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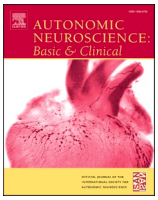

Stress and central autonomic network

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ABSTRACT

The central autonomic network (CAN) plays a critical role in the stress response, which is triggered by challenges on the homeostasis (physiological stressors) or unpleasant social or environmental situations. This review focuses on the role of areas of the CAN including the insular and anterior cingulate cortices, extended amygdala, hypothalamus, periaqueductal gray and locus coeruleus in the stress response. These areas are interconnected and affect sympathetic or parasympathetic output via their influence on premotor or preganglionic autonomic neurons in the lower brainstem and spinal cord. The insula integrates multiple inputs to create a sense of the physiological state of the body, whereas the anterior cingulate initiates predictive visceromotor commands. The amygdala and bed nucleus of the stria terminalis provide automatic emotional tagging and trigger automatic survival responses to threat via their outputs to the hypothalamus, periaqueductal gray, and lower brainstem. Several regions of the hypothalamus, including the paraventricular nucleus, dorsomedial nucleus and lateral hypothalamic area participate in different patterns of stress response according to the type of stimulus and projections to premotor and preganglionic autonomic neurons. The periaqueductal gray initiates different patterns of autonomic, pain modulatory, and motor responses, including the "fight or flight" or "playing dead" responses. The locus coeruleus promotes emotional learning in the amygdala associated with states of anxiety. Neurons of the C1 area of the rostral ventrolateral medulla elicit sympathoexcitatory responses to internal stressors such as hypoxia and inflammation. The ventromedial medulla, including the nucleus raphe pallidus, initiates sympathoexcitatory responses to social and other external stressors.

1. Introduction

The central autonomic network (CAN) involves a group of interconnected areas of the telencephalon, diencephalon, and brainstem that control the sympathetic outputs via preganglionic neurons in the brainstem vagal nuclei and in the spinal cord [1,2]. One of the major function of these areas is the stress response triggered by challenges from the internal or external environment [3]. Stress implies an adaptative process with integration of signals from the environment and promotion of physiological and behavioral changes allowing the organism to adapt to homeostatic challenges [4]. The stress response varies according to the type of stressor and includes not only autonomic but also humoral responses such as activation of the adrenocortical axis as well as changes in respiration and motor function [5,6]. The components of the CAN include the insular and anterior cingulate cortices; centromedial nucleus of the amygdala (CeM) and the bed nucleus of the stria terminalis (BNST); several nuclei of the hypothalamus; the periaqueductal gray matter in the midbrain (PAG); the parabrachial (PB)/Kölliker-Fuse complex in the pons; the nucleus of the solitary tract (NTS); the medullary intermediate reticular zone encompassing the rostral ventrolateral medulla (RVLM, including the C1 area) and caudal ventrolateral medulla; and the rostral ventromedial medulla (RVMM) and medullary raphe (Fig. 1). This review will focus on the role of different components of the CAN in the stress response. These components are extensively interconnected and only some of the major connections will be emphasized here.

2. Sources of stimuli initiating the stress response

Different types of interoceptive, humoral, and exteroceptive signals may reach the CAN and trigger the stress response. Interoception refers to the sense of the physiological state of the body conveyed by visceral receptors and nociceptors [7]. Interoceptive afferent inputs are conveyed by lamina I in the dorsal horn or the NTS and are relayed either directly or via the PB to the hypothalamus, amygdala, and insular cortex (via the thalamus) [2,8]. For example, changes in blood pressure,

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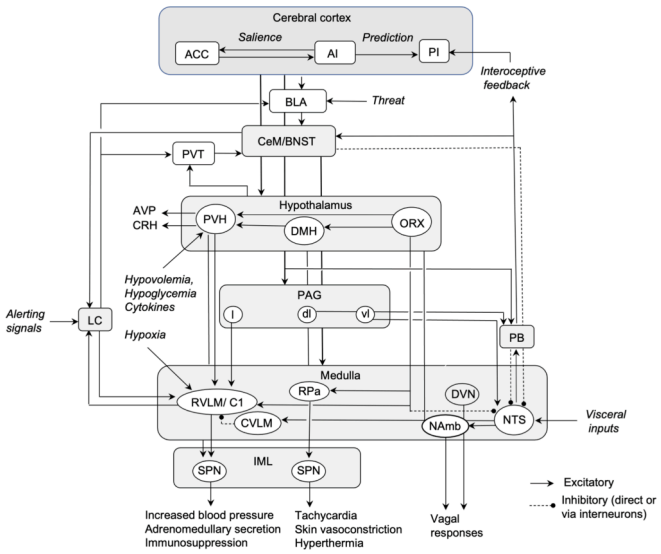

