An Honest Reckoning With the Amygdala and Mental Illness

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Anxiety disorders are a leading source of human misery, morbidity, and premature mortality. Existing treatments are far from curative for many, underscoring the need to clarify the underlying neural mechanisms. Although many brain regions contribute, the amygdala has received the most intense scientific attention. Over the past several decades, this scrutiny has yielded a detailed understanding of amygdala function, but it has failed to produce new clinical assays, biomarkers, or cures. Rising to this urgent public health challenge demands an honest reckoning with the functional-neuroanatomical complexity of the amygdala and a shift from theories anchored on "the amygdala" to models centered on specific amygdala nuclei and cell types. This review begins by examining evidence from studies of rodents, monkeys, and humans for the "canonical model," the idea that the amygdala plays a central role in fear- and anxiety-related states, traits, and disorders. Next, the authors selectively highlight work indicating that the canonical model, while true, is overly simplistic and fails to adequately capture the actual state of the evidentiary record, the breadth of amygdala-associated functions and illnesses, or the complexity of the amygdala's functional architecture. The authors describe the implications of these facts for basic and clinical neuroimaging research. The review concludes with some general recommendations for grappling with the complexity of the amygdala and accelerating efforts to understand and more effectively treat amygdala-related psychopathology.

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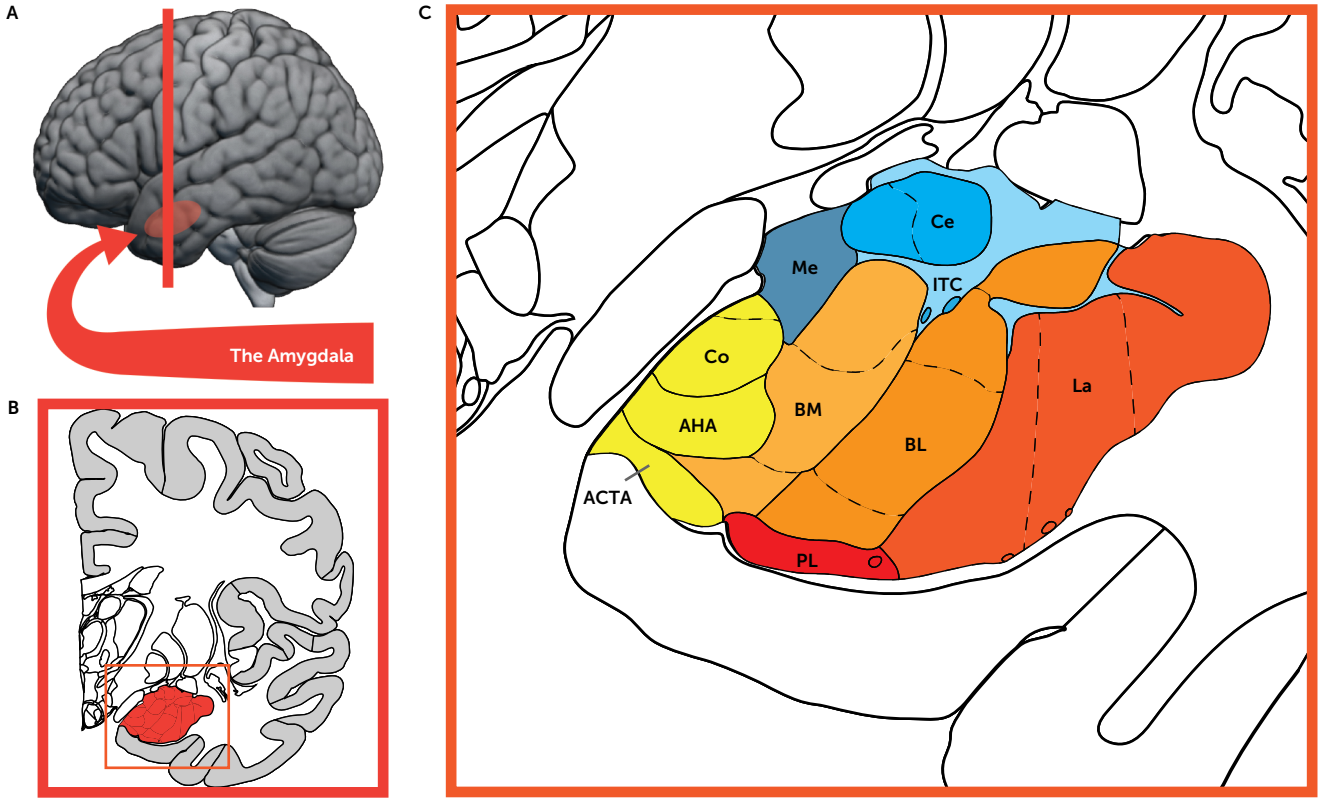
Fear and anxiety are evolutionarily conserved features of mammalian life that help protect us from harm (1, 2). But when expressed too strongly or pervasively, they can be crippling, even fatal (3–5). Anxiety disorders impose a staggering burden on global health, afflicting ~360 million individuals annually (6). In the United States alone, roughly one in three individuals will experience a lifetime disorder, service utilization is surging, and direct health care costs exceed $40 billion annually, drawing the attention of clinicians, scientists, the media, and policy makers (7–13). Existing treatments were developed decades ago and have limited effectiveness, durability, and tolerability, underscoring the need to clarify the neural systems governing the expression of fear and anxiety (14–17). Although many regions contribute, the amygdala—an almond-shaped collection of nuclei buried beneath the temporal lobe—has received the lion's share of scientific attention (Figure 1). Over the past two decades, this intense scrutiny has yielded a much more detailed understanding of amygdala function, but it has failed to produce new clinical assays, biomarkers, or cures. Rising to this urgent challenge demands an honest reckoning with the functional-neuroanatomical complexity of the amygdala and a shift from conceptual models centered on "the amygdala" to models centered on specific nuclei and cell types. We begin by examining evidence for the "canonical model," the idea that the amygdala plays a crucial role in all manner of fear- and anxiety-related states, traits, and disorders. Next, we highlight work indicating that the canonical model, while true, is overly simplistic and fails to adequately capture the nuance of a burgeoning empirical literature, the breadth of amygdala-associated functions and disorders, or the complexity of amygdala architecture revealed by animal models (for detailed reviews, see references 18–21). We then describe the implications of this complexity for the design and interpretation of basic and clinical neuroimaging research and for understanding and developing better treatments for psychiatric illness. We have come to believe that shifts are required in how neuroimagers approach the study of fear and anxiety. Nevertheless, we emphasize here and reiterate later that we are not fundamentally pessimistic about the human neuroimaging enterprise—such work is a necessary complement to animal models, and there are valuable clues to be gleaned from the close study of the human brain in sickness and in health (1, 22, 23). We conclude by outlining some general recommendations for grappling with the complexity of the amygdala and accelerating efforts to understand and more effectively treat amygdala-related psychopathology.

FIGURE 1. The human amygdala[a]



[a] The amygdala is an almond-shaped collection of more than dozen nuclei buried beneath the medial temporal lobe. Panel A shows the location of the amygdala within the human brain. The vertical red line indicates the location of the coronal schematic shown in panel B, which illustrates the location of the amygdala relative to other subcortical regions. Panel C shows the amygdala nuclei; note that some nuclei are not visible at this location. ACTA=amygdalocortical transition area; AHA=amygdalohippocampal area; BL=basolateral nucleus; BM=basomedial nucleus (accessory basal); Ce=central nucleus; Co=cortical nucleus; ITC=intercalated cells; La=lateral nucleus; Me=medial nucleus; PL=paralaminar nucleus. Portions of the figure were adapted with permission from the Allen Institute for Brain Science human reference atlas (262).

THE CANONICAL MODEL OF "THE AMYGDALA"

In the minds of many scientists and even the public, the amygdala is synonymous with fear and anxiety (24–27). And in fact, converging lines of evidence indicate that the amygdala 1) is anatomically poised to trigger signs of fear and anxiety; 2) is sensitive to a wide variety of noxious and potentially threat-relevant stimuli, and variation in amygdala function is associated with dispositional risk for anxiety disorders, depression, and related internalizing illnesses (28); 3) exerts bidirectional control over signs and symptoms of fear and anxiety; and 4) contributes to the development, maintenance, and treatment of internalizing illness.

