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The central extended amygdala guides survival-relevant tradeoffs: Implications for understanding common psychiatric disorders

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ABSTRACT

To thrive in challenging environments, individuals must pursue rewards while avoiding threats. Extensive studies in animals and humans have identified the central extended amygdala (EAc)—which includes the central nucleus of the amygdala (Ce) and bed nucleus of the stria terminalis (BST)—as a conserved substrate for defensive behavior. These studies suggest the EAc influences defensive responding and assembles fearful and anxious states. This has led to the proliferation of a view that the EAc is fundamentally a defensive substrate. Yet mechanistic work in animals has implicated the EAc in numerous appetitive and consummatory processes, yielding fresh insights into the microcircuitry of survival- and emotion-relevant response selection. Coupled with the EAc's centrality in a conserved network of brain regions that encode multisensory environmental and interoceptive information, these findings suggest a broader role for the EAc as an arbiter of survival- and emotion-relevant tradeoffs for action selection. Determining how the EAc optimizes these tradeoffs promises to improve our understanding of common psychiatric illnesses such as anxiety, depression, alcohol- and substance-use disorders, and anhedonia.

1. Optimizing survival-relevant tradeoffs in a challenging world

The natural world is an unforgiving place, where opportunities to acquire resources, reproduce, and explore must be balanced against ubiquitous threats of predation, starvation, and injury (Blanchard et al., 2011; Blanchard and Blanchard, 2008; Mobbs et al., 2009, 2015). An animal that grazes with reckless abandon might enjoy the short-term benefits of better nutrition, but it's more likely than its vigilant conspecifics to be injured or killed by a predator (Cooper et al., 2015; Evans and Stempel et al., 2018). Conversely, an animal that tends to forgo its meals and flee at the faintest sign of danger might avoid predators in the short term, but it will eventually suffer malnourishment. Survival-relevant tradeoffs like these pervade the natural world (Fig. 1A, *left*), and the central nervous system evolved to manage them. The human brain also manages *emotion*-relevant tradeoffs, for example the decision of whether to socialize with others or avoid them (Fig. 1A, *right*). While some trepidation in approaching others can be adaptive, an extreme bias toward avoidance can be maladaptive and characteristic of anxiety-related psychopathology (Fox and Kalin, 2014; Shackman et al., 2016). Importantly, the same avoidant behavior could result from any of several biases in the response-selection process (Fig. 1B). How might this selection process be organized in the brain to promote survival in a world of innumerable possibilities? We posit that the brain dynamically integrates sensations, memories, homeostatic signals, preferences, expectations, and other factors into an *n*-dimensional feature space where weighted environmental and interoceptive evidence (i.e., $E * W_k^T$) for survival- and emotion-relevant responses can be represented as values (i.e., $V[R_k]$) and compared (Fig. 1C). The brain must then resolve the feature space to select and trigger adaptive physiology, cognition, and behavior that promote survival and optimize well-being by striking the best balance between risks and rewards.

What constitutes "adaptive" depends on the feature-space inputs, which are unique to individuals at a given moment: Grazing for a few extra seconds as a predator approaches might be adaptive if an animal is especially hungry, if the quality of its food source is high, if its surroundings favor last-second escapes, if nearby conspecifics diffuse the likelihood of being attacked, if the predator is frail or immature, and so on. As the value of each input waxes and wanes, perturbations in the feature space nudge the probability of action selection toward one response or another. Input from a plethora of brain regions shapes the feature space. To avoid "paralysis by analysis" in the management of these high-stakes tradeoffs, specific substrates must integrate across this

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feature space to rapidly select the most adaptive response. The EAc is well-positioned for this role.

2. Evidence for an evolutionarily-conserved role for the EAc in defensive behavior

In the crucible of natural selection, the primacy of survival has spurred the evolution of defensive adaptations across phylogeny. In mammals, the EAc is a conserved neural substrate that responds to both innate and learned threats. Situated at the center of a distributed network of brain regions that promote fitness in challenging contexts (Fox et al., 2015b; Mobbs et al., 2015), the EAc receives robust direct and indirect input from contextual, sensory, regulatory, and evaluative regions (de Olmos and Heimer, 1999; Swanson and Petrovich, 1998). Two of its major subcomponents—the Ce and the BST—form a functionally coupled circuit (Oler et al., 2012; Oler and Tromp et al., 2017; Tillman et al., 2018; Gorka et al., 2018; Avery et al., 2014) and exhibit similar patterns of gene expression (Bupesh et al., 2011; Fox et al., 2015b; Lein et al., 2007), neurochemistry (Gray and Magnuson, 1992), cellular composition (McDonald, 1982, 1983), and structural connectivity (Fox et al., 2015; Oler and Tromp et al., 2017; Roy et al., 2009). Direct projections from the EAc to effector regions including the periaqueductal gray (PAG) and parvocellular reticular formation (PCRt) trigger selected responses (Han et al., 2017; Tovote et al., 2016). The EAc is therefore well-positioned to synthesize environmental and interoceptive inputs into a meaningful gestalt, rapidly select optimal defensive responses, and launch those responses into action (Fox et al., 2015b; Mobbs et al., 2015).