Fig. 1. Interactions between the different components of the central autonomic network involved in the stress response.
The stress responses are integrated at the levels of the cerebral cortex, amygdala, hypothalamus, periaqueductal gray (PAG), pons, and medulla (gray boxes), via descending projections affecting several nuclei within these levels (thick lines). Selective nuclei within each level (white ovals) have specific connections that mediate different aspects of the stress response via descending output to premotor and preganglionic neurons of the medulla and spinal cord (thin lines). These connections are complex, and only important examples are depicted in the figure. At the cortical level, the dorsal posterior insula (PI) is the primary interoceptive cortex whereas the anterior insula (AI) and anterior cingulate cortex (ACC) process behaviorally salient information and participate in autonomic control via descending outputs to the amygdala, hypothalamus, and brainstem. Emotionally salient information, including threatening stimuli, is processed at the level of the basolateral amygdala (BLA), which via the centromedial nucleus of the amygdala and the bed nucleus of the stria terminalis (CeM/BNST) provide outputs to the hypothalamus, PAG, pons, and medulla. The CeM/BNST also receives aversive information via the parabrachial nucleus (PB) which relays visceral afferent information from the nucleus of the solitary tract (NTS). These visceral inputs interoceptive feedback to the cerebral cortex, which is used to correct visceromotor prediction errors. Alerting signals reach the cerebral cortex, CeM/BNST, and other areas via the locus coeruleus (LC), in part via the paraventricular nucleus of the thalamus (PVT), which also relays visceral information from the PB (not shown). Different portions of the hypothalamus and PAG participate in the stress response. The paraventricular nucleus (PVH) has a central role in response to hypoglycemia, hypovolemia, cytokines, and other internal challenges and initiates sympathoexcitatory responses via projections to the rostral ventrolateral medulla, including the C1 area (RVLM/C1) and to sympathetic preganglionic neurons (SPNs) of the intermediolateral cell column (ILM). The PVH also contains magnocellular neurons that secrete arginine vasopressin (AVP), and parvocellular corticotrophin releasing hormone (CRH) neurons that activate the corticoadrenal axis. The dorsomedial nucleus (DMH) generate autonomic, respiratory, and neuroendocrine responses to psychological stressors; the sympathoexcitatory responses are mediated by neurons of the nucleus raphe pallidus (RPa) projections to the IML. The orexin (ORX) ORX neurons of the lateral hypothalamus and perifornical region send excitatory projections to the PVH, DMH and to brainstem autonomic and respiratory nuclei promoting sympathetic cardiovascular activation, respiratory responses to hypercapnia, and attenuation of the baroreflex via inputs to the NTS.
The PAG consists of several columns, lateral (l), dorsolateral (dl), and ventrolateral (vl) that mediate different autonomic, pain modulatory, and motor responses according to the type of challenge. The lateral and dorsolateral PAG initiate fight-or-flight responses; the lateral PAG via projections to the RVLM/C1 area and the dorsolateral PAG via input to the lateral PB inhibit the baroreflex. The ventrolateral PAG column inhibits the sympathoexcitatory neurons of the RVLM and activates the baroreflex at the level of the NTS and the vagal preganglionic neurons of the nucleus ambiguus (NAmb). In addition to inhibition of the RVLM/C1 via the caudal ventrolateral medulla (CVLM), the NTS inhibit stress responses via projections to the BNST and CeM (not shown). Some stress responses are associated with increase vagal output to the heart via the NAmb, and to the gastrointestinal tract via the dorsal motor nucleus of the vagus (DVN).

