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Freezing revisited: Coordinated autonomic and central optimization of threat coping

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Abstract| Animals have sophisticated mechanisms for coping with dangers. Freezing is a unique state that, upon threat detection, allows evidence to be gathered, response possibilities to be previsioned and preparations to be made for worst case fight or flight. We propose that – rather than reflecting a passive fear-state – the particular somatic and cognitive characteristics of freezing help to conceal overt responses, while optimizing sensory processing and action preparation. Critical for these functions are the neurotransmitters noradrenaline and acetylcholine, which modulate neural information processing and also control sympathetic and parasympathetic branches of the autonomic nervous system. However, the interactions between autonomic systems and the brain during freezing, and the way that they jointly coordinate responses, remain incompletely explored. We review the joint actions of these systems and offer a novel computational framework to describe their temporally harmonized integration. This reconceptualization of freezing has implications for its role in decision making under threat and for psychopathology.

[H1] Introduction

Animals are endowed with elaborate repertoires of defensive actions that allow them to respond as optimally as possible to the dangers they face. Successfully responding to a threat involves a cascade of potential behavioural responses that are organized according to its perceived immediacy[1–4]. Beyond 'safety' (the stage at which no threat is present) three stages in this cascade are traditionally distinguished[5–8]. 'Pre-encounter threat' responses are associated with the possibility, but no immediate evidence, that a predator might be present. For instance, a grazing deer, upon hearing a noise in the forest, will raise its head and scan the environment to ascertain the possible presence of a wolf. 'Post-encounter threat' responses arise upon detection of a not-yet-attacking predator. Here, the deer will usually and strikingly 'freeze', remaining as immobile as possible. Finally, 'circa-strike' responses are the responses prey take when actually confronted with an immediate threat (often referred to as 'flight, fight or fright' responses). Most likely, our deer will shoot off as fast as possible to escape.

Traditional views conceptualized threat anticipatory freezing merely as a passive fear state[9–11]. However, there is increasing acknowledgement that this behaviour is not passive and may differ from the fright-related immobility that is observed after the dreaded thing has happened[1,7,12,13]. In this article, we propose that post-encounter freezing involves complex cognitive operations aimed at assessing the nature of the threat and planning for appropriate responses, as well as complex somatic processes geared towards action preparation. Crucial aspects of such preparation are that bodily

responses should remain concealed, to avoid inadvertently alerting the predator, and that cognitive responses be sharpened, which involves minimizing exteroceptive and interoceptive sources of noise[14–16].

Strikingly, such a coordination of cognitive and somatic responses must involve a tight integration between the activity of three distinct nervous systems: the CNS, the autonomic nervous system (ANS) and the sensory-somatic nervous system. An important question is therefore how this integration takes place. We suggest that such integration critically depends on the coordinated chemical modulation of the activity of these three nervous systems. Among the neurotransmitters that are thought to mediate this regulation, acetylcholine (ACh) and noradrenaline (NA) are the most prominent. However, as is common in the brain, the neurons that release ACh and NA also release other neurotransmitters and/or cotransmitters. In addition, in the CNS, two other neuromodulators — dopamine and serotonin — play important roles in coordinating vigorous defensively-oriented cognition and action; however, they are less directly involved in the ANS and its coordinated function with the CNS and so will not be the focus of this article.

Here, we outline the descending and ascending control mechanisms that jointly orchestrate the unique anticipatory state of freezing associated with post-encounter threat. Descending control leads to reduction of motion, heart rate (bradycardia) and breathing rate; ascending control leads to sharpened cognition and sensation, while maintaining the state of freezing. We then provide a theoretical account, discussing the computational principles (including information processing and control-theoretical aspects)[18], that may underlie the action and interaction of ascending and descending control . This model of temporally-tuned central and autonomic balance implies that disease may occur when the systems are discoordinated. Our reconceptualization of threat-anticipatory freezing[12] as enabling a temporally and chemically tuned orchestration of cognitive, sensory and behavioural responses challenges the traditional views that relegate this state to being merely a read out of passive fear and shows how it may be central to decision making under threat. The evidence base underlying our hypotheses is diverse. Many details of defensive reactions are species specific[19]; however, the information gathering and processing demands associated with post-encounter threat may be more general. Most data come from rodents, but there are also broadly consistent findings in rabbits, and in non-human and human primates. We will note particularly when the results described are from experiments in humans.

[H1] Autonomic and central control

Upon detection of potential threat (the ‘post-encounter threat’ stage described above), activation of the sympathetic arm of the ANS promotes increased heart rate, breathing and muscle tone, in

preparation for action. Neurons of the sympathetic ganglia exert their effects directly (or indirectly via the adrenal gland) mainly through the release of NA, which can act as both a neurotransmitter and a hormone. Within the CNS, NA is mainly produced by the locus coeruleus (LC), through which it exerts the above descending influences on the ANS, while at the same time exerting ascending modulation of cognitive functions including arousal, attention and perception[17,20]. Particularly relevant for the post-encounter threat state is the role of the LC in interrupting or resetting ongoing processing in the light of unexpected events that impose potentially dramatically new and changed demands on information processing[21,22]. Thanks to its widespread projections in CNS and ANS, the LC is ideally located to orchestrate links between ascending and descending control systems during post-encounter threat states (**Fig. 1**). The LC is activated both directly and indirectly[23,24] by connections from the nucleus tractus solitarus (NTS), a target of input from the vagal nerve (which reports on the state of the body and itself releases NA in the amygdala)[25,26].

Parasympathetic nervous system activity during the post-encounter threat stage acts to reduce motion, heart rate and breathing (**Fig. 1**), mainly through the release of ACh. This parasympathetic response is mainly coordinated by the vagal nuclei (the nucleus ambiguus (NAm) and the dorsal motor nucleus of the vagus (DMV); **Fig. 1**), which, like the LC, receive afferent information from the NTS[20]. However, the parasympathetic response is also modulated by limbic (amygdala) and frontal (medital prefrontal cortex (mPFC) and anterior cingulate cortex (ACC)) regions via relays in the hypothalamus (specifically, the paraventricular nucleus (PVN)) and the bed nucleus of the stria terminalis (BNST)[27,28]. Within the CNS, there are many cholinergic nuclei, including the nucleus basalis of Meynert in the basal forebrain (BF) and the laterodorsal tegmental (LDT) and pedunculopontine nuclei (PPT) of the midbrain. The LDT and PPT project predominantly to subcortical, brainstem and spinal cord regions (**Fig. 1**) and have connections with several visceral and somatic medullar and cranial nerves and spinal cord nuclei, including the NA[29,30].These cholinergic nuclei are thus ideally suited to modulate integration between ascending pathways and descending parasympathetic control systems during freezing. For example, cholinergic PPT neurons affect functions such as locomotion[31] and breathing through their connections to the spinal cord, brainstem and medulla[29], but also impact cognitive functions by acting as a relay station for spinal cord sensory afferents to the thalamus and the basal ganglia[30]. Although the range of cognitive functions mediated by these cholinergic nuclei is far from clear, and we cannot here do justice to the richness of what is known, there is cross-species evidence that these neurons are involved in sustained attention[32,33] and in prioritizing bottom-up or stimulus-driven activity over top-down input[34].

