining the expression of distinct defensive responses and identify key elements in the neural circuitry driving them. Systematically linking anxiety symptoms to perturbations in psychobiologically-grounded patterns of conserved defensive responding could begin to address limitations in phenomenology-based clinical conceptualizations of anxiety (Kotov et al., 2017; Insel et al., 2010), and thus inform our understanding of pathological anxiety and its treatment (Hyman, 2014; Xia and Kheirbek, 2020).

1. Defining features of pathological anxiety

Anxiety disorders are prevalent, chronic, impairing, and associated with adverse outcomes (Kessler and Wang, 2008; Stein et al., 2017; Beesdo et al., 2009; Shackman and Fox, 2021). In psychiatric nosology, they encompass several diagnoses, with diagnostic distinctions centering primarily on the types of objects or settings that are perceived as threatening, and which evoke a range of symptoms such as tension and physiological arousal, hypervigilance and worry cognitions, and avoidance behaviors (APA, 2013; World Health Organization, 2019).

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https://doi.org/10.1016/j.neubiorev.2023.105305
Received 9 July 2022; Received in revised form 22 June 2023; Accepted 3 July 2023
Available online 5 July 2023

For example, symptoms may be evoked by social situations that involve potential scrutiny (social anxiety disorder), by circumscribed objects or situations (e.g., specific phobias), or in relation to separation from attachment figures (separation anxiety disorder) (APA, 2013).

Yet, despite these diagnostic distinctions, clinical observations and empirical work consistently indicate limited disorder specificity in symptom presentation (i.e., significant homotypic and heterotypic comorbidity), diagnostic reliability and validity, familial aggregation and genetic loci, pathophysiology, and treatment targets or response (Shackman and Fox, 2021; Cummings et al., 2014; Cuthbert and Insel, 2013; Hofmann and Hayes, 2019; Shear et al., 2007; Purves et al., 2020; Smoller, 2016; Kotov et al., 2021, 2022). These lines of evidence suggest that anxiety disorders likely share *common* mechanistic perturbations, etiology, and phenomenology, potentially arising from a shared biological or psychosocial diathesis (Smoller, 2016; Craske et al., 2009; Barlow et al., 2004; Gray and McNaughton, 2000; Chavanne and Robinson, 2021). Identifying common mechanisms and patterns of symptom manifestation in pathological anxiety, rather than focusing on relatively weak diagnostic distinctions, could significantly promote our understanding of 'core' pathological processes; this, in turn, could guide mechanistic research towards treatment development (Barlow et al., 2004, 2017).

What might constitute a core process in pathological anxiety? Psychiatric nosology generally highlights reported symptoms pertaining to "excessive fear and anxiety" as defining features and diagnostic criteria of anxiety disorders (APA, 2013). While the terms 'fear' and 'anxiety' are broadly used to distinguish emotional responses to imminent threat from anticipation and preparation for future threat, respectively (Craske et al., 2009; Barlow, 2002; Lang et al., 2000; Perusini and Fanselow, 2015; Tovote et al., 2015; LeDoux and Pine, 2016), the precise nature of this distinction in terms of theoretical considerations, underlying neural circuitry, clinical expression, and other facets, is still very much a matter of debate (Perusini and Fanselow, 2015; Tovote et al., 2015; LeDoux and Pine, 2016; Grogans et al., 2023). Elusive distinctions limit the utility of these terms as the basis for describing core processes in pathological anxiety, especially when it comes to linking quantitative, psychobiological research in lab models to clinical classification (Perusini and Fanselow, 2015).

Instead, 'fear' and 'anxiety' symptoms may be understood as commonly reflecting maladaptive defensive responses to potential threat (or stressors) observed across anxiety disorders. Considerable translational research indicates that objects or settings signaling potential threat, such as danger to one's life and health, or loss of caregivers, social standing, or resources (Marks and Nesse, 1994; Beauchaine and Zisner, 2017), elicit a cascade of threat-anticipatory defensive responses observed across multiple levels (e.g., molecular, synaptic, physiological, and cognitive) that is subserved by partially conserved neural circuitry, and promotes survival by driving defensive behaviors (Cisek, 2019; Fox and Shackman, 2019; Shackman and Fox, 2021; Beauchaine and Zisner, 2017; Silva et al., 2016; Borkovec, 1985; Hur et al., 2020). Thus, we may begin to link specific clinical symptoms of anxiety to specific patterns of exaggerated and pervasive expression of otherwise normative anticipatory, defensive responses to potential threat (Grupe and Nitschke, 2013; Kenwood et al., 2022; Shackman and Fox, 2021; Craske et al., 2009; Rosen and Schulkin, 1998; Mineka and Oehlberg, 2008; Mobbs et al., 2020). The focus on responses to *potential* threat is further underscored by recent work associating pathological anxiety with aberrant anticipation, rather than ultimate experience, of aversive events (Grupe and Nitschke, 2013; Abend et al., 2021a, 2020). Linking anxiety symptoms to patterns of conserved defensive responses may help bridge clinical terminology and psychobiological processes increasingly delineated in translational neuroscience research.

Among threat-anticipatory responses, emerging evidence indicates the centrality of excessive *cognitive* (e.g., vigilance, worry cognitions) and *physiological* (autonomic arousal) defensive responses in anxiety symptom presentation, regardless of specific source of potential threat (Insel et al., 2010; Craske et al., 2009; Barlow, 2002; Lang et al., 2000; LeDoux and Pine, 2016; Borkovec, 1985; Zinbarg, 1998; Bar-Haim et al., 2007); their excessive expression may then promote exaggerated execution of defensive behaviors (e.g., avoidance) observed across anxiety disorders (Craske et al., 2009; Barlow et al., 2004; Abend et al., 2021b; Linke et al., 2021; Bijsterbosch et al., 2014). In other words, while different objects and situations may be perceived as posing potential threat, the exaggerated expression of otherwise normative cognitive, physiological, and behavioral defensive responses is *shared* across disorders (Blanchard et al., 2011; APA, 2013; Gray and McNaughton, 2000; Marks and Nesse, 1994; Rosen and Schulkin, 1998; Etkin and Wager, 2007; Martin et al., 2014). Moreover, individuals who tend to show enhanced cognitive responses to threats also show enhanced physiological responses (Abend et al., 2021b), suggesting these are parts of a shared defensive mechanism (Rosen and Schulkin, 1998). Together, it may be posited that pathological anxiety reflects a tendency for enhanced defensive responsivity, manifesting particularly in the physiological, cognitive, and behavioral domains (Rosen and Schulkin, 1998; Craske, 1999); these responses are expressed too strongly or pervasively that they become maladaptive, distressing, and impairing, constituting what is referred to clinically as anxiety symptoms (Kenwood et al., 2022; Rosen and Schulkin, 1998; Blanchard, 2017).

2. Threat imminence continuum

Considerable cross-species research demonstrates that defensive responses to threat are organized along a threat imminence continuum, typically comprising a pre-encounter, post-encounter, and circa-strike phases (Perusini and Fanselow, 2015; Mobbs et al., 2020; Adolphs, 2013; Fanselow et al., 1988; Blanchard and Blanchard, 1989; McNaughton and Corr, 2004; Mobbs et al., 2019). Thus, distinct responses have evolved to anticipate threat and minimize harm, such as vigilance, acute physiological responding, and avoidance behavior; these are differentially and dynamically expressed as a function of physical or temporal threat proximity, and are orchestrated and carried out by conserved neural circuitry (LeDoux, 2012; Fox and Shackman, 2019; Mobbs et al., 2020; McNaughton and Corr, 2018). Importantly, recent work begins to extend such insights to humans, providing a strong translational, empirical and conceptual framework for describing human defensive responding (Blanchard, 2017; Shuhama et al., 2019; Mobbs, 2018; Hamm, 2019; Mobbs and Kim, 2015; Shackman et al., 2016a).

Under the assumption that pathological anxiety reflects the propensity for exaggerated expression of normative responses to potential threat (Kenwood et al., 2022; Rosen and Schulkin, 1998; Blanchard, 2017; Shuhama et al., 2019; Levy and Schiller, 2021), and that such responses may be organized by threat imminence (Blanchard, 2017; Adolphs, 2013; Fanselow et al., 1988; Mobbs, 2018), distinct anxiety symptoms could be systematically linked to aberrant expression of imminence-dependent defensive responses, providing a model for dynamically contextualizing symptoms within a wider translational framework of response to threat (Craske et al., 2009; McNaughton and Corr, 2004; Hamm, 2019; Krueger and DeYoung, 2020). An organization of anxiety symptoms that is grounded in conserved psychobiological mechanisms may be useful in two key respects. First, drawing from considerable translational research, it may begin to systematically describe the manifestation of pathological anxiety with greater temporal precision (Kotov et al., 2017; Insel et al., 2010; Robinson et al., 2019). Anxiety symptom presentation, much like physiological, behavioral, and subjective responses to aversive events, shows temporal variability (Burke et al., 2005; Lapate and Heller, 2020; Pfaltz et al., 2010). The fact that symptom presentation is not static complicates phenomenological descriptions of pathological anxiety, as reflected in its relatively loose nosological definition (APA, 2013; World Health Organization, 2019); it is also acknowledged by influential theories on the dynamic nature of emotion and in the emergence of denser symptom assessment strategies (e.g., ecological momentary assessment) (Lapate and Heller, 2020; Walz

and Nauta, 2014; Davidson, 2015; Maciejewski et al., 2015; Trull et al., 2015). Thus, an anxious individual will not chronically exhibit a specific set of symptoms, such as worry and arousal; however, current nosology insufficiently specifies which and when specific symptoms do arise. The proposed framework anchors the expression of symptoms to the perceived presence of specific threats and the imminence-dependent defensive responses they evoke, delineating which symptoms are expected at different times. For instance, an important public speaking event (conferring the threat of potential social rejection) is expected to differentially elicit exaggerated physiological tension, worry, passive and active avoidance behaviors, acute physiological arousal, and even panic, as the threat becomes increasingly imminent. As such, extant nosology may be complemented by predictions of when different symptoms are expected to emerge.