The Amygdala Is Anatomically Poised to Orchestrate States of Fear and Anxiety

The amygdala lies at the center of a web of brain regions, and it is uniquely well-positioned to use information from sensory, contextual, and regulatory regions to guide the assembly of emotional responses via dense projections to the downstream regions that directly mediate the behavioral (e.g., passive and active avoidance), physiological (e.g., cardiovascular and neuroendocrine activity, startle), and cognitive (e.g., vigilance, associative learning, long-term memory) features of fear and anxiety (29–31).

Amygdala Function Is Sensitive to Threat and Covaries With Dispositional Risk for Internalizing Illness

Studies of rhesus monkeys (*Macaca mulatta*) afford an opportunity to obtain concurrent measures of naturalistic defensive behaviors, neuroendocrine activity, and brain metabolism in response to ethologically relevant threats, including explicit cues of potential danger (e.g., an unfamiliar human intruder's profile) and more diffuse contexts (e.g., a novel testing cage)—something that would be challenging to accomplish in humans. Using [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) in samples encompassing as many as 592 individuals, Kalin, Fox, and colleagues have demonstrated that amygdala activity (glucose metabolism) covaries with heightened behavioral inhibition (e.g., freezing) and cortisol responses to such threats (32–37). Amygdala metabolism is moderately stable over time and context and, as such, represents a trait-like feature of brain function (36). Fox and colleagues showed that amygdala metabolism during exposure to an unfamiliar human intruder's profile showed an intraclass

correlation (ICC) of 0.64 over 1.1 years, similar to the concurrent stability of defensive responses to threat in young monkeys (ICC=0.72) (34, 38, 39) and the 5-year stability of neuroticism/negative emotionality, a prominent dispositional risk factor for internalizing illnesses, in humans (partial R=0.60; N=56,735) (31, 40).

Like the anxiety disorders, anxious temperament or "trait anxiety" reflects a mixture of nature and nurture in humans and nonhuman primates (33, 41, 42). Work in monkeys demonstrates that the neural circuitry underlying trait-like variation in anxiety can be similarly fractionated. Although heritable, amygdala metabolism appears to be more closely related to the variation in anxious temperament that is explained by differences in early-life experience (h^2=0.29, r_g=n.s., N=592) (33). In contrast, functional connectivity between the amygdala and the neighboring bed nucleus of the stria terminalis (BST) appears to be more closely associated with the heritable variation in anxious temperament and, hence, to the intergenerational transmission of internalizing risk from parents to their offspring (h^2=0.45, r_g=0.87, N=378) (43).

Among humans, the amygdala is recruited by a broad spectrum of noxious and potentially threat-relevant stimuli, both learned and unlearned, including aversive scenes and odors, Pavlovian threat cues (CS+), uncertain- and certain-threat anticipation, horror movies, an approaching tarantula, pain, and photographs of angry, fearful, and untrustworthy faces (22, 44–58). Increased amygdala activation is, in turn, associated with elevated levels of threat-elicited distress and psychophysiological arousal (22). More recent work has leveraged machine learning approaches to show that the amygdala is also a key element in whole-brain multivoxel patterns or "signatures" that predict the intensity of negative affect triggered by noxious stimuli (i.e., in individuals not used for signature training [59]) and that distinguish Pavlovian threat (CS+) from safety (CS−) (52, 60, 61).

Like monkeys, human adults and youths with a more anxious, neurotic, or shy disposition are prone to more intense or persistent activation in the amygdala. This has been observed both at "rest," in the absence of an explicit task, and in response to novelty, task-irrelevant negative emotional faces, aversive images, and Pavlovian threats (41, 53, 62–65). For example, Kaczkurkin et al. (66) used a large peri-adolescent youth data set (N=875) to show that, on average, adolescent females are marked by a more anxious temperament than adolescent males and that this difference statistically reflects elevated resting perfusion in the amygdala (sex → resting amygdala activity → disposition). Amygdala–temperament associations appear to be more pronounced following acute stress inductions (67) and are amplified among individuals with lower social support (68), another risk factor for internalizing illness (31).

The Amygdala Exerts Bidirectional Control Over Fear- and Anxiety-Related States and Traits

Lesion and other loss-of-function experiments (e.g., optogenetic inhibition) in rodents demonstrate that the amygdala is mechanistically critical for orchestrating defensive responses to a variety of threats, learned and unlearned, certain and uncertain (19, 22, 69–74). The amygdala is also critical for mounting species-typical avoidance and escape responses to naturalistic threats, such as a robotic virtual predator (75).

Other work in mice suggests a role for the amygdala in anxious temperament and related emotional traits. For example, Ahrens et al. (76) showed that anxious, behaviorally inhibited mice are characterized by tonically elevated amygdala activity, consistent with FDG-PET and perfusion fMRI studies in humans and monkeys (36, 66, 77, 78). In an elegant series of experiments, Ahrens et al. demonstrated that amygdala activity is sensitive to uncertain danger (unpredictable shock) and is both necessary and sufficient for heightened defensive responses to novelty and diffuse threat (open field).

While our understanding of the primate amygdala lags behind that of rodents, work in monkeys and humans suggests that it is mechanistically crucial for mounting defensive responses to threat. In monkeys, fiber-sparing (excitotoxic) lesions of the amygdala attenuate defensive behaviors and endocrine responses to both conditioned and innate threats, including unfamiliar conspecifics (79–82).

These observations dovetail with work in humans. Patient SM, for example (83), is marked by near-complete bilateral destruction of the amygdala and shows a profound lack of fear and anxiety—whether measured objectively or subjectively—to both diffusely threatening contexts (e.g., traversing a haunted house, where the timing and nature of threat encounters is uncertain) and acute threats, including spiders, snakes, horror films, Pavlovian threat cues, "jump scares" in the haunted house, and even real-world assault. Notably, SM also shows profoundly low levels of dispositional fear and anxiety—whether indexed by self-report, family report, clinician report, or daily diary (83–85).

Other work has examined the consequences of amplifying amygdala activity. Work in monkeys shows that manipulations that increase amygdala metabolism can potentiate freezing and other signs of threat-evoked anxiety (80), consistent with rodent studies (76). Likewise, electrical stimulation of the human amygdala has been shown to elicit conscious feelings of fear and anxiety, accompanied by tachycardia and surges in electrodermal activity (86). Inman et al. (86) describe an individual ("subject 8") who experienced intense fear and anxiety in response to 6-volt stimulation in the right amygdala: "It was, um, it was terrifying, it was just . . . it was like I was about to get attacked by a dog . . . like someone unleashes a dog on you, and it's just like it's so close, and you feel like you're going to s— your pants. It's terrifying." At 8 volts, he asked to terminate the stimulation, saying, "That was so scary it was nauseating. It's like, um, I went zip-lining a few weeks ago . . . and this was worse." Such feelings were dose-dependent, absent during intermixed sham trials, reproducible across sessions, and broadly

consistent with earlier microstimulation observations (87–89). Taken with the loss-of-function data, this suggests that circuits centered on the amygdala exert bidirectional control over many of the core signs and symptoms of fear- and anxiety-related states and traits.

Amygdala Hyperreactivity Is Associated With Internalizing Illness and Normalized by Treatment

Several lines of evidence indicate that the amygdala plays a prominent role in the pathophysiology of anxiety disorders and depression.

