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Translational cross-species evidence of heart-related dynamics in threat learning

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ABSTRACT

Fear engenders a vast array of autonomic responses in organisms, which are elicited by the presence of threat. Among these responses, heart rate is influenced by the presence of dangerous events as well but can be modulated based on environmental and internal circumstances. This process, while present across different species, may be subtended by partially different neural mechanisms. Here, we outline a perspective regarding the similarities between human and rodent evidence, which suggests the role of the prefrontal cortex and the insula as central hubs in the modulation of threat responses. However, current disparities between human and animal research preclude drawing definitive parallels, motivating further research with sophisticated neuroimaging and *in vivo* calcium imaging. Finally, clarifying the cross-species convergence of autonomic regulation may help refine translational models of anxiety and its treatment. Thus, we provide a conceptual framework to bridge cross-species differences and summarize the key brain areas underlying threat-induced autonomic changes, with emphasis on their translational relevance for psychopathology.

1. Neural patterns of rodent and human learned threat

In the animal kingdom, a remarkable phenomenon emerges when confronted with potential threats. Individuals of several species exhibit a myriad of autonomic responses, encompassing physiological changes like alterations in heart rate, pupil dilation, and fluctuations in skin conductance (Bolles, 1970; Fanselow and Helmstetter, 1988). While unconditioned fear responses emerge in the presence of immediate danger, learned threat involves the association of previously neutral stimuli with aversive outcomes. In addition, behavioral adaptations come into play, exemplified by the instinctual choices of fight, flight, or freeze (Borkar and Fadok, 2024; Roelofs, 2017). Cognitive responses also manifest, with individuals experiencing states of anxiety, distress, and even panic. This structured interaction of autonomic, behavioral, and cognitive processes constitutes a finely tuned survival mechanism across species (Adolphs, 2013). Therefore, by integrating these diverse aspects, organisms can effectively detect, assess, and respond to danger in their environment. These adaptive reactions collectively optimize the chances of survival, enabling animals to navigate hazardous situations and endure impending threats (Flavell et al., 2022; Maren and Quirk, 2004). The aim of this review is to synthesize translational evidence on the neural mechanisms that modulate heart-related dynamics during threat learning in humans and rodents. Therefore, we focused on key brain structures including the prefrontal cortex, insula, amygdala, and hippocampus, and examine how their coordination shapes autonomic and behavioral responses to threat, highlighting species-specific differences and limitations in current methodologies, with a view toward improving future translational models.

Threat conditioning is a psychological process in which an individual learns to associate a neutral stimulus with a threat-inducing event, leading to the development of a fear response (Bach et al., 2023; LeDoux, 2014; Lonsdorf et al., 2017). Evidence suggests that threat conditioning

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elicits a variety of psychophysiological changes, among which heart rate dynamics constitute a crucial and unique physiological response among different species (Battaglia, Nazzi, Lonsdorf, et al., 2024; Signoret-Genest et al., 2023). When an individual is exposed to a conditioned stimulus, like a neutral sound coupled with an aversive event, the brain triggers the response of the autonomic nervous system. In this context, it regulates visceral functions including heart rate through two complementary branches: the sympathetic and parasympathetic systems. Sympathetic activation increases heart rate via noradrenergic signaling to the sinoatrial node (SA-node) of the heart. On the other hand, parasympathetic activity, primarily mediated by the vagus nerve, decreases heart rate. Consequently, response to an aversive event may prompt either an increment or reduction in heart rate, priming the body for fight-or-flight reactions. Although it is well known that threats typically induce tachycardia - an acceleration of heart rate - to prepare the body for action, recent evidence has shown that, prior to this, threat triggers a transient bradycardia - a slowing of the heart rate - via vagal activation, known as fear-induced bradycardia (Battaglia et al., 2022; Castegnetti et al., 2016). Crucially, both cardiac responses support defensive adaptation: tachycardia facilitates mobility and action readiness, while bradycardia enhances perceptual focus and stillness in anticipation of the subsequent action (for a comprehensive review on this phenomenon see Battaglia, Nazzi, Lonsdorf, et al., 2024). This threat learning system operates alongside safety learning, the process by which neutral stimuli acquire predictive value for the absence of threat, enabling adaptive inhibition of fear responses in non-threatening contexts (Laing and Harrison, 2021). While threat conditioning involves associative learning of danger signals, safety learning represents an active form of conditioned inhibition that requires discrimination between threat and safety cues, engaging distinct neural circuits (Tashjian et al., 2021).