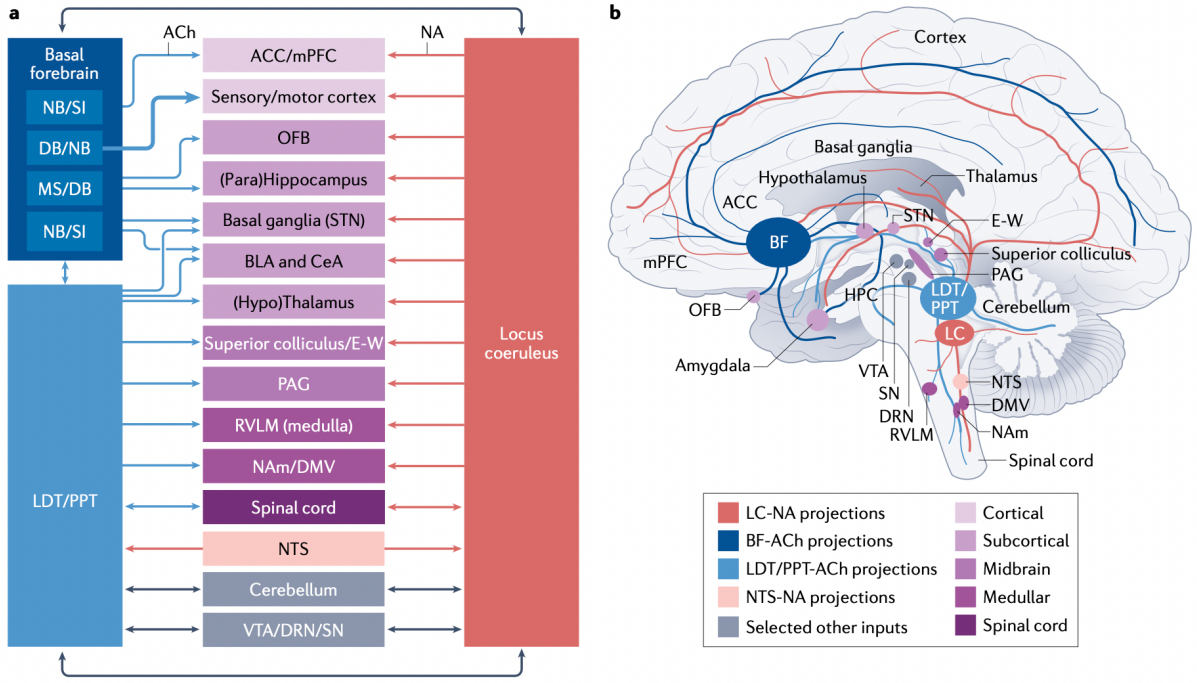

Fig 1: Ascending and descending control systems involved in freezing. a| Schematic illustrating the ascending and descending output circuits of the central noradrenaline (NA) and acetylcholine (ACh) hubs: the locus coeruleus (LC), the basal forebrain (BF) and the laterodorsal tegmental and/or pedunculopontine nuclei (LDT/PPT)[20,30,194–197]. Blue is used to indicate regions and connections that use ACh as their primary neurotransmitter, whereas red indicates regions and connections that primarily act via NA. However, we note that these neural systems should not be identified narrowly with ACh and NA as there are more neurotransmitters and/or co-transmitters involved in their activation/inhibition effects. The arrows show projections from these areas to key brain regions, with those areas receiving overlapping projections depicted in purple (with the shade of purple indicating their location within the nervous system). For simplicity, reciprocal inputs from these projection regions to the LC, BF and LDT/PPT are not shown. Selected additional sources of input to the LC and LDT/PPT are also shown. BF projections to primary sensory and motor areas are strong and highly specialized and are therefore indicated using a thicker arrow[195]. The cell bodies of the BF neurons are distributed across a series of nuclei, including the medial septal (MS) nucleus, the diagonal band (DB) nuclei; the nucleus basalis (NB), and the substantia innominata (SI)[198]. **b|** An illustration of some of the main projections from the LC, BF and LDT/PPT in the human brain[24,43–46]. Note that the some of the projections are inferred based on findings in animals, the illustrations are not intended to show all circuits innervated by these regions and the thickness of the lines is intended to illustrate main (thick) versus smaller (thin) projections but is not proportional to projection strengths. These neural systems are proposed to be the critical effectors for the psychophysiological, cognitive and behavioural effects described in this article. ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex; OFB, olfactory bulb; STN, subthalamic nucleus (STN); BLA, basolateral amygdala; CeA, central nucleus of the amygdala; SC, superior colliculus (SC); E-W, Edinger–Westphal nuclei; PAG, periaqueductal gray; RVLM, rostoventrolateral medulla; NAm, nucleus ambiguous; DMV, dorsal motor nucleus of the vagus; NTS, nucleus tractus solitatus; VTA, ventral tegmental area; DRN, dorsal raphe nuclei; SN, substantia nigra.