heart rate, and blood gases are conveyed from baroreceptors, cardiac receptors, pulmonary receptors, and carotid and aortic chemoreceptors via the glossopharyngeal and vagus nerves to different subnuclei of the NTS [5]. Some afferent signals can induce immediate reflex adjustments of the end-organs via projections from specific NTS subnuclei to premotor sympathetic neurons of the RVLM including the C1 area, vagal nuclei, or respiratory pattern generators [6]. A second major source of information to the CAN is provided by humoral signals from the blood and cerebrospinal fluid [6]. Some signals, such as blood temperature or circulating steroids can directly affect neurons in the CAN; others, such as circulating angiotensin II or cytokines act via circumventricular organs such as the area postrema and subfornical organs that lack a blood brain barrier, or via paracrine mechanisms mediated by signals from the cerebral microvasculature [9]. The third major input to the CAN originates from forebrain areas involved in processing of interoceptive signals, including the CeM/BNST, anterior insula, and anterior cingulate cortex [10,11].

3. Cortical areas, interoception, and autonomic control

The anterior insula and anterior cingulate cortex (ACC) are nodes of the so-called salience network involved in processing of behaviorally salient information [12], and participate in autonomic control via descending outputs to the amygdala, hypothalamus, and brainstem (Fig. 1) [11]. The anterior insula receives inputs via the mid-insula from the dorsal posterior insula, which is the primary interoceptive cortex [12]. The anterior insula integrates interoceptive signals with emotional and cognitive processing and is involved in attention of the physiological state of the body [7]. The ventral anterior insula (frontoinsular cortex) and the pregenual ACC contain large layer 5 projection neurons, called von Economo neurons, which project to the PAG, PB and other areas of the CAN [13]. Recent models of interoception and emotion incorporate the Bayesian concepts of predictive coding [14,15]. In one such model, projection neurons in the anterior insula and pregenual ACC targeting autonomic control areas generate predictions about physiological states that are sent via cortico-cortical projections to the posterior insular cortex [15]. In the posterior insula, these visceromotor simulations are compared to afferent interoceptive inputs, and this

comparison generates a prediction error signal that is sent back to the anterior insula and ACC to refine interoceptive predictions [15]. These prediction errors trigger both emotional feelings and homeostatic responses [14,16]. Emotion constitutes both a psychological and physical reaction that is critical for survival and control of behavior [17]. They are experienced as strong feelings and produce physiological changes that prepare the body for immediate action via coordinated activation of survival, arousal, and reward and motivation circuits [17]. The stress responses do not require the explicit mental representation of the emotional state [16,17].

4. The extended amygdala and automatic survival responses

The amygdala provides automatic tagging of the valence (positive or negative) and intensity of innate stimuli such as pain, conditioned stimuli, and environmental stimuli (including social stimuli such as face expression) and thereby their behavioral relevance [18]. Cortical, thalamic, and other subcortical inputs reach the basolateral complex of the amygdala, which projects to the central nucleus of the amygdala, including the centrolateral nucleus and the CeM [19]. The CeM and the BNST form a functional continuum referred to the medial extended amygdala [20]. These areas have an important role in responses to threat and other anxiety provoking stimuli via projections to the hypothalamus, PAG, and brainstem autonomic nuclei (Fig. 1); they trigger automatic survival responses [20]. A major source of aversive information to the amygdala is the PB, which conveys pain and visceral sensation directly to the CeM [21]. The CeM sends dense GABAergic and peptidergic projections to the hypothalamus, PAG, PB, NTS, RVLM and vagal nuclei. Via these projections, the amygdala may elicit sympathetic or parasympathetic activation, secretion of stress hormones, and innate motor responses [22,23]. Some of the effects of CeM projections may be indirect; for example, GABAergic inputs inhibit barosensitive neurons of the NTS leading to increase blood pressure [24]; there are also direct (presumably glutamatergic) projections from the CeM to barosensitive neurons of the C1 area [24]. Neurons of the extended amygdala, like those in the paraventricular nucleus of the hypothalamus (PVH) express corticotrophin releasing hormone (CRH), which is a common mediator of stress responses [25].