Studying these complementary processes through heart rate dynamics provides valuable insights into the physiological mechanisms underlying threat learning and its modulation. Although these concepts have long been firmly established in scientific literature, it is important to acknowledge the possibility of variations in functional neuroarchitecture of the brain between humans and rodents when facing aversive events, along with technical limitations from using functional neuroimaging in humans, in particular for the prefrontal and insular cortices.

In rodents, evidence has proposed a key role of the insular cortex in regulating brain function, heart rate changes, and behavioral responses to threats. Klein et al. (Klein et al., 2021) has proposed that in rodents, the complex orchestration of responses to contextual danger signals involves a multifaceted interplay involving the insular cortex. This suggestion is particularly significant as it highlights the insular cortex as a critical component alongside historically acknowledged subcortical brain structures such as the amygdala and hippocampus in these psychophysiological processes (Christianson, 2021; Klein et al., 2021). Accordingly, the amygdala is relevant for threat evaluation, and the hippocampus contributes to contextual encoding and memory integration, providing spatio-temporal information to the prefrontal-amygdala circuit (Orsini et al., 2011; Sánchez-Bellot et al., 2022). Specifically, Klein's research demonstrated that the insular cortex not only plays a crucial role in integrating information related to modulation of heart rate dynamics, transmitted via vagal projections, but it also facilitates the induction of freezing behavior as a defensive response having direct projections with the amygdala (Nicolas et al., 2023). Therefore, the integration of these processes, potentially within the insular cortex, may contribute to the modulation of responses to danger. In this context, the insula has been proposed as a crucial component in a cortical circuitry of higher-order functioning, exerting an indirect influence on behavior through the recruitment of executive resources and psychophysiological responses (Gogolla et al., 2014; Park et al., 2024). Also, Klein's findings indicate that the reactivity of the insula to a cue associated with threat is influenced by the integration of predictive information conveyed by the threat-conditioned stimulus, which is further modulated by negative bodily feedback signals during freezing responses. Moreover, the differential responsiveness of the insula to the conditioned stimulus may arise from the stronger negative bodily feedback signals received by the insula during frequent episodes of freezing, which is a characteristic behavior observed in high-fear animals.

In rodents, the insular cortex receives robust inputs from specific thalamic and brainstem nuclei responsible for transmitting visceral and cardiovascular signals from the periphery to the brain (Gehrlach et al., 2020; Livneh and Andermann, 2021). Besides its role in threat processing, evidence also supports its central role in the elaboration of safety-related information in rodents (Christianson et al., 2008; Christianson and Greenwood, 2014). Also, evidence from studies conducted on humans and other animals has implicated the insula in threat and extinction learning, as well as the acquisition of safety-related information. Importantly, subcortical structures including the Periaqueductal Gray (PAG) and hypothalamus play central roles in threat expression, especially in the execution of freezing, escape, and stress-responsive behaviors, in down streaming projections of prefrontal and insular signaling (Brydges et al., 2013; Casanova et al., 2018; Fullana et al., 2016; Napadow et al., 2008; Thayer and Sternberg, 2006). Notably, functional distinctions exist between its anterior and posterior subdivisions: while the anterior insula is well-established as a fear-response region (Laing et al., 2022; Savage et al., 2020), the posterior insula has been implicated as a key mediator of safety-related outputs, such as fear inhibition (Foilb et al., 2016). These subdivisions may reflect a functional gradient from viscero-sensory representation in the posterior insula to interoceptive awareness, as the conscious perception of internal bodily states such as heartbeat, respiration, or gut sensations, and salience integration in the anterior insula. In particular, the posterior insula receives raw bodily signals such as blood pressure or gastric distension, while the anterior insula translates these signals into conscious feelings of internal emotional states, like fear or anxiety (Craig, 2011; Gu et al., 2013). Therefore, these findings might shed light on the comprehensive nature of the insular cortex's involvement in coordinating both physiological and psychological reactions to potential threats in the animal kingdom (Biggs et al., 2020). Hence, the foremost contribution of the insular cortex would be closely associated with the guidance of behavior, signifying that it occupies a paramount position within a high-level regulatory process (see Fig. 1). Within this animal framework, the insular cortex might serve as an important hub where predictions about bodily states are formulated, and its output serves to fine-tune subcortical processes (Q. Wang et al., 2022).