Second, considerable translational research and theory delineate the conserved mechanisms orchestrating and triggering imminence-dependent defensive responses (Perusini and Fanselow, 2015; Mobbs et al., 2020; Adolphs, 2013; LeDoux and Daw, 2018). Harnessing such explanatory power towards providing a sound psychobiological basis for anxiety symptoms could substantially improve our mechanistic understanding of pathological anxiety, guided to date primarily by categorical definitions provided by psychiatric nosology (Insel et al., 2010; Kotov et al., 2022; Tiego et al., 2023). Precise mapping of symptoms to underlying circuitry could provide more tractable and robust biomarkers needed for neuroscience-guided research on pathophysiological mechanisms and treatment (Xia and Kheirbek, 2020; Krueger and DeYoung, 2020; Abi-Dargham and Horga, 2016; Garcia-Gutierrez et al., 2020; Venkatasubramanian and Keshavan, 2016).

In the next sections, a framework linking anxiety symptoms to aberrant expression of imminence-dependent defensive responses is described. The focus in defensive responding is on the cognitive, physiological, and behavioral domains, due to the centrality of such responses in anxiety symptomatology and the relative ease with which these can be assessed both in the lab and by patients. First, distinct patterns of cognitive and physiological responses expressed along the threat imminence continuum, and the distinct defensive behaviors they drive, are characterized. Next, findings linking exaggerated expression of imminence-dependent defensive responses to pathological anxiety are reviewed. Finally, key elements in the neural circuitry underlying defensive responding are described.

3. Threat imminence and defensive responses

Extensive translational research delineates several phases of encounter with potential threat (Mobbs et al., 2020; Adolphs, 2013; Fanselow et al., 1988; Blanchard and Blanchard, 1989). These phases are associated with specific defensive responses, as described next.

3.1. Pre-encounter

Pre-encounter constitutes a state in which no concrete threat is currently present, but one is possible and thus anticipated (Fiddick, 2011; Hamm et al., 2016). As such, it is a context-activated state reflecting greater likelihood of threat encounter in the current spatial or temporal context, initiated through species-specific innate responses (e.g., by open field, darkness, or predator odor) or learned through past experiences (i.e., context conditioning) (Davis et al., 2010; Grillon, 2008). It is typically modeled experimentally in humans using paradigms involving context-based induction of uncertain-threat delivery, such as context-conditioning and threat-of-shock paradigms in which subjects are experientially or verbally informed about context-dependent, temporally-unpredictable aversive stimuli such as electric shocks (Chavanne and Robinson, 2021; Davis et al., 2010; Grillon, 2002; Grillon et al., 2019).

Cognitively, the pre-encounter phase is characterized by vigilance (Hamm, 2019; Wieser et al., 2016), mediated by increased sensory gain (Cornwell et al., 2017), to facilitate detection of potential threats. Such responding is coupled by increased tonic physiological arousal, e.g., elevated skin conductance levels, increased muscle tone, and potentiation of startle reflexes, likely to facilitate rapid *encounter* phase responding (see below) (Grillon, 2008; Troger et al., 2012; Ho et al., 2020; Kastner et al., 2016). A sustained pre-encounter state may manifest behaviorally in restlessness and tension reflecting prolonged preparation for action, and attempted avoidance of the threat context, and may be accompanied by reduction in appetitive behaviors such as food intake or sexual activities which may be deemed as lower priority (Mobbs et al., 2020; Hamm, 2019; Kalin, 2017; Grillon et al., 2006). Together, the key function served by the *pre-encounter* phase is detection of potential danger in the environment and sustained preparation for response (Hamm, 2019; Grillon, 2008, 2002; Grillon et al., 2006; Robinson et al., 2012).

3.2. Encounter

When one is in a *pre-encounter* context, and an object conferring potential threat is spotted, the *encounter* phase is initiated, interrupting and "resetting" ongoing behavior (Roelofs and Dayan, 2022; Dayan and Yu, 2006); phasic arousal then promotes rapid assessment of potential threat value towards execution of defensive behaviors, if necessary (Blanchard et al., 2011; Gray and McNaughton, 2000; Roelofs and Dayan, 2022; LeDoux, 2000). Examples of this are an animal in an open field spotting a potential predator, or a person walking down a dark alley noticing a sudden movement. Thus, the encounter phase promotes state transition from *pre-* to *post-encounter* with a specific potential threat (Blanchard et al., 2011; Lang et al., 2000; Corr, 2013; Gross and Canteras, 2012; Livermore et al., 2021; Bolles and Fanselow, 1980). Of note, translational literature typically combines the *encounter* and *post-encounter* phases (described next); here, these phases are separated since specific anxiety-relevant processes in humans may be identified in each.

Arousal and action preparation are accompanied by phasic physiological responding, e.g., increased perspiration, heart rate, breathing, and muscle tone, driven by the sympathetic branch of the autonomic nervous system (Roelofs and Dayan, 2022; Ojala and Bach, 2020; Bradley, 2009); such insight is derived primarily from cross-species research probing threat learning processes that involve conditioned, experience-driven changes in threat value ascribed to cues (Mineka and Oehlberg, 2008; LeDoux and Daw, 2018; LeDoux, 2000; Maren, 2001). Time-course analysis further suggests that encounter-driven phasic physiological arousal may precede threat assessment (Hamm, 2019; Abend et al., 2022a; Wendt et al., 2017), potentially indicating that this initial response plays a role in promoting preparation for action, even before it is known if one is ultimately needed (Livermore et al., 2021; Bradley, 2009). Aside from reflexive responses (e.g., startle) (LeDoux and Daw, 2018), encounter in animals and humans involves initial behavior *inhibition*. Such 'attentive defensive freezing' (inhibition of overt behaviors) may serve to evade detection by potential predators while also providing the opportunity for detailed assessment and selection of appropriate defensive behaviors (Gray and McNaughton, 2000; Blanchard, 2017; McNaughton and Corr, 2018; Hamm, 2019; Kalin, 2017; Roelofs and Dayan, 2022). Elaborate threat assessment depends on attention allocation which facilitates processing object features (Blanchard et al., 2011; Mogg and Bradley, 2018; Wieser and Keil, 2020); this enables estimation of threat value computed from factors such as its type, proximity, magnitude (or cost), probability of striking, and broader context (Blanchard et al., 2011; Blanchard, 2017; McNaughton and Corr, 2018; Hamm, 2019; Tashjian et al., 2021; Drabant et al., 2011).

The evolved ability to generate and maintain powerful and realistic future *representations* of potential threat through mental simulation of action-outcomes (LeDoux and Daw, 2018) is adaptive as it enables preparation for more distal danger in complex settings. Such imagery and simulation have been shown to elicit robust cognitive and emotional responses, impact neural plasticity, and activate relevant sensory-motor brain regions (Reddan et al., 2018; Holmes and Mathews, 2010, 2005). Thus, invoked imagery of potential negative outcomes (e.g., social

embarrassment during public speaking) can serve as robust threats even without physically being in the relevant situations or perceiving the threat (Lang et al., 2000; Ottaviani, 2018; Ottaviani et al., 2016; Moulton and Kosslyn, 2009). As such, we may consider such imagined and stimulated threat as *encountered* threat, requiring assessment of features such as threat magnitude (cost) and probability of occurring, which accordingly elicit relevant defensive responses (see *post-encounter*) (Ottaviani, 2018; Ottaviani et al., 2016; Moulton and Kosslyn, 2009; Loewenstein et al., 2001). While threat assessment of an object that is physically perceived may be relatively simpler as relevant physical features are clearly observed, assessment of distal, simulated threats may be complicated by difficulty in accurately estimating such features, including occurrence probability. The inherent uncertainty in such estimation (Grupe and Nitschke, 2013), especially given limited knowledge, could prolong this process and call for its repeated initiation.

More broadly, the *encounter* phase may entail the resolution of approach-avoid conflicts, arguably more common than threat-only settings, by weighing estimated potential threat and reward values to determine the adaptive motivated behavior to pursue given a certain situation (Gray and McNaughton, 2000; McNaughton and Corr, 2018; Livermore et al., 2021; Averbeck and Murray, 2020). Thus, desired things invoke approach behavior which increases the likelihood of attaining them (Dranias et al., 2008; Cisek, 2019), but in many cases this also entails potential threat and associated avoidance motivation that conflict with the approach motivation (e.g., eating sugar-rich foods). The arbitration of such conflicts may be particularly nuanced and prolonged in humans, given the expanded capacity for generating complex representations of abstract, multi-faceted, and often ambiguous stimuli, settings, and action outcomes (Gray and McNaughton, 2000; McNaughton and Corr, 2018). Internal computation and weighing of potential threat and reward values determine eventual behavior selection, such that greater threat value may result in *passive avoidance*, a defensive response that prioritizes inaction at the cost of forgone rewards.

