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The role of the locus coeruleus in the generation of pathological anxiety

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Abstract

This review aims to synthesise a large pre-clinical and clinical literature related to a hypothesised role of the locus coeruleus norepinephrine system in responses to acute and chronic threat, as well as the emergence of pathological anxiety. The locus coeruleus has widespread norepinephrine projections throughout the central nervous system, which act to globally modulate arousal states and adaptive behavior, crucially positioned to play a significant role in modulating both ascending visceral and descending cortical neurocognitive information. In response to threat or a stressor, the locus coeruleus–norepinephrine system globally modulates arousal, alerting and orienting functions and can have a powerful effect on the regulation of multiple memory systems. Chronic stress leads to amplification of locus coeruleus reactivity to subsequent stressors, which is coupled with the emergence of pathological anxiety-like behaviors in rodents. While direct in vivo evidence for locus coeruleus dysfunction in humans with pathological anxiety remains limited, recent advances in high-resolution 7-T magnetic resonance imaging and computational modeling approaches are starting to provide new insights into locus coeruleus characteristics.

Keywords

Locus Coeruleus, Pathological Anxiety

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Introduction

Pathological anxiety can be defined as a fear-like or defensive physiological and behavioral state that persists in a non-threatening environment (Eysenck, 1992; Rosen and Schulkin, 1998). Pathological anxiety is a core feature of anxiety disorders as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5), including generalised anxiety disorder (GAD), social anxiety disorder (SAD) and panic disorder, and post-traumatic stress disorder (PTSD). These disorders represent the most prevalent class of psychiatric disorders in the United States, with an anxiety disorder showing around an 18% 12-month prevalence rate (Kessler et al., 2005b) and they act as a major risk factor for suicide (Eysenck, 1992; Kessler et al., 2005b; Rosen and Schulkin, 1998). Specific phobia and social phobia have the highest prevalence rates, followed by PTSD, GAD and panic disorder (Kessler et al., 2005b) (Table 1). Panic disorder and GAD, both archetypal examples of disorders of pathological anxiety, represent the sixth leading cause of years lived with disability worldwide (Kessler et al., 2005b)

The Research Domain Criteria (RDoC) initiative (Insel et al., 2010) aims to deconstruct traditional diagnostic categories into constituent domains and constructs that are relevant and testable across species and units of analysis. This approach is aimed to ultimately provide more fundamental measures for diagnostics and treatment determination. Human anxiety disorders are commonly conceptualised as disorders of maladaptive response to acute threat (fear) and potential threat (anxiety), both within the RDoC negative valence systems domain. Threatening environmental stimuli or 'stressors' typically induce complex behavioral, neural and endocrine responses, including both fear and anxiety, which are highly conserved across species (Blanchard et al., 2001; Romero, 2004; Ulrich-Lai and Herman, 2009).

Threats or stressors activate brainstem nuclei, particularly the locus coeruleus (LC). The LC has widespread norepinephrine (NE) projections throughout the central nervous system (CNS) thought to primarily function to globally modulate behavior and arousal states. NE has myriad central functions including regulation of CNS cells and circuits (O'Donnell et al., 2012). The LC is the major producer of NE in the CNS and LC activation produces

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Table 1. Characterisation of human anxiety and stress-related disorders.

Human anxiety disorder	Core symptoms (DSM-5)	Research domain criteria (RDoC) domain / construct	Average age of onset (years)	Prevalence (%, SE)				Female:male ratio
				Total	Serious	Mod	Mild	
Panic disorder	• Recurrent unexpected panic attacks. • At least one of: – Persistent concern about having additional attacks – Worry of the implications or consequences of the attack – A significant change in behavior related to the attacks • Absence of agoraphobia/presence of agoraphobia • The panic attacks are not caused by the direct physiological effects of a substance or medical condition. • The panic attacks are not better accounted for by another mental disorder.	Negative valence systems / potential threat ('anxiety'), acute threat ('fear'), sustained threat.	30.3; 95% CI = 26.09 to 34.59	2.7 (0.2)	44.8 (3.2)	29.5 (2.7)	25.7 (2.5)	2.1
Specific phobia	• Excessive or unreasonable, persistent and intense fear triggered instantaneously by a specific object or situation, out of proportion to the actual danger. • Avoidance or extreme distress. • The phobia significantly impacts school, work or personal life.	Negative valence systems / potential threat ('anxiety'), acute threat ('fear'), sustained threat.	11.0; 95% CI = 8.25 to 13.65	8.7 (0.4)	21.9 (2.0)	30.0 (2.0)	48.1 (2.1)	1.8
Social anxiety disorder (or social phobia)	• Marked and persistent fear of social or performance situations and scrutiny that will be humiliating or embarrassing. • Exposure to the feared social situation provokes anxiety or panic attack. • The person recognises that the fear is excessive or unreasonable. • The feared social or performance situations are avoided or endured with distress. • The avoidance, anxious anticipation or distress interferes with occupational or academic functioning, social activities or relationships, or there is marked distress. • The fear or avoidance is not due to the direct physiological effects of a substance or a general medical condition and is not better accounted for by another mental disorder.	Negative valence systems / potential threat ('anxiety'), acute threat ('fear'), sustained threat.	14.3; 95% CI = 13.27 to 15.41	6.8 (0.3)	29.9 (2.0)	38.8 (2.5)	31.3 (2.4)	1.6

(Continued)

Table 1. (Continued)

Human anxiety disorder	Core symptoms (DSM-5)	Research domain criteria (RDoC) domain / construct	Average age of onset (years)	Prevalence (%, SE)				Female:male ratio
				Total	Serious	Mod	Mild	
Generalised anxiety disorder	• Excessive anxiety and worry (apprehensive expectation) about a number of events or activities (such as work or school performance). • The worry is difficult to control. • The anxiety and worry are associated with three (or more) of the following symptoms: – Restlessness – Being easily fatigued – Difficulty concentrating – Irritability – Muscle tension – Sleep disturbance • The focus of the anxiety and worry is not confined to features of another mental disorder. • The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning. • The disturbance is not caused by the direct physiological effects of a substance or a general medical condition.	Negative valence systems / potential threat ('anxiety'), acute threat ('fear'), sustained threat. Cognitive systems / cognitive control. Arousal and regulatory systems / arousal, sleep-wakefulness.	34.9; 95% CI = 30.88 to 39.01	3.1 (0.2)	32.3 (2.9)	44.6 (4.0)	23.1 (2.9)	1.7
Post-traumatic stress disorder	• Exposure to a traumatic event in which the person experienced, witnessed or was confronted with event(s) that involved actual or threatened death or serious injury to self or others. • The traumatic event is persistently re-experienced as recurrent and intrusive distressing recollections of the event, including images, thoughts or perceptions. • Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness. • Persistent symptoms of increased arousal as indicated by two (or more) of: – Difficulty falling or staying asleep – Irritability or outbursts of anger – Difficulty concentrating – Hypervigilance – Exaggerated startle response	Negative valence systems / potential threat ('anxiety'), acute threat ('fear'), sustained threat. Cognitive systems / attention, working memory. Arousal and regulatory systems / arousal.	26.6; 95% CI = 22.13 to 31.06	3.5 (0.3)	36.6 (3.5)	33.1 (2.2)	30.2 (3.4)	1.9
Any anxiety disorder			21.3; 95% CI = 17.46 to 25.07	18.1 (0.7)	22.8 (1.5)	33.7 (1.4)	43.5 (2.1)	1.5

Demographic and feature domain characteristics of disorders characterised by pathological anxiety. Information obtained from Ditlevsen and Elklit (2012); Kessler et al. (2005a, 2012); Lijster et al. (2017).