Neuroimaging studies of threat-anticipation tasks in humans, and human neuroimaging papers that use the words "fear" and "anxiety," often report significant activation in the Ce and BST (Fig. 2A, *top*, adapted from Fox and Shackman, 2019, p. 60, Fig. 2; Hur et al., 2020; Shackman and Fox, 2016; Somerville et al., 2013; Hur et al., in press). In nonhuman primate (NHP) neuroimaging studies, individual differences in rhesus neuroendocrine and behavioral reactivity to potential threats are associated with increased [18 F]fludeoxyglucose (FDG) metabolism in the Ce and BST (Fig. 2A, *bottom*; Fox et al., 2008, 2015a; Oler et al., 2010), as well as increased functional connectivity between these regions (Fox et al., 2018; Oler and Tromp et al., 2017). Loss-of-function studies tell a similar story and induce a "threat blind" phenotype in NHPs: rhesus monkeys with gross amygdala lesions, which include the Ce, exhibit more affiliative and sexual behaviors toward intact conspecifics (Emery et al., 2001; Machado and Bachevalier, 2008), are more likely to consume unpalatable foods (Machado et al., 2010), and more readily interact with novel and potentially dangerous objects (Bliss--Moreau et al., 2010, 2011; but see Charbonneau et al., 2021). Similarly, rhesus monkeys with spatially-precise Ce lesions show blunted freezing in response to potential threats and are quicker than intact conspecifics to reach past a snake and retrieve food rewards (Kalin et al., 2004). In rodents, decades of fear-conditioning and threat-related studies have built a foundation for investigating threat processing and have been instrumental to the formulation, testing, and refinement of hypotheses regarding individual responses of the Ce and BST to phasic and sustained threats (Davis et al., 2010; Walker et al., 2009; Walker and Davis, 2008; Marcinkiewcz et al., 2016; Tovote et al., 2016; Perusini and Fanselow, 2015). Despite long-standing evidence of its role in non-defensive processes (e.g., Aggleton, 2000; Baxter and Murray, 2002; Whalen and Phelps, 2009), the sheer volume of studies implicating the EAc in threat processing could lead one to conclude that it is fundamentally a defensive substrate.