3.3. Post-encounter

Encounter phase computations of threat value guide the *post-encounter* execution of appropriate defensive behaviors given available options (e.g., the presence of escape routes) and current goals (Blanchard et al., 2011; Mobbs et al., 2020; Fanselow et al., 1988). For example, a concrete threat of high proximity or magnitude calls for acute *active avoidance*, a prototypical, highly-conserved defensive response that reduces the likelihood of harm by preventing contact with the threat through actively removing oneself from the source of imminent danger (Cisek, 2019; Gray and McNaughton, 2000; Cain, 2019; LeDoux et al., 2017; Choi and Kim, 2010). Given adequate space and escape routes, animals will flee an approaching predator (Choi and Kim, 2010); likewise, humans will create distance from a potential attacker. Cross-species research indicates that the likelihood of eventual execution of behavior scales with proximity and magnitude of the identified threat (Mobbs et al., 2020; Mobbs, 2018; Hamm, 2019; Wendt et al., 2017; Choi and Kim, 2010; Hashemi et al., 2019). This scaling is accompanied by changes in autonomic responding reflecting sympathetic activation (e.g., increasing skin conductance, and muscle tone) alongside inhibitory parasympathetic activation (e.g., bradycardia, hypoventilation, and motor inhibition), and these are moderated by available behavioral options (Hamm, 2019; Abend et al., 2022a; Wendt et al., 2017; Benke et al., 2017; Klumpers et al., 2017; Meyer et al., 2019). Parasympathetic dominance is understood to act as a brake, allowing for increasing action preparation, but not execution; a threshold-based shift to sympathetic dominance (and parasympathetic withdrawal) occurs as behavior execution is necessary for safety, enabling its initiation (Roelofs and Dayan, 2022; Drabant et al., 2011; Roelofs, 2017; Evans et al., 2018).

The ability to maintain representations of more distal threats that do not yet require immediate, acute active avoidance provides space and time for more complex forms of avoidance to diminish the danger (LeDoux and Daw, 2018; Roelofs and Dayan, 2022; Pittig et al., 2020). For example, animals may use defensive burying to create distance from a fairly nearby threat (De Boer and Koolhaas, 2003); in other settings, animals and humans may exhibit defensive aggression or submissive behaviors towards a potential attacker to diminish the chances of being attacked (Weinshenker and Siegel, 2002; Herrnstein and Hineline, 1966; Gilbert, 2000; Russell et al., 2011). The evolved ability to mentally simulate future threats conferring sufficient potential danger to invoke defensive behaviors (e.g., social embarrassment during an upcoming public speaking event), provides opportunities for more instrumental, deliberative behaviors in the service of diminishing the future danger (Mobbs et al., 2020; Shuhama et al., 2019; LeDoux and Daw, 2018; Moulton and Kosslyn, 2009; Schubert et al., 2020). Such behaviors are often more elaborate, slow, and require action simulation to determine expected outcomes (LeDoux and Daw, 2018; Pittig et al., 2020), such as preparing and rehearsing a planned presentation (to avoid social embarrassment and rejection) or locking the front door (to avoid home invasion). The time afforded by mental simulation of future threats allows for iterative simulated (encounter-phase) threat assessment to diminish the chosen defensive behavior if it sufficiently reduced the perceived danger, or switch to simple active avoidance if mitigation failed and the threat has become highly proximal (Roelofs and Dayan, 2022; Livermore et al., 2021). As noted above, within the context of motivational conflict, reward-driven approach behaviors may be intertwined with instrumental active avoidance, generating cautious approach (risky foraging) (Gray and McNaughton, 2000; Mobbs and Kim, 2015; Choi and Kim, 2010).

3.4. Contact

Situations in which the threat is already in direct contact (i.e., attack; also referred to as circa-strike[1]), and preventative avoidance behaviors were not successful, invoke the immediate execution of acute, conserved, and stereotypic defensive behaviors, such as protean escape (uncoordinated flight burst, differing from active avoidance), defensive attack, and tonic immobility ("playing dead", as opposed to risk assessment-associated freezing during encounter, depending on available options (Gray and McNaughton, 2000; Mobbs et al., 2020; Blanchard and Blanchard, 1989; McNaughton and Corr, 2004; Hamm, 2019; Kalin, 2017; Silva and McNaughton, 2019). The all-or-none nature of activation of these simple, conserved behaviors suggests a threshold that is crossed following rapid, coarse computation (Mobbs et al., 2020; Evans et al., 2018). While post-encounter involves monotonically increasing physiological preparation for active avoidance execution, cross-species research indicates that threat contact is accompanied by phasic, systemic sympathetic discharge of physiological responses to support these acute behaviors, such as perspiration, hyperventilation, and tachycardia (Craske et al., 2009; Marks and Nesse, 1994; Hamm et al., 2016). In contrast, cognitive responses may be dampened since there is not enough time to carry out more sophisticated threat computations and nuanced goal-directed behaviors (Gray and McNaughton, 2000; Mobbs et al., 2020; Qi et al., 2018).

In summary, evidence gleaned from cross-species research supports a dynamic organization of defensive responses by threat imminence, whereby as a potential threat becomes increasingly imminent, defensive responses are differentially expressed. Of note, some responses may be observed in multiple phases, reflecting common supporting functions; for example, increased physiological arousal, to facilitate behavior execution, may be observed in all phases, but shows distinct temporal dynamics across phases (e.g., tonic, phasic, or monotonically increasing).

[1] The term 'circa-strike' is often used for the most threat-imminent phase of defensive responding. The term 'contact' was chosen here to disambiguate from preceding proximal-threat responses during post-encounter.

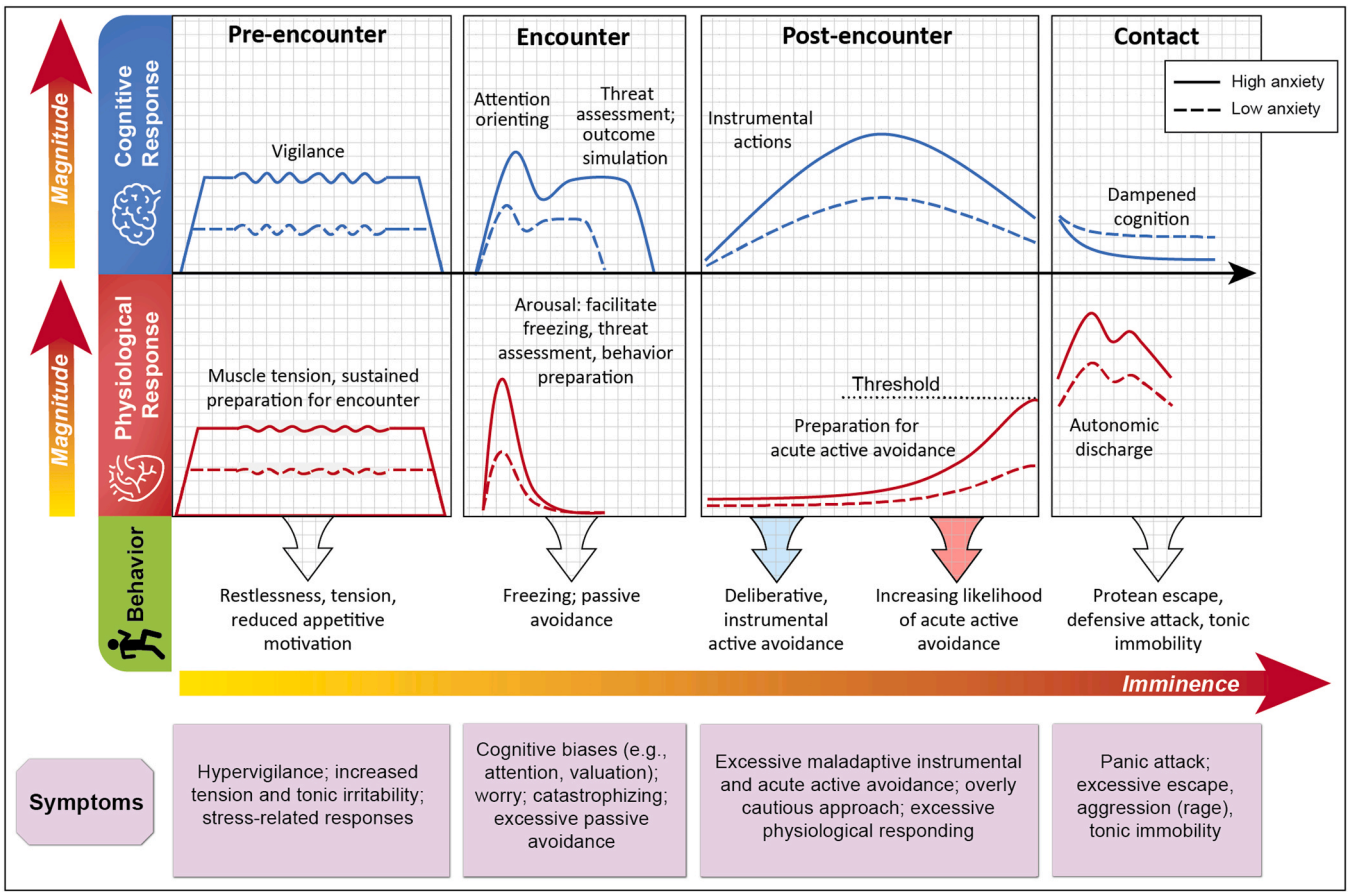


Fig. 1. Phases of threat imminence (defined along horizontal axis) are described in terms of magnitude of expression (vertical axis; from low to high magnitude) of cognitive (blue) and physiological (red) defensive responses, the behaviors they drive (green), and how these may be linked to anxiety symptoms and related responses (purple). Note that some symptoms may potentially occur in more than one phase. Solid and dashed lines describe expected intensity for individuals characterized by high and low levels of anxiety, respectively (note that anxiety severity, and magnitude of defensive responses, likely reflects a continuum).