Similarly, in the theoretical framework of human threat conditioning, evidence suggests that threat responses are not solely the result of a subcortical circuit, such as the amygdala, hippocampus, and hypothalamus, but also involve cortical areas. In particular, humans present a sophisticated anatomical-functional interplay between the prefrontal cortex and heart-related dynamics that mediate behavioral, cognitive, and autonomic responses when facing an imminent threat (Battaglia et al., 2022; Battaglia and Thayer, 2022). The prefrontal cortex, with its executive functions and regulatory abilities, acts as a hub in coordinating and integrating the processes involved in recognizing and responding to threatening stimuli (Gilmartin et al., 2014; Kredlow et al., 2022), but is also involved in positive affect processing of safety signals (Harrison et al., 2017). This coordinated functioning ensures the appropriate encoding and processing of information related to potential threats, allowing organisms to adaptively navigate and survive in their environments (see Fig. 1). Furthermore, there is compelling causal evidence suggesting that when one of these nodes is functionally impaired, it can result in abnormal threat learning (Battaglia et al., 2020; Richter et al., 2021).

2. Neurovisceral integration model of fear across species

Considering the evidence in both humans and rodents, the

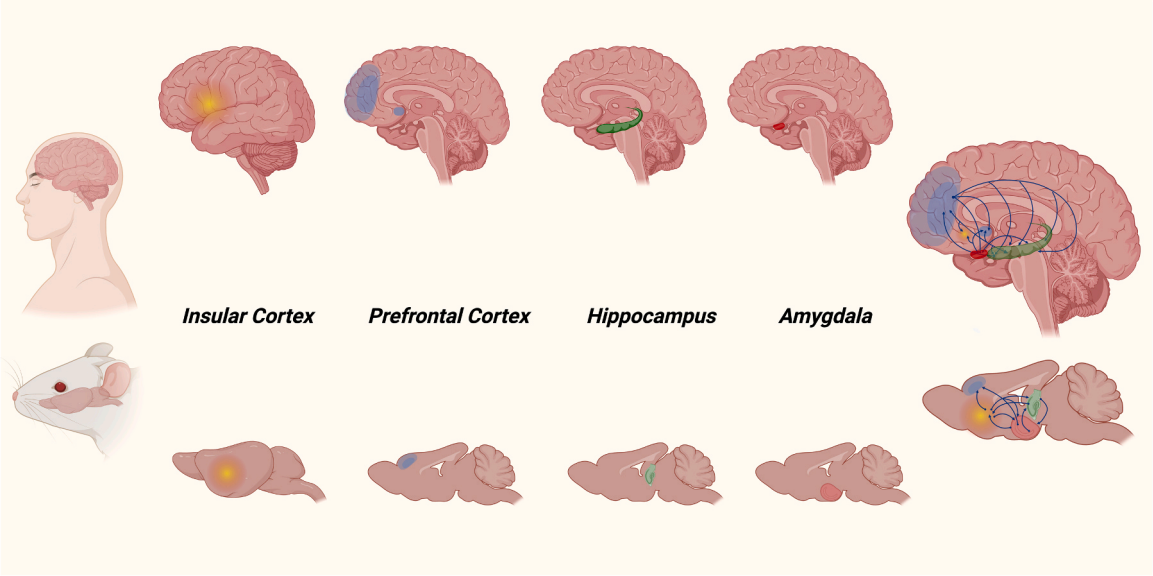

Fig. 1. Neuroanatomical location of the threat learning network in the human and rodent brain. From left to right in the image, we observe the representation of the entire brain followed by specific regions, including the insular cortex, prefrontal cortex, hippocampus, and amygdala, depicted for both human (upper) and rodent (lower) brains. On the right side, we find a simplified schematic illustrating the functional connectivity underlying threat learning, highlighting the interconnections between these crucial regions across species. This visualization demonstrates how different areas interact in various cross-species manners to facilitate threat-learning processes. (Q. Wang et al., 2022; Chin et al., 2023; Kredlow et al., 2022; Teed et al., 2022). Created in BioRender.com.