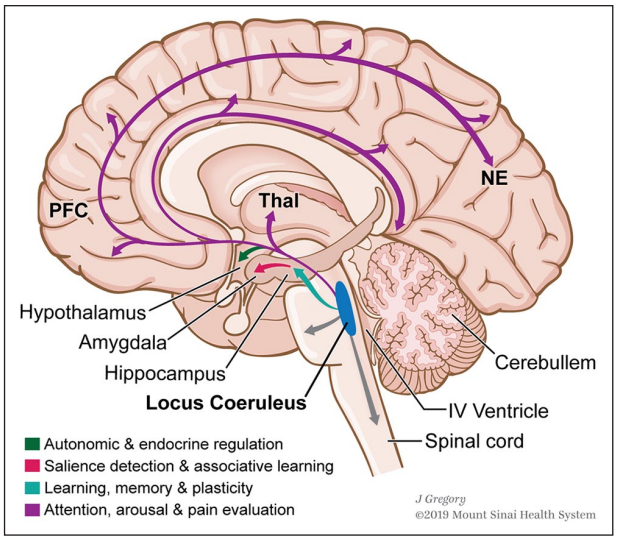

Figure 1. Major locus coeruleus (LC) projections throughout the central nervous system play distinct functional roles.
Ascending LC projections innervate the hypothalamus for autonomic and endocrine regulation; the amygdala for salience detection and associative learning; the hippocampus to influence learning, memory and plasticity; and the cortex, for regulation of attention, arousal and the cognitive evaluation of pain. Descending LC projections (gray) reach the periaqueductal gray and other brainstem nuclei, as well as the spinal cord.

NE release throughout the cortex, acting as a single global regulator (O'Donnell et al., 2012). Tonic, continuous activity of the LC is low during sleep, intermediate during active wake and high in states of distress or anxiety (Atzori et al., 2016). Acute threats also engage the sympathetic nervous system for the behavioral 'fight or flight' response (hypothalamus–pituitary–adrenal (HPA) axis), which elevates circulating glucocorticoids for a coordinated physiological and behavioral response (Charmandari et al., 2005) (Figure 1). A 'normal' or adaptive response to threat can present as freezing or motor arrest, often used as a primary proxy of fear in rodents or somatomotor agitation or exertion. Both responses are coupled with increased vigilance and arousal, critical for the alerting, orienting and fear learning functions required in a dangerous or uncertain environment (Cardinal et al., 2002; Sara and Bouret, 2012). These partly reflexive responses are collectively referred to as 'bottom-up' responses and are critical for an adaptive response to a dynamic environment. Higher order frontal cortical systems provide 'top-down' regulation of these responses to blunt or regulate the response to threat if the environment is perceived to be safe (Bishop et al., 2004). While the recruitment of brainstem nuclei responsible for alerting and orienting is critical for a normal, adaptive response to threat, the excessive or overactive engagement of these structures is associated with a maladaptive threat response or a prolonged anxious state (Berridge and Waterhouse, 2003; Ulrich-Lai and Herman, 2009). Alongside this excessive bottom-up response, there can be also deficient cortical top-down regulation of subcortical and midbrain structures, leading to an inability to down-regulate the physiological and behavioral threat response.

In rodents, pathological anxiety can be modeled as a variety of anxiety-like behaviors, each potentially modeling a component of human anxiety disorders. While animal models can capture certain phylogenetically conserved responses to stressors, such as risk aversion and reduced exploratory behaviors, the vast cognitive gap that exists between laboratory animals and humans limits the translation of a wide range of complex psychological characteristics of the human stress response or experience of pathological anxiety. Induction of anxiety-like behaviors in rodents, for example, via genetic manipulation, chronic repeated stress or with predator interactions, is not translatable to humans. Likewise, specific human-experienced stressors, including complex childhood trauma or neglect, financial or work stressors and extreme social judgment cannot be modeled in animals. Furthermore, key clinical features such as worry, rumination, intrusive thoughts, nightmares or catastrophising cannot be modeled in animals. Thus, although animal models can generate multiple translatable features, they do not reflect the full repertoire of symptoms that characterise a human anxiety disorder.

While our ability to measure these constructs differs between humans and rodents, rodent models can provide considerable insight into the pathophysiology of human disorders in some respects. Some primary behavioral anxiety-like examples include excessive fear-like behaviors, such as freezing and reduced social interaction (Rosen and Schulkin, 1998). More translational measures that can be captured by animal models and observed in humans include faster fear learning, reduced extinction learning, reduced exploratory behavior and increased risk aversion (Park and Moghaddam, 2017). Cognitive-behavioral human measures that mirror translational pre-clinical models include fear learning (Lissek, 2012), attentional bias (Shechner et al., 2012), as well as physiological or neural activity during anticipation of negatively valenced stimuli (Bishop et al., 2004). Other biological measures such as pupil dilation and 3-methoxy-4-hydroxyphenylglycol (MHPG) – a major metabolite of NE – can be measured in both humans (Murphy et al., 2014; Raskind et al., 1984; Southwick et al., 1993) and pre-clinical models (Aston-Jones and Cohen, 2005; Gilzenrat et al., 2010; Joshi et al., 2016; Korf et al., 1973a, 1973b). To date, there is predominantly indirect evidence of LC's role in human pathological anxiety, however more recent work with ultra-high field 7-T magnetic resonance imaging (MRI) is enabling direct examination of the human LC in vivo (Morris et al., 2020; Priovoulos et al., 2018).

This review aims to synthesise the pre-clinical and clinical literature to date related to a hypothesised role of the LC in responses to acute and chronic threat, as well as the emergence of pathological anxiety. By first defining its role in critical cognitive processes, like attention, learning and memory, we aim to lay the groundwork for an understanding of its role in response to threat to inform dimensional (RDoC) mechanistic models across human anxiety disorders with the ultimate goal of improving treatments for these disabling conditions.