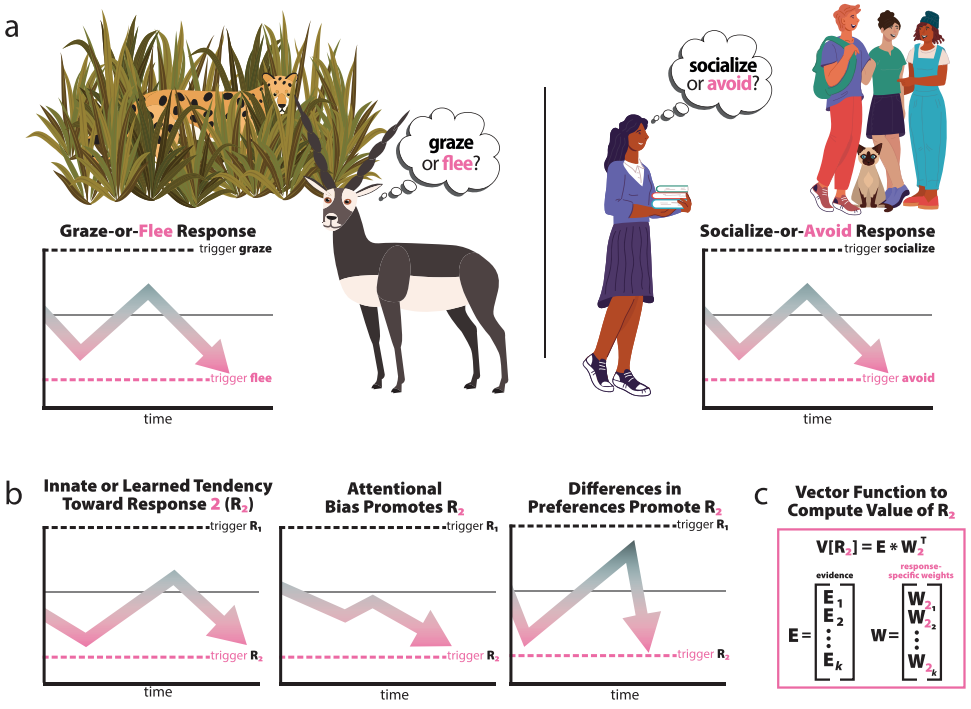

Fig. 1. In nature and society, behavior is characterized by risk-vs-reward tradeoffs. **a**) Adaptive responses are selected from competing options. A hungry gazelle detects a predator and must select between grazing and freezing (*left*)—neither of which is inherently maladaptive. This selection process can be defined as a function of the value of each response, i.e., f(V[R_1], V[R_2]). While we are agnostic about the specific computations underlying the tradeoffs inherent to response selection, these choices can be conceptualized with simplified drift-diffusion models (DDM; Ratcliff and McKoon, 2008) in which responses are triggered as accumulating evidence surpasses a decision threshold, represented here as dashed lines bisected by a grey line indicating the indifference point. In humans, the systems that underlie these survival-relevant selection processes can select emotion-relevant responses (*right*). **b**) Different underlying processes can trigger the same response. Even with a simplified two-option DDM—which has been useful for characterizing multi-alternative valuation decisions (Krajbich and Rangel, 2011)—different underlying processes can bias individuals toward the same response: an innate or learned tendency toward one response over another (*left*), an attentional bias that leads to disproportionate accumulation of evidence in favor of one response over another (*middle*), or differences in the valuation of evidence between responses (*right*) illustrate sources of bias toward response R_2. **c**) Response selection as a computational process in an *n*--dimensional feature space. The value of any response (e.g., V[R_2]) can be conceptualized as the product of all available evidence (e.g., [E_1, E_2... E_k]) times the context-specific weight afforded to each piece of evidence (e.g., [W_{21}, W_{22}... W_{2k}]^T). In the case of our gazelle, E_1 might represent predator proximity, and W_{22} the gazelle's sensitivity to predator proximity in the context of escape decisions. Of note, the weights may comprise a sparse matrix; that is, many pieces of evidence may have no (or little) bearing on a specific response.