Amygdala activation:

1. Is elevated in children, adolescents, and adults with internalizing disorders and in individuals with a positive family history (90, 91). Parallel effects have been reported for "resting" amygdala perfusion (66). Three recent coordinate-based meta-analyses (CBMAs), collectively encompassing thousands of participants, provide consistent evidence of amygdala hyperreactivity in individuals with major depressive disorder and/or anxiety disorders (92–94). In the most nuanced CBMA, McTeague et al. (93) observed significant amygdala hyperreactivity to "emotional" tasks among individuals with interview-verified anxiety or depression diagnoses. Ancillary analyses suggested that these effects were largely driven by studies of negative faces and scenes. Amygdala hyperreactivity was also evident in a comprehensive recent CBMA focused on anxiety disorders and emotional tasks (95).
2. Is amplified by exposure to the same kinds of stressors and psychological pathogens (e.g., combat, childhood maltreatment) that can precipitate acute illness in at-risk individuals (90, 96–98). For example, a recent CBMA encompassing more than 3,000 participants indicated that adversity exposure is associated with exaggerated reactivity of the amygdala to emotional tasks (99).
3. Prospectively predicts heightened internalizing symptoms among adolescents and emerging adults exposed to stress, trauma, or negative life events (100–102). For example, McLaughlin et al. (103) showed that adolescents marked by a more reactive amygdala at baseline experienced heightened posttraumatic symptoms 9 months after exposure to the terrorist attack at the 2013 Boston Marathon. Among young children, amygdala activation has been shown to prospectively predict the worsening of internalizing symptoms (62).
4. Is attenuated by clinically effective pharmacological (e.g., benzodiazepine, SSRI) treatments for anxiety and depression (90, 104–107), consistent with work in rodents (108, 109). Amygdala reactivity is dampened by moderate doses of ethanol (110), a well-established anxiolytic that, like the benzodiazepines, enhances inhibitory neurotransmission in the amygdala (111–113). The discontinuation of antidepressant treatment often triggers relapse, and new work suggests that individuals who exhibit a "rebound" in amygdala reactivity at the time of discontinuation are more likely to relapse (114).
5. Is attenuated by cognitive-behavioral therapy (CBT) in anxiety patients (107, 115, 116) and by cognitive reappraisal (a core element of CBT) in psychiatrically healthy individuals (117).

Collectively, these observations suggest that heightened amygdala function contributes to the development and maintenance of pathological fear, anxiety, and depression. Despite this progress, it has become increasingly clear that things are not so simple. To develop a more complete and useful understanding of amygdala function, we first need to reckon with its anatomical complexity.

A NEUROANATOMICAL PERSPECTIVE ON "THE AMYGDALA"

The amygdala was discovered and named by Burdach in the early 19th century, decades before Nissl, Golgi, and Cajal developed the stains needed to resolve cellular details and 150 years before the advent of the chemical tracers needed to study long-range connectivity (118). As these tools became available, neuroanatomists recognized that "the amygdala" is an anatomical concept that lumps together at least 12 different nuclei, each containing millions of functionally and structurally distinct cells (20, 118, 119). Differences in the contribution of these nuclei to fear, anxiety, and other behaviors reflect differences in cellular composition and connectivity (118). The overall composition of amygdala nuclei ranges from "striatal-like," in the case of the central (Ce) and medial (Me) nuclei, to "cortical-like," in the case of the basal (Ba) and lateral (La) nuclei (often grouped together as "BLA"). Although both regions contain mixtures of inhibitory (GABAergic) and excitatory (glutamatergic) neurons, the Ce and Me primarily contain inhibitory neurons that project to subcortical and brainstem nuclei, whereas the La and Ba primarily contain excitatory neurons with robust bidirectional connections to the cortex. Recent work in humans and monkeys indicates that Ce neurons, whether inhibitory or excitatory, show different profiles of gene expression when compared to their La counterparts, as indexed by single-nucleus RNA sequencing (120). In fact, the Ce is more similar to the extra-amygdalar BST—in terms of gene expression, cytoarchitecture, neurochemistry, connectivity, embryonic development, and many aspects of function—than it is to the La (21, 22, 48, 121, 122). Based on these kinds of neuroanatomical similarities, Alheid and Heimer (121) proposed an alternative anatomical concept—the "extended amygdala"—that encompasses a mixture of amygdalar and extra-amygdalar regions, including the Ce, Me, BST, portions of the sublenticular extended amygdala (an archipelago of cell islands lying between the substantia innominata and lenticular nucleus), and parts of the nucleus accumbens shell that neighbor the BST (20, 121). In short, even a cursory inspection of these kinds of anatomical data

makes it clear that "the amygdala" is neither a natural kind nor a singular unit—that it combines disparate regions (Ce/Me vs. BLA) and omits similar ones (e.g., BST)—suggesting that the canonical model is too simplistic.

NEW HUMAN DATA AND SHORTCOMINGS OF THE CANONICAL MODEL

From a human neuroimaging perspective, the canonical model—which implies that the amygdala is *the* neural center for fear and anxiety—suffers from two notable shortcomings. First, associations with fear- and anxiety-related constructs, while statistically significant, are often weaker and less generalizable than often assumed. Second, the canonical model fails to adequately capture the breadth of functions and disorders supported by the amygdala, suggesting that the amygdala's contribution to fear and anxiety may be more nuanced and complex than the model suggests. To be clear, these limitations do not fundamentally undermine the canonical model, but they do raise conceptual and practical concerns, and they underscore the need to adopt approaches that more fully embrace the functional and anatomical complexity of the amygdala.

Associations With Fear and Anxiety Are Often Modest and Inconsistent

Basic neuroscience research. Much of the groundbreaking work to understand the function of the rodent amygdala focused on its role in Pavlovian conditioning (123). Guided by this work, the first wave of human fMRI studies reported heightened amygdala activation to Pavlovian threat cues (CS+ > CS−), suggesting an evolutionarily conserved functional-neuroanatomical system (124, 125). But replicating these observations—which were based on a grand total of 19 participants—has proved challenging, with many groups reporting null effects (54, 126, 127) or even amygdala deactivation (CS+ < CS−) (127, 128). Similar inconsistencies are evident in the instructed threat-of-shock literature (44, 95, 129, 130). While the mechanistic status of the human amygdala in Pavlovian threat conditioning was never in any real doubt (131), for much of the past decade, it was unclear whether this association could be reliably detected in human fMRI studies. While differences in methodology and sample composition certainly contribute (132, 133), a more substantive answer to this question only recently emerged. Leveraging a well-powered sample (N=601) and a region-of-interest approach, Wen et al. (51) showed that many of these inconsistencies reflect a mixture of weak statistical effects, rapid habituation, and the field's tendency to aggregate heterogeneous amygdala nuclei. They showed that statistically significant but numerically negligible amygdala activation is evident using a conventional analytic approach, which entails aggregating across all acquisition trials and nuclei (Cohen's d=0.12). Effects were stronger in the first four trials of the acquisition phase (Cohen's d=0.51), particularly the first trial (before the association is learned), but even here the authors' power analyses indicated that ~80 participants are required to consistently detect differential amygdala reactivity at a liberal threshold (CS+ > CS−; 75% power; alpha=0.01, uncorrected). Trial-by-trial analyses revealed significant deactivation within ~10 trials, and this effect was especially pronounced in the BLA. During the extinction phase, heightened amygdala activation was evident only for the first 1–2 trials. These findings, which dovetail with rodent electrophysiological work, strengthen claims of conserved amygdala function and reinforce the importance of going beyond "the amygdala" to examine individual nuclei or circumscribed sets of nuclei (e.g., BLA). They also highlight the value of examining more fine-grained temporal dynamics. Yet, the need to focus on such a limited number of trials raises serious concerns about psychometric reliability and casts doubt on the utility of this approach for psychiatric neuroimaging association studies (134–136).

Individuals with an anxious, shy, or neurotic disposition are more likely to develop internalizing disorders, and if they do, they may experience a more severe and treatment-resistant course (31). Although early human fMRI studies indicated that these risk-conferring dispositional phenotypes are associated with exaggerated amygdala reactivity to emotional faces (137–139), four recent large-sample studies (Ns, 213–1,256) failed to replicate these associations (44, 140–142). This suggests that relations between dispositional risk and amygdala reactivity to emotional faces are either negligible or, as with the Pavlovian literature, require specialized approaches to detect (143, 144). There are hints that amygdala–disposition associations are stronger for faces that are task-irrelevant, unattended, or presented outside of conscious awareness (64, 137, 145). Whether this is generally true and whether these associations are sufficiently consistent and strong to warrant further investment is unclear. Weak and inconsistent associations are not limited to emotional face paradigms. Early work suggested that individuals with an anxious or neurotic disposition show heightened amygdala reactivity during periods of threat anticipation, as with Pavlovian threat conditioning and instructed threat-of-shock paradigms (146). With one exception (53), subsequent studies—many featuring relatively large samples (Ns, 50–220)—have reported null effects (reviewed in reference 44).