Afferents and efferents of the LC-NE system

The LC projects to myriad cortical, subcortical and brainstem nuclei to rapidly and globally modulate neural function (Bremner et al., 1996a, 1996b). It also receives widespread innervation. Extensive work characterising LC afferents and efferents has been largely conducted in animal models. Ascending LC-NE projections diverge into four bundles (Jones et al., 1977) to innervate (1) hypothalamus (Asakura et al., 2000; Jones et al., 1977), particularly the lateral portion including periventricular nucleus and

supraoptic nucleus, important for autonomic and endocrine regulation (Jones et al., 1977); (2) ventral and central nucleus of the amygdala (Asakura et al., 2000; Jones et al., 1977), important for salience detection and associative learning (Campese et al., 2017; Chen et al., 1992; Sears et al., 2013); (3) the 'diagonal band', medial septum and hippocampus (Haring and Davis, 1985; Jones et al., 1977; Loughlin et al., 1986), that influences learning, memory and plasticity (Ehlers and Todd, 2017; Harley, 1987; Sara, 2009); and (4) the corpus callosum, reaching the cingulum and beyond throughout the cortex (Jones et al., 1977), for regulation of attention, arousal and the cognitive evaluation of pain (David Johnson, 2003; Sara and Bouret, 2012; Scherder et al., 2003; Willis and Westlund, 1997). LC-NE neuron lesions reduce NE in most of these regions, particularly hypothalamus and cerebral cortex (Neophytou et al., 2001). The LC also projects to the bed nucleus of the stria terminalis (BNST) (Asakura et al., 2000), cerebellum (Bremner et al., 1996b), lateral habenula (Purvis et al., 2018) and extensively to the olfactory bulb (Shipley et al., 1985). Descending LC projections pass into the medial forebrain bundle including the periacqueductal gray (PAG), tegmentum and raphe nuclei (Jones et al., 1977). Posterior-ventral LC projects through the length of the spinal cord (Jones and Yang, 1985; Loughlin et al., 1986) and targets parasympathetic neurons of the vagus dorsal motor nucleus (Westlund and Coulter, 1980).

Afferent inputs to the LC are less extensive than its efferents. Midbrain and brainstem projections to LC derive primarily from the ventrolateral (Ennis and Aston-Jones, 1986), rostral (Aston-Jones et al., 1991a) and dorsomedial medulla (Aston-Jones et al., 1991b) – regions that play a major role in the regulation of sympathetic control and behavioral orienting. It receives bidirectional inputs from the ventral tegmental area (VTA) (Deutch et al., 1986; Ornstein et al., 1987), which modulate depressive phenotypes (Isingrini et al., 2016; Weiss et al., 2005; Zhang et al., 2018, 2019), and from suprachiasmatic nucleus (SCN) (Legoratti-Sanchez et al., 1989) for circadian-based regulation of arousal (Aston-Jones et al., 2001). Other brainstem inputs to the LC derive from the hypothalamic paraventricular nucleus (PVN), PAG, raphe nuclei, as well as from the spinal cord, with limited inputs from neighboring nuclei to create a local circuit (Aston-Jones et al., 1991b; Cedarbaum and Aghajanian, 1978). Cortical and subcortical projections to LC originate from insula, central nucleus of the amygdala (Cedarbaum and Aghajanian, 1978), dorsolateral and dorsomedial prefrontal cortex (PFC) (Arnsten and Goldman-Rakic, 1984) and from prelimbic PFC – which may be indirect (Aston-Jones et al., 1991b; Jodo et al., 1998).

The widespread network of the LC system is therefore crucially positioned to play a significant role in modulating both ascending visceral feedback and descending cortical cognitive processing to mediate both psychological and physiological operations (Berntson et al., 2003). There is a growing consensus that distinct projections mediate distinct behaviors, suggesting that the LC is comprised of independent modules (Uematsu et al., 2017). Functionally distinct cell modules have been demonstrated to have specific anatomical projections with distinct functions (Hirschberg et al., 2017; Llorca-Torralba et al., 2019; Uematsu et al., 2015, 2017). For example, discrete projections can have opposite physiological and behavioral effects: amygdala projections can enable aversion learning, whereas PFC projections can enable extinction learning (Uematsu et al., 2017). Similarly, ascending and descending projections can have opposite functions: spinal projections can be analgesic and anti-nociceptive, whereas PFC projections can exacerbate pain responses (Hirschberg et al., 2017). In rodents, there appears to be a developmental genetic basis for some of these functional distinctions (Robertson et al., 2013, 2016). LC projections throughout the cortex are not homogeneous, and they show distinct biochemical and electrophysiological properties, governing varying levels of NE release (Chandler et al., 2014). Further work supports this model of modularity by indicating that LC cell populations are functionally distinct ensembles, since their spiking activity are largely asynchronous (Totah et al., 2018). Interestingly, strong aversive stimuli can cause a robust, unified LC-NE response across most LC cells (Uematsu et al., 2017), suggesting that the LC can provide both specific mediation of discrete behaviors and global mediation of general arousal. This highlights the nexus at which the LC operates and its crucial role as a modulator of highly conserved behavioral responses, discrete higher order cognitive functions and global arousal.

LC modulation of arousal, attention and memory formation

Arousal and attention

Adaptive responses to dynamic environments require intact functioning of attentional and memory-formation systems. Adept attentional direction is required for appropriate memory formation, and a correctly formed memory is required to guide appropriate attention direction. Both of these systems are under tight regulation by the LC, particularly in response to threat-related stimuli or events (Anisman et al., 2000; Ehlers and Todd, 2017; Sara and Bouret, 2012).

For normal attentional function, tonic firing of the LC in the range of 1–3 Hz is needed. Lower than normal activity is associated with hypoarousal and attention deficits, whereas higher tonic firing is associated with hyperarousal and anxious states (Howells et al., 2012). In the normal state and in the absence of threat, the tonic LC-NE system sustains vigilance and orienting functions (David Johnson, 2003). At an early, basic level, LC projections to vestibular nuclei mediate vestibulo-ocular and vestibulospinal reflexes for alerting and vigilance (Balaban, 2002, 2016; Peng et al., 2016). The ability of the LC to direct attention to a given cue seems unrelated to valence (Berridge and Waterhouse, 2003): the LC responds to all novel stimuli and mediates general attentional orienting (Sara and Bouret, 2012; Usher et al., 1999). The central LC-NE system therefore alerts or primes the organism in response to any significant external event (Svensson, 1982). Interestingly, LC lesions reduce exploratory behavior, but only in novel environments (Harro et al., 1995). This, coupled with evidence from electrophysiological studies in primates, suggests that the LC may play a major role in regulating the switch between goal-directed (exploit) and exploratory behaviors in novel environments (Usher et al., 1999).

The LC generally becomes activated in states of heightened vigilance, when a disruptive stimulus requires reorienting behavior (Aston-Jones et al., 1991a). Single unit recordings show that the LC responds to a stimulus predicting a noxious air puff in freely moving cats, but shows no activation during prediction of reward (Rasmussen and Jacobs, 1986). It has been suggested that phasic LC-NE activity acts as a global 'interrupt' function to orient attentional and cognitive processing to salient or, specifically,

threatening situations (David Johnson, 2003) and its activity is closely related to cortical excitability for wide-scale behavioral and cognitive priming (Sara and Bouret, 2012). However, while the LC responds to all novel stimuli (Berridge and Waterhouse, 2003), and stimuli that require a response (Rajkowski et al., 2004), responses generally habituate over time if the stimulus is not aversive (Sara and Bouret, 2012), implicating a special function for threat. In support of this, LC-NE response to novel light is higher in rodents with greater fear-potentiated startle (Anisman et al., 2000). However, the frontal cortex has the ability to suppress LC activity over time (Sara and Herve-Minvielle, 1995).