neurovisceral integration model (Thayer and Lane, 2000) provides a comprehensive framework for understanding the elaborate interplay between the central autonomic network (CAN) and its regulation of various cognitive, behavioral, and physiological processes associated with a wide range of emotions, as evidenced by the analysis of heart rate variability (HRV) patterns - a measure of the variation in time intervals between heartbeats, reflecting autonomic flexibility and emotional regulation (Thayer and Sternberg, 2006). Central to this model is the pivotal role exerted by cortical structures as prefrontal, cingulate, and insular cortices as key brain regions involved in executive functions, monitoring, decision-making, and emotional regulation. Crucially, these cortical brain regions exert descending control to the subcortical structures implicated in modulating heart rate and defensive behaviors (i.e. ventro-medial PFC-PAG pathway). Through their intricate connectivity with limbic structures, these areas exert a sophisticated modulatory influence on autonomic activities, predominantly exerting inhibitory effects via the parasympathetic nervous system (PSNS) while simultaneously activating circuits within the sympathetic nervous system (SNS) (Napadow et al., 2008) (see Fig. 2.).

Within the framework of human threat learning, we extensively examined the evidence of this phenomenon and put forth a comprehensive theoretical model called the neurovisceral integration model of fear (NVI-f) (Battaglia and Thayer, 2022). The NVI-f expands on the original neurovisceral integration model by incorporating dynamic threat learning and extinction processes, thereby emphasizing the role of predictive and inhibitory control in autonomic regulation during fear learning. This model serves as a conceptual framework to interpret the underlying physiological pathways and processes involved in threat-related responses in humans. Based on this human-based model, in threatening situations, sympatho-excitatory subcortical circuits are disinhibited leading to higher threat responses, in which the prefrontal cortex together with the amygdala exerts excitatory control of the parasympathetic outflow (Bach and Melinscak, 2020). This suggests that after an initial threat identification, high-level cognitive areas and the amygdala determine the functioning of the parasympathetic system by regulating in succession the nucleus ambiguus and the dorsal nucleus, which innervates the vagus nerve, until it reaches the sinoatrial node of the heart, determining the fear-induced bradycardia, directly through