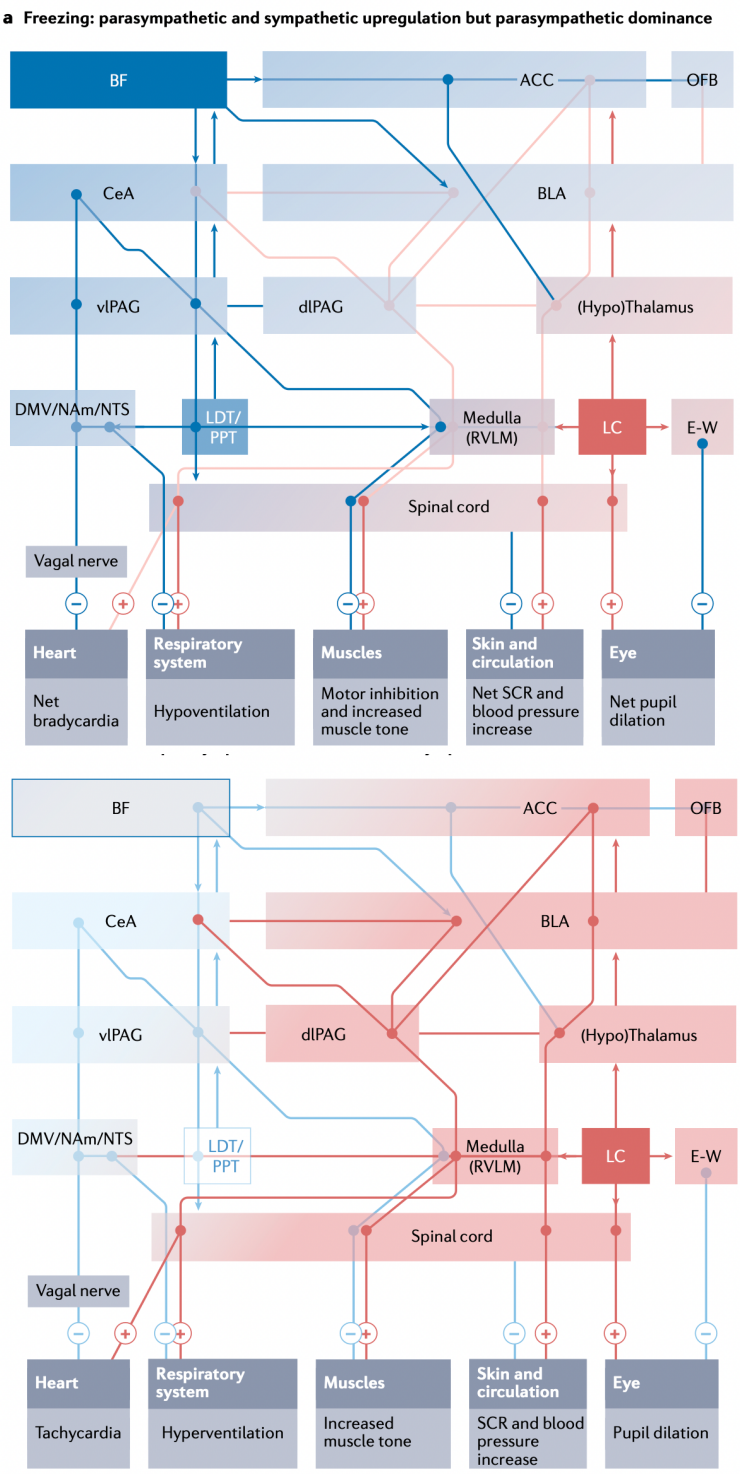

Fig. 2: Neuromodulation of autonomic balance during freezing and the switch to action. The schematics illustrate the changes in activity that take place in CNS regions and circuits involved in descending control of autonomic balance during freezing and the switch to action. Boxes depicting brain regions are organized from cortical (at the top) to subcortical, spinal cord and peripheral effectors (at the bottom), with boxes shaded in red and blue indicating the regions that are primary sources of the neuromodulators noradrenaline (NA) and acetylcholine ACh, respectively. In these schematics, blue and red lines are used to illustrate the connections between regions (with arrowheads used to indicate connections that have a specific directionality) that drive parasympathetic activity and those that drive sympathetic activity, respectively. The relative brightness of the lines reflect the hypothesized dominance of either parasympathetic or sympathetic pathways at each stage. + indicates activation and - inhibition. **a|** Freezing is associated with concurrent sympathetic and parasympathetic upregulation, with the latter being dominant. Projections from the basal forebrain (BF) and the midbrain pedunculopontine nuclei (PPT) and laterodorsal tegmental nuclei (LDT) reduce heart rate via parasympathetic innervation of ventrolateral periaqueductal grey (vlPAG), rostroventrolateral medulla (RVLM) and vagal nuclei (specifically, the nucleus ambiguus (NAm) and the dorsal motor nucleus of the vagus (DMV)). Cholinergic PPT/LDT projections also contribute to motor inhibition, predominantly by innervating vlPAG, and RVLM, the latter of which can directly inhibit spinal cord motor neurons. The influences of cholinergic BF projections on freezing are less well spelled out but seem to be mediated via the amygdala[53,66] and olfactory bulb OFB[198] (the latter in turn feeds breathing signals to the anterior cingulate cortex (ACC), which maintains the state of freezing[74] by controlling breathing[71] and cardiovascular responses[55]). During freezing, the predominantly sympathetically regulated muscle tone and skin conductance responses (SCR) are largely preserved due to the activity of concurrent sympathetic projections originating from the locus coeruleus (LC). The LC projects to the hypothalamus and almost every region displayed in the illustrations[17] and upregulates sympathetic activity, with effects that include pupil dilation. This

effect remains relatively dominant over the simultaneous effects of ACh projections from the Edinger–Westphal nuclei (which drive pupil contraction via the parasympathetic system)[43]. The concurrent sympathetic and parasympathetic effects on breathing involve both the nucleus tractus solitatus (NTS) and PAG–medullar–spinal cord connections and typically lead to hypoventilation (although fast but superficial breathing can also occur during freezing)[56,57]. Heart rate is reduced during freezing as a net effect of dominant parasympathetic innervation of the heart[44,45]. **b|** The switch from freezing to action involves parasympathetic withdrawal and increased sympathetic activation, resulting in increased heart rate, breathing and SCR and pupil dilation as well as increased NA-driven activation of the dorsal lateral periaqueductal grey (dlPAG) and spinal cord motor neurons. The switch to action may be generated both at the level of the PAG, orchestrated by the CeA[9], as well as by higher level signals from the ACC[98]. Via connections to the vagal nuclei and via RVLM connections, the LC inhibits parasympathetic control of cardiovascular functions including vasoconstriction. To keep the figure clear, please note not all existing connections are indicated.

[H1] Descending and ascending control

Post-encounter threat poses particularly challenging problems both at the level of CNS and within the ANS. Body and brain have to become prepared for fast and potentially decisive action and yet this preparation has to happen covertly. There is thus a need for what looks like a paradoxical integration between activation and inhibition. As we will outline below, at higher cortical levels, orchestration of this integration appears to involve regions of the ACC; at a lower (more sub-cortical) level, orchestration comes from the dorsal lateral periaqueductal grey (dlPAG) and ventrolateral periaqueductal grey (vlPAG) and from ascending and descending control systems that are mainly mediated by NA and ACh. The amygdala plays important roles at both levels (**Fig. 1 and Fig. 2**).

[H2] Descending control

[H3] Sympathetic upregulation versus parasympathetic inhibition

As noted above, various defensive actions are ultimately influenced and realized by the sympathetic branch of the ANS, with phasic autonomic activation wrought by the LC. During post-encounter threat, these actions are duly prepared, in a way we detail below. However, the essence of this condition is that action decisions are often not immediately clear, for instance in the case of an ambiguous situation or approach-avoidance conflict. Thus, concurrent upregulation of the parasympathetic branch of the ANS acts as at least a temporary inhibition on the execution of the bulk of these actions.

Across species, a fast subcortical road to sympathetic activation, and to the coordinated engagement of relevant neural structures for processing the potential danger, involves the hypothalamus and the amygdala[17]. In particular, the basolateral amygdala (BLA), which enjoys strong connections with

cortical and subcortical sensory input regions[35–37] and receives input from the LC, plays a key role in the initial detection and during the processing of a threat during post-encounter state of freezing[17,20]. The BLA usually exerts its effects via intra-amygdala connections with the central nucleus of the amygdala (CeA)[38]. Projections from the CeA to the LC and hypothalamus activate viscera, with effects including increased heartrate, muscle-tone, breathing, pupil dilation and sweating, that would generally occur in the absence of parasympathetic inhibition. At the same time, projections from the CeA to the dlPAG prepare immediate fight-or-flight reactions during post-encounter states via rostroventrolateral medulla (RVLM)–spinal cord projections[39]. For example, CeA cells expressing corticotropin-releasing factor (CRF) would mediate conditioned flight-reactions via this pathway across species[11,38].

There are at least two further LC-driven routes that would contribute to fast defensive action. First, direct LC–spinal cord connections can rapidly activate the skeletal musculature via the actions of NA at ventral horn α1-adrenoceptors[40,41]. Second, LC projections to the superior colliculus (SC) can enhance defensive reactions to looming stimuli[42] by engendering rapid pupil dilation (relevant for the detection of such stimuli[43]) and through direct SC-dlPAG connections[39].

During freezing, this active sympathetic preparation is accompanied by significant autonomic inhibition by the parasympathetic branch of the ANS, which we here suggest allows for covert information gathering and processing. The parasympathetic response successfully counteracts the sympathetically driven activation of spinal cord projections that are important for movement and visceral functions (such as heart rate increases) and involves the activation of projections from the vlPAG and RVLM to cholinergic neurons in the NA and the dorsal motor nucleus of the vagus (DMV) and, through the vagus nerve, to the heart[29,44,45]. This results in net bradycardia and hypoventilation during freezing. Indeed, conditioning studies coupling threat of shock as the unconditioned stimulus (US) to a conditioned stimulus (CS) demonstrated that sympathetically driven tachycardia is inhibited by parasympathetic activity upon CS presentation, an effect that is not present during pseudo-conditioning (where US–CS combinations are not systematically paired and sympathetic upregulation occurs alone)[46]. However, in both animals and humans, the dominance of the parasympathetic over the sympathetic branch of the ANS during freezing is not complete. For instance, increased muscle tone, pupil dilation and skin conductance continue to a large extent during post-encounter threat, consistent with the predominant sympathetic innervation of these systems[43,47] (**Fig. 2**).