Learning and memory

The LC plays a critical role in learning and memory formation, especially for threat-related learning. Multiple neural systems subserve distinct learning and memory processing, broadly including hippocampal context-dependent associative learning, stimulus discrimination, declarative memory and working memory (Olton et al., 1979; Sutherland and McDonald, 1990), amygdala-mediated affective or biologically significant incentive-based associative learning (Phelps, 2004; Sutherland and McDonald, 1990) and dorsal striatal reinforcement-based motor learning (McDonald and White, 1993). The LC-NE system seems to modulate each of these distinct learning and memory systems. First, LC-NE projections to hippocampus regulate long-term potentiation (LTP) and hippocampal plasticity (Harley, 1987), allowing arousal to influence learning (Sara, 2009), to engender subsequent attentional biases (Ehlers and Todd, 2017). Second, an intact direct functional LC-NE projection to the amygdala is necessary for Pavlovian threat learning (Sears et al., 2013) and aversive Pavlovian-to-instrumental transfer (Campese et al., 2017), and NE activity in the amygdala enhances passive-avoidance memory consolidation (Chen et al., 1992). Finally, there are fewer LC-NE terminals in the dorsal striatum, although the dorsal striatum shows high NE turnover rates and interactions between LC-NE neurons and the striatal dopaminergic system seems to mediate the behavioral effects of methamphetamine (Ferrucci et al., 2013; Fornai et al., 1996a, 1996b). Together these findings demonstrate that the LC can have a powerful effect on the regulation of multiple memory systems, including hippocampal plasticity for generation of threat-related attentional biases and amygdala-mediated associative learning for aversive events.

Role of LC in response to acute threat

Threatening environmental cues or events induce a coordinated response (Carrasco and Van de Kar, 2003) that is designed to heighten vigilance and prepare a rapid and flexible behavioral response. Threat or perceived stress increases NE release and HPA axis activation which induces hypothalamic corticotrophin-releasing factor (CRF) release and adrenal production of glucocorticoids including cortisol (Carrasco and Van de Kar, 2003; Makino et al., 2002). CRF and NE work together to promote the response to stress (Gresack and Risbrough, 2011) – inhibiting feeding, increasing blood pressure, stimulating adrenocorticotropic hormone (ACTH) and elevating sympathetic tone (Bailey et al., 2003; Laugero et al., 2001). Altogether these systems prepare the organism for an acute behavioral response. CRF also increases tonic LC firing rate and NE release (Asakura et al., 2000; Fan et al., 2009; Jedema and Grace, 2004), while NE also directly activates the HPA (Calogero et al., 1988), creating a feed-forward system important for anxiety pathogenesis (Owens et al., 1993).

While the role of the HPA axis has been well-defined as a key coordinating system that responds to threat or stress, a significant body of work underscores the critical role of the LC in this response too. It is clear that the LC rapidly responds to threatening stimuli. LC activity increases in monkeys (Grant and Redmond, 1984) and rats within 15 min (Silveira et al., 1993) and 30 min (Day et al., 2004; Sands et al., 2000) after an aversive or threatening stimulus. LC activation occurs following a range of threats or stressors, including the elevated plus maze (Silveira et al., 1993), acute and chronic-restraint stress (Sands et al., 2000), lipopolysaccharide (LPS)-induced sickness (Lacosta et al., 1999), forced swim and a single electric shock (Bruijnzeel et al., 2001), and the impact on increased LC excitability can be long lasting (Borodovitsyna et al., 2018). Threatening predator odor, an ecologically relevant stressor that elicits innate anxiety responses, induces activation of LC (Day et al., 2004; Hayley et al., 2001), BNST, PVN and PAG (Janitzky et al., 2015), leading to anti-predatory responses (Sobrinho and Canteras, 2011). Pain and acute noxious stimuli also activate central NE circuits in rodents (Kowalski et al., 2014) and in humans, as measured by pupilomotry (Chapman et al., 2014).

In humans, subliminal fear activates the LC, alongside higher cortically mediated orienting responses (Liddell et al., 2005). Anticipation of threat engages arousal and increases brainstem auditory evoked potentials (Baas et al., 2006) and pupil dilation (Clewett et al., 2018), both thought to be indirect measures of LC activation, although pupil dilation can be governed by other systems besides NE (Nelson and Mooney, 2016; Reimer et al., 2016). Finally, in humans, even psychological or perceived stress increased LC connectivity with amygdala (van Marle et al., 2010). The LC-NE system is therefore thought to govern a rapid warning response to stress (Lanius et al., 2017).

Other threat response systems

The LC is not, of course, the only neural threat response system. It is worth noting that other cortical and subcortical regions participate in a wider ‘threat circuit’, including amygdala and medial PFC, which are extensively reviewed elsewhere (Simpson et al., 2001; Taylor and Whalen, 2015) (Figure 2). Briefly, the amygdala has been most widely implicated in threat processing (Derntl et al., 2009; Harmer et al., 2006; Isenberg et al., 1999; Johansson and Hansen, 2002; Loughead et al., 2008; Oya et al., 2002), although it seems to serve a higher order, integrative threat learning function compared to the LC’s more rapid alerting function. The amygdala is a site of convergence of exteroceptive information from cortex and thalamus and visceral information from subcortex (Bremner et al., 1996a), where conditioned associations can be formed, activating learned fear responses (Cardinal et al., 2002). Indeed, there is evidence that the amygdala is recruited during early stages of fear learning (Bishop et al., 2007; Davidson, 2002). More generally salient events increase amygdala activation (both appetitive and aversive) (Fitzgerald et al., 2006) and the release of extrahypothalamic CRF, suggesting it drives attention to salient events rather than acting as a specific threat signal (Merali et al., 1998). The medial PFC (in humans, comprised of orbitofrontal cortex, ventomedial PFC, dorsomedial PFC and