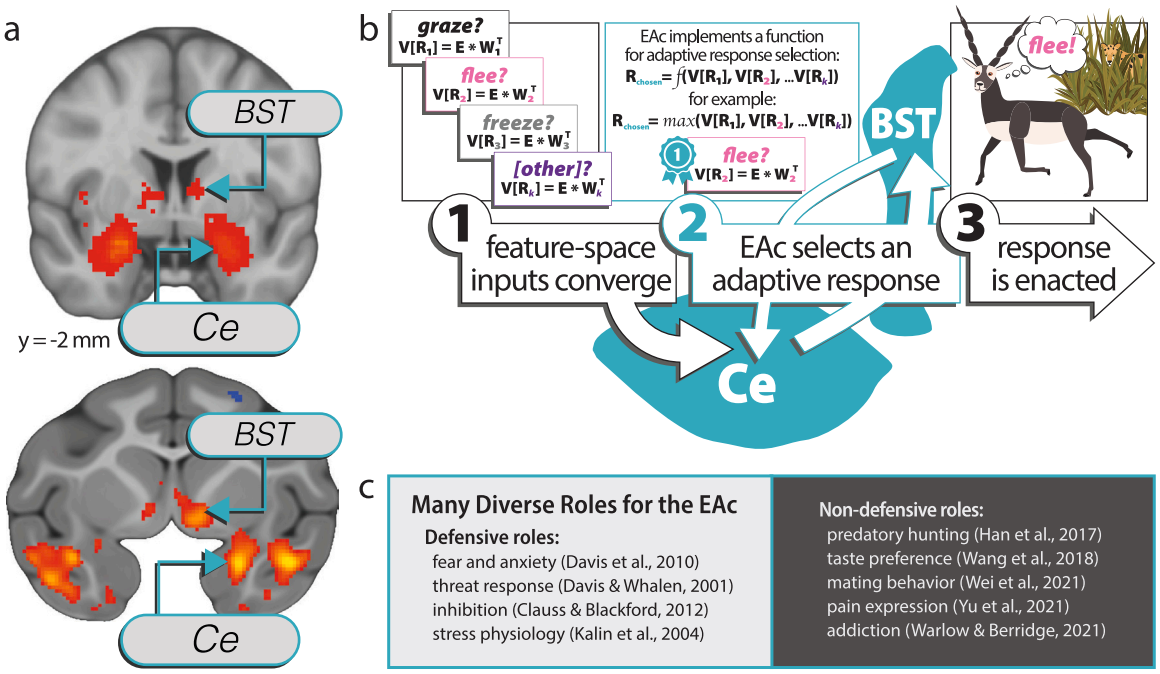

Fig. 2. The EAc selects defensive and non-defensive responses. **a**) Studies of humans and rhesus monkeys implicate the EAc in uncertain threat response. As reported in Shackman and Fox (2016), a *Neurosynth*-enabled (Yarkoni et al., 2011) automated meta-analysis of "fear" and "anxiety" neuroimaging studies in humans reveals Ce and BST activation (*top*), and large-scale (N = 592) nonhuman primate neuroimaging studies of response to uncertain threat (Fox et al., 2015a) show that rhesus anxious temperament predicts elevated EAc metabolism during exposure to an uncertain threat represented by an unfamiliar human intruder (*bottom*). **b**) Feature-space model of EAc-implemented function for selecting between graze (R_1), flee (R_2), and freeze (R_3) responses based on the weighted valuations of those responses in each context. In this simplified three-choice model, 1) feature-space inputs encoding salient, weighted environmental and interoceptive evidence converge on the EAc; 2) the EAc represents and resolves the feature space through an unknown selection function (shown here as a placeholder function to represent what is almost certainly a more complicated process; see Krajbich and Rangel, 2011) to guide survival-relevant and emotion-relevant tradeoffs for action selection and adaptive physiology; and 3) instructions to enact the winning response are pushed downstream to effector regions capable of triggering changes in physiology, cognition, and behavior. **c**) An illustrative list of defensive and non-defensive EAc roles highlights the EAc's involvement in diverse response sets. Of note, we use the terms "defensive" and "non-defensive" to be inclusive of physiological, cognitive, and behavioral changes, as well as the phenomenological states that elicit EAc involvement.

3. Rodent studies uncover the EAc's diverse roles in survival-related response selection

In the past decade, methodological advances have endowed researchers with tools that enable cell type-specific targeting, millisecond-resolution observation, and bidirectional control of neural populations (Chen et al., 2013; Deisseroth, 2011; Resendez and Stuber, 2015; Roth, 2016; Fox and Shackman, 2019). Coupled with well-validated threat assays, these methods are elucidating the mechanisms that subserve threat processing and have uncovered intermingled populations of EAc

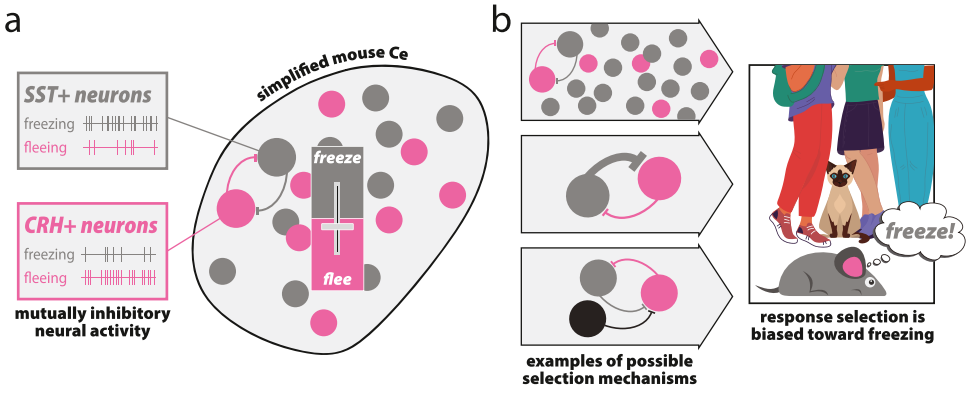

Fig. 3. Genetically dissociable microcircuits provide a substrate for response selection through the implementation of a selection function (e.g., f(V[R_1], V[R_2],.V[R_k]; see Fig. 2B). **a**) Mutually inhibitory neural activity in the mouse Ce. A competitive inhibitory microcircuit composed of intermingled, competing populations of SST+ and CRH+ neurons select between freezing and fleeing responses, respectively. The activity of either population generates strong inhibitory postsynaptic currents that suppress the other population, thereby serving as a rapid, winner-take-all mechanism for selecting between active and passive threat response. **b**) Possible mechanisms for response selection. Several distinct mechanisms could dispositionally bias an individual toward passive threat response (i.e., maladaptive freezing), characteristic of behavioral inhibition (Roelofs, 2017; Roelofs et al., 2010; Roelofs and Dayan, 2022); for example: a preponderance of SST+ neurons (*top*), disproportionately strong SST+ to CRH+ projections (*middle*), or the presence of a third population of neurons that co-inhibits CRH+ neurons (*bottom*). Importantly, while we have highlighted the SST+ and CRH+ microcircuit in the mouse Ce, it is likely that imbalances in other microcircuits—for example, the aforementioned "CeL_{on}"/PKCδ- and "CeL_{off}"/PKCδ + microcircuit—could drive similar tendencies. We hypothesize similar alterations in other EAc regions, such as the BST.
Adapted from Fadok et al. (2017).