[H3] Sculpting the freezing response

During freezing, cholinergically-induced bradycardia and hypotension have been suggested to be driven via activation of local muscarinic receptors in the vlPAG[44]. Indeed, early rodent studies consistently showed that electric stimulation of vlPAG neurons produces bradycardia and that this may occur via a relay in the RVLM[48–51]. In line with these observations, stress exposure-elicited bradycardia was shown to be mediated by activation of cholinergic receptors in the vlPAG that activate a monosynaptic pathway to the medullar NA[45]. Activity in the vlPAG also inhibits sympathetic upregulation by the LC, resulting in a more general decrease in arousal[20]. Finally, cholinergic activation of muscarinic receptors in the BNST has been shown to drive bradycardia during freezing, presumably via medullar connections[52]. In line with a role in threat detection under ambiguous conditions, the involvement of the BNST in freezing and autonomic responses is specific for conditioned (threat-anticipatory) and not for unconditioned stress-responses (reviewed in REF[53]). These lower level controllers of heart rate are complemented by higher level controllers in the brain, such as the ACC and vmPFC. The involvement of the ACC and vmPFC in cardiovascular control has been shown in humans as well as rats[54,55] and presumably involves their regulation of the parasympathetic aspect of the baroreflex[27], mediated by muscarinic receptors in the ACC[55].

Cholinergic mechanisms in the midbrain, particularly the ventral medulla and PAG, are also known to play a key role in the regulation of breathing[56], though PAG activation has been linked to both hyper- and hypo-ventilation.[57] There is a close coupling between respiration and heart rate, and restrained breathing under threat has been linked to bradycardia in humans as well as animals [57–61]. The innervation of the spinal cord, midbrain and brainstem by cholinergic PPT neurons also plays an important role in modulating breathing[29].

Inhibition of motor output arises from the inhibition of spinal cord motor neurons via amygdala–vlPAG–medullar connections[11,62–64]. (it is noteworthy that vlPAG–medullar connections are also involved in opioid-mediated analgesic responses during freezing[49,65]). Cholinergic BF projections (specifically those arising in the nucleus basalis (NB)) to the amygdala play a role in the expression of freezing[66] and startle modulation[67]. This more general motor inhibition suppresses actions of any sort; however, as specific flight or fight responses are being elicited or prepared, more focally targeted inhibition is necessary — both because these responses may be more potent (and so require greater repression), and because they may need to be disinhibited once the animal enters the circa-strike state.

One potential route to such targeted motor inhibition is via the CeA. It is known that somatostatin-positive cells in the CeA project directly to GABAergic interneurons in the vlPAG, allowing for a disinhibitory enhancement of principal neurons in the vlPAG[11,62–64] that produce freezing via medullar–spinal cord connections[64] (**Fig. 1**). But the CeA can also induce activation of glutamatergic cells in the dlPAG that reduce freezing through their projections to GABAergic vlPAG cells[64]. CeA

somatostatin-positive cells can also directly inhibit the CRF-releasing cells in the CeA that mediate active fight and flight responses in the dlPAG[11]. In particular, cholinergic projections from the PPT to the CeA, brainstem, PAG and spinal cord may play a role here, as they are known to affect locomotion and freezing[68] (reviewed in REF[31]). Direct evidence that these projections are involved in targeted inhibition at the level of the PAG stems from at least two studies showing that microinjection of a cholinergic agonist into the vlPAG in guinea pigs and rats increased the duration of tonic immobility episodes[69] and freezing[70] respectively, whereas ACh inhibition in the dorsolateral part (dlPAG) was associated with fight-or-flight related actions, presumably via action disinhibition[70].

[H3] Maintaining the freezing response

Although the above mentioned amygdala–PAG circuit (**Fig. 2a**) is critical in initiating the freezing response, the mPFC and ACC have been implicated in the maintenance of freezing[71]. The slow breathing rhythm that is typical of freezing in animals is accompanied by the transmission of slow wave theta oscillations (4Hz), generated in the brainstem, to mainly dorsal parts of the mPFC and ACC via the olfactory bulb (OFB)[71]. This process is thought to enhance perception, which is essential during post-encounter freezing[72]. Indeed, a slow breathing rhythm can optimize sensory processing by the OFB during olfactory sampling, as well as enhancing other sensory processes in humans[72]. The mPFC, including ACC, is ideally situated to sustain freezing, in part due to its influence over cardiovascular control, but mostly by exerting top-down control over the breathing rate (presumably via connections with the amygdala and PAG)[71,73]. Indeed cortical slow-wave activity in the mPFC of mice (including ACC) can also drive freezing, presumably by synchronizing 4Hz oscillations in ACC–amygdala circuits[74]. Similarly, dmPFC entrainment to slow wave oscillations that stem from the olfactory cortex and peak in synchrony with inhalation was shown in humans using intracranial recordings[75]. Stimulus presentation during the inhalation phase of respiration has been associated with enhanced cognitive performance in tasks involving fear discrimination and memory retrieval[75], suggesting that breathing control may also both sustain freezing and optimize perception in humans. Although cholinergic receptors in the ACC play a role in controlling parasympathetic cardiovascular responses in rodents[55], it remains to be shown whether this is also the case for ACC-driven changes in breathing and immobility.

It is unknown how long freezing can last in humans. However, from animal studies we know that the initial sympathetic and concurrent parasympathetic upregulation can be initiated within a few hundred milliseconds, whereas the threat-related state of parasympathetic dominance can last anywhere from seconds to tens of minutes. Indeed, there are reports of freezing episodes lasting 30 minutes in rats under threat of shock [76].

[H2] Ascending control

Along with the richly balanced descending control of the motor and autonomic systems during freezing (**Fig. 2A**), there are changes in the state of the CNS that are caused by ascending neuromodulatory systems. These affect the neural structures that regulate the descending control systems and also affect aspects of perception and cognition that are important in post-encounter threat. The altered information processing that occurs during this state of freezing has been suggested to put an organism into a state that is conducive to sensory intake[1,77–80] by interrupting ongoing processing and reorienting attention and cognition (see below).

In humans, investigations are accumulating into altered sensory processing during freezing-related bradycardia[81], although there is currently little evidence for causality. Initial evidence for a link between freezing-related bradycardia and optimized visual-motor behavior comes from an eye-tracking study demonstrating more focused eye-gaze during post threat-encounter bradycardia and showing that this is linked to faster flight responses[82]. In addition, a perceptual decision study showed that bradycardia during freezing under threat of shock was linked to improved processing of coarse visual features[83], increased upregulation of visual cortex activity and increased activity in backward projections from the amygdala to the visual cortex[84]. Further, bradycardia has been linked to faster perceptual decision-making and stronger modulation of cardiac rhythms has been found to be related to the ability to maintain response speed as decision complexity increases in both young and older adults [85]. In animals, other sensory processes have also been found to be upregulated during freezing. For instance, the OFB acts to optimize odor sensing and the transmission of sensory information to the ACC in mice[71]. The OFB receives cholinergic input from the BF, which can further increase the detection (via active sensing) and discrimination of odors[86], as well as olfactory perceptual learning[87]. It has been suggested for both animals and humans that neural rhythms entrained to the sort of respiratory patterns evident in freezing are also involved in enhancements of sensory processing (see above)[72,73].