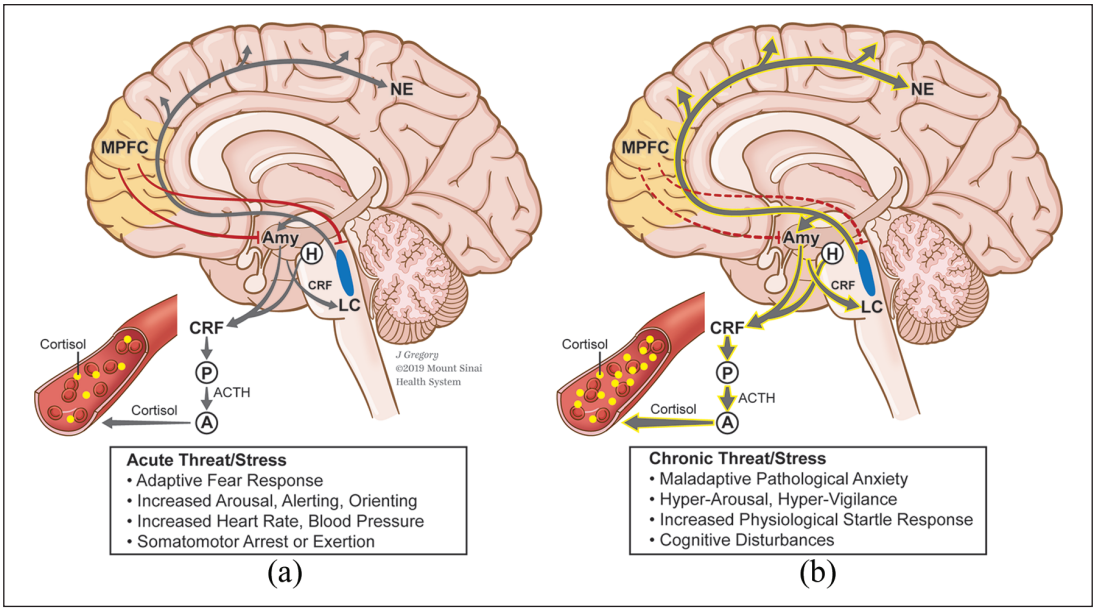

Figure 2. Central actions of the locus coeruleus (LC) in the regulation in threat reactivity.
(a) The adaptive response to acute threat involves a rapid, coordinated response in order to prepare the organism for an acute physiological response and behavioral activation. This involves hypothalamus–pituitary–adrenal (HPA) axis activation, hypothalamic corticotrophin-releasing factor (CRF) release and production of cortisol, which reaches body tissues via peripheral vasculature. Rapid LC activation and norepinephrine (NE) release also occurs, with NE targets throughout the cortex leading to global modulation of arousal and attention. Other NE targets in the amygdala (Amy) and medial prefrontal cortex (MPFC) mediate threat learning and reciprocally regulate the LC (red lines). (b) Chronic threat or stress leads to widespread changes in the central LC-mediated response to subsequent stressors. Chronic stress leads to LC hyperactivity, increased NE in LC, amygdala, hippocampus, MPFC and increased HPA axis activity via reduced HPA regulation. Excessive cortisol and NE relate to maladaptive physiological signs of hyper-arousal and reduced regulation of the LC by the MPFC (dotted red lines), which additionally contribute to reduced regulation of pathological anxiety. Gray lines indicate LC and HPA projections.

anterior cingulate cortex (ACC)), which has reciprocal projections with both the amygdala (Aggleton et al., 1980; Carmichael and Price, 1995; Ghashghaei and Barbas, 2002) and the LC, regulates and updates learned negative associations via extinction learning or re-learning new safe/neutral associations (Delgado et al., 2008; Milad et al., 2005; Milad and Quirk, 2002). Optimal emotion regulation requires concomitant activation of medial PFC and deactivation of amygdala (Delgado et al., 2008; Wager et al., 2008), which mitigates anxiogenesis (Bishop et al., 2004; Hare et al., 2008; Hariri et al., 2003; Pezawas et al., 2005; Simpson et al., 2001). In addition, the dorsolateral PFC also plays a regulatory role on medial PFC and amygdala threat or stress-related responses, reducing interference by negative emotion for adaptive cognitive control, important for resilience (Liston et al., 2009; Ochsner et al., 2004; Sinha et al., 2016). While these cortical regions respond to threat or stressors and downregulate the negative emotional and autonomic response to stress, acute threat or stress also has a detrimental effect on PFC function, via increased NE which engages alpha-1 adrenergic receptors to reduce PFC function (Arnsten, 2015), resulting in cortical atrophy, dendritic deterioration and overall reduction in cognitive control of emotion (Arnsten, 2009).

Role of LC in the development of pathological anxiety

Thus far, we have highlighted the 'normal' or adaptive role of the LC in response to acute threat. The following sections describe the hypothesised role of the LC in responses and processes that lead to maladaptive or pathological states.

Chronic stress

Chronic or repeated stress in rodents can be used as a model for human disorders of pathological anxiety and depression. These rodent studies demonstrate that the LC is involved in several different types of stress response. First, after prolonged restraint stress (30–60 min), LC activity (C-fos) increases (Keshavarzy et al., 2015). Second, chronic or repeated stress (corticosterone administration; Fan et al., 2014) increases tyrosine hydroxylase (TH) in the LC and norepinephrine transporter (NET) in the hippocampus, amygdala and PFC (Fan et al., 2014), leading to increased anxiety and defensive behaviors. After chronic long-term stress, not only does LC activity increases but also its subsequent sensitivity to stress increases. Chronic stress induces amplification of LC reactivity and increased NE release to subsequent stressors in rats (Jedema et al., 2001), possibly related to reduced LC auto-inhibition after stress (Jedema et al., 2008) and blunting of HPA axis regulation in a feedback-facilitation cycle (Makino et al., 2002).

In addition, in rat models of chronic stress, increased NE in the PFC causes further cortical atrophy and dendritic restructuring, resulting in reduced cognitive and attentional control (Liston et al., 2006, 2009). While it is probably too much to assume that the cellular observations made in rats directly translate to the human data, it is nevertheless important to recognise that chronic stress-induced plasticity in the PFC exists across species. These

stress-induced alterations could be pathologically exacerbated in patients with PTSD (Bremner et al., 1997).

The emergence of anxiety-like behaviors in rodents

There is considerable evidence indicating a link between increased LC activity and the development of pathological anxiety-like behaviors in animals. For example, anxiety, fear and behavioral inactivation in rats are associated with increased LC activity (Kryzhanovskii et al., 1991). More causal evidence emerges from studies showing that LC activation produces greater anxiety and fear-like behavior (via neurokinin 1 receptors; Hahn and Bannon, 1999) in both rodents (Boulenger and Uhde, 1982) and monkeys (Bunney and Tallman, 1980). Furthermore, increased LC activity and TH expression is associated with the onset of anxiety-like behaviors in a rodent model of chronic pain (Alba-Delgado et al., 2013). This LC-mediated onset of anxiety behaviors is partly mediated via projections to amygdala (McCall et al., 2017) and amygdala CRF inputs to LC, which increases tonic LC activity that promotes anxiety-like behaviors in mice (Curtis et al., 2002; McCall et al., 2015; Van Bockstaele et al., 1998). The increased tonic LC activity appears to be sufficient to induce acute anxiety-like behavior following stress (McCall et al., 2015; Sciolino et al., 2016; Zerbi et al., 2019). Furthermore, transgenic mice with increased LC catecholaminergic neuron density have increased anxiety-like and panic behaviors (Dierssen et al., 2006).

LC lesions seem to reduce anxiety- or fear-like behavior (Boulenger and Uhde, 1982), increase fear extinction (Tsaltas et al., 1984) and do not affect appetitive sucrose conditioning (Tsaltas et al., 1984), indicating its specific role in threat processing. Reduction of alpha2A adrenoreceptor expression in the LC also reduces anxious behavior during the elevated plus maze in rats (Shishkina et al., 2002). Furthermore, blocking the LC increase in TH expression following stress reduces anxiety behaviors (Lee et al., 2012a, 2012b). The specificity of this effect is demonstrated by a studies showing that selective inhibition of LC-NE neurons during stress precludes generation of anxiety-like behaviors in rodents (McCall et al., 2015). Further work has shown that acute stress causes persistent increases in LC firing consistent with long-term expression of anxiety-like behavior in rats (Borodovitsyna et al., 2018). Together these rodent studies strongly indicate the critical role of the LC in anxiety pathogenesis.