neurons that function as substrates for the selection of defensive responses. For example, cell type-specific manipulations within the mouse Ce have identified a competitive inhibitory microcircuit—comprised of intermingled corticotropin releasing hormone-positive (CRH+) and somatostatin-positive (SST+) neurons—that rapidly selects between fleeing and freezing (Fadok et al., 2017; Fig. 3A). Similarly, distinct cell types have been implicated in competitive responses to learned vs. unlearned threats (Isosaka et al., 2015). Other studies have characterized a lateral Ce (CeL) microcircuit that gates conditioned freezing through projections to the medial Ce (CeM; Botta et al., 2015; Ciocchi et al., 2010; Haubensak et al., 2010). This work shows that "CeL_{off}" neurons—which express the anxiety-associated genetic marker protein kinase C-delta (PKCδ +)—form a reciprocal inhibitory microcircuit with intermingled "CeL_{on}"/PKCδ-negative (PKCδ-) neurons. Threat conditioning increases the basal firing rate of the "CeL_{off}"/PKCδ + population, leading to stronger local inhibition of CeL-CeM projections and increased threat generalization—a transdiagnostic feature of anxiety disorders (Lissek et al., 2010, 2014; Morey et al., 2020; Holley and Fox, 2022). These findings dovetail with work in NHPs demonstrating that levels of the transcript encoding for PKCδ in the CeL is associated with individual differences in threat responding (Kovner et al., 2020).

To understand *how* EAc alterations promote pathological anxiety, we need to carefully consider its broader role in arbitrating survival-relevant tradeoffs (i.e., as a function of V[R_i], or f(V[R_1], V[R_2]; see Fig. 2B, C). For instance, researchers have shown that chemogenetic inhibition of CeL PKCδ + neurons—the same cells that appear to play a mechanistic role in threat generalization—induces risky feeding behavior in mice, as measured by the consumption of bitter tastants that control animals tend to reject (Cai et al., 2014; Ponserre et al., 2020). Other studies have shown that gustatory cortical projections to the Ce encode—and, when manipulated, can even *reverse*—the hedonic value of bitter tastants (Wang et al., 2018). These studies of consummatory behavior are especially interesting in the context of survival-relevant tradeoffs, since aversion to bitterness is an evolved safeguard against the consumption of toxic substances (Bachmanov et al., 2014). Intriguingly, they also hint toward the versatility of the EAc's microcircuitry; that is, the ability of some populations of neurons to bidirectionally control divergent survival behaviors (e.g., eating, threat reactivity) depending on the current context (and experimental probe/assay). Context-dependent repurposing of microcircuits would be an efficient solution to the demands of flexibly responding to the innumerable feature-space perturbations that increase or decrease the adaptiveness of specific emotion-relevant responses. For example, while it may be *generally* maladaptive to graze while predators are nearby, *specific* constraints—such as life-threatening malnutrition—may reshape the feature space so radically that grazing becomes the optimal response. In this case, perhaps "CeL_{on}"/PKCδ- neurons suppress "CeL_{off}"/PKCδ + neurons to reduce threat responding and promote risky feeding, triggering a "Hail Mary" response as an alternative to imminent death. It is also possible, however, that this appearance of multifunctionality could arise as a product of within-cell-type heterogeneity, and that intermingled groups of ostensibly specific EAc neurons might be further functionally dissociable (e.g., see Zeng, 2022).

An increasing number of studies remind us that the EAc is not a solely defensive substrate. For example, researchers investigating the neural substrates of predatory hunting have begun to dissect the Ce's involvement in prey pursuit and capture. By stimulating the axon terminals of intermingled populations of Ce neurons in mice, Han and colleagues (2017) identified parallel pathways that control appetitive locomotion and consummatory behaviors: a Ce-PAG pathway motivates prey pursuit, while a Ce-PCRt motivates prey consumption. Even in sated animals, activating the Ce-PAG pathway triggers immediate predatory hunting of live or artificial prey, whereas activating the Ce-PCRt pathway triggers immediate biting attacks against these targets, as well as fictive feeding in the absence of prey. Fascinatingly, activating the Ce-PCRt pathway *does not* trigger attacks against other mice, indicating that it is not an indiscriminate "rage circuit," but rather a context-specific circuit for food consumption. Furthermore, in the Kash Lab, researchers investigating the molecular substrates of binge eating discovered a population of prepronociceptin (*Pnoc*)-expressing neurons in the Ce that project food-palatability information to the ventral BST, parabrachial nucleus (PBN), and nucleus of the solitary tract (Hardaway et al., 2019). Activation of Ce *Pnoc* neurons was sufficient to motivate real-time place preference—a widely used index of reward value. Notably, the consequences of manipulating these neurons were specific to reward: inhibiting these cells failed to induce anxious behavior in the open field test, elevated plus maze, or other anxiogenic assays. Other work demonstrates that even the Ce's putatively "escape-related" CRH+ neurons can motivate reward seeking in specific contexts. For example, mice will optogenetically self-stimulate "escape-related" CRH+ Ce cells, suggesting an increase in appetitive motivation or hedonic pleasure (Kim et al., 2017). Self-stimulation of these cells has also been shown to increase the amount of effort that rats will expend to obtain sucrose rewards, implying a role in incentive motivation (Baumgartner et al., 2021). Other studies have implicated the EAc in a spectrum of roles ranging from mating behaviors (Wei et al., 2021) and social interaction (Flanigan and Kash, 2020), to binge drinking (Rinker et al., 2017) and nociception (Yu et al., 2021).