4. Anxiety symptoms and excessive expression of defensive responses

According to the proposed framework, pathological anxiety reflects a tendency for exaggerated expression (i.e., greater magnitude and persistence) of otherwise normative defensive responses (Kenwood et al., 2022; Rosen and Schulkin, 1998; Blanchard, 2017). As such, as a threat becomes increasingly imminent, an anxious individual will show excessive expression of expected imminence-dependent defensive responses which follow the same organizing scheme (Fig. 1; Box 1). In other words, pathological anxiety as a disposition will dynamically vary in expression as a function of imminence of relevant threats. In the next section, empirical work linking specific anxiety symptoms to imminence-dependent defensive responses is reviewed.

4.1. Pre-encounter

Studies indicate that anxiety is associated with enhanced expression of defensive responses associated with *pre-encounter* states. Specifically, findings demonstrate exaggerated cognitive (e.g., hypervigilance, worry) and physiological (elevated autonomic levels) responding in such contexts, potentially reflecting excessive efforts to predict, detect, and prepare for aversive events (Grupe and Nitschke, 2013; Lang et al., 2000; Grillon, 2008, 2002; Abend et al., 2022a; Armstrong and Olatunji, 2012; Gorka et al., 2017; Robinson et al., 2013a; Roth et al., 2008). Thus, key clinical features of anxiety disorders such as heightened vigilance and muscle tension "in preparation for future danger" (APA, 2013) may be framed as aberrant *pre-encounter* responses. Likewise, excessive avoidance of contexts perceived as conferring threat is prominent in pathological anxiety, such as avoidance of social settings or separation from caregivers (APA, 2013; Kalin, 2017; Grillon et al., 2006; Neueder et al., 2019). Related maladaptive behaviors that arise during anticipation of potential threat, such as restlessness, difficulty relaxing, and tonic irritability, are observed in anxiety and may potentially be attributed to this phase (APA, 2013; Silver et al., 2021; Keeton et al., 2009). Relatedly, key aspects of "stress" may correspond to preparation for threat encounter, incldiuing Lu et al. (2021) stress-induced reduction in appetitive motivated behaviors (Hollon et al., 2015; Arnaldo et al., 2022; Pizzagalli, 2014), reflecting prioritization of survival functions, which is observed in anxiety and has been proposed as a possible mechanism linking anxiety and depression (Winer et al., 2017; Herhaus et al., 2022; Grillo, 2016). Enhanced *pre-encounter* responding may potentially promote stronger subsequent *encounter* and *post-encounter* responses (i.e., biased threat assessment leading to exaggerated avoidance behaviors), as reflected in context-potentiated startle responses (Grillon, 2002; Cornwell et al., 2017; Robinson et al., 2013a; Bublatzky and Schupp, 2012; Mkrtchian et al., 2017). Such a prepotent downstream effect is inherently adaptive as the cost of false-positive response cascade initiation is relatively low given the threat associated with the context (Nesse, 2005; Marks and Nesse, 1994).

States of sustained anticipation of potential threat can also impair certain cognitive functions such as working memory and attention control in healthy individuals, and could potentially account for such cognitive deficits observed in anxiety patients (Robinson et al., 2013a; Bishop, 2007; Moran, 2016; Pessoa, 2009; Hur et al., 2019). As noted

above, these deleterious effects may reflect the prioritization of threat detection over other goal-directed processes (Robinson et al., 2012, 2013b), although it remains a matter of debate whether such effects are specific to processing of threat (vs. non-threat) stimuli and which specific functions are affected and in what way (Robinson et al., 2013a; Anderson and Britton, 2020; Stout et al., 2020, 2013; Ward et al., 2020). For example, some work finds states of anticipation of unpredictable threat to impair attention control and other cognitive processing while other research finds improvement (Robinson et al., 2013b; Choi et al., 2012; Edwards et al., 2010; Miller and Patrick, 2000). Finally, subjective intolerance of the uncertainty associated with occurrence of future threat (e.g., if and when it will materialize) is a trait found to strongly relate to anxiety severity, suggesting a role for biased certainty and confidence in threat estimation in pathological anxiety (Grupe and Nitschke, 2013; Brosschot et al., 2016; de Lafontaine et al., 2022; Tanovic et al., 2018; Morriss et al., 2022).

4.2. Encounter

Different forms of excessive physiological, cognitive, and behavioral responses to threat observed in pathological anxiety may be attributed to aberrant defensive responses associated with the *encounter* phase. Stronger phasic physiological responses and attentive freezing in response to encounter with cues signaling potential threat have been linked to anxiety severity, particularly in fear-learning and unpredictable-threat paradigms which assess responses to onset of conditioned cues and startle probes, respectively (Roelofs and Dayan, 2022; Ojala and Bach, 2020; Lissek et al., 2005; Duits et al., 2015; Abend et al., 2022b). Learning theories specifically implicate aberrant fear conditioning and extinction of such cued responses in pathological anxiety (Duits, 2015; LeDoux, 2000; Milad and Quirk, 2012; Mineka and Oehlberg, 2008). Recent work also indicates that anxious individuals show stronger initial physiological responses to *detection* of potential-threat cues, occurring prior to actual threat assessment (Abend et al., 2020, 2022a); such findings support the notion of general enhanced encounter responsivity in pathological anxiety, at the cost of excessively high rates of unnecessary, false-positive initiation of the defensive response cascade (Nesse, 2005).

Observations of threat-related biases in otherwise normative cognitive processes underlying threat detection and assessment have inspired influential cognitive models of pathological anxiety, e.g (Wieser and Keil, 2020; Eysenck, 1992; Rapee and Heimberg, 1997). For example, evidence from emotional face paradigms suggests associations between anxiety severity and excessive allocation of attention to, and visual processing of, encountered threat cues, although inference is complicated due to inconsistent findings and effect sizes (Box 1) (Bar-Haim et al., 2007; Wieser and Keil, 2020; Armstrong and Olatunji, 2012; Abend et al., 2018; Michalowski et al., 2015; Clauss et al., 2022; Bantin et al., 2016). Considering threat imminence may begin to resolve such discrepancies, as early attention allocation during threat encounters may reflect enhanced threat vigilance (Armstrong and Olatunji, 2012), followed by threat avoidance during post-encounter (sustained attention) (Lisk et al., 2019; Mogg et al., 2004). Biases in several processes involved in threat valuation and probability assessment are commonly observed across anxiety disorders. These include, for example, inflated estimates of negative outcome likelihood and cost, and interpretation of ambiguous cues as conferring greater threat value (Grupe and Nitschke, 2013; Lissek et al., 2014; Hazlett-Stevens and Borkovec, 2004; Richards et al., 2001). Such biases have conceivably been "rewarded" through evolution as they ultimately promote survival, as noted above; however, in most situations, they result in unnecessary defensive mobilization, leading to functional impairment and distress, as observed in anxiety (Nesse, 2005).

As noted, we may begin to consider mental imagery and simulation of aversive outcomes as eliciting *encounter* responses within the threat-imminence framework. Much like physically perceived objects, imagery of future, simulated outcomes calls for assessment of threat levels to determine appropriate defensive responses. Cognitive biases in threat assessment of future outcomes could lead to inflated estimations of threat magnitude and probability of occurrence (Grupe and Nitschke, 2013) which then manifest as pessimistic expectations and catastrophizing cognitions associated with the clinical symptom of excessive worry observed across anxiety disorders (Grupe and Nitschke, 2013; Barlow, 2002; Holmes and Mathews, 2010; Moulton and Kosslyn, 2009; Davey and Wells, 2006; Wells, 1997). Difficulty in accurately estimating future threat magnitude and probability, especially in situations of significant uncertainty, could lead to repetitive invocation of threat assessment processes, contributing to the persistent and intrusive nature of worry in anxiety (Barlow, 2002; Shuhama et al., 2019; Davey and Wells, 2006; Wells, 1997). Similarly, worry has been suggested to reflect maladaptive attempts to simulate actions that will sufficiently mitigate the threat (problem solving) (Bishop and Gagne, 2018). Prioritized, repetitive threat assessment and preparation for defensive behavior may further be associated with observed deficits in cognitive flexibility and decision making in anxiety (Park and Moghaddam, 2017; Butts et al., 2013), as well as potentially underlie threat-related obsessive tendencies, a defining feature of obsessive-compulsive disorder (OCD) (APA, 2013); indeed, OCD is highly comorbid with anxiety disorders (Bartz and Hollander, 2006).

4.3. Post-encounter

Anxiety-related biases in encounter-phase threat appraisal, such as inflated threat cost and probability (Grupe and Nitschke, 2013), could lead to stronger downstream mobilization of defensive behaviors (Zorowitz et al., 2020; Arnaudova et al., 2017). Indeed, excessive expression of post-encounter defensive responses and their behavioral outcomes is a central feature across anxiety disorders (APA, 2013; Craske et al., 2009; Barlow, 2002; Abend et al., 2021b; Davey and Wells, 2006).

As noted, increasing proximity of a concrete, identified threat is associated with changes in sympathetic physiological responding to facilitate execution of active avoidance (Hamm, 2019). Indeed, excessive phycological responses to proximal threats are defining features of pathological anxiety (APA, 2013). For example, experimental manipulations of post-encounter threat proximity show that approaching internal/-interoceptive threats (i.e., induced dyspnea) and external/exteroceptive threats (i.e., noxious thermal stimulation) lead to exaggerated increases in physiological responses and execution of active avoidance in anxiety patients (Hamm, 2019; Abend et al., 2022a; Benke et al., 2017). Aside from acute forms of active avoidance, pathological anxiety is also associated with excessive expression of other, more complex and nuanced behaviors aimed at diminishing threat, such as defensive aggression, and submissive behavior (APA, 2013; Davis et al., 2010; Ottaviani et al., 2016; Russell et al., 2011; Schubert et al., 2020; Lau et al., 2012).