Mechanistic work has also revealed effects that are inconsistent with a simplistic version of the canonical model. Amygdala lesions do not completely abolish threat-elicited freezing, and not all manipulations that increase amygdala activity increase anxious or fearful behaviors (81). For example, in monkeys, overexpression of neurotrophin-3 in the dorsal amygdala *increases* Ce metabolism, but *decreases* anxious temperament (147). Although microstimulation of the human amygdala can produce signs and symptoms of fear and anxiety, and these are the most commonly evoked emotions, conscious feelings are infrequently triggered and are by no means confined to fear; in fact, feelings of sadness, guilt, joy, and happiness have been reported (86–89). This

heterogeneity likely reflects, in part, variability in the intensity and nuclear location of stimulation (86).

Conversely, loss-of-function research indicates that the human amygdala is not necessary for experiencing all forms of fear and anxiety. In a seminal study (148), patient SM and two other patients with bilateral amygdala lesions experienced frank panic attacks, reported intense feelings of fear, anxiety, and panic, and showed elevated signs of arousal in response to CO_2 inhalation, a well-validated interoceptive threat. Taken with the data reviewed above (in the section "The Canonical Model of 'The Amygdala'"; e.g., 83), these observations suggest that although the amygdala can be critical for organizing fear and anxiety in response to many external threats (but perhaps not all; e.g., as with Pavlovian "overtraining"), it is *not* necessary for triggering emotional response to CO_2-triggered air hunger, an endogenous threat.

Clinical neuroimaging research. Overlapping concerns apply to the clinical neuroimaging literature.

1. To ensure an adequate number of studies, CBMAs of the clinical neuroimaging literature have been compelled to "lump" across diagnoses, ages, and tasks, precluding inferences about diagnostic or symptom specificity (92–94). Among individuals with anxiety disorders, a recent CBMA demonstrated amygdala hyperreactivity to emotion perception and generation tasks (95). While this was true when collapsing across diagnoses, in disaggregated analyses it was only evident for specific phobia and social anxiety disorder. Whether this reflects genuine diagnostic differences or an artifact of systematic differences in statistical power and fMRI tasks is unknown (149).
2. Early research suggested that amygdala activation is associated with the severity of internalizing symptoms (150, 151). Yet, more recent studies with substantially better power (Ns, 229–28,638) indicate that amygdala reactivity to negative emotional faces and Pavlovian threat cues is unrelated to concurrent anhedonia, depression, fear, or general distress symptoms (128, 152), consistent with null effects for dimensional measure of anxious temperament and neuroticism/negative emotionality (44). Whether this reflects a genuinely null effect, an artifact of aggregating amygdala nuclei, or suboptimal fMRI assays is unclear. In several well-powered studies (Ns, 592–875), significant associations with basal measures of activity in the dorsal amygdala have been consistently observed (33, 66). Although this provides an empirical rationale for prioritizing the Ce and neighboring nuclei for mechanistic follow-on studies, the magnitude of these associations is too modest for clinical application or therapeutics development.
3. In a groundbreaking study (N=340), Swartz et al. (100) showed that heightened amygdala reactivity to fearful and angry faces predicts the worsening of anxiety and anhedonia symptoms in young adults exposed to negative life events. While scientifically useful, here again, the magnitude of this prospective association (d=0.33, r^2=0.027) is too weak to be useful for screening, diagnosis, or other clinical applications centered on individuals (for online visualization tools, see 153, 154). More generally, null effects are not uncommon in prospective studies. For example, Peng et al. recently reported that amygdala reactivity to Pavlovian threat cues is unrelated to the longitudinal course of internalizing symptoms across a 2.5-year follow-up (N=279) (155). Whether this reflects the use of a whole-amygdala region of interest and conventional analyses of the Pavlovian paradigm (see above) or a failure to measure and model negative life event exposure is unknown.
4. Early studies suggested that amygdala reactivity is dampened by cognitive reappraisal in healthy individuals and by CBT in patients with internalizing disorders (115–117). Yet, Bo et al. (55) recently failed to detect significant amygdala down-regulation in a well-powered reappraisal study (N=358), even when examining specific amygdala nuclei. This is consistent with null effects in recent CBMAs of the CBT neuroimaging literature (55, 156, 157).

Is the amygdala a key player in fear- and anxiety-related states, traits, and disorders? Undoubtedly. Is there any value to clinical neuroscience research? Yes, work conducted over the past two decades has yielded steady advances in our understanding of what the amygdala does and does not contribute to the expression and experience of fear and anxiety in rodents, monkeys, and humans. Nevertheless, the data reviewed in this section provide a sober reminder that most of the work remains to be done, and they raise concerns that neuroimagers have relied too heavily on underpowered samples, a limited number of suboptimal workhorse tasks (e.g., emotional faces), and analytic approaches that disregard anatomical heterogeneity and temporal dynamics, weakening associations with psychiatric phenotypes (1, 91). The degree to which modest brain–behavior associations reflect cellular heterogeneity within amygdala nuclei remains unclear, a point we return to later.

The Human Amygdala Is Not Specific to Fear and Anxiety

The amygdala's robust contributions to fear and anxiety often overshadow its role in other behavioral functions and psychiatric illnesses. The field has long recognized that the amygdala contributes to a variety of non-threat functions (27, 158–160), and human neuroimaging studies show that the amygdala is robustly engaged by a variety of positive stimuli, including erotica, food and drug cues, music, pleasant odors, happy faces, and humorous stimuli (56, 161–170). The amygdala also appears to play a key role in directing eye gaze to the parts of the face most diagnostic of others' intentions and inner states (31, 171). Likewise, detailed studies of patient SM and other individuals with circumscribed damage indicate

that the amygdala plays a critical role in aspects of social perception and decision making, theory of mind, the emotional modulation of declarative memory, and loss aversion for rewards (172, 173). Convergent evidence comes from work in monkeys, where fiber-sparing lesions of the amygdala disrupt normative preferences for viewing conspecific faces (174) and lead to aberrant visual inspection of faces (175).

From a clinical perspective, the amygdala is now known to contribute to a wide variety of neuropsychiatric disorders—not just internalizing illnesses. Among these, temporal lobe epilepsy and autism spectrum disorder (ASD) are perhaps the most familiar (88, 176). Youths with ASD show aberrant trajectories of neuroanatomical maturation in the amygdala (177, 178) and alterations in gaze-dependent amygdala reactivity to faces (171, 179, 180). Other work suggests a role in psychosis. A recent CBMA demonstrated that individuals with schizophrenia show exaggerated amygdala reactivity to emotionally neutral stimuli (181), while those with heightened paranoia show elevated amygdala perfusion at rest (182, 183). Other work suggests that the amygdala plays an important, though often overlooked role in substance use disorders and obesity (e.g., 184). For example, feelings of hunger have been shown to amplify amygdala reactivity to food cues in unselected samples, and to amplify reactivity to drug cues in users (185–187). Furthermore, heightened amygdala reactivity to drug cues is attenuated by successful attempts to cognitively downregulate craving intensity, consistent with a causal role (188). More recently, the amygdala has been implicated in the development of neurodegenerative disorders, including Alzheimer's and Parkinson's disease (189–191). While many of these associations are modest in size, they underscore the amygdala's relevance to a broad range of illnesses.

Taken together, these observations make it clear that the amygdala is not a fear and anxiety center; it is a key contributor to a panoply of practically and psychiatrically important behaviors, symptoms, and illnesses. Recent work in rodents has provided some valuable clues about the cellular mechanisms that potentially underlie this diversity of functions and phenotypes.