Like the Ce, the BST is enriched with distinct neuron populations that mediate several physiological and behavioral features of defensive responding (Kim et al., 2013), making it a priority target for dissecting the mechanisms of anxiety disorders. Moreover, structural and functional sex dimorphism in the BST (Allen and Gorski, 1990; Bredewold and Veenema, 2018; Dumais et al., 2016; Urien and Bauer, 2022) hint at this region's potential relevance to the sex differences in the prevalence of anxiety disorders, which are more common among women than men (Lebow and Chen, 2016; Bandelow and Michaelis, 2015). Although less is known about the BST's role in reward and another non-defensive processes, it boasts deep molecular heterogeneity, and its neurons express a range of neuropeptide markers that enable fine-grained modulation of physiological and behavioral survival-related tradeoffs (Gungor and Paré, 2016; Giardino et al., 2018). In mice, for instance, parallel circuits comprised of genetically distinct, lateral hypothalamus (LH)-projecting BST neurons are differentially involved in promoting defensive and appetitive behaviors: one circuit, comprised of CRH+ neurons, promotes avoidance, whereas the other, comprised of cholecystokinin-positive (CCK+) neurons, promotes feeding and mate approach (Giardino et al., 2018). Intriguingly, the latter population may play a key role in addiction (Giardino and Pomrenze, 2021) and appears to interact with estradiol-2 in the presence of cocaine and opioids to reinforce drug-seeking behavior (Ma and Giardino, 2022). This not only highlights the involvement of the BST in non-defensive responding, but also underscores the importance of studying sex as a biological variable in neuroscientific research.

These findings motivate our view that distinct alterations across or within several EAc circuits could give rise to nearly indistinguishable clinical phenotypes, for instance by increasing avoidance (Choi and Kim, 2010; Giardino et al., 2018), dampening incentive motivation (Mahler and Berridge, 2012; Warlow and Berridge, 2021; Baumgartner et al., 2021), shaping hedonic values (Wang et al., 2018), moderating reward-reinforcement signaling (Hardaway et al., 2019), or some combination thereof.

Taken together, recent studies of predation and reward demonstrate that the EAc plays a critical role in both aversive and appetitive survival-related functions—and that the functional "identity" of specific neuron populations is highly context dependent. On balance, these observations render views of the EAc's specificity to threat processing untenable and require us to fundamentally reconsider what the EAc is doing in threatening contexts.

4. Biological degeneracy ensures partial redundancy for EAc-mediated processes

The EAc does not have a monopoly on selecting between survival-relevant tradeoffs. For instance, in a laboratory paradigm used to induce panic via the inhalation of carbon dioxide (CO_2)-enriched air, even patients with focal bilateral amygdala damage can mount adaptive panic responses (Khalsa et al., 2016). And in freely-behaving mice, a feed-forward excitatory circuit projecting from the dorsomedial superior colliculus (dMSC) to the PAG encodes threat levels and initiates rapid escapes in response to threat stimuli that are parametrically modulated for saliency (Evans and Stempel et al., 2018). Redundancies and "emergency brakes'' are to be expected, since evolution favors biological *degeneracy*—that is, "the ability of elements that are structurally different to perform the same function or yield the same output" (Edelman and Gally, 2001, p. 13,763)—over single points of failure. This is consistent with survival as a core determinant of brain evolution across phylogeny. Still, the EAc is uniquely poised to function as an arbiter for survival-relevant tradeoffs. It integrates a wealth of information from myriad regions necessary to encode a survival-relevant feature space (i.e., by computing f(V[R_1], V[R_2], …V[R_k]), forms numerous microcircuits capable of rapidly selecting between competing physiological and behavioral responses, and projects to regions that can trigger those responses. Importantly, it is precisely these physiological and behavioral tradeoffs that are shared between survival- and emotion-relevant responses. Therefore, we expect the function of the EAc in survival to be particularly relevant for understanding pathological anxiety and other psychiatric illnesses characterized by prominent alterations in emotion and motivation (e.g., depression, alcohol- and substance-use disorders, anhedonia). While the EAc is not *required* to mount innate, largely reflexive responses like those we've described here, it seems to be involved in processing both learned (Li, 2019; Fadok et al., 2017; Sanford et al., 2017; Yu et al., 2017) and unlearned (Isosaka et al., 2015) threats. The Ce exhibits activity-dependent synaptic plasticity (Samson and Paré, 2005), and our work in nonhuman primates suggests that it represents the contributions of learning and experience to the risk of developing anxiety disorders (Holley and Campos et al., 2022; Fox et al., 2015a).