A more distal negative outcome that does not require immediate coping offers time for more complex forms of instrumental avoidance that will mitigate the threat (Sangha et al., 2020). Excessive execution of such behaviors is observed in pathological anxiety and may disrupt normative appetitive behaviors (APA, 2013; Herres et al., 2021); for example, in an effort to minimize potential social embarrassment, anxious individuals may spend excessive amounts of time in preparation and rehearsal before public speaking (APA, 2013). Similarly, perfectionism in school settings may be viewed as excessive means to diminish academic threat (e.g., not achieving academic goals) and is highly correlated with anxiety severity (Limburg et al., 2017). As with repetitive threat assessment, and perhaps due to it, excessive execution of certain instrumental defensive responses (e.g., excessive hand washing) may underlie OCD-related compulsions (APA, 2013; Bartz and Hollander, 2006).

Alternatively, rather than actively utilizing instrumental actions to mitigate future threat, individuals often engage strategies for effortful emotion regulation, i.e., sets of actions aimed to influence one's own

emotional experience (Gross, 1998). Anxiety is specifically associated with increased use of maladaptive regulation strategies, such as distraction, emotional avoidance, and suppression (Cisler et al., 2010; Kelly and Forsyth, 2009; Schäfer et al., 2017). These may reflect forms of post-encounter, 'internal' active avoidance behavior to diminish defensive responsivity to simulated, imagined negative outcomes which may be experienced as distressing, rather than actions to cope with the threat itself.

Within the context of approach-avoid conflicts, exaggerated threat valuation during the encounter phase (Grupe and Nitschke, 2013) should increase the tendency for passive avoidance behavior (i.e., diminished approach behavior) (Blanchard et al., 2011; Grupe and Nitschke, 2013; Bishop and Gagne, 2018; McNaughton et al., 2016). Indeed, excessive passive avoidance is a salient and impairing feature of pathological anxiety, whereby individuals prefer to forgo potential rewards (e.g., positive social interactions) due to the risk of aversive outcomes (e.g., social rejection) (APA, 2013; Livermore et al., 2021; Bishop and Gagne, 2018; Loijen et al., 2020; Aupperle and Paulus, 2010). Such maladaptive behavioral tendencies, especially to novel objects or situations, are observed at young age as childhood *behavioral inhibition* temperament (Kalin, 2017; Barker et al., 2015; Henderson et al., 2015) which confers greater risk for later pathological anxiety (Tang et al., 2020; Clauss and Blackford, 2012).

From a reinforcement learning perspective, major theories further propose that excessive and pervasive use of avoidance behavior, both in passive and active forms, precludes determination of (likely) eventual safety and the integration of such information into future threat assessments (LeDoux et al., 2017; Mowrer and Lamoreaux, 1946; Krypotos et al., 2015; Craske et al., 2018). This impedes normative extinction of learned threat contingencies, or correction of inaccurate beliefs, contributing to the persistence and maintenance of heightened threat responding in pathological anxiety (Blanchard et al., 2011; Pittig et al., 2020; Treanor and Barry, 2017; Bouton et al., 2001). For example, a non-anxious individual bitten once by a dog will extinguish their acquired fear of dogs through subsequent encounters with friendly dogs; an anxious individual is more likely to remain fearful since subsequent encounters elicit avoidance, precluding linking dogs with the experience of safety.

4.4. Contact

Acute physiological discharge and stereotypic defensive behaviors associated with threat contact are referred to clinically as panic attacks (APA, 2013; Barlow, 2002; Blanchard, 2017; Hamm, 2019; Hamm et al., 2016). In line with the notion of pathological anxiety reflecting excessive defensive responding, panic attacks indeed feature prominently across anxiety disorders in situations where danger is perceived as immediate and all but certain (APA, 2013; Barlow, 2002; Hamm et al., 2016; Bouton et al., 2001). As such, panic attacks may reflect excessive instantiation of perceived threat contact, which favors enduring many false-positives for a rare, actual danger (Nesse, 2005). The selection of which defensive behavior to pursue has been shown to depend on available options. Thus, laboratory studies demonstrate greater rates of escape behavior in anxiety patients in face of immediate, but escapable, threat (Hamm, 2019; Hamm et al., 2016). In contrast, excessive tonic immobility (or defensive immobilization) in anxiety is associated with threat contact situations perceived as inescapable (Moskowitz, 2004); relatedly, inescapable peritraumatic tonic immobility predicts later post-traumatic stress disorder (PTSD) symptoms (Van Buren and Weierich, 2015; Bovin et al., 2008; Lima et al., 2010). Defensive attack may correspond to reactive aggression and rage episodes observed in individuals with anxiety, as well as related conditions such as (phasic) irritability and PTSD (APA, 2013; Johnco et al., 2015).

5. Neural circuitry supporting defensive responding

The conserved nature of defensive responding offers opportunities for leveraging insight from translational, cross-species neuroscience research to identify potential pathophysiological mechanisms in anxiety (LeDoux and Pine, 2016; Adolphs, 2013; Mobbs, 2018; Robinson et al., 2019; LeDoux and Daw, 2018); but see (LeDoux and Pine, 2016; Fanselow and Pennington, 2017). As the scope of potentially relevant brain regions is wide (Grogans et al., 2023), this review is necessarily selective, and will focus on the most intensively scrutinized circuits (Fig. 2). It should be noted that inference on phase-specific functions is still limited due to experimental designs that do not allow for clear dissociations.

5.1. Pre-encounter

Translational research in rodents and humans focusing on contexts conferring potential threats implicates a network that includes hippocampus and amygdala, and contiguous cortices, in encoding and retrieving associations between environmental, interoceptive, and temporal contexts and aversive outcomes (Blanchard et al., 2011; Chavanne and Robinson, 2021; Maren et al., 2013; Marks et al., 2021; Zidda et al., 2018). Studies in humans invoking induced, sustained potential-threat anticipation compared to safe settings point to key involvement of amygdala and bed nucleus of stria terminalis (BNST) in such states, and their modulation of sensory gain in other regions to facilitate responsiveness to incoming information (Hamm, 2019; Grillon, 2008; Arnsten, 2009; Davis and Whalen, 2001; Shackman et al., 2016b). Electrophysiology work shows, for example, anxiety-related enhanced early processing of auditory stimuli, evidenced through mismatch negativity-evoked responses linked to auditory cortices and brainstem processing, and visual stimuli, assessed via effects on early-visual components to visual stimuli measured over occipital visual areas (Hamm, 2019; Robinson et al., 2013a). Importantly, anxiety-related effects on early processing in threat contexts are observed to both threat and neutral stimuli (Hamm, 2019; Robinson et al., 2013a), suggesting a potential-threat-induced hypervigilant state that impacts general sensory processing of incoming stimuli.

Complementing this work, recruitment of anterior insula and dorsomedial PFC and anterior cingulate cortex (ACC), as well as dorsal attention network nodes (e.g., dorsolateral PFC and parietal cortex), has been observed in humans and non-human primates when anticipating unpredictable threat, with variation in their coactivation linked to anxiety and modulation of physiological responses (Robinson et al., 2019, 2012; Balderston et al., 2020; Morriss et al., 2021). As such, it has been implicated in adaptively promoting and maintaining attentional vigilance and preparation for action, while its excessive activation has been suggested to contribute to pathological anxiety (Kenwood et al., 2022; Chavanne and Robinson, 2021; Davis et al., 2010; Robinson et al., 2013a). Not with standing these findings, additional research is required to directly link neural circuitry function to physiological and behavioral pre-encounter responses.

5.2. Encounter

A large body of research, primarily in rodents and humans, examines the circuitry subserving encounter responses. Initial object detection initiates activation of the sympathetic branch, primarily via widespread ascending and descending locus coeruleus (LC) noradrenergic projections (Roelofs and Dayan, 2022; Dayan and Yu, 2006). This facilitates phasic physiological responding, such as increased heart rate, through interactions of LC and amygdala with hypothalamus and other downstream structures, that accompany preparation for immediate mobilization of acute defensive behaviors subserved by amygdala-dorsal periaqueductal gray (PAG) and LC-spinal cord paths (Silva et al., 2016; Roelofs and Dayan, 2022; Dayan and Yu, 2006; Jones and Yang, 1985). Concurrently, LC and amygdala nuclei modulate cognitive functions by promoting cortical excitability that facilitates arousal, perception, and attention allocation (Roelofs and Dayan, 2022; Dayan and Yu, 2006; Pessoa, 2010). These activating effects are counteracted by