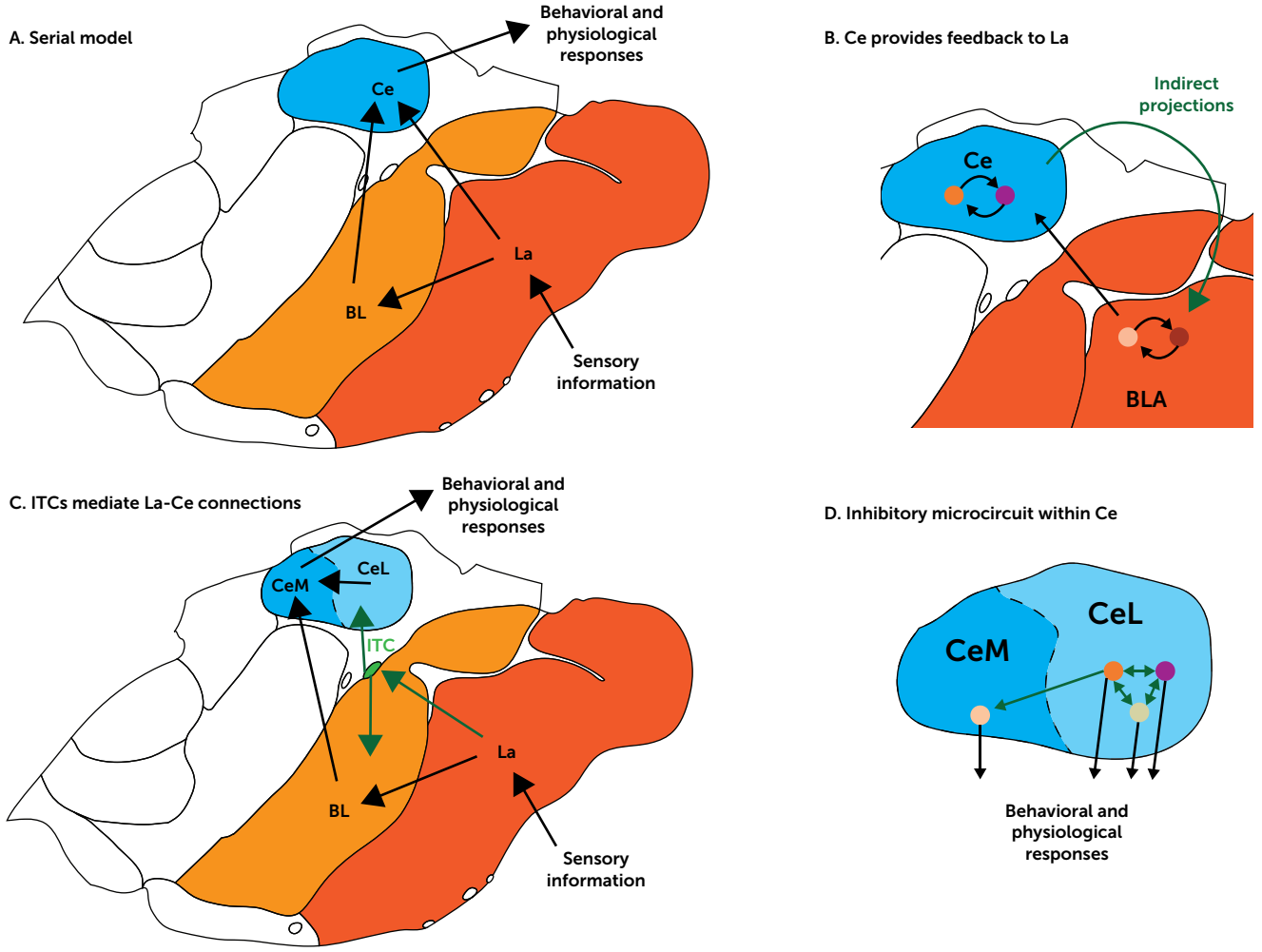
NEW INSIGHTS FROM RODENT MODELS OF THE AMYGDALA

Seminal work in rats and rabbits by LeDoux, Kapp, Davis, and others (123, 158, 192) led to a detailed understanding of the amygdala's role in Pavlovian threat learning and set the stage for the canonical model as we currently know it. Early theories emphasized the serial flow of information from La, the sensory gateway to the amygdala, to Ce, the major output station of the amygdala (123, 192). Pavlovian associative memories are formed in La, where information about a tone or another benign conditioned stimulus (CS+) and a shock unconditioned stimulus (US) converge. With sufficient pairings, this convergence induces synaptic strengthening in La, enabling the formerly neutral CS to trigger preparatory defensive responses via projections to Ce, which serves as a relay to downstream effector regions (Figure 2A). Although the serial model was an important milestone in the scientific study of the amygdala, it has become increasingly clear that it, too, is incomplete. Building on new data, theorists have summarized this updated understanding with different sorts of simplified schematics, each incorporating features that were unknown or overlooked by the serial model. First, La learning depends on indirect feedback from Ce, which is at odds with the serial-relay view (Figure 2B) (193, 194). Second, the intercalated cells (ITCs)—small clusters of cells nestled along the border of Ce and Ba/La—and other amygdala nuclei participate in Pavlovian threat learning (Figure 2C) (195, 196). Direct projections from La to Ce are relatively modest, and much of the communication happens via intermediate nuclei, including the ITCs and Ba. ITCs relay information from La to Ce and are modulated by input from frontal regions during acquisition and extinction (prelimbic and infralimbic cortex, respectively, in rodents) (195). Third, other amygdala nuclei can, in coordination with frontal regions, influence defensive responding. For example, the basomedial nucleus can decrease freezing elicited by both learned (Pavlovian threat) and unlearned (open-field) triggers (197). Likewise, Me can initiate freezing and other defensive responses to a variety of naturalistic threats (198). Fourth, like the overarching canonical model, the serial-relay model of Pavlovian threat conditioning makes no attempt to incorporate the role of amygdala nuclei (including La, Ba, and Ce) in non-threat functions, including reward (199–201), social behavior (202, 203), olfaction (204), aggression (205), and others (159, 206, 207).

The fact that the La, Ba, Ce, and other amygdala nuclei each contribute a range of functions—both threat and non-threat—highlights the need to grapple with the anatomical complexity lying *within* these nuclei. Within each nucleus, cells can be grouped into functionally distinct populations based on their patterns of gene expression and/or connectivity. Studies in rodents have leveraged projection and cell type–specific opto- and chemogenetic manipulations to identify microcircuits that contribute to a rich variety of threat-related and non-threat behaviors (19, 207–211). In some cases, this work has revealed intermingled cellular populations with distinct, even opposing, influences on behavior (22). Here, we selectively highlight a few illustrative examples of these new insights. Studies of mouse BLA have revealed overlapping groups of Ce- and nucleus accumbens–projecting neurons that are required for threat and reward learning, respectively (199, 212, 213, 214). Other work demonstrates that stimulation of different groups of intermingled Ce neurons can trigger a variety of defensive and non-defensive responses, including prey pursuit and capture (215), eating (216, 217), taste preferences (218), and pain (219).

From a neuroimaging perspective, these observations raise questions about whether and how we can discern

FIGURE 2. Amygdala microcircuits[a]



[a] Influential models developed in the late 20th and early 21st century emphasized the serial flow of information from La, the sensory gateway to the amygdala, to Ce, the major output station (panel A) (25). Ce triggers defensive responses via efferent projections to subcortical and brainstem effector regions. More recent evidence has produced a new generation of schematics. Some emphasize the flow of feedback from Ce to BLA (193, 194) (panel B), and some emphasize the ITCs' role in mediating the flow of information from La to Ce (panel C) (195, 196). Still others focus on the role of inhibitory Ce microcircuits in selecting defensive responses to threat (panel D) (19, 208, 210, 211). BL=basolateral nucleus; BLA=lateral, basolateral, and basomedial nuclei; Ce=central nucleus; CeL=lateral division of Ce; CeM=medial division of Ce; ITC=intercalated cells; La=lateral nucleus.

intranuclear differences in cellular function. After all, the engagement of different cellular populations is not necessarily associated with differences in bulk activation, as indexed by fMRI. In the BLA, for example, one can imagine that the recruitment of threat- and reward-sensitive cells leads to similar overall levels of activity (see the online supplement). Importantly, the complexities of microcircuit architecture can further complicate relations with bulk activation. In the Ce, for instance, the same threat can recruit distinct groups of somatostatin (SST+) and corticotropin-releasing hormone (CRH+) cells to trigger freezing or escape, respectively (220). Critically, SST+, CRH+, and protein kinase Cδ (PKCδ+) cells are mutually inhibitory; that is, increasing the activity of one attenuates the others (Figure 2D) (19, 208, 210, 211). In short, different behaviors and tasks, each mediated by distinct Ce cellular populations, could result in identical changes in bulk activation.