Another potential read-out of altered stimulus processing in the post-encounter state is the magnitude of fear-potentiated startle (FPS). This is the heightened response to a startling (typically) auditory, visual or tactile stimulus as a result of being in a fearful state. In rodents, FPS is initiated via the brainstem (specifically the nucleus reticularis pontis caudalis (PnC)), a key input hub for the integration of affective modulatory information[88]. Importantly FPS is modulated by the CeA[88] — the core output region initiating defensive responding[46,89]. Fine-tuning of this modulatory input is achieved predominantly by inputs from the BLA, BNST and PAG[88,89]. Indeed, in humans, the strength of FPS modulation is correlated with the extent of parasympathetic dominance [90,91]. This in line with rodent work showing that FPS is potentiated during freezing[92,93]. It is known that FPS is influenced by

ACh and decreases, for instance, in the face of the injection of a muscarinic antagonist into the VTA[94] or the administration of the non-selective cholinergic antagonist carbachol to the nucleus accumbens[95]. This picture fits the notion of increased threat-anticipatory sensory sensitivity and action-preparedness during attentive freezing (**Fig. 3**). Unpredictable threat can also potentiate startle as part of anxiety potentiated startle (APS). This would putatively arise during orienting, which is the initial cessation of ongoing activity, to alert and reset cognitive processing that takes place immediately upon threat detection (see **Fig. 3**, **Fig. 4**)[96].

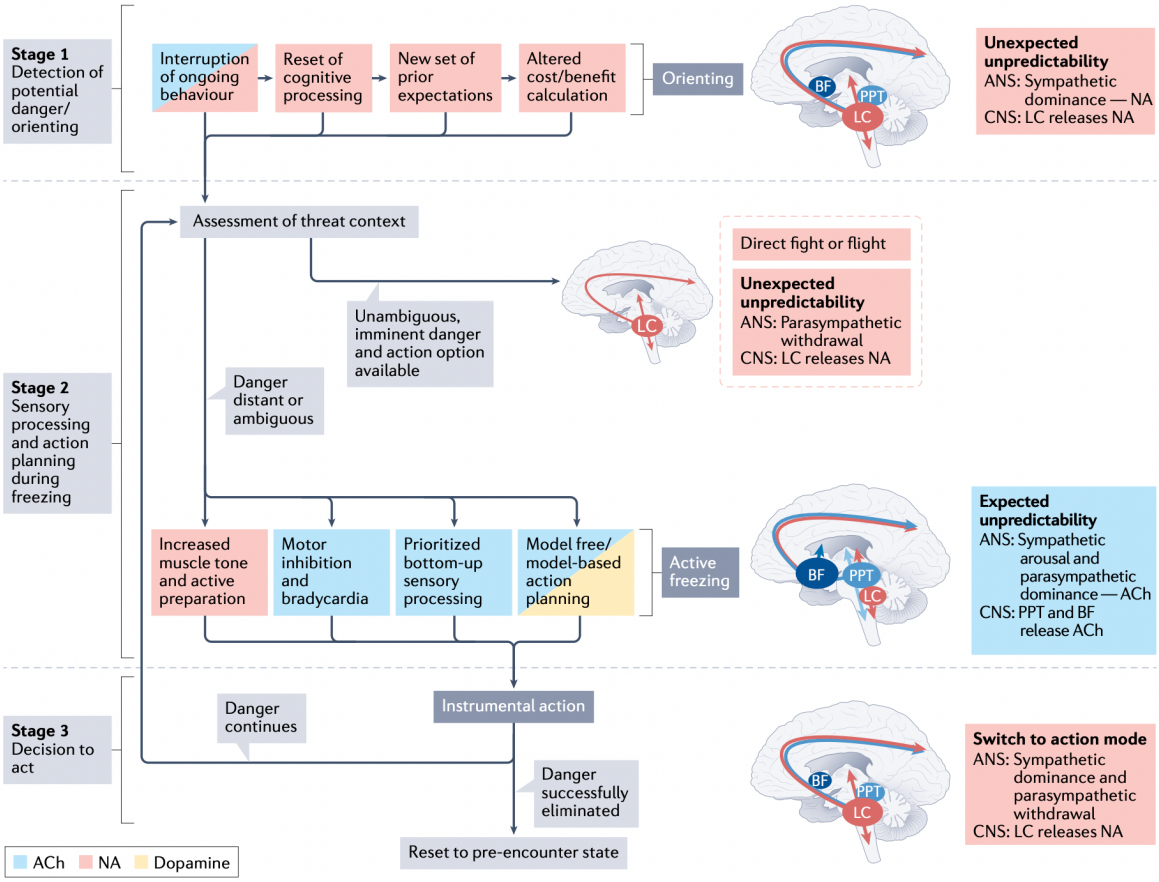

Fig 3. Information processing and control-theoretic considerations pertaining to freezing. The figure presents a flow diagram illustrating what we hypothesize to be the predominant cognitive, behavioural and neuromodulatory characteristics of the post-encounter stages of orienting, freezing and acting. These three stages respectively facilitate the initial detection of the potential danger (a form of unexpected uncertainty), which can be followed by immediate fight or flight in case the danger is unambiguous, imminent and action options are available or, alternatively, by freezing associated with motor inhibition and upregulated sensory and cognitive processing of the danger (typically associated with expected unpredictability). Finally a decision about the actions appropriate to maximize the chance of a successful outcome leads to an instrumental action, which is an instance of expected predictability. These three stages are arranged in a loop, within which there may be short-cuts and which can end and start again, depending on whether or not the danger has been successfully eliminated or averted. Thus, a new phase of attentive freezing can occur even after a potentially temporarily successful or unsuccessful action or encounter. The diagram illustrates the fact that each stage is served by a unique balance between sympathetic and parasympathetic systems, innervated among others by neurons releasing noradrenaline (NA – in red) and acetylcholine (ACh – in blue), respectively. The relative dominance of these chemical modulators in each stage is also illustrated in the brain images to the right, which illustrate the synchronized ascending and descending control that occurs via important relay structures, including the locus coeruleus (LC) and pedunculopontine nuclei (PPT). Other neuromodulators, notably dopamine (DA), are also involved.