There is, however, also contradictory evidence suggesting that reduced LC activity is associated with anxiety. Abolishing LC activity with desipramine increased anxiety behaviors (immobility) (Weiss et al., 1994), and destruction of LC terminals increased anxiety-like behavior in the form of reduced exploration of novel environments (Itoi et al., 2011; Kask et al., 2000) in rodents. This inconsistency in findings of reduced LC activity associated with anxiety may be explained by the specific behavioral measure affected by LC-NE lesions: immobility and reduced exploration. Evidence indicates that LC-NE lesions alter freezing time in rats without affecting the initial locomotor (running and jumping) response to conditioned and unconditioned aversive stimuli, indicating LC lesions may relate to defense rather than behavioral activation for aversive avoidance (Neophytou et al., 2001). However, while the LC has a global function in mediating arousal to strongly aversive stimuli, distinct sub-modules can have distinct and opposite functional roles in mediating learning or responses to aversive stimuli (Hirschberg et al., 2017; Llorca-Torralba et al., 2019; Uematsu et al., 2015, 2017). The distinct roles of the LC-NE system in active versus passive aversive avoidance require further study.

Role of the LC in risk factors for pathological anxiety

Insight into the role of the LC in pathological anxiety can be discerned via examining risk factors for the development of pathological anxiety. For examples, Wistar Kyoto rodents are bred to be susceptible to certain types of stress and exhibit anxiety-like behaviors with excessive responses to stressors. These rats show reduced inhibitory control of the LC (less sensitive alpha-2 adregnergic receptors in LC and reduced inhibitory GABA input), implicating a shift toward enhanced excitatory capacity of the LC as a key mechanism of anxiety (Bruzos-Cidon et al., 2015). Rodents bred to exhibit high anxiety behaviors also show increased activity of the LC, PAG, hypothalamus, as well as reduced activity of the ACC after stress (Salchner et al., 2006). Furthermore, transgenic rats with reduced glial angiotensinogen and enhanced anxiety behaviors show coincident higher LC activity and increased locomotor response to novelty (Ogier et al., 2016). Finally, rat offspring from stressed dams, a risk factor for susceptibility to anxiety, show higher fear responses and corticosterone reactivity, alongside increased LC, amygdala and striatal reactivity and reduced medial PFC reactivity to stress (Sadler et al., 2011). Together, these findings in rodents highlight the role of genetic and prenatal environmental factors that modulate LC and frontal cortical reactivity to stressors. These factors pose clear risk for exaggerated anxiety responses in rodents. Interestingly, in seeming contradiction to these findings, Maudsley non-reactive rats (which are resilient to anxiety) show higher basal LC neuronal activity and a burst-like pattern of firing (Verbanac et al., 1994). More work needs to be done to tease apart the contributions of tonic versus phasic LC firing and specific modular regulation of activity.

Biological sex

Biological sex can also act as a risk factor for pathological anxiety and implicate LC as a differentiating factor in mediating anxiety behaviors. Female rats have larger and more complex LC than males (Bangasser et al., 2011; Valentino et al., 2012) and the constitution of receptor sites on LC structures also seems to differ between sexes. CRF receptors in the cortex (Bangasser et al., 2010) and LC (Bangasser, 2013) are differentially expressed between sexes, making females more sensitive to CRF. Higher female sensitivity to CRF in the LC is linked with more hyperarousal and symptoms of pathological anxiety (Bangasser, 2013). Interestingly, selective LC-NE glucocorticoid receptor ablation in female, but not male rats, results in heightened anxiety-like behaviors (Chmielarz et al., 2013). Chronic alcohol administration also induces anxiogenesis with increased LC activity and in female but not male rats (Retson et al., 2015). Finally, early life stress increases astrocyte function in the LC which leads to anxiety symptoms in female, but not male mice (Nakamoto et al., 2017). Together, these findings indicate that heightened

vulnerability to stressors in females may be in part governed by specific differences in LC structural and molecular composition, rendering females more susceptible to pathological anxiety.

Inflammation

Finally, inflammation may mediate the link between LC function and anxiety behaviors. For example, LPS injected into the LC increases astrocyte function and anxiety-like behavior in mice (Nakamoto et al., 2017). Inflammation can also serve as a high-risk state for the development of pathological anxiety. Monoarthritis (a hyper-inflammatory state in rodents) is associated with an anxiety-like phenotype, with increased activation in LC and PFC (Borges et al., 2014) and systemic interleukin-2 injections increases NE in many LC target regions (Lacosta et al., 2000). In a rodent model of anorexia, increased inflammation coincides with increased LC activity and anxiety behaviors (Scharner et al., 2017). Conversely, reducing neuro-inflammation can reduce LC damage and anxiety-like behaviors in a mouse model of Alzheimer's disease (Braun and Feinstein, 2017). The LC itself seems to have a regulatory, anti-inflammatory effect, acting as a neurotrophic and neuroprotective modulator in a normal state (Feinstein et al., 2016; Lee et al., 2016; Wang et al., 2015). However, the LC's anti-inflammatory and neuroprotective capacity is reduced following stress (Lee et al., 2016), indicating one mechanism by which the LC mediates the normal and abnormal response to stressors – via neuroimmune regulation.

Role of LC in human patients with pathological anxiety

Patients with pathological anxiety experience clinical symptoms and cognitive disturbances that point toward an underlying disturbance in LC function. Panic disorder is characterised by the recurrent unexpected onset of 'panic attacks', a sudden and rapid state of intense fear or sympathetic nervous system arousal, in the absence of any environmental threat, substance or other provoking disorder (American Psychiatric Association, 2013). Individuals with panic disorder also fear future attacks and avoid situations that might trigger an attack, such as crowded public transport. GAD is a condition of excessive, non-specific anxiety or worry, often coupled with restlessness, irritability or fatigue, as well as concentration difficulties (American Psychiatric Association, 2013). SAD is more specific than GAD, characterised by a persistent, excessive fear of social or performance situations in particular, including maladaptive worry about social scrutiny and embarrassment (American Psychiatric Association, 2013). PTSD, previously classified as an anxiety disorder and now classified as a trauma- and stressor-related disorder (Friedman, 2013), can develop in individuals exposed to event(s) that threatened death or serious injury, in which the trauma is re-experienced via nightmares, flashbacks or unwanted memories (American Psychiatric Association, 2013). Patients with PTSD experience negative alterations in mood and cognition, as well as states of heightened physiological arousal and exaggerated startle responses, alongside more general difficulties with concentration and exaggerated avoidance behaviors (American Psychiatric Association, 2013).

Early evidence indicated that patients with PTSD and panic disorder, given yohimbine (an $\alpha 2$ adrenergic receptor antagonist) or CO_2 (increases LC-NE), show increased anxiety and panic symptoms (Charney et al., 1984; Gorman et al., 1984; Southwick et al., 1993), implicating a role for LC-NE in anxiety symptoms in humans. PTSD has since been conceptualised as a disorder stemming from conscious and subconscious hyper-response to threat, associated with hyperarousal and a hyper-active 'alarm system' neural response including from the LC, amygdala and PFC (Lanius et al., 2017). In support of this model, PTSD patients show more exaggerated heart-rate responses, skin conductance, eye blink responses and LC blood-oxygen-level-dependent (BOLD) activation to loud sounds (Naegeli et al., 2018), as well as higher LC and insula BOLD responses to fearful stimuli (Morey et al., 2015) compared to trauma-exposed controls. There is also evidence linking PTSD with distorted fear learning governed by overactive of LC and insula to fearful stimuli and with increased LC connectivity with amygdala, striatum and insula during direct threatening eye gaze (Steuwe et al., 2015). Contradictory to this model is evidence that patients with PTSD show reduced LC size and reduced LC-NE reuptake availability (Arango et al., 1996; Bracha et al., 2005). However, this may be explained by differences in tonic versus phasic LC responses. For example, there is evidence for increased NE activity in PTSD in response to stressors but not during rest (Bremner et al., 1999). Finally, there is evidence for reduced PFC-mediated cognitive–emotional control during stress in PTSD: traumatic images invoke reduced medial PFC and ACC area 24 blood flow (positron emission tomography (PET)) in patients (Bremner et al., 1999) and patients have reduced ACC response when exposed to emotional conflict (Kim et al., 2008), implicating a mechanism of heightened LC reactivity to threat alongside blunted cortical regulation.