Interim Conclusions

The amygdala encompasses more than a dozen nuclei, each containing intermingled populations of cell types. Over the past decade, work in mice has revealed that these cells contribute to a broad array of threat- and non-threat functions and behaviors. These are often mediated by dynamic interactions between cell types within microcircuits that are situated within and across amygdala nuclei (and other regions of the brain). With this new knowledge in hand, the modest and inconsistent associations between neuroimaging measures of "the amygdala" and psychiatrically relevant phenotypes in humans are hardly surprising. The canonical model of "the amygdala" is insufficient, and studying "the amygdala" is nearly always the wrong level of analysis. The challenge for the neuroimaging community is to embrace and leverage this functional-neuroanatomical complexity.

IMPLICATIONS OF AMYGDALA CELLULAR HETEROGENEITY AND OPPORTUNITIES FOR ACCELERATING CLINICAL RESEARCH

A central goal of psychiatry and clinical psychology is to prevent or cure psychiatric illness. Yet, billions of dollars of research have largely failed to uncover new assays, biomarkers, or treatments. Research focused on "the amygdala" cannot to rise to this challenge. Based on what we now know about amygdala cells and microcircuits, the mapping between brain and psychiatric phenotypes likely reflects a mixture of "many-to-one" and "one-to-many" associations (221). Many-to-one refers here to perturbations of multiple cell types that can produce similar behavioral disturbances. For instance, alterations to Ce-projecting BLA neurons, ITCs, or SST+ Ce neurons can all influence Pavlovian threat conditioning. One-to-many refers to perturbations to different cell types within a single nucleus that can have dramatically different behavioral consequences (e.g., SST+ vs. CRH+ neurons in Ce) (220) and perturbations of the same cell type that could impact different outcomes, depending on the larger circuit in which they are embedded (e.g., CRH+ cells are involved in both escaping threat and approaching reward) (220, 222). To the extent that different amygdala-implicated disorders (see the section "New Human Data and Shortcomings of the Canonical Model," above) are marked by different signs and symptoms, this likely reflects distinct cellular substrates. Conversely, to the extent that different patients with a particular amygdala-implicated disorder or different disorders share overlapping symptoms, this may reflect shared cellular substrates. The same implications apply to the development of new therapeutics.

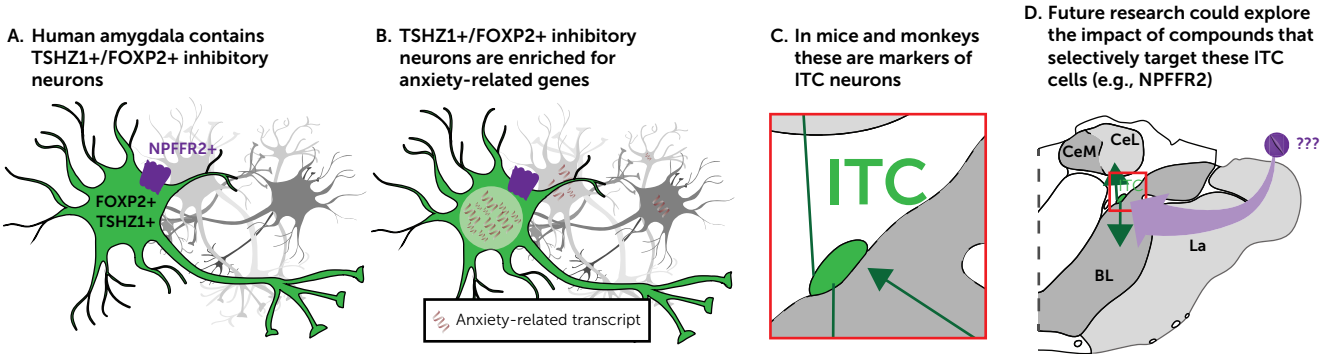
Recent insights into the cellular complexity of the amygdala also have implications for the interpretation of gene association studies. Like other brain regions, cell typing in the amygdala is often based on patterns of gene expression. Gene association studies indicate that thousands of genetic variants contribute to amygdala-relevant disorders (223–228). The impact of these genes on psychopathology is proximally mediated by their influence on neural cells. Genes that are uniquely expressed in specific amygdala cell types are likely to have circumscribed phenotypic consequences, whereas those that are expressed across different types of amygdala cells are likely to have a broad impact, and genes that are expressed in both amygdala and non-amygdala cells will have the broadest and least specific behavioral consequences. These insights can help make sense of evidence that many psychiatric disorders are coheritable and rely on overlapping sets of genes (229, 230). In short, understanding what cell types are impacted and how they contribute to psychopathology has the potential to guide the development of novel therapeutics, a point we develop further below.

Cells are the fundamental building blocks of the brain and are shaped by a combination of genetic and experiential processes. Cell types provide a natural biological platform for accelerating our understanding of neuropsychiatric illness and for developing more effective treatments with fewer off-target effects. Consider Parkinson's disease. While it has long been recognized that Parkinson's reflects the loss of dopamine neurons in the substantia nigra pars compacta, it was unclear which cells were most vulnerable, and the underlying molecular processes remained enigmatic. Recent work identified a single class of cell types that are disproportionately affected, which in turn highlighted a set of specific molecular processes that appear to mediate heightened genetic risk (231). Other work has begun to exploit information about cell types to create precisely targeted gene therapies for disorders of the retina and inner ear (232, 233). From a therapeutics perspective, treatments that target a cell type for excitation or inhibition are attractive because they can address multiple candidate etiologies, all of which ultimately act at the level of the cell. For example, disruption of a receptor, the regulation of its expression, or its intracellular signaling could all potentially result in the same functional outcome. Even if they do not directly address the underlying cause, a cell type–targeted treatment could effectively address any or all of them by simply inhibiting the cell, either tonically or in an activity-dependent manner (234).

To achieve the promise of cell-type treatments for amygdala-related disorders, we must first develop a taxonomy of human cell types and understand the degree to which they are conserved across mammalian species. Efforts are ongoing and underscore the complexity of the mammalian brain (235–243). Even comparatively "simple" regions, such as primary motor cortex, contain more than 50 unique cell types (235). Although there is no agreed-upon comprehensive taxonomy for amygdala cell types, data from multiple groups suggest that this heterogeneity goes beyond commonly used chemoarchitectonic (e.g., GABAergic vs. glutamatergic), cytoarchitectonic (e.g., projection vs. medium spiny), or expression-based (e.g., SST+ vs. CRH+) classifications (242–245). Moreover, there is no guarantee that the amygdala cells mediating threat-elicited freezing in mice (e.g., SST+) perform the same functions, or even exist, in humans (120). Indeed, comparative work has begun to reveal a mixture of conserved and, perhaps, human-unique cell types in the amygdala (120).