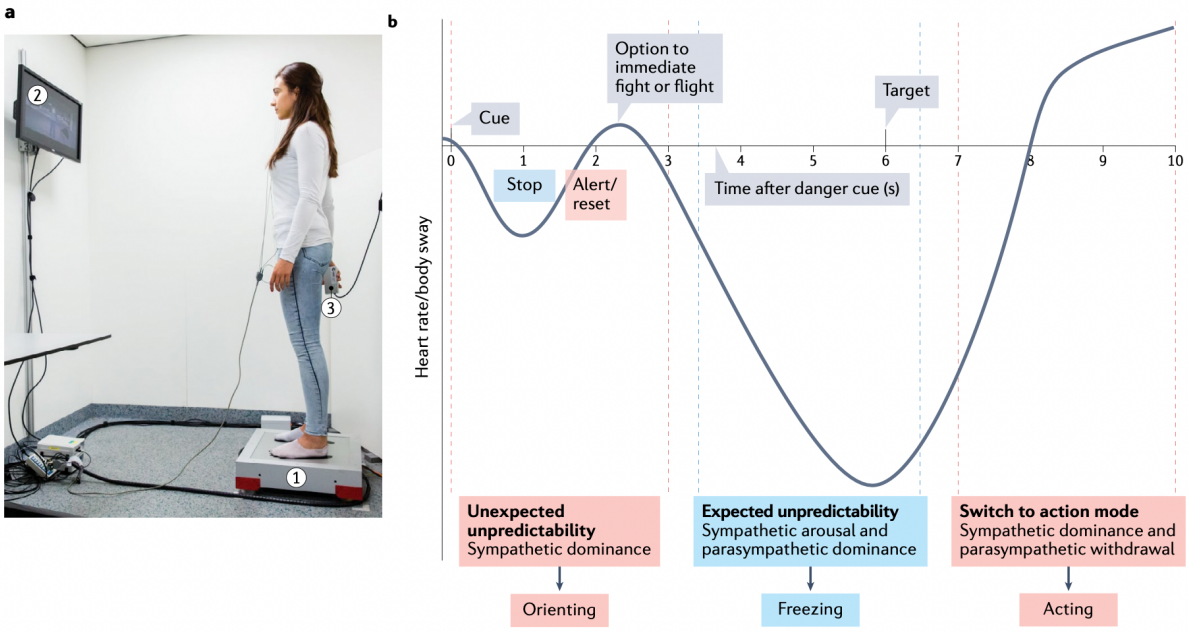

Fig 4. Measuring freezing in humans. As in animals, threat-anticipatory freezing in humans is expressed as reduced heart rate and immobility (see **Fig 2**). **a**| The increased muscle tone and reduced motion that are typical for freezing are reflected in a reduction in body sway, which can be assessed continuously by measuring subtle shifts in the center of pressure over time, using a stabilometric force platform (1). Typically in humans reductions in body sway are assessed when a visual cue is presented on the display (2), that signals threat of a subsequent shock, that can be avoided by a button press (3). **b**| Schematic illustration of the characteristic body sway and heart rate patterns that occur in a typical active threat of shock paradigm: a cue (presented at time 0) signals threat of a shock and elicits a typical orienting-related reduction (to stop ongoing behavior) and subsequent increase (facilitating fast reset of ongoing cognitive processing and alerted cost benefit calculation) in both measures. This is followed by a longer lasting reduction (freezing) that ends after target presentation (here indicated at Time 6 sec) signaling the option to act (for instance to approach or avoid)[98,112,199]. Part **a** is reproduced, with permission, from Hashemi et al.[98].

[H2] Unfreezing

As we have noted, it is the degree of motor reduction and bradycardia that mark out the parasympathetically dominated freezing state from the sympathetically dominated fight-or-flight states[8,97]. Parasympathetic withdrawal therefore plays an important role in shifting from threat-anticipatory state of freezing, during which actions have been prepared, to actual execution of action, when this becomes necessary. This tips the net balance of autonomic activity to sympathetic dominance, reflected by tachycardia[8,98–100]. Such a switch is necessary either to enable Pavlovian or automatic active fight/flight actions or to enable instrumental or goal-directed actions, which may afford extra context dependence (see **Fig. 2**, **Fig. 3** and **Fig. 4**).

Whereas the switch to Pavlovian fight/flight may involve connections between the CeA and the PAG[9,64], subdivisions of the ACC, and in particular the perigenual ACC (pgACC) and its connections to the amygdala and PAG have been implicated in the switch to goal-directed actions[10,98,101,102] and the

LC[103–105]. The human pgACC region in which increased activity was observed[98] in the switch to goal-directed action upon threat imminence is located at the ventral and dorsal separation of the ACC sites that innervate the parasympathetic and sympathetic branches of the ANS respectively[106], and so may be in an ideal anatomical position to alter the net balance between these two branches. This area not only receives information about the state of freezing (such as heart and breathing rate), but is also known to be involved in the maintenance of freezing (by controlling breathing and the parasympathetic component of the cardiovascular response, for instance)[27,71]. This makes the ACC ideally suited to prepare the body for switching to action. Interestingly, various parts of the ACC are implicated in calculations about and the execution of cognitive control[107–109], including the rather essential stay versus go decisions that are ubiquitous in the context of foraging[110,111] and involve abstractly similar computations to those involved in evaluating the necessity of freezing against the opportunity for other actions (such as fight or flight).

Although one might think that freezing and inhibition would be detrimental to the alacrity and accuracy of subsequent action, it actually appears that the opposite is true. Within bounds, human studies showed the stronger the magnitude of bodily immobility, bradycardia and PAG activity under threat of shock, the faster the reaction times for subsequent correct responses[98,112]. Threat anticipatory freezing may therefore be seen as a highly effective preparatory state for action[8].

[H1] Computational considerations

As we have described, the responses of both the CNS and the ANS in the post-encounter threat state are richly structured. They therefore raise various information processing and control-theoretic considerations[3,7,113–115]. Some of these considerations are relatively computationally abstract; others depend on the particulars of the operation of the neural systems involved. Equally, while for some stages of the post-encounter response we have a good idea about the mechanisms that implement the processing in the CNS and ANS, for others (notably the planning stage), we know less.

[H2] Detection of potential danger

The initial detection of danger will often begin during the pre-encounter threat state. At this stage, animals will predominantly be engaging in other activities, such as foraging, but will expend at least some effort on periodic threat assessment, at least in environments where danger is possible[115,116]. In fact, the animals may face an approach/avoidance conflict depending on the likelihood of the arrival of a danger to a location. If they do approach a source of food, for example, they then face an exploit/assess/plan conflict, since the time available for foraging will be reduced by the time taken up

by safety-related tasks. These include direct searching or checking for threats, engaging in planning of what to do if a danger arrives[117] and using some form of replay (the offline activation of patterns of activity in the brain that reflect its knowledge of the environment) to stamp situationally-appropriate defensive actions into a reflex-like or habitual instrumental controller[7,116,118–120] that can act quickly given the advent of post-encounter or circa-strike threat. Conveniently, replay has been shown to happen during periods of quiet wakefulness or even food consumption[121–124]; and particularly involves coordination between hippocampal and cortical structures[125,126].

There are at least four likely consequences of detection of potential danger, portions of which may proceed in parallel. The first is a fast reorienting, allowing limited resources (including both attention and action) to be brought to bear on the threat (see **Fig. 3**). This is facilitated by the very fast operation of cholinergic neuromodulation (see also **Fig. 4**) and may also involve NA in the CNS,[21,22] whose extremely widespread delivery makes it ideal for this task (although its relative sloth has given pause for thought[127]).

A second, related consequence is the interruption and reset of any ongoing information processing (**Fig. 3**). This is necessary to allow a new mode of processing appropriate either to post-encounter or circa-strike threat, depending on the defensive distance. It is also statistically appropriate: information was hitherto being collected under the assumption that no danger was immediately present, an assumption that has been falsified by the detection of the threat. Integrative information processing, such as that involving diffusion-to-bound-like mechanisms[128] must also be reset, since the intermediate decision variables that are used in such mechanisms will have been invalidated. These are again putative effects of NA in the CNS[21,22].