Studies implicating LC in other human disorders of pathological anxiety are less numerous than those in PTSD. LC dysfunction has been implicated in SAD (Marazziti et al., 2015), and worry in GAD has been associated with reduced heart-rate variability (indicating parasympathetic withdrawal) and increased LC–amygdala connectivity (Meeten et al., 2016). The amygdala has been more widely studied in these disorders. For example, phobia is associated with enhanced amygdala activation to threat (Bertolino et al., 2005), suggested to be involved in vigilance-avoidance processing (Larson et al., 2006), which reduces after therapy (Alpers et al., 2009; Goossens et al., 2007). Panic disorder has also been associated with the 'extended fear network' including brainstem, cingulate, insula, PFC and amygdala (Sobanski and Wagner, 2017), which cause both physiological and psychological (threat anticipation) symptoms (Windmann, 1998). Other cortical and subcortical regions implicated in human pathological anxiety are more extensively reviewed elsewhere (Simpson et al., 2001; Taylor and Whalen, 2015).

Anxiolytics

Clinical pharmacology on known anxiolytics is another area of research that implicates the function of the LC-NE system in human pathological anxiety. The alpha-1 adrenergic receptor antagonist, prazosin, is effective for treating PTSD (Koola et al., 2014; Raskind et al., 2000) and stress-induced craving in alcohol dependence (Fox et al., 2012). Beta-adrenergic receptors are also

necessary for the development of anxiety-like behaviors (Gorman and Dunn, 1993; Wohleb et al., 2011) and regulate the induction of stress-induced gene expression in the brain in mice (Roszkowski et al., 2016). Beta-adrenergic receptor antagonism ('beta-blockers') prevents the development of anxiety-like behaviors in mice (Gorman and Dunn, 1993) and humans (Jefferson, 1974), particularly for somatic symptoms (Harris and Aston-Jones, 1993; Hayes and Schulz, 1987; Kelly, 1980; Noyes, 1982). While there is limited evidence for the efficacy of beta-blockers for treating PTSD (Amos et al., 2014) and performance anxiety in healthy individuals (Liebowitz et al., 1985), more recent studies indicate a novel pathway for treating anxiety disorders with beta-blockers. First described by Nader et al. (2000) in 2000, memory reconsolidation is a process whereby memories that are re-activated become labile and vulnerable to manipulation. Several studies have now demonstrated that distribution of *traumatic* memory reconsolidation with beta-blockers is feasible in humans and effective at relieving PTSD symptoms (Brunet et al., 2008; Evers, 2007; Kindt et al., 2014), although wider replication is currently lacking (Wood et al., 2015). While this novel direction for treatment of pathological anxiety in humans is promising, further work is needed to more directly target LC-NE system dysfunction with pharmacotherapies. One small study of three panic disorder patients showed that inhibition of the LC with the alpha2 agonist, clonidine, resulted in reduced panic and anxiety symptoms (Valenca et al., 2004).

While evidence for targeting LC-NE dysfunction for the treatment of pathological anxiety in humans is largely indirect, more direct evidence from pre-clinical studies implicates modulation of the LC-NE system function as a direct target for a variety of anxiolytics.

First, endogenous neuropeptide Y (NPY) is anxiolytic and reduces the behavioral responses to stress (Desai et al., 2014; Eaton et al., 2007; Kask et al., 2002). A network including LC, amygdala, PAG and hippocampus seems to mediate the anxiolytic effects of NPY (Heilig, 2004; Kask et al., 2002). More specifically, NPY given directly to the LC reduces anxiety and increases exploratory behaviors in rats (Kask et al., 1998) and anxiety-like behavior produced by LC terminal destruction can be attenuated by NPY administration (Kask et al., 2000). NPY given immediately before (Sabban et al., 2015a; Serova et al., 2013) or after (Sabban et al., 2015b) stress (forced swim, elevated plus maze, LC activation) reduces stress-induced physiological and behavioral manifestations of anxiety including ACTH, corticosterone and LC-TH expression (Sayed et al., 2018, #1; Serova et al., 2013}. Interestingly, stress causes a reduction of NPY in LC, nucleus accumbens (Nac) and PVN (Desai et al., 2014), indicating a mechanism by which stress leads to reduced resilience against anxiogenesis.

Benzodiazepines, which are commonly used for anxiolysis, bind to LC neurons (Hellsten et al., 2010) and reduce LC neuronal activity (Soderpalm and Engel, 1989), stress-induced increase in NE (Gray, 1996; Ida et al., 1985; Tanaka et al., 2000), CRF (Skelton et al., 2000) and the neuroendocrine responses to stress (Carrasco and Van de Kar, 2003). Diazepam has been shown to reduce LC responses to negative stimuli (Rasmussen and Jacobs, 1986). In contrast, non-BZ anxiolytics increase LC activity (Sanghera and German, 1983; Trulson and Henderson, 1984).

Chronic selective serotonin reuptake inhibitors (SSRIs), which are antidepressant and anxiolytic, reduce LC-NE neuron firing in control (Szabo and Blier, 2002) and perinatal-protein deprived rats (Sodero et al., 2004). SSRIs seem to reduce LC firing at a rate consistent with their therapeutic effects (Szabo et al., 2000). The SSRI fluoxetine also reduces glucocorticoid receptor expression in LC (Heydendael and Jacobson, 2010). Another non-SSRI antidepressant, imipramine, also reduces stress-induced LC activation (de Medeiros et al., 2005). Selective serotonin-norepinephrine reuptake inhibitors (SNRIs) such as milnacipran, which has also shown to have anxiolytic effects (Dell'Osso et al., 2010), may also activate LC to release 5HT for anxiolysis (Bourin et al., 2005).

Finally, exercise has been shown to reduce anxiety and stress-related markers, and increase galanin in LC (Salim et al., 2010; Sciolino and Holmes, 2012; Sciolino et al., 2015). Exercise or galanin has been shown to reduce stress-induced anxiety behaviors (Sciolino et al., 2015). Chronic galanin antagonism blocked the resilience-inducing influence of exercise (Sciolino et al., 2015).

Future directions in approaches to studying the LC in humans

Emerging advances in neuroimaging technology and computational modeling are starting to highlight pathways by which the LC can be studied in humans in vivo. Advances in MRI acquisition protocols, resolution afforded by higher field MRI and data denoising strategies will allow the investigation of LC structure and function with enhanced spatial and temporal precision.