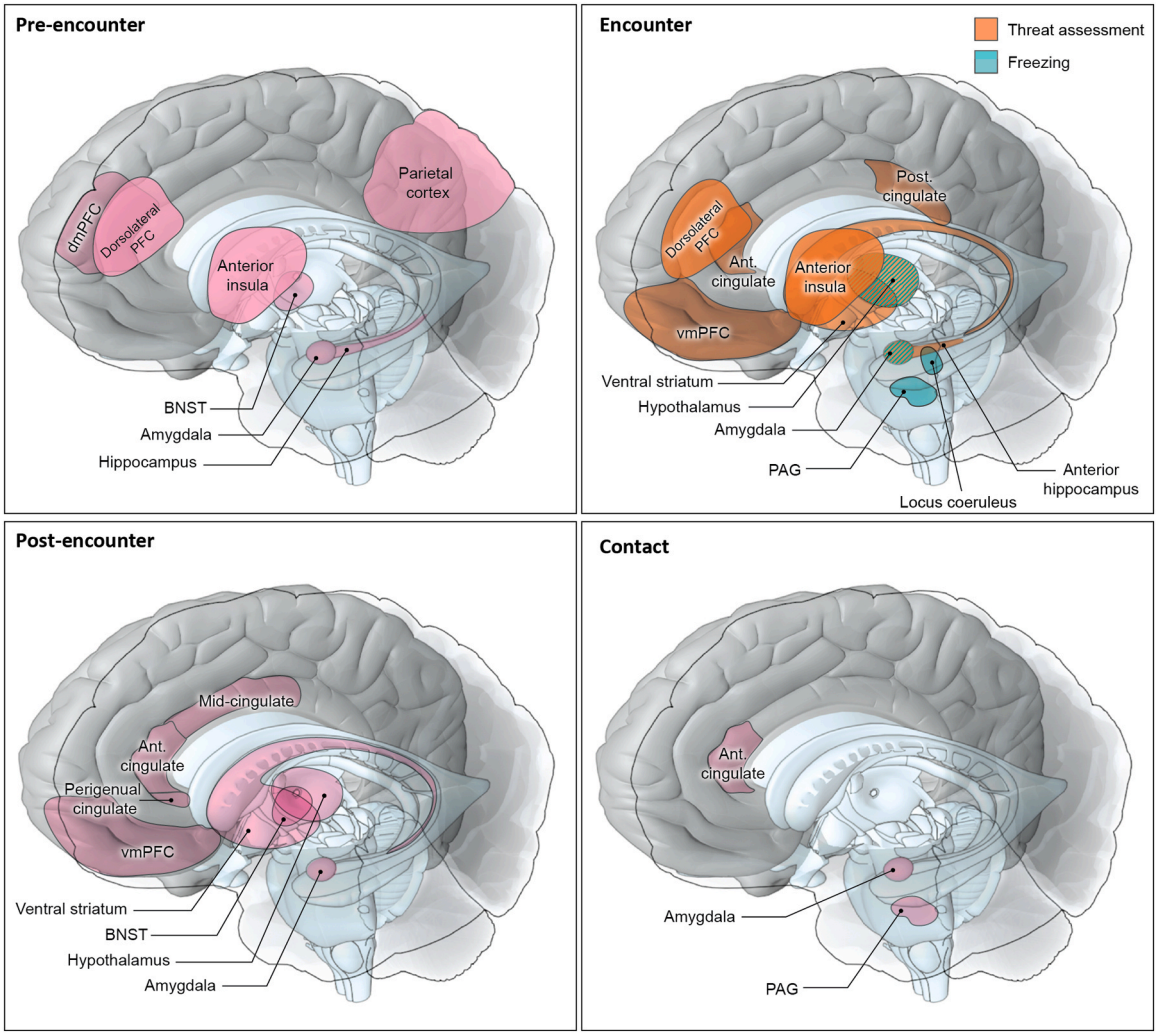


Fig. 2. Brain structures and regions hypothesized to play key roles in defensive responses associated with each phase of threat imminence. Additional structures and regions are likely involved; the subset depicted here has been more strongly associated with anxiety. Note: dmPFC = dorsomedial prefrontal cortex; PFC = prefrontal cortex; BNST = bed nucleus of the stria terminalis; Ant. = anterior; Post. = posterior; PAG = periaqueductal gray.

parasympathetic branch function involving basal forebrain and ventral PAG pathways, providing rapid inhibition of responding and attentive freezing behavior (Roelofs and Dayan, 2022; Deolindo et al., 2011; Tovote et al., 2016). This sympathetic-parasympathetic balance enables more elaborate assessment of threat levels and nuanced selection of behavior when threat is ambiguous or during approach-avoid conflicts (see below) (Roelofs and Dayan, 2022).

A key role in detailed processing of threat-relevant cues (e.g., conditioned cues) is attributed to basolateral and central amygdala activity, particularly in conjunction with ventromedial prefrontal cortex (vmPFC), as revealed from research in rodents, non-human primates, and humans (LeDoux and Daw, 2018; Shackman et al., 2016b; Fox et al., 2015; Milad and Quirk, 2012; Phelps, 2006; Hagihara et al., 2021; Fullana et al., 2016; Bruhl et al., 2014). This circuit is part of a broader network mediating threat valuation and selection of motivated behaviors that considers multiple object features given internal and external contexts, with key subcortical nodes additionally including ventral striatum, hypothalamus, and ventral hippocampus (LeDoux, 2000; Averbeck and Murray, 2020; Pessoa, 2010; Phelps, 2006). Research in rodents, non-human primates, and humans further suggests the integration of subcortical input in vmPFC/orbitofrontal cortex and septum, anterior cingulate, and anterior insula during valuation-driven cognitive functions such as encoding of future aversive and appetitive outcomes and probability, conflict monitoring, and mediation of approach-avoid conflict resolution and broader decision making (Grupe and Nitschke, 2013; McNaughton and Corr, 2018; Fiddick, 2011; Corr, 2013; Tashjian et al., 2021; Drabant et al., 2011; Pujara et al., 2019; Bissonette et al., 2014; Rangel and Hare, 2010; Keefer et al., 2021). Activation of posterior cingulate cortex during potential-threat encounter (Meyer et al., 2019; Fullana et al., 2016; Mobbs et al., 2010; Limbachia et al., 2021; Murty et al., 2022) may reflect the relevance of environmental context and spatial information during threat assessment (Vogt et al., 1992; Pearson et al., 2011). Aberrant function in this circuitry has been linked to threat-related biases in such cognitive functions (Grupe and Nitschke, 2013; McNaughton et al., 2016; Aupperle and Paulus, 2010; Pelletier and Fellows, 2021) as well as to pathological anxiety, and particularly with respect to aberrant amygdala connectivity with vmPFC and dorsal PFC, potentially indicating dysregulated threat assessment (Kenwood et al., 2022; Kalin, 2017; Aupperle and Paulus, 2010; Gold et al., 2020, 2016; Etkin et al., 2011; Myers-Schulz and Koenigs, 2012). Cross-species work further suggests that aberrant reinforcement-based updating of threat value, subserved in part by amygdala-vmPFC function, is linked to anxiety, and hypothesized to play a key role in its etiology and treatment (Kenwood et al., 2022; Levy and Schiller, 2021; Abend et al., 2022b; Milad and Quirk, 2012; Casey et al., 2015).

Limited literature directly examines mental imagery of potential negative outcomes associated with abstract or distal potential threats. Extant work on negative imagery and worry cognitions suggests the

involvement of nodes of the 'default mode network' (DMN), primarily including anterior and posterior cingulate cortices, and their interaction with emotion regulatory cortical regions such as lateral PFC (Bijsterbosch et al., 2014; Weber-Goericke and Muehlhan, 2019; Makovac et al., 2020; Wilson-Mendenhall et al., 2013). Additional work further implicates amygdala and PAG activation and functional connectivity with DMN hubs and lateral PFC during induced threat imagery and worry (Shuhama et al., 2016; Meeten et al., 2016).

5.3. Post-encounter

Expression of physiological responses to a specific, proximal threat have been robustly and causally linked to vmPFC, and particularly its caudal sector, via its regulation of downstream structures including amygdala, hypothalamus, and brainstem nuclei, as shown in non-human primates and humans (Kenwood et al., 2022; Kalin, 2017; Myers-Schulz and Koenigs, 2012; Alexander et al., 2020; Orem et al., 2019). The maintenance of parasympathetic dominance until acute active avoidance execution is deemed necessary has been associated with ACC and adjacent mPFC regions (Roelofs and Dayan, 2022; Hashemi et al., 2019; Bagur et al., 2021). Complementing such work, rodent and human research suggests that the amygdala and perigenual cingulate cortex, adjacent to vmPFC and ACC, mediate the shift from parasympathetic to sympathetic dominance which facilitates the execution of active avoidance (Roelofs and Dayan, 2022; Livermore et al., 2021; Hashemi et al., 2019). vmPFC has likewise been linked to gating of acute active avoidance through projections to ventral striatum, a key structure implicated in executing motivated behaviors, as part of a circuit that also includes amygdala nuclei, anterior insula, multiple cingulate sectors, and premotor cortices (Tovote et al., 2015; Hur et al., 2020; Mobbs et al., 2020; Shackman et al., 2016a; Livermore et al., 2021; Diehl et al., 2019). Indeed, function in different nodes in this network has been shown to be dynamic and sensitive with respect to threat proximity (Hur et al., 2020; Mobbs et al., 2020; Adolphs, 2013; Hamm, 2019; Meyer et al., 2019). For example, research across species shows that as a threat is perceived to get closer, amygdala, BNST, and anterior/mid-cingulate and motor cortices are increasingly engaged, potentially to support the expected execution of active avoidance (Hur et al., 2020; Hamm, 2019; Wendt et al., 2017; Meyer et al., 2019; Qi et al., 2018; Rahman et al., 2021; Mobbs et al., 2009, 2007); conversely, some work shows parametrically decreasing activation in vmPFC and posterior cingulate cortex with threat proximity (Meyer et al., 2019; Mobbs et al., 2010). Of note, studies implicate PAG in preparation and execution of active avoidance in humans (Mobbs et al., 2020; Wendt et al., 2017; Hashemi et al., 2019; Meyer et al., 2019; Hur et al., 2019), potentially via interaction between its ventral and lateral divisions (Silva and McNaughton, 2019); however, these findings need to be reconciled with animal work linking PAG specifically to contact-driven escape (Diehl et al., 2019).

Anxiety severity has been found to moderate the association between amygdala-vmPFC intrinsic functional connectivity and magnitude of proximity-dependent increases in physiological response (Abend et al., 2022a). Similarly, anxiety moderates connectivity among amygdala, BNST, and vmPFC during cued anticipation of unpredictable outcomes (Clauss et al., 2019; Williams et al., 2015). Converging work in animals shows that induced vmPFC over-activation (mimicking pathophysiological states) results in increased amygdala and hypothalamus activity accompanied by altered physiological responses to post-encounter threat (Alexander et al., 2020), highlighting the importance of this region in orchestrating the expression of active avoidance.