The third consequence of detection is to establish a new set of prior expectations (**Fig. 3**) about the environment. Of course, if the precise nature of the potential danger is uncertain (a rustle in the forest could be either malign or benign), then these new expectations might be quite vague. This operation can perhaps be seen as a form of task-switching, which is known to engage a variety of prefrontal neural mechanisms[129,130] that have also been associated with the reset aspects of NA[21].

A final consequence of detection is that the cost/benefit calculation of sensation, cognition and action changes (**Fig. 3**). When it is of existential importance for the animal to act appropriately in the face of a credible danger[131], the actual and opportunity costs of collecting information about the threat, working out what (if anything) to do about it and, ultimately, to do whatever is necessary, are putatively far outweighed by the benefits of avoiding damage or predation. The quantification of this expected (possibly net) benefit of information processing is exactly a computational index of arousal [132,133], namely, the animal is aroused to the extent that it has the opportunity to improve its likely lot.

We suggest that arousal likely follows initially and predominantly from NA released by LC neurons: the ascending projection of which will engage sensory and cognitive resources, while the descending projection to the sympathetic branch of the ANS sets the stage for fast and effective action.

[H2] Sensory processing and planning

Having detected the threat, the relatively stark question for the animal is whether or not it has also been detected, with the predator chasing or attacking. If so, more extreme circa-strike measures such as rapid escape may be required (**Fig. 3**) without affording the opportunity for controlled information processing and planning[134]. If the threat situation is still ambiguous or the predator still at a distance, then the prey can enter the freezing-based post-encounter threat state. Here, as we have noted, the control theoretic demands are to collect sufficient information about the threat in order to be able to plan effective methods for addressing it, and to specify and prepare the required actions.

At this stage, we suggest that simultaneously activated sympathetic and parasympathetic freezing has a number of particularly desirable characteristics. First, and most obviously, the animal is immobile and thereby potentially less detectable by a predator. Reducing the rate or depth of breathing will also help with this. Immobility confers the additional benefit of making it easier for the animal to gather information, since there will be no sensory consequences of its own actions to cancel, no need to compute the spatial locations of the threat relative to a non-stationary baseline and no excess sources of internal, physiological noise coming from the actions. Reducing heart and breathing rate also reduces physiological noise which enhances perception[135,136]. Finally, animals may be prone to Pavlovian misbehaviour[137] — that is, evolutionary preprogrammed responses that could be deleterious. Immobility will also prevent a headlong rush towards those.

Several other neural and peripheral systems must also coordinate during freezing. For example, the effect of sympathetic activity on pupil dilation might operate in close conjunction with a cholinergically-mediated preference for the detection of coarse sensory features[83]. This would emphasize detection over fine discrimination, which would be appropriate at least at the first stages of working out more about the nature of the threat. It has also been suggested that NA, by signaling unexpected (or at least substantially underexpected) uncertainty (such as cases of substantial model failure evidenced by allowing a predator on the scene) can automatically elicit signals of expected uncertainty (associated with the release of ACh), since the animal will realize that something is amiss with its model, which it will therefore need to update[22,138]. There is a direct path from the LC to the BF that might mediate this effect but NA-releasing neurons from the NTS also project to the BF. According to this hypothesis, it would then be the expected uncertainty that leads to an upweighting of relevant bottom-up sensory information over (apparently incorrect) prior expectations[22,138,139]. The

collection of this information is, as noted, one of the key features of the post-encounter threat state of freezing. Expected uncertainty also affords the opportunity for learning[140], although this is presumably mostly relevant after the immediate threat has been countered.

Another speculative facet of the coactivation of CNS systems that use NA and ACh as their primary transmitters is the simultaneous engagement of two different forms of arousal: NA-driven systems are associated with the benefit of cognition and action and ACh-driven systems with a continuing need to resolve the limited and uncertain understanding the animal might have of the situation (and thus a lack of a clear and obvious plan for defence). Taking this speculation one step further, it is possible that ACh signaling prevents over-arousal that might lead to cognitive failure due to excess NA. This would be a cognitive analogue of the physical freezing state – optimizing preparation rather than reckless action.

What type of information processing needs to be energized (and improved[33])? A formal description of the problem of choosing appropriate actions in the face of large amounts of uncertainty is provided by a partially observable Markov decision process (or POMDP)[141]. In conventional versions of this, agents calculate and then execute policies, which are systematic ways of acting to gain more information (a form of active observation) or to change the agent's circumstance in the world that optimize a function such as the probability of survival. These calculations — which determine things such as when the information accumulated is sufficient to ensure that the risks of waiting to collect more outweigh those of acting prematurely and thus potentially inaccurately – are tremendously difficult to perform exactly, even for computers[142]. Therefore, a wealth of heuristic algorithmic approaches is necessary, and these are likely to be tailored to perform well in particular circumstances. In general, neuromodulators are involved in controlling the use and form of these heuristics in the light of such things as the actual and opportunity costs of time and cognition; this is sometimes known as meta-control[143,144].

As an example of these approaches, diffusion-to-bound decision-making[145] offers a simple, threshold-based, method for deciding when to stop accumulating sensory information and execute an action. This is optimal in some very particular circumstances (as a sort of sequential likelihood ratio test[146]) and is a good heuristic in many other cases too. It has been suggested that the urgency to act, which is determined by the relationship between the rate of accumulation and the threshold, is itself influenced by neuromodulators, including NA[127,147].

Another important class of heuristics derives from the existence of systematically different routes to specifying policies, well described by model-based and model-free forms of reinforcement learning [148]. Model-based methods (also coarsely known as system 2 or 'slow' reasoning[149]) learn an internal

representation (a cognitive map[150]) of their environment (for instance during safe and pre-encounter states) and use this to plan ahead, perhaps through a form of pre-play[151,152,153]. Model-based choice is highly flexible (and has been related to goal-directed decision-making in animals[154]); however, the calculations required can be slow and place large demands on limited resources such as working memory.

Model-free methods (also known as system 1 or 'fast' reasoning), by contrast, attempt to learn suitably far-sighted policies from experience. Reinforcement learning includes various techniques for doing this, such as temporal difference learning[155], some of which apparently have rather transparent neural substrates[156]. Once learned, these policies can be executed immediately. Of course, learning from actual experience of mortal threat is particularly challenging, which could explain the requirement for the time for processing afforded by freezing. However, as mentioned above, off-line training [118,119] during pre-encounter states might allow knowledge to be transferred from the model to enable an effective, as well as cheap and fast, reflex-like, model-free policy[7,120].

Model-based and model-free calculations, which are known to be at least partially separated in the brain[157], can be integrated in various ways. The same sorts of calculations that determine whether enough external information has been gathered to license a decision can be used to decide whether sufficient internal information processing[158] has occurred to decide whether and how to act. Again, neuromodulators might play a role in this determination, both in the uncertainty assessment and evaluation[22] and (in the appetitive case) in signaling the opportunity cost associated with the time spent performing model-based calculations[159]. This opportunity cost may be reported by relatively slowly-changing dopamine concentrations[160–162].

There is very much more to learn about the heuristics that animals apply, particularly under the sort of stress engendered by post-encounter states. It is known that the ACC plays a critical role in cognitive control and, in particular, in the sort of stay versus go decisions that have been richly studied in the context of foraging[111,163,164], but apply here too. As noted above, the ACC has a role in the switch from freezing to goal-directed instrumental control, potentially via removing the parasympathetic brake on action. By contrast, the switch from freezing to the emergency condition of fight/flight is presumably engendered by sensory cues associated with the more proximal approach of the danger, and is mediated via the central nucleus of the amygdala and the PAG[9,64,98,165].