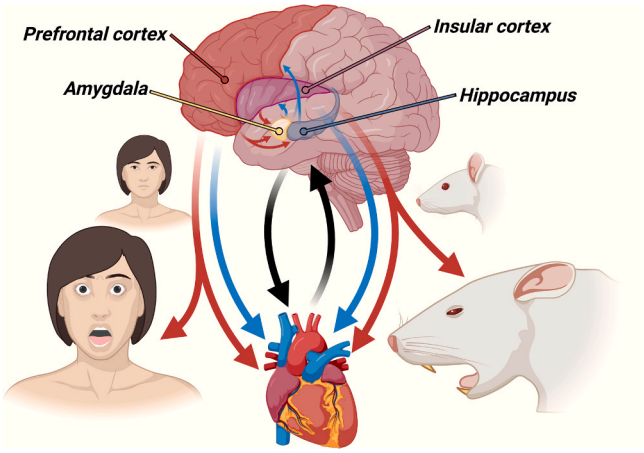

Fig. 2. Expression and modulation of threat-related psychophysiological and behavioral responses. In both humans and rodents, these are regulated by a network that includes the prefrontal cortex, the insular cortex, the amygdala, and the hippocampus. This regulation is driven by a functional interplay of neurovisceral information (represented as black arrows) that is then conveyed to the prefrontal cortex in humans and the insula in mice, which exert activating (red arrows) and inhibitory (blue arrows) projections. Moreover, these two areas share connections with subcortical structures, highlighting their role as relay stations in threat-related learning. Created in BioRender.com.

vagal control (Battaglia and Thayer, 2022). In accordance with the NVI-f model, it is proposed that higher-level cognitive cortical structures, specifically the prefrontal cortex, exert control over the functioning of subcortical structures such as the amygdala and hippocampus. This control leads to neurovisceral physiological changes through the involvement of sympathetic and parasympathetic projections, which in turn modulate various aspects of heart-related dynamics. Even though the role of the insula in this process has been contemplated in the theoretical model, there is currently limited empirical evidence in humans to support its involvement alongside other brain regions. One of the key limitations that prevent adequately addressing this issue is the

disparity between investigation methods across human and non-human research, the latter of which can access large-scale recordings and circuit-level manipulations with enhanced precision on the temporal and spatial level. Whereas invasive methods in rodents allow for fine-grained manipulation and recording of subcortical circuits, human studies often rely on indirect signals with limited spatial and temporal resolution (Barron et al., 2021; Flores et al., 2018). Additionally, the procedures used to investigate threat learning can differ substantially among species, leading to obstacles in drawing potential similarities (Flores et al., 2018). Thus, this may have prevented research from defining the precise role of the insula in regulating heart dynamics in humans as well, which could be as important as it is in other animals such as rodents.

Notwithstanding, the neurocircuitry underlying heart rate regulation and skin conductance responses when facing threat are only partially overlapping in humans, suggesting that these systems rely on the engagement of different brain regions. Specifically, compared to electrodermal activity, heart rate modulation is predicted by reduced ventromedial prefrontal cortex and insula activity (Eisenbarth et al., 2016). Additionally, in negative emotional states, heart rate modulation is characterized by bilateral insular activity alongside subcortical structures (Hiser et al., 2021; Kuniecki et al., 2003). This evidence, alongside emerging research in rodents, suggests that the insular cortex may play a role in the regulation of heart-related threat responses in humans as well.

Consequently, while it is evident that the dynamic interplay between cortical and subcortical structures is responsible for shaping the acquisition and expression of threat learning, accurately determining the functional weight of the involved areas, let alone their hierarchical order in regulating threat responses accompanied by changes in heart rate, remains a challenge.

The evidence discussed here provides valuable insights into possibly different neural mechanisms behind threat learning. Therefore, it is reasonable to suggest that the regulation of threat-related responses may be subtended by different roles and hierarchical structures of the brain areas involved. The crucial differentiation lies in the specific cortical contributions to the regulation of this process between humans and rodents. In humans, the prefrontal cortex plays a central role, functioning as the orchestrator that exerts top-down control over other cortical regions, including the insula. This activation subsequently influences subcortical structures, ultimately extending down to the medulla. In rodents, the insula acts as a key region in integrating heart-related, bottom-up signals to regulate affective states (Hsueh et al., 2023), as well as other sensory, emotional, motivational, and cognitive inputs (Gogolla, 2017; Klein et al., 2021), suggesting its central role alongside the prefrontal cortex in threat responses regulation (see Fig. 1). These functional characterizations highlight possible interspecies overlap in how threat-learning processes are organized and regulated.