Once cell types are identified, we need to identify the types that are most relevant to psychiatric symptoms and disorders. This can be accomplished by fusing cell type taxonomies with data from human genome-wide association studies. For example, Kamboj et al. (120) leveraged such data to identify La and Ce cell types that are relatively enriched for the genes linked to anxiety disorders and other amygdala-related illnesses (Figure 3). Focusing on relative enrichment has the advantage of down-weighting cell types that are enriched for nonspecific psychopathology-linked genes. This approach revealed a group of ITC cells that were enriched for genes associated with neuroticism/negative emotionality, anxiety disorders, and depression. As described above (in the section "New Insights From Rodent

FIGURE 3. Identifying and understanding the role of amygdala cell types in anxiety disorders[a]



[a] As shown in reference 120, single-nucleus RNA sequencing (snRNA-seq) can be used to identify evolutionarily conserved cell types, along with putative marker genes (TSHZ1 and FOXP2) and G protein–coupled receptors (NPFFR2) (panel A). Data from large-scale genome-wide association studies can be leveraged to identify cell types that show relative enrichment of disorder-associated genetic variants (panel B). Spatial sequencing and in situ hybridization can be used to confirm cellular location (panel C). Together, these data can be integrated with rodent microcircuit studies to prioritize cell types for mechanistic follow-up studies, including experimental therapeutics research (panel D). BL=basolateral nucleus; Ce=central nucleus; CeL=lateral division of Ce; CeM=medial division of Ce; ITC=intercalated cells; La=lateral nucleus.

Models of the Amygdala"), work in rodents indicates that ITCs play a key role in processing Pavlovian threat and can be modulated by prefrontal biasing signals. Taken together, these observations prioritize ITCs as a target for mechanistic follow-up work. Basic research in animals can leverage cell type–specific perturbation and recording tools to clarify their role in local microcircuits and their relevance to psychiatrically relevant behavioral phenotypes. While challenging, human translational research can assess whether cell type–specific hypotheses are fruitful for understanding the macroscopic function of the human amygdala and other brain regions (see the online supplement for additional details and examples). Together, these basic and translational studies can be used to prioritize the cell types that are most likely to be involved in psychiatric disorders.

Prioritized cell types provide a target for therapeutics development. Efforts to develop improved tools for targeted interventions are ongoing. This includes the development of viral vectors that can be delivered across the primate blood-brain barrier (246–250), the identification of enhancers, promotors, and other regulators to restrict expression to specific amygdala cell types (e.g., 251), and innovations in genetically encoded cargo that could be used to modulate the activity of these cells at the scale of the human brain (e.g., designer receptors exclusively activated by designer drugs) (252–257). Pharmacological treatment strategies can also target cell types, by identifying receptors that are enriched on the cell type of interest. For example, Kamboj et al. (120) showed that anxiety-related ITCs are enriched for neuropeptide FF receptor 2 (NPFFR2), and preclinical research hints that NPFFR2 treatments may buffer the effects of stress (258–261) (Figure 3). While systemic pharmacological approaches are more likely to have adverse off-target effects than gene therapies (via their impact on other cell types in and outside of the amygdala), this provides another potential pathway to developing new treatments for maladaptive fear and anxiety.

More broadly, this body of work showcases some ways in which cell types can be leveraged to generate novel hypotheses about the neurobiological mechanisms underlying amygdala-related psychopathology and inform the development of new treatments. The utility of this approach is likely to increase over time as more data and consensual cellular taxonomies become available for the amygdala and other regions.

CONCLUSIONS

Amygdala-related disorders impose a staggering burden on public health, and existing treatments are far from curative for many (6, 11). Addressing this burden will require the development of interventions that are more effective, durable, and tolerable. Rising to this challenge requires a frank recognition of the strengths and weaknesses of the theoretical canon that has built up around "the amygdala" and an embrace of models centered on nuclei and cell types. Translational work in animals can be used to develop hypotheses that can be tested in healthy and diseased humans. Although this path will require exceptional creativity and effort, it is clear that we must begin to more honestly reckon with the amygdala's functional-neuroanatomical complexity if we are going to understand its role in neuropsychiatric disease.

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Supplementary Note: Cell-type informed neuroimaging task design

Different amygdala-activating tasks likely recruit distinct cellular populations

As detailed in the main report, work in rodents makes it clear that different stimuli, tasks, and behavior are dependent on distinct types of amygdala cells, often within the same nucleus. This is likely true of the human amygdala as well. As such, different stimuli, tasks, and behavior represent non-equivalent probes of amygdala functional neuroanatomy. In fact, recent work from our group and others shows that variation in amygdala activation is weakly correlated across amygdala-activating tasks (Grogans et al., 2024; Villalta-Gil et al., 2017). Variation in amygdala reactivity to emotional faces, for instance, tells us next-to-nothing about amygdala reactivity to anticipated threat (**Figure S1**). Likewise, activation in the amygdala and other regions shows task-dependent associations with psychiatric phenotypes. A recent CBMA of anxiety disorders reported dramatically different neural "hits," depending on whether illness was viewed through the lens of "emotional" or "cognitive" tasks (Chavanne & Robinson, 2021). Among first-year university students, photographs of delicious food and erotica both robustly recruit the nucleus accumbens (NAC), but variation in food reactivity selectively predicts freshman weight gain, whereas erotica reactivity selectively predicts sexual desire and number of sexual partners (Demos et al., 2012). Anticipated threat potently activates the BST, a key division of the EA. Photographs of fearful and angry faces produce an even stronger effect. Yet only uncertain-threat is associated with variation in the risk-conferring N/NE phenotype (Grogans et al., 2024). These kinds of observations are consistent with the idea that different neuroimaging tasks recruit different sets of cells and that it is the activity of these cells, not the region, that co-varies with psychiatric phenotypes. As such, the choice of task is critical for understanding the neural systems governing variation in risk, resilience, symptom severity, and diagnostic status.

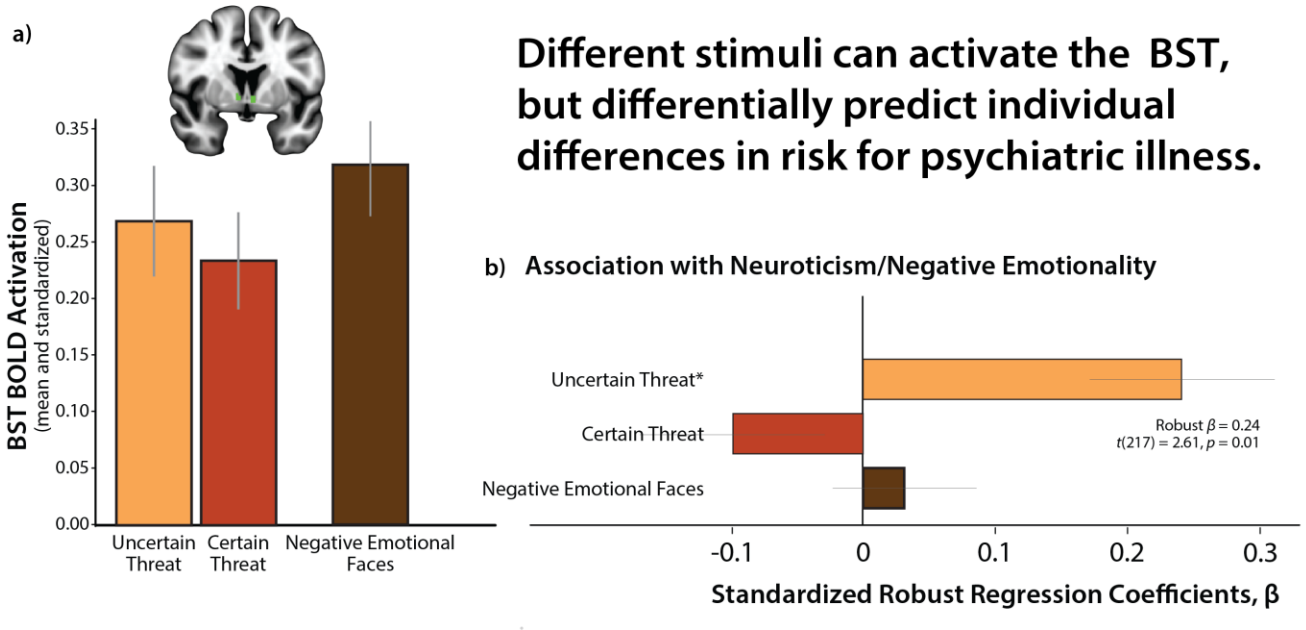

FIGURE S1. Different stimuli can activate the same region, but differentially predict risk for psychiatric illness. (a) Uncertain-threat anticipation, certain-threat anticipation, and negative emotion faces all activate the BST. Bars depict mean standardized ROI activation relative to the respective baseline conditions for each ROI (spatially unsmoothed data). Whiskers depict standard errors. Inset depicts the anatomically defined BST (*green*). **(b)** Yet BST BOLD activation is only associated with variation in the risk-conferring N/NE during the anticipation of uncertain threat (*orange*). Other associations were not significant. Bars depict standardized coefficients for each robust regression model. Whiskers indicate standard errors. Adapted with permission from (Grogans et al., 2024). Abbreviation—BST, bed nucleus of the stria terminalis.