[H2] Decision to act

Further control-theoretic reasons for the autonomic co-contraction that is observed during freezing are revealed when we consider the stage at which a decision is made to act. In particular, we suggest that

this co-contraction means that output can be far faster: withdrawal of an activated system is likely to be far more expeditious than engagement of an active system from baseline, when a full cascade of peripheral and central-cognitive processes still has to be realized. In the case of switching from freezing to action, parasympathetic withdrawal may enable fast execution of the already sympathetically-driven prepared action[98] (see **Fig. 2**, and **Fig. 3**). We speculate that this might be true either for habitual or goal-directed instrumental actions that address the threat in a manner sensitive to inference and learning, or for Pavlovian fight/flight actions.

[H1] Conclusions and future directions

Considering the post encounter threat state from neural, psychological and computational perspectives has shown how the most obvious external characteristic of this state — a particular form of active freezing arising from co-activation of the normally opposed sympathetic and parasympathetic branches of the ANS — could have various advantages from the viewpoints of both information processing and fast Pavlovian or instrumental action. Descending control of this state is quite well understood, and the potential benefits of expending effort on enhancing unbiased, bottom-up, sensory processing and engaging in planning are easy to observe. However, the roles of ascending neuromodulators in engaging these forms of appropriate information processing are less clear. Certainly, various of the modes of action of ACh and NA in the CNS are in a position to achieve some of this; but much remains to be discovered by precisely recording and manipulating the candidate circuits within the timeframes of the detection, evaluation and action stages.

One important source of ideas is evolutionary theory. For instance, the polyvagal theory of the phylogeny of the ANS[166–168] suggests that it progressed in three stages. The first, associated with an unmyelinated vagus nerve, allowed metabolic activity to be depressed in response to threat and also controlled aspects of digestion. The second stage was associated with the sympathetic nervous system, which organized energized behaviour for fight or flight. The third stage was associated with a myelinated vagus nerve and allowed for more flexible and sophisticated responding. It has been suggested that the last stage is particularly involved in the evolution of somatic regulation in a social context[167]; but the evolutionary layering of the competition and cooperation between the inhibitory and activating aspects of the different branches of the ANS is notable. It would be interesting to understand the parallel evolution of cholinergic and noradrenergic neuromodulation in the CNS[169].

NA and ACh are certainly not unique in playing roles as neuromodulators in the defensive cascade. Dopamine is involved in aversive processing in various ways, with specific groups of dopaminergic neurons reporting on negative outcomes[170,171]. In the third stage of our model, shown in **Fig. 3**,

dopmaine activity may affect the choice of vigorous defensive actions[172–174] through a rather complex relationship to its well-explored relationship with appetitive processing[116]. Equally, though also subject to many intricacies, serotonin is implicated in processing and learning about aversive situations and circumstances[175–177]. In particular, it has been proposed that serotonergic neurons in the dorsal raphe and the vlPAG are involved both in inhibiting fight/flight panic responses and in activating the link between the CeA and the vlPAG that is involved in mediating the freezing response[178,179]. Consistent with this, humans with a polymorphism in the serotonin transporter gene (*SLC6A4*) that reduces its expression, as well as *Slc6a4* knockout rats, have exaggerated bradycardia and freezing, which in both species was mediated by increased functional coupling in the amygdala-vlPAG pathway in the face of threat[63]. In general, serotonin is associated with behavioural inhibition and patience[180–185], which could be seen as broader facets of a state of freezing or immobility. Nevertheless, there is evidence that serotonin's activity and effects change from inhibition to invigoration as aspects of threat and danger increase[186], perhaps in concert with the anatomical switches that we have detailed in the transition from freezing to more active responding. Future studies should investigate the interactions between neurotransmitter systems, and the switch to action in particular[187].

Along with the advantages of autonomic co-contraction that we have mentioned are problems in regulating a careful balance between two highly activated, but opposed, systems. We might expect substantial individual differences in the ability to do this. Indeed, there is evidence that some people show tachycardia and hyperventilation rather than bradycardia and hypoventilation, in the context of aversive conditioning[188–191], and it has been suggested that this distinguishes people for whom preparing for the subsequent defensive action is more important from those who instead stress the sort of defensive attention that well characterizes the freezing state[60,79]. Whether this distinction correlates with vulnerability to or experience of psychiatric dysfunction is an important open question (**Box 1**).

Many potential experimental directions arise directly from the computational analysis described above. Tests of our hypotheses will benefit from burgeoning advances in measurement methods[192,193]. In particular, we need to understand how well adapted the enhanced sensory processing during post-encounter freezing is to the nature of the potential threat and predictions about its future behavior. Likewise, it would be interesting to study how other knowledge about the potential risk/reward associated with different potential plans of action, perhaps built during pre-encounter threat states, is integrated with immediate sensory information. There is more to learn about the assessment of the remaining planning that can be fit into the time available, and indeed what sort of learning about all of these facets happens after the event, given survival. Finally, a psychiatric perspective encourages examination of individual differences in these various characteristics, occasioned by such things as different risk sensitivities. From a CNS perspective, given the potential roles for all the major

ascending neuromodulators that we have discussed (along with their cotransmitters), perhaps the most significant gap is in our understanding of the loci and effect of interactions between these systems during freezing.

In summary, although freezing might seem a rather simple protective response to a dangerous circumstance, we argue that it is really a delicately balanced state in which competition and cooperation between neurotransmitters and neuromodulators in the autonomic and central nervous systems provides the opportunity and means for exquisitely regulated sensory reception and information processing, affording animals the best chance of improving their fate.

Box 1: Clinical considerations. In line with rodent and primate work[200,201], several studies have linked stronger freezing reactions to threat to increased internalizing symptoms, including anxiety[97,99–101,113,202]. Moreover, a pattern of reduced initial (not later) freezing-responses has been shown to be linked to aggression[199]. Increased freezing tendencies have also been observed as a function of trauma and stress-exposure[203,204]. The notion that regulating a careful balance between defensive states may be tricky and that subtle deviations may be linked to risk for psychopathology was recently supported by a prospective longitudinal study. In this study, deviations from normal in infant freezing —both exacerbated freezing or no freezing at all in response to a moderately threatening situation — were predictive of the development of internalizing symptoms in early and late adolescence, respectively[205]. Likewise, increased amygdala activity during threat anticipatory freezing was linked to increased vulnerability to develop post traumatic stress disorder in police officers[202].

Patients with anxiety-related disorders display chronically elevated autonomic activity[206], which may underlie characteristic decision-making biases, including increased avoidance[207]. Interesting in this respect are recent findings linking bodily freezing and freezing related bradycardia to instrumental avoidance and value integration during approach–avoidance decision making[112,208]. Further investigation is needed to determine how far this is related to interoception. There are complex interactions between ANS states and interoceptive cardiac and respiratory awareness that in turn link to psychopathological states[209,210].

Information processing during post-encounter threat is also likely to be altered in conditions such as anxiety. For instance, pre-existing or induced anxiety can be associated with enhanced response inhibition[211,212] and an earlier transition to escape from slowly approaching threats[213]. Elements of the interaction between the cortex and the amygdala that we have described as playing a critical role in post-encounter threat may also differ under anxiety[214]. Assumptions about the controllability of the circumstance likely also play a critical and psychiatrically relevant role, adding ‘flop’ as an additional option to fight/flight/freeze/fright if there is nothing else for it[215].

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interest.