Overall, despite the technical limitations of most studies using functional neuroimaging, it can be suggested that there are dissimilarities rather than neuroanatomical functional differences between animal and human threat processing circuits. Building upon the NVI-f model, it is possible to expand that in rats, the insular cortex, rather than the prefrontal cortex as posited in humans, may serve as the primary structure governing the regulation of threat responses. The existing body of evidence demonstrates a convergence of findings, supporting the significant involvement of the vagus nerve as the principal functional mediator of the peripheral nervous system in the regulation of cardiac activity in both animal models (Gail et al., 2023; Haberbusch et al., 2022) and humans (Soltani et al., 2023). However, there remains a contentious debate surrounding the precise central nervous system structure responsible for orchestrating threat learning mechanisms and their associated expression in humans and rodents. In any case, the solid evidence coming from studies carried out in rodents and humans is suggestive of the key role of the insula in this process, possibly as a relay station for interoceptive signals from the body (Gehrlach et al., 2020). To ultimately resolve this scientific dispute, future investigations should leverage advanced neuroimaging techniques, sophisticated physiological measurements, and state-of-the-art optogenetic approaches. These cutting-edge methodologies hold promise for disentangling the intricacies of the prefrontal cortex and the insular cortex in their respective roles as potential determinants of threat learning modulation, particularly within the human brain.

3. Translational implications

Expanding further on this matter, it is crucial to consider the implications of potential interspecies differences in the context of translational research and modeling of fear-related disorders in humans. Understanding the similarities and divergences in the neural circuits underpinning threat learning between rodents and humans is fundamental for developing more effective and targeted therapies for anxiety disorders, post-traumatic stress disorder (PTSD), and other fear-related conditions (Craske et al., 2018; Fenster et al., 2018; Verbitsky et al., 2020). For example, there is evidence that there are projections necessary for threat memory consolidation conserved in humans and mice (Florido et al., 2024), as well as partially overlapping mechanisms between the two species when it comes down to the development of PTSD as supported by altered amygdala-insula connectivity (Andero et al., 2013). Moreover, while rodent-based animal models have provided valuable insights into the basic mechanisms of threat learning, translating these findings to humans requires careful consideration of the potential differences in neural architecture and function, including limitations in human neuroimaging resolution (e.g., 3-Tesla fMRI) compared to invasive techniques used in animals. These methodological disparities highlight the need for cautious interpretation when bridging species-level findings, particularly regarding the roles of the prefrontal cortex and insula. For now, the apparently more prominent role of the prefrontal cortex in humans suggests that therapeutic interventions might benefit from a greater focus on enhancing executive functions and cognitive control. Conversely, the importance of the insular cortex in rodents highlights the need to further explore its role in integrating sensory and interoceptive information in humans during threat processing.

Moreover, these interspecies potential differences raise intriguing questions about the evolutionary development of threat circuits. The increased complexity and the central role of the prefrontal cortex in humans suggests the possibility of an evolutionary adaptation allowing for more sophisticated regulation of threat responses in complex social and environmental contexts. Beyond the expansion of the prefrontal cortex in humans, evolutionary changes have also occurred in regions such as the insular cortex and subcortical structures like the amygdala. These modifications may contribute to species-specific threat responses, potentially explaining differences in how these same areas are involved differently in humans versus rodents (Chin et al., 2023). This evolutionary perspective could provide valuable insights into the unique vulnerabilities of humans to anxiety and fear-related disorders, as well as potential pathways for their treatment. For example, neuroimaging evidence in individuals with PTSD, anxiety disorder or panic disorder show reduced PFC activity and disrupted prefrontal-amygdala connectivity during threat processing, linked to excessive autonomic arousal (Langhammer et al., 2025; Teed et al., 2022; H.Y. Wang et al., 2024 or for a comprehensive review see Kredlow et al., 2022). Therefore, a promising area for future research is the exploration of how these differences in neural circuits influence the efficacy of various therapeutic approaches. For example, exposure-based therapies, widely used for anxiety disorders, might act through slightly different mechanisms in humans compared to animal models (Knowles and Tolin, 2022). Understanding these differences could lead to more refined and personalized treatment protocols (Battaglia et al., 2023a, 2023b). In humans, the advent of advanced neuroimaging techniques such as 7-Tesla functional