5. Characterizing response-selection mechanisms in the EAc

We hypothesize that the EAc encodes an *n*-dimensional feature space, where multiple inputs from across the brain converge to form an integrated view that enables adaptive responding to both threats and opportunities. The EAc is hypothesized to play a critical role in normative fear and anxiety (Davis et al., 2010; Fox et al., 2015b; Fox and Shackman, 2019), as well as anxiety-related psychopathology (Avery et al., 2016; Clauss, 2019; Morey et al., 2020; Shackman and Fox, 2021). Although scores of studies document the relationship between alterations in the EAc and differences in threat processing, an expanding mechanistic literature reminds us that the EAc is not threat-specific, and that it guides survival-relevant response selection more broadly. Importantly, lesion studies that find preferential deficits in threat responding do not imply that this region is uninvolved in triggering other responses. The historical tendency to focus on threat processing could reflect experimental biases, or some underlying threat-bias in the EAc's response selection mechanisms. Characterizing the EAc's response selection mechanisms will help to clarify the relationships between neurobiology and psychiatric disorder. It is possible, for instance, for dissimilar mechanisms to have the same net effect, thereby promoting a somewhat uniform anxious phenotype via distinct EAc alterations. In fact, we *expect* this to be the case, and to contribute to the challenges in the pharmacological treatment of anxiety disorders (Garakani et al., 2020; Koen and Stein, 2011). For example, a competitive microcircuit that selects between two mutually exclusive behaviors, such as the Ce CRH+ /SST+ microcircuit that selects between fleeing and freezing (Fadok, 2017), could feature any of several alterations that would dispositionally bias an individual toward one behavior over another. A maladaptive bias toward defensive freezing, which is thought to underlie temperamental behavioral inhibition and the risk to develop anxiety-related psychopathology (Fox and Kalin, 2014), could be driven by 1) a preponderance of SST+ neurons (Fig. 3C, *top*), 2) disproportionately strong inhibitory SST+ projections onto CRH+ neurons (Fig. 3C, *middle*), or 3) the tendency of a third population of neurons to inhibit CRH+ neurons (Fig. 3C, *bottom*). Similar outcomes could arise via alterations in the aforementioned "CeL_{on}"/PKCδ- and "CeL_{off}"/PKCδ + microcircuit. These illustrative mechanisms might respond differently—or not at all—to a common intervention, underscoring a major barrier to the development of one-size-fits-all treatments.

The implications of this within-region cell-type heterogeneity present a challenge for the neuroimaging community. A voxel, the smallest unit of spatial resolution in functional magnetic resonance imaging (fMRI), may represent the activation of hundreds of thousands of neurons. Because of this, blood oxygen level-dependent signal (BOLD) responses collected from intermingled neuron populations that form competitive microcircuits for response selection might look identical in the scanner even when subjects exhibit opposite responses to a given stimulus. But because this heterogeneity is unlikely to be uniform across voxels, it can also lend to the development of hypotheses that move beyond univariate relationships between regional signals and fear/anxiety measures. For example, based on findings from mice, we might hypothesize that the voxels of the basal and lateral regions of the amygdala each contain some mixture of reward- and threat-sensitive cells. With this hypothesis in mind, we might not expect to see differences in activation across these amygdala voxels in a straightforward test of reward vs threat. However, we might expect multivoxel pattern analysis (MVPA; Norman et al., 2006) to reveal *dissociable patterns* of activation that are characteristic of reward or threat processing, because each voxel has a different mixture of cell types. By parametrically modulating reward or threat information, we may be able to detect changes in patterns—not in any one voxel, but across voxels. Such research could extend MVPA's many contributions (e.g., Chang et al., 2015; Frick et al., 2014; Liu et al., 2015; Norman et al., 2006; Woo et al., 2017) by evaluating hypotheses that posit a conserved organization of reward- and threat-sensitive cells across species. This approach could also be coupled with pharmacological methods: By combining perturbations of the EAc's feature space (i.e., by modulating reward or threat evidence) with drugs believed to target a subset of cell types, we should be able to test hypotheses derived from rodent literature concerning the relationship between specific cell types and the function of the EAc. Such drugs may be useful for these studies, even if they have side-effects or lack clinical efficacy, and include those that target specific serotonin (Sharp and Barnes, 2020), oxytocin (Quintana et al., 2021), and CRH receptors (Zorrilla and Koob, 2010), among others (e.g., neuropeptide Y, cannabinoids, vasopressin, substance P, etc.). These examples illustrate the types of approaches we expect to enable key advances in precision psychiatric diagnostics and treatment in the years to come. Creative study design centered on cross-modality approaches such as these are needed to help blunt the enormous public-health burden of anxiety disorders (Beddington et al., 2008) and improve the effectiveness and availability of treatment to the untold millions who suffer their effects (Bandelow and Michaelis, 2015; U.S. Burden of Disease Collaborators et al., 2018).