5.4. Contact

The expresssion of acute, contact-driven defensive behaviors is similar across a variety of species, suggesting the involvement of highly-conserved circuitry (Mobbs et al., 2020). PAG, through amygdala and hypothalamus paths, has been robustly implicated in generating escape, aggression, and tonic immobility across species (Mobbs et al., 2020; McNaughton and Corr, 2004; Evans et al., 2018; Silva and McNaughton, 2019; Qi et al., 2018). Electrical stimulation of PAG in humans evokes acute physiological responding (e.g., increased sweating, heart rate, and respiratory rate), as well as fear of death and desire to flee, which closely resemble panic attacks (Schenberg et al., 2014). Further, PAG structural and neurochemical abnormalities are associated with a proneness for panic attacks in patients (Del-Ben and Graeff, 2009). Medial sections of PFC, including ACC, and insula additionally project to PAG (Faull and Pattinson, 2017); given their roles in threat assessment (see above), these regions may mediate the initiation of contact-driven defensive behaviors (Roelofs and Dayan, 2022).

The findings reviewed above suggest the involvement of several conserved neural circuits in imminence-dependent defensive responding, and indications for anxiety moderation of aspects of these circuits. These findings also show that some brain structures, as well as activated biological systems (e.g., autonomic physiology), are involved in multiple imminence phases, potentially pointing to shared original functionality that, over time, became more intricately controlled to support distinct functions (Cisek, 2019). Additional research is needed to link anxiety to specific aberrant function in defensive response circuitry, and test different theoretical models. For example, a central, restricted mechanistic perturbation (e.g., amygdala dysfunction (LeDoux, 2000)) may give rise to aberrant function of multiple defensive responses; alternatively, it may be the case that functional perturbation independently spans multiple, distributed brain systems (Grupe and Nitschke, 2013). Considering threat imminence in study designs may allow for stronger inference on the involvement of specific circuitry in different forms of aberrant defensive responding (Box 2).

6. Summary

Here, it is posited that anxiety symptoms could be understood as reflecting the excessive, maladaptive expression of otherwise normative threat-anticipatory defensive responses, and as such could be organized by threat imminence. Such an organization could enhance our theoretical understanding of pathological anxiety by providing a testable framework within which different aspects of symptom presentation and psychobiological correlates are hypothesized to occur and interact.

From a clinical perspective, this framework may begin to resolve challenges in anxiety phenomenology (e.g., individuals are not expected to continually express a certain subset of symptoms; rather, different symptoms are expressed over time as a specific threat is becoming, or is perceived as becoming, more imminent), imprecise terminology (e.g., 'fear' vs 'anxiety'), and high comorbidity (since anxiety may reflect a tendency for defensive responsivity, similar symptom expression patterns are expected for different sources of harm). By generating more specific expectations of symptom expression, treatments may be developed to target specific symptoms with greater precision (Box 2).

A symptom framework rooted in partially conserved biological mechanisms also lends itself to translational neuroscience research on pathophysiology (Box 2). Anxiety research in humans may benefit from focusing on symptoms that correspond to conserved patterns of defensive responses as these may track more closely with function in specific neural circuits (Kenwood et al., 2022; Robinson et al., 2019). For example, a circuit containing the amygdala, hippocampus, and vmPFC has been robustly linked to defensive responses in animals and humans and to pathological anxiety (Kenwood et al., 2022; Milad and Quirk, 2012; Hagihara et al., 2021; Myers-Schulz and Koenigs, 2012), but further refinement is needed in order to link function within it to distinct, symptom-relevant responses. Likewise, induction of context-based *pre-encounter* states elicits robust insula, ACC, and BNST activation in humans and animals (Chavanne and Robinson, 2021); such findings could guide research linking function in this circuitry to *pre-encounter* symptoms such as hypervigilance and heightened tension

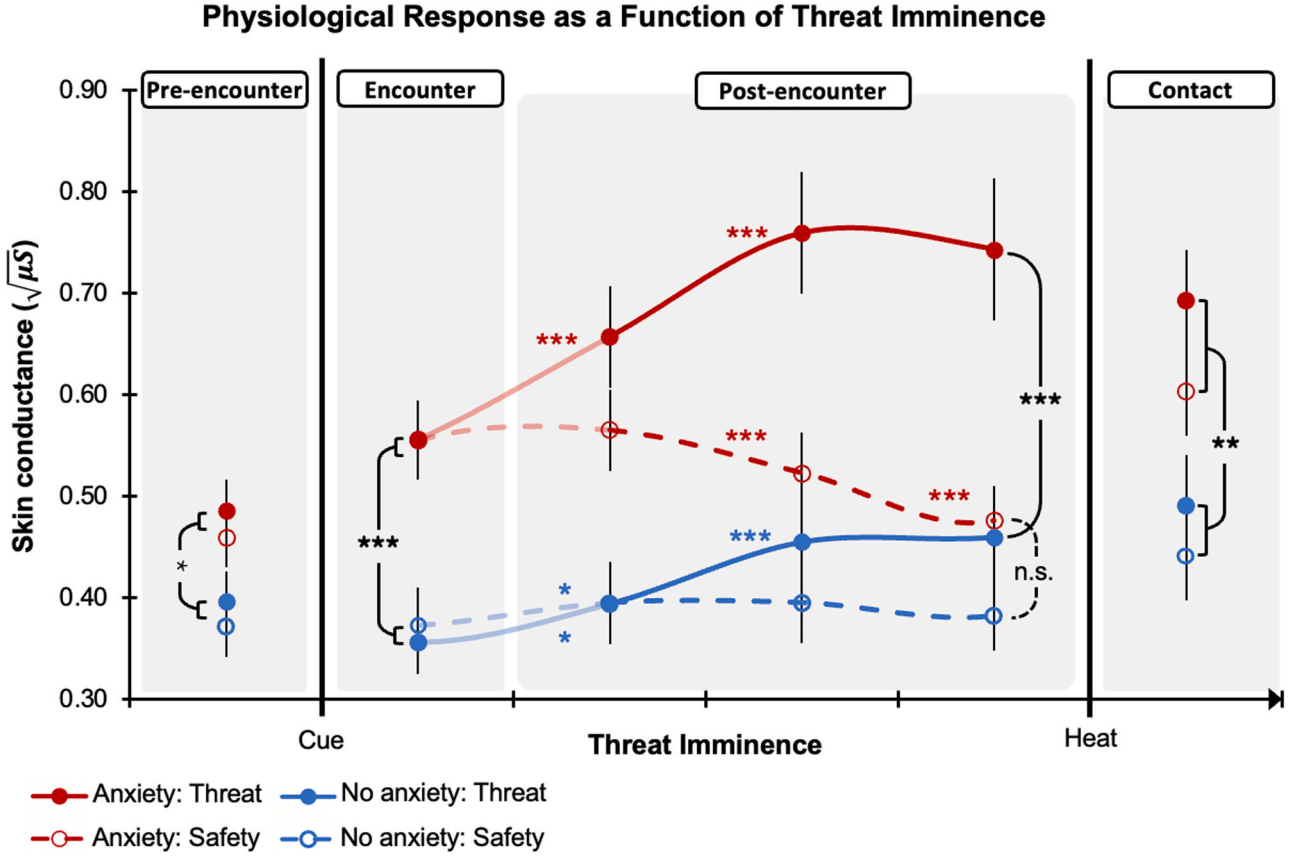
(Robinson et al., 2013a). Reliable cross-species biomarkers may then pave the way for development of novel targeted interventions (Xia and Kheirbek, 2020; Abi-Dargham and Horga, 2016).

Finally, it should be noted that the proposed framework does not attempt to replace other models of pathological anxiety; rather, it is intended to complement and integrate other conceptualizations of psychopathology that emphasize different theoretical and methodological considerations. Thus, this framework attempts to link the detailed phenomenology offered by psychiatric nosology (APA, 2013), with biologically-inspired approaches, such as Research Domain Criteria (RDoC) (Insel et al., 2010; Cuthbert, 2015) which aims to classify psychopathology based on dimensions of observable behavior and neurobiological measures. These perspectives are considered in light of comparative biology and evolutionary perspectives on anxiety (Nesse, 2005; Adolphs, 2013; Mobbs, 2018; LeDoux, 2000), as well as cognitive and motivational-behavioral models of anxiety (Gray and McNaughton, 2000; Barlow, 2002; Wells, 1997; McNaughton et al., 2016). Finally, this framework aligns with the rationale behind reductionist classification approaches that attempt to identify core, shared elements among different symptom manifestations, such as the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2021). Together, the proposed framework draws from the many perspectives on anxiety and the unique advantages each offers to form an integrative approach to understanding anxiety symptoms.

Box 1: empirical data on threat imminence, defensive responding, and pathological anxiety

As an example of research linking imminence-dependent defensive responding and anxiety, in recent work (Abend et al., 2022a), we examined physiological responding in 50 youths who were either free of any psychiatric diagnoses (healthy group) or diagnosed with social, separation, and/or generalized anxiety disorder (unmedicated, treatment-seeking; anxiety group). All participants completed a task whereby instructed cues signaled the upcoming delivery of non-painful (safety) or highly painful (threat) thermal stimulation. This design enabled us to compare groups in terms of responses at different threat-imminence phases, as shown in the accompanying Figure. Physiological response was quantified in sequential bins as average skin conductance signal relative to its tonic level.