Leveraging insights gleaned from animal models mandates coordinated approaches

Early neuroimaging research was notably effective at bringing animal research to bear on our understanding of the human mind and brain (Büchel et al., 1998; Kastner & Ungerleider, 2000; Knutson et al., 2001; LaBar et al., 1998; Postle et al., 2000). Leveraging tasks and hypotheses adapted from studies of working memory, reward anticipation, and Pavlovian conditioning in rats and monkeys, this work (a) confirmed that homologous regions are involved across species and (b) laid the groundwork for understanding how these regions contribute to human-specific faculties (e.g., verbal working memory). As our understanding of the mouse amygdala brain continues to deepen, this kind of coordinated cross-species approach remains critical. Delivering on the promise of translational research will require cleverly incorporating insights from rodent studies of cell-types into human neuroimaging studies. This can be achieved by designing tasks that specifically target particular cell-types or, at minimum, developing tasks and analytic approaches humans that are strongly rooted in animal research and adequately validated. Tasks aimed at understanding fear and anxiety, for instance, should produce robust increases in distress and psychophysiological arousal (Fox et al., 2018). Likewise, based on work in rodents, we probably would not expect to see a robust effect of Pavlovian- or instructed-threat cues on amygdala activation when aggregating across disparate nuclei (Grogans et al., 2024; Wen et al., 2022). Instead, we might predict nucleus-specific changes in bulk activation, multivoxel patterns of activation, or functional connectivity.

This is not hypothetical; this kind of conceptual approach has been successfully deployed in other areas of cognitive neuroscience. For example, it has been used to understand how concepts are encoded in the brain. To do so, researchers built on the identification of hippocampal "grid cells" in mice, cells that fire any time a mouse traverses specific hexagonal locations in two-dimensional space (Rowland et al., 2016). Neuroimaging work confirmed that humans show similar grid-like activation patterns when navigating a two-dimensional virtual-reality environment (Doeller et al., 2010). This work was then extended to show that grid-like neural codes are also engaged when humans navigate two-dimensional "conceptual spaces," as when comparing individuals on their level of competence and popularity (Aronov et al., 2017; Bao et al., 2019; Constantinescu et al., 2016; Liang et al., 2024; Park et al., 2021). These data illustrate how neuroimaging research can be used to understand the contribution of cell-types identified in animals to species-general and human-specific behaviors.

Challenges for amygdala-related task design

Cell-type targeted neuroimaging research requires concrete predictions about the expected activity of specific cell-types and tasks with high face or process validity. For example, one could use Pavlovian-threat/extinction tasks with parameters that closely match those used in rodents (face validity) or tasks that involve adjudicating between Ce-dependent behaviors (process validity). The neuroimaging outcome must be well aligned with predictions derived from animal models. If one expects mutually inhibitory cellular populations, then bulk increases in Ce activation will be insufficient.

Novel computational models and data analytic strategies—like those used to study grid-codes—must be developed for interrogating amygdala cells. For example, rodent models indicate that threat and reward are processed by different sets of anatomically overlapping and mutually inhibitory cells in the La. As such, one would not predict differential levels of overall La activation when contrasting threat and reward trials (**Figure S2**). However, these cells are not uniformly distributed. Different voxels likely contain varying mixtures of the two cell-types. From the perspective of fMRI, this will be associated with distinct multivoxel patterns of activation (**Figure S2**). In the absence of strong evidence that these cells are similarly distributed across individuals, it will be fruitful to identify multi-voxel patterns at the individual level, as is often done in studies of vision, attention, and working memory (e.g., Lewis-Peacock & Postle, 2008). Rodent models also show that threat- and reward-sensitive cells in La differentially project to Ce and NAC, respectively. This suggests that it will also be fruitful to explore potential differences in task-related functional connectivity in humans. These examples illustrate the kinds of cell-type targeted predictions that could be tested in human fMRI studies (for additional examples, see Drzewiecki & Fox, 2024).

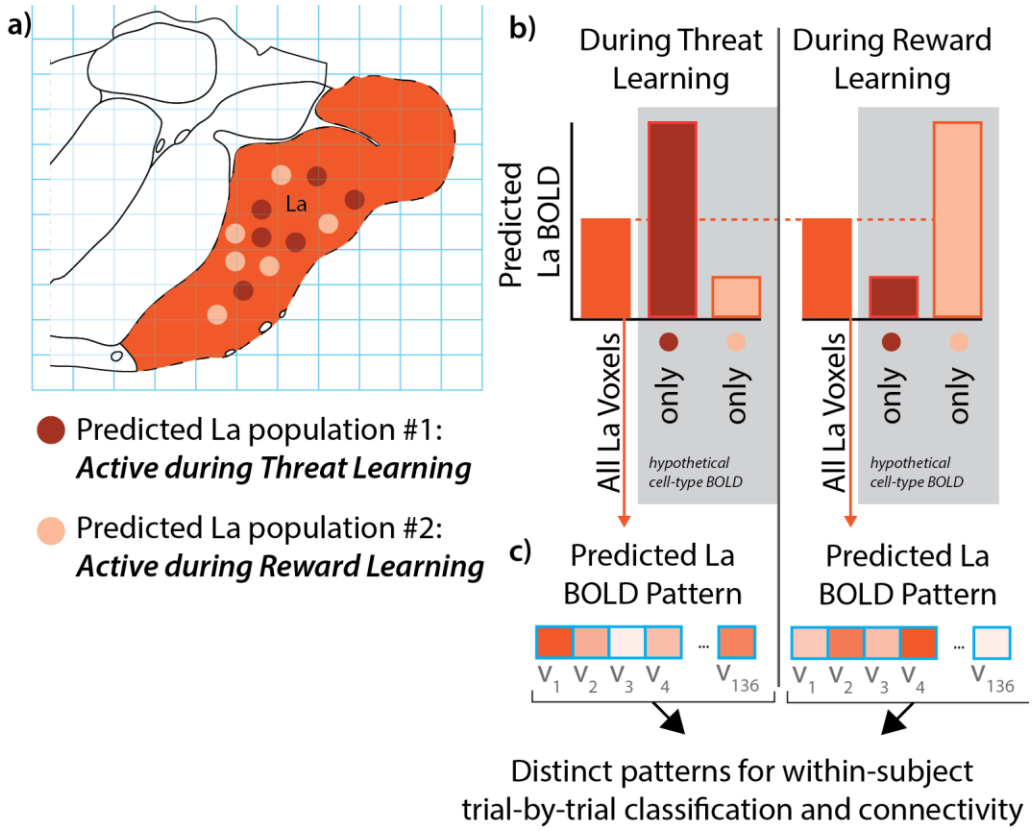

FIGURE S2. Translating cellular insights gleaned from animal models to human neuroimaging. (a) Rodent models have identified intermingled populations of mutually inhibitory La cells that are active during threat and reward learning, respectively. **(b)** This would be expected to yield similar levels of overall La activation across conditions. **(c)** However, because different voxels contain varying ratios of threat- and reward-sensitive cells, we would expect that the multivoxel pattern of La activation would differ across trials as a function of trial type. Rodent models suggest that threat-and reward-sensitive cells differentially communicate with other brain regions, and this could be explored in humans using measures of task-related functional connectivity. Note: Together, the left and right La encompass ~136 2-mm^3 fMRI voxels. Abbreviation—BOLD, blood-oxygen-level-dependent fMRI signal; La, lateral nucleus; v#, voxel.

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