6. Toward an improved understanding of common psychiatric disorders

In a seminal review, Rangel, Camerer, and Montague (2008) laid out the processes necessary for action selection to take place in the brain, noting that each process is experimentally tractable: (1) representation of a problem, (2) assignment of values to possible options, (3) selection

and implementation of a winning option, (4) evaluation of the outcome, and (5) feedback to enable learning and refinement. These functions are not unique to a single brain region. Here, we have argued that the EAc integrates salient environmental and interoceptive features in an *n*-dimensional space (akin to steps 1 and 2, above), and guides adaptive responses to challenges and opportunities alike by resolving that feature space to select winning strategies (akin to step 3, above). Although it lies beyond the scope of our mini-review, recent work suggests that the EAc is well-suited to perform steps (4) and (5), for example, via inputs from the PBN (Palmiter, 2018) and ventral tegmental area (Li, 2019), respectively. Moreover, the EAc is differentiated from other brain systems involved in action selection by its direct projections to the effector regions that can induce specific aspects of an emotional response, including species-typical physiological changes (e.g., cardiorespiratory and skin-conductance responses) and behaviors (escape, pursuit, freezing, etc.).

The EAc is uniquely poised to perform survival- and emotion-relevant action selection, and so it is a priority target for understanding psychiatric disorders characterized by prominent alterations in emotion or motivation. However, our expanding knowledge of its neuron populations and their multifunctional, context-dependent involvement in defensive and non-defensive processes should give us pause as we carefully rethink what these findings mean for the study of mental illness. This may require a conceptual reframing of how EAc alterations contribute to pathophysiology. Here, we have proposed approaching survival- and emotion-relevant tradeoffs (Fig. 1) as the outputs of an *n*-dimensional feature space that is encoded and resolved by the EAc (Fig. 2B). This computational approach to understanding survival- and emotion-relevant response selection in the EAc is intended to complement and integrate with other theories of how the brain implements these tradeoffs (e.g., Mobbs et al., 2015; Perusini and Fanselow, 2015; LeDoux and Pine, 2016; etc.).

A major implication of this conceptual reframing is that the same disordered phenotype could arise from alterations in distinct cellular/molecular substrates, which presents challenges for the development of effective treatments. Because the mechanism(s) that the EAc uses to compare feature vectors for survival- and emotion-relevant decisions are presently unknown (Fig. 2B, *middle*), investigations that parametrically modulate feature-space inputs will be especially valuable in elucidating the mechanisms that select between the EAc's response sets—and, when imbalanced, contribute to maladaptive responding (Fig. 3B). Importantly, there are likely to be *many-to-one* and *one-to-many* relationships between biological dysregulation and psychopathology. As outlined in Fig. 3, multiple, distinct biological mechanisms within the EAc could lead to the same output. (Similarly—although not discussed in detail here—a common CeL alteration might differentially bias physiological, cognitive, and behavioral outputs via distinct alterations in downstream mechanisms, for example in regions innervated by CeM outputs). A current challenge for human research is to develop and test hypotheses derived from animal studies to understand the role of the EAc in human psychopathology. To that end, studying the EAc's non-defensive functions in phylogenetically close NHP species (e.g., Parkinson et al., 2001) will be instrumental in understanding how mechanistic discoveries in rodents relate to the disordered emotion-relevant responses common to clinical populations. A focused effort toward characterizing how the EAc's feature-space inputs are encoded and what the comparison process for response selection entails will enable targeted manipulations of specific cells, genes, and molecules and uncover clinical entry points in the development of new interventions for a range of common psychiatric disorders.

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