During *pre-encounter*, when onset of cues that may signal threat was expected, the anxiety group showed greater responding than the healthy group. This group effect became stronger during *encounter* (that is, to onset of cues signaling threat or safety); no cue effect was observed at that point, suggesting that anxious individuals' enhanced encounter arousal is relatively non-specific and occurs *prior* to threat differentiation. The presence of a group effect but no cue effect highlights exaggerated responding at the cost of many false-positives (safety trials). During the *post-encounter* epoch, the groups showed different patterns of arousal. Among anxious individuals, arousal increased as threat became more proximal, and decreased as the safe outcome became more proximal, with threat differentiation becoming maximal at the moment of highest outcome proximity. This pattern was substantially attenuated in the healthy group. Importantly, group effects on physiological responses also manifested as dimensional associations with continuous symptom severity scores. Finally, response to the painful stimulation itself, i.e. *contact*, was significantly greater in the anxiety group. Together, these findings indicate different anxiety-related and imminence-dependent patterns of defensive responding, underscoring the value of considering dynamic responses across the threat imminence continuum.



Changes in physiological response by threat imminence in individuals with and without anxiety disorders. Threat-imminence phases were defined as epochs (demarcated in gray boxes) relative to cue and thermal stimulation onset in which skin conductance was indexed. Data

points and lines reflect response to threat (highly painful heat; solid lines) and safety (non-painful heat; dashed line), for the anxiety (red) and healthy comparison (blue) groups. Data presented reflect physiological activation already accounting for individual differences in local tonic (baseline) responding. Distance between X-axis ticks is 2 s. *Note*: * , $p < 0.05$, * *, $p < 0.01$, * ** , $p < 0.001$. Colored asterisks reflect within-group changes; black asterisks reflect between-group effects. Data adapted from prior work (Abend et al., 2022a).

Reviews and meta-analyses examine links between anxiety severity and magnitude of specific cognitive and physiological responses during different phases of encounter with potential threat. *Pre-encounter* is typically modeled using sustained unpredictable-threat (relative to safety) paradigms that robustly elicit elevated subjective anxiety (Robinson et al., 2019; Grillon et al., 2019). Meta-analysis of functional imaging studies indicates an overlap between such induced states in healthy individuals and findings in anxiety patients that manifests primarily in anterior and mid-cingulate and inferior frontal gyrus (IFG)/insula cortices (Chavanne and Robinson, 2021). Given the purported roles of cingulate and IFG in selection and control of behavior (Cavanagh and Shackman, 2015) and of the insula in representing salience and mediating physiological homeostasis (Oppenheimer and Cechetto, 2016), such findings may potentially reflect anxiety-related enhanced motor and somatic preparation for action should salient stimuli be detected in a context in which potential threat might occur (Chavanne and Robinson, 2021).

Several meta-analyses examine cognitive responding in anxiety that may correspond to the *encounter* phase (although it may be difficult to sufficiently distinguish those from *post-encounter* processes). Anxiety was found to moderately relate to bias towards threat in early allocation of attention measured using reaction-time (ß=0.08 in 1291 youths (Abend et al., 2018); d= 0.45 assessed across 2263 individuals and various anxiety disorders (Bar-Haim et al., 2007)) and (eye-tracking-derived) initial fixations (g=0.47, N = 1085 (Armstrong and Olatunji, 2012)) measures; with a bias away from threat in sustained attention processes (free-viewing dwell time in youths with anxiety disorders, g=0.26, N = 798 (Lisk et al., 2019)); with interpretation bias (self-generated text to ambiguous scenarios in youths with anxiety disorders; d=0.62, N = 11,507 (Stuijfzand et al., 2018)); and with behavioral measures of conditioned fear over-generalization (g=0.24, N = 867 across anxiety disorders (Cooper et al., 2022)).

Physiologically, comparison of anxiety patients to controls (N > 2000) indicated excessive responding (skin conductance response or electromyography startle response) to conditioned safety, d= 0.30, and threat, d= 0.35, stimuli during the conditioning and extinction phases of fear learning, respectively (Duits et al., 2015), which may primarily reflect learned *encounter* responses. That is, across fear learning paradigms, the assessment of threat value ascribed to reinforced cues changes (increasing threat during conditioning; decreasing threat during extinction) in an anxiety-dependent manner. Neurally, meta-analyses of fMRI studies examining neural responses to anxiogenic stimuli (Ns=1993, 873, and 327 including patients and controls) reveal differences in circuitry components implicated in encounter responses, including amygdala, insula, vmPFC, and ACC, as well as parietal cortex (which may reflect attentional components) (Bruhl et al., 2014; Gentili et al., 2016; Ipser et al., 2013). fMRI meta-analyses of responses to conditioned and extinguished threat cues in healthy individuals likewise reveal consistent ACC, insula, and vmPFC, as well as PAG, hippocampus, and additional structures implicated in threat assessment (Fullana et al., 2016, 2018), but a meta-analysis comparing anxious and healthy individuals is needed to identify specific pathophysiology.

Meta-analysis of acute social stress, comparable to imminent-threat *post-encounter*, indicated sex-dependent effects on cortisol release in 372 anxiety patients and controls (SMD=0.50 (Zorn et al., 2017)). Here, as well, imaging studies on specific *post-encounter* and *contact* processes in anxious individuals are needed to enable meta-analytic inference on neural circuitry. Together, extant meta-analytic findings using behavior, eye-tracking, physiology, and neuroimaging (where available) indicate consistent anxiety-related differences in patterns of imminence-specific responses to potential threat.

Box 2: implications for research

Practical considerations for research can be drawn from the organization of anxiety symptoms by threat imminence. Given that specific symptoms may reflect excessive expression of distinct imminence-dependent defensive responses, it is critical to qualify which phase or process is evoked and modeled in experimental paradigms. For example, paradigms examining cued (learned or instructed) physiological responses to threat typically index responses as an aggregate across a window of several seconds, which may encompass multiple effects related to *pre-encounter*, *encounter*, and *post-encounter*. Collapsing responses across several phases may diminish sensitivity to detect expected pathological anxiety effects on conditioned responses to threat (vs. safety) cues, potentially contributing to inconsistent findings observed across studies (Abend et al., 2020; Lissek et al., 2005; Duits et al., 2015; Dvir et al., 2019); analysis of conditioned response dynamics could potentially improve detection of anxiety effects (Abend et al., 2022a) (Box 1).

Relatedly, studies commonly aim to engage "threat processing" neural circuitry, broadly defined, by presenting pictures of different emotional faces. Yet, such manipulations may primarily elicit *encounter* responses characterized by a general, non-specific initial response to cue detection, with threat-based differentiation in responses emerging only later (Abend et al., 2022a; Leuchs et al., 2019; Krause et al., 2018); this may account for issues relating to small effect sizes (Haller et al., 2022). Modeling neural activation in a phase-specific manner (e.g., using a phasic impulse model for *encounter* responses, and a sustained- or increasing-response model for *post-encounter* activation) could potentially better capture the underlying psychobiological processes (Hur et al., 2020).

Physiological responses provide primary readouts in research on defensive responding (Ojala and Bach, 2020). Given phase-specific response patterns (e.g., tonic vs phasic responding), it is important to consider which readout to use to capture the process of interest. For example, eye-blink startle response has been consistently used for indexing anxiety effects during evoked threat-anticipatory states or contexts, such as variants of threat-of-shock tasks (Robinson et al., 2019; Grillon, 2008). In contrast, skin conductance response and pupil dilation may capture phasic responses to onset of cues signaling potential threat, and thus may be particularly useful in paradigms targeting *encounter* responses (Ojala and Bach, 2020; Newsome et al., 2023). Temporal changes (e.g., increase or decrease) in skin conductance levels, pupil dilation, muscle

tone, and heart rate may be useful in capturing response dynamics during *post-encounter* epochs in which the threat is becoming increasingly proximal (Hamm, 2019; Abend et al., 2022a; Krause et al., 2018). As noted, different models of neural (BOLD) responses may likewise be differentially suited to capture processes of interest (Hur et al., 2020).

In addition to basic and clinical research on normative and pathological defensive response mechanisms, the proposed framework can potentially guide research on treatment for pathological anxiety (Robinson et al., 2019). For example, cognitive-behavioral therapy (CBT) is a first-line treatment for anxiety but shows variable response rates (Loerinc et al., 2015), highlighting the need for improving treatment efficacy. Given that CBT emphasizes maladaptive cognitions and behaviors, it may be complemented by a symptom framework that enables patients and therapists to better anticipate, and target, cognitive and behavioral symptoms when these are expected to manifest as a function of imminence of a relevant, identified threat. This approach is in line with therapeutic protocols that integrate different treatment modules depending on symptom presentation (Weisz et al., 2012), as different modules may be applied to phase-specific symptoms. Further, it could pave the way for standardized, multi-modal measurements of symptom severity, previously proposed as means to generate more accurate assessment of functioning and treatment response (Loerinc et al., 2015). Finally, given the conserved nature of defensive responding, considerable translational research aims to improve anxiety treatment through cross-species behavioral and pharmacological research (Grillon, 2008; Craske et al., 2018). Specifying mechanisms that are central to the aberrant expression of defensive responses in each threat-imminence phase could inform research on developing targeted treatments (e.g., drugs that diminish *pre-encounter* potentiation of *encounter* responses that may drive further "downstream" excessive responding).

Data Availability

No data were used for the research described in the article.

Acknowledgements

I would like to thank Daniel S. Pine, Ellen Leibenluft, Julia O. Linke, Simone P. Haller, Katharina Kircanski, and Naomit Lily Omri for valuable conversations and insightful suggestions, and the Editors and Reviewers for their time and helpful contributions. This work was supported by the Brain & Behavior Research Foundation (Young Investigator award 28239) and (in part) by the Intramural Research Program of the National Institute of Mental Health (ZIAMH002781-15).

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