The past few years have provided in vivo characterisation of the LC in awake humans that reliably correlates to post-mortem analyses of relative LC size, cell distribution, location, age-related size alteration and disease-specific structural changes, notably for Alzheimer's disease (Chan-Palay and Asan, 1989; Kelly et al., 2017; Theofilas et al., 2017). The T1-weighted turbo spin echo (TSE) technique is the current gold standard of LC structural imaging in humans, offering contrast in the LC due to the presence of neuromelanin (NM), which is MR-visible due to a magnetisation transfer (MT) contrast mechanism. NM contrast has been shown to be a reliable indirect measure of the number of LC cells – providing the basis for in vivo studies of LC microstructure (Betts et al., 2019; Clewett et al., 2016). The metabolic activity of the LC has also been captured with functional MRI, albeit with large voxel sizes. Validation of LC functional MRI (fMRI) has come from reference to simultaneously acquired pupilometry, showing that pupil diameter and LC BOLD activation are tightly correlated (Alnaes et al., 2014; Elman et al., 2017; Murphy et al., 2014). These advances have demonstrated the rapid improvement in fMRI resolution and sensitivity. Nonetheless, while current structural imaging of the LC uses high in-plane resolution (~0.4 mm), it also has large slice thickness (~3 mm). This means that while LC can be localised in the brainstem, the characterisation of its size and shape is still not optimised. Similarly, current functional MRI of LC involves image acquisition at standard voxel sizes of ~3 mm to attain good functional sensitivity. Recent work using high-field MRI and computational segmentation algorithms has been used to measure LC structure and volume with sub-millimeter resolution (Morris et al., 2020). This was successfully performed in human subjects with and without pathological anxiety, demonstrating

enlarged LC in patients, associated with poorer attentional control and higher anxious arousal (Morris et al., 2020). Further applications of this work in larger sample sizes and using fMRI will be critical for the translation of the wealth of pre-clinical work described, to clinical settings.

Recent advances in computational modeling approaches are also providing new insights into LC function. Several computational frameworks suggest two underlying modes of LC function. One mode in which tonic LC activity mediates exploration via an increase in gain in sensory representations and general arousal, and the second mode in which phasic LC activity optimises behavior in light of current task performance, recruiting insula-based salience detection and PFC decision-making systems (Aston-Jones and Cohen, 2005; Dowman et al., 2016). Optimal task performance and learning requires an accurate representation of certainty in the environment, which is suggested to be computed by NE and acetylcholine (Yu and Dayan, 2005), both of which modulate general arousal-related pupil dilation (Larsen and Waters, 2018). Indeed, pupil dilation has been linked with the reliability or stability of information in the environment (Nassar et al., 2012), critical for optimal environmental navigation. However, this link between pupil sensitivity and optimal computation of environmental features in an unstable world seems to be disturbed in patients with high trait anxiety (Browning et al., 2015). Together, these computational models provide new and potentially integrative insights into LC and NE function, and their potential disturbance in human disorders of pathological anxiety. Harnessing computational models based on known physiological and biological systems will enable development and understanding of small and large-scale networks that ultimately direct behavior.

Summary

The LC is critically placed to modulate both ascending visceral feedback and descending cortical cognitive processing to mediate both psychological and physiological operations (Berntson et al., 2003). While threat or perceived stress broadly increases sympathetic tone and HPA axis activation (Carrasco and Van de Kar, 2003; Makino et al., 2002), it also recruits LC activity and NE release throughout the CNS. Direction of attention and memory formation, particularly for threat-related stimuli and events, are both under tight regulation by the LC. Indeed the LC responds rapidly to a range of threatening stimuli, including even the mere anticipation of threat (Baas et al., 2006; Clewett et al., 2018), subliminal fear (Liddell et al., 2005) or perceived stress (van Marle et al., 2010) and the broader LC-NE system governs an 'alarm system' response to stress (Lanius et al., 2017) across species.

Moreover, chronic or repeated stress (Fan et al., 2014) increases LC, hippocampal, amygdala and PFC activity (Fan et al., 2014) and leads to anxiety and defensive behaviors (Li et al., 2018). After chronic stress, not only does LC activity increase but its sensitivity to subsequent stressors also increases (Jedema et al., 2001), possibly due to reduced LC auto-inhibition after stress (Jedema et al., 2008). Resultant increased tonic LC activity and LC catecholaminergic neuron density is sufficient to lead to anxiety and panic in rodents (Dierssen et al., 2006; McCall et al., 2015). This coincides with human evidence of hyperarousal and exaggerated physiological responses to threat centered on LC (Lanius et al., 2017; Morey et al., 2015; Naegeli et al., 2018). Together this suggests a mechanism by which repeated stress can lead to LC dysregulation and therefore maladaptive exaggerated fear or pathological anxiety responses.

Future innovation in human neuroimaging and neural circuit modeling will advance the investigation of LC structure and function in vivo, allowing greatly enhanced precision for characterising the LC in humans.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: In the past 5 years, Dr. Murrough has provided consultation services and/or served on advisory boards for Allergan, Boehreinger Ingelheim, Clexio Biosciences, Fortress Biotech, FSV7, Global Medical Education (GME), Impel Neuropharma, Janssen Research and Development, Medavante-Prophase, Novartis, Otsuka and Sage Therapeutics. In the past 12 months, Dr. Murrough has provided consultation services and/or served on advisory boards for Boehreinger Ingelheim, Clexio Biosciences, Global Medical Education (GME) and Otsuka. Dr. Murrough is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders and on a patent pending for the use of ezogabine and other KCNQ channel openers to treat depression and related conditions. The Icahn School of Medicine (employer of Dr. Murrough) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine or esketamine for the treatment of depression. The Icahn School of Medicine is also named on a patent related to the use of ketamine for the treatment of PTSD. Dr. Murrough is not named on these patents and will not receive any payments. Dr. Charney is named as co-inventor on patents filed by the Icahn School of Medicine at Mount Sinai (ISMMS) relating to the treatment for treatment-resistant depression, suicidal ideation and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. and it has and will receive payments from Janssen under the license agreement related to these patents for the treatment of treatment-resistant depression and suicidal ideation. Consistent with the ISMMS Faculty Handbook (the medical school policy), Dr. Charney is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO has received regulatory approval for treatment-resistant depression, ISMMS and thus, through the ISMMS, Dr. Charney will be entitled to additional payments, beyond those already received, under the license agreement. Dr. Charney is a named co-inventor on several patents filed by ISMMS for a cognitive training intervention to treat depression and related psychiatric disorders. The ISMMS has entered into a licensing agreement with Click Therapeutics, Inc. and has and will receive payments related to the use of this cognitive training intervention for the treatment of psychiatric disorders. In accordance with the ISMMS Faculty Handbook, Dr. Charney has received a portion of these payments and is entitled to a portion of any additional payments that the medical school might receive from this license with Click Therapeutics. Dr. Charney is a named co-inventor on a patent application filed by the ISMMS for the use of intranasally administered Neuropeptide Y (NPY) for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. Dr. Charney is a named co-inventor on a patent application in the United States, and several issued patents outside the United States filed by the ISMMS related to the use of ketamine for the treatment of PTSD. This intellectual property has not been licensed. The remaining authors disclose no conflicts of interest.

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