neuroimaging and non-invasive neurostimulation offers new opportunities to probe and potentially modulate these circuits more precisely. Techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) could be used to specifically target regions like the prefrontal or insular cortex, allowing for a more direct assessment of their causal role in threat learning and symptoms expression in humans (Borgomaneri et al., 2021). It is also crucial to consider how these differences in neural circuits might influence pharmacotherapy for threat-related disorders. Many psychotropic drugs were initially developed and tested on animal models, primarily rodents (Schwarting et al., 2024). Awareness of the differences in neural organization could guide the development of more targeted drugs that consider the specificities of human threat circuits (Belzung, 2014; von Mücke-Heim et al., 2023).

Finally, this field of research traditionally underscores the importance of an integrative approach that combines animal and human studies. While animal models continue to provide invaluable insights into basic neural mechanisms, human studies are essential for validating and refining these models in the context of human cognitive and emotional complexity. Furthermore, sex differences may play a significant role in both threat processing and HRV. In general, sex-related differences have been observed in autonomic and emotional responses to threat, with variations potentially influenced by hormonal factors such as estrogen and progesterone (Florido et al., 2021; Hamidovic et al., 2020). These differences can impact both the perception of threat and the physiological regulation of arousal. For example, female rodents often show distinct patterns of fear learning and extinction, while human studies have reported sex-specific differences in baseline HRV and its modulation during stress. Given these findings, it is important to consider sex as a biological variable when interpreting results and designing future studies. (Florido et al., 2024; Gammie, 2022; Velasco et al., 2022). Integrating various evidence from different species, coupled with the use of advanced data analysis and computational modeling techniques, could lead to a more comprehensive and nuanced understanding of threat circuits and their functioning in both normal and pathological conditions.

4. Conclusion and future directions

Combining human and animal studies of threat learning, the evidence supports the central role of prefrontal and insular cortices in regulating autonomic responses. Rodent studies suggest the insula plays a primary role in relaying interoceptive feedback, while human evidence suggest a primary prefrontal control. To this end, bridging the gap between animal models and human threat processing remains a critical challenge in neuroscience and clinical psychology (Flores et al., 2018; Haaker et al., 2019). The continued exploration of the functional roles of prefrontal and insular cortices, along with their interactions with subcortical regions, promises to yield significant advances in our understanding of threat learning and regulation. This knowledge could contribute to improved treatments of threat-related disorders, leading to more effective, personalized therapeutic approaches that address the unique complexities of human threat processing.

In conclusion, by integrating these insights it can be possible to develop more sophisticated, species-sensitive models of threat learning that inform both our theoretical understanding and clinical interventions: define better targets for current and future advanced methods, with the aim of establishing a more comprehensive and precise understanding of the complex neural mechanisms underlying threat learning and its regulation (Battaglia, Nazzi, and Thayer, 2024). Consequently, it will be possible to disentangle the eventual contrast between animals and humans concerning how prefrontal and insular cortices engage with subcortical regions in the involute process of threat learning.

CRediT authorship contribution statement

SB and JFT conceived the idea. SB wrote the manuscript and designed the figures. RGA and JFT provided critical revisions. All authors approved the final version of the manuscript.

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Declaration of Competing Interest

The authors declare no competing interests.

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Data availability

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

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