5. The hypothalamus as a pattern generator of the stress response

The hypothalamus has an integrative role and functions as a pattern generator of autonomic, endocrine, and behavioral responses. It consists of several nuclei that participate in circuits involved in maintenance of bodily functions at key set points (homeostasis), and adaptation to internal or external stressor (allostasis) [26,27]. The two hypothalamic effector systems activated by stress are the sympathetic-adrenomedullary and the hypothalamic-pituitary-adrenal (HPA) axis [26]. Several hypothalamic areas trigger autonomic responses to stress, including the PVH, dorsomedial nucleus (DMH), and lateral hypothalamic/perifornical areas containing orexin (ORX, hypocretin) neurons [28].

The PVH is a complex and heterogenous nucleus composed of different groups of neurons and plays a central role in response to internal stressors such as hypoglycemia, hypovolemia, and inflammation [5]. Autonomic PVH neurons project to the IML, RVLM and NTS and control sympathetic outflow to the heart, kidneys and other organs (Fig. 1) [5]. Magnocellular PVH neurons producing arginine vasopressin (AVP) project to the posterior pituitary for storage and release in response to increase in osmolarity, hypovolemia, or both [29]. These neurons are activated by neurons in the circumventricular organs, such as the subfornical organ, in response to increase osmolarity, circulating angiotensin II, and others signals [29]. Parvocellular CRH neurons of the PVH are essential to initiate the stress response. These neurons send projections to the median eminence to activate adrenocorticotropic hormone (ACTH) release from the anterior pituitary and ultimately increase the release of glucocorticoids from the adrenal cortex during acute stress [30]. Parvocellular CRH neurons also synthesize AVP, which acts synergistically with CRH to amplify the release of ACTH [31]. Another role of AVP released into the hypothalamo-hypophyseal portal circulation is the alteration of the set-point of feedback inhibition of the HPA axis by adrenal glucocorticoids on type II receptors in subcortical structures causing greater and more prolonged elevations of adrenal corticosteroid concentrations in the blood [32–34]. The acute increase in glucocorticoids mobilizes energy in response to homeostatic challenge and promotes adaptation via their actions on synapses, circuits, and behavior [35]. On the other hand, chronic elevation in glucocorticoids can cause deleterious pathophysiological changes, including heart failure [4,34]. Glucocorticoids also inhibit the production of brain cytokines by suppression of the locus coeruleus (LC) activity and inhibition of proinflammatory downstream signal transduction cascades in glial cells [36]. It should be noted that forebrain afferents to parvocellular CRH neurons may be either excitatory or inhibitory. For example, inputs from the CeM/BNST may activate the HPA axis whereas those from the prefrontal cortex and the hippocampus have an inhibitory effect via GABAergic neurons surrounding the PVH [37,38].

The DMH is a key region in triggering a highly coordinated response to actual or potentially threatening stimuli in the external environment, such as psychological stressors [28,39]. The DMH receives inputs from the cortex, amygdala, and other forebrain regions and is critical for generating autonomic, respiratory, and neuroendocrine responses to psychological stressors (Fig. 1); the DMH also receives an input from the dorsolateral column in the PAG, which is another key region involved in the integration of stress-evoked cardiorespiratory responses, as discussed below [28]. The DMH triggers sympathoexcitatory responses via inputs to the RVMM, RVLM and nucleus raphe pallidus (RPa), either directly or via the PAG, leading to activation of preganglionic neurons that elicit tachycardia and vasoconstriction [5,28,39]. In response to emotional stressors, there is an asymmetric activation of the amygdala, DMH and PAG; this asymmetric cardiac modulation could predispose to stress-induced cardiac arrhythmias [40]. The DMH modulates autonomic and neuroendocrine responses that not only promote heat-conservation [41,42] but also mediate stress induced hyperthermia via outputs to the RPa [43]. The DMH is also a critical region for integration of respiratory responses to stress; DMH neurons augment respiratory activity via connections with neurons in the perifornical area that project to brainstem respiratory neurons [28].

The ORX neurons of the lateral hypothalamus and perifornical region promote cardiovascular and respiratory responses associated with behavioral arousal, reward and motivated behavior, and stress [44,45]. These neurons send excitatory projections to the PVH, DMH and to brainstem autonomic and respiratory nuclei (Fig. 1) [45]. Orexin promotes sympathetic cardiovascular activation and respiratory responses to hypercapnia, and attenuates the baroreflex [45]. ORX neurons are recruited both by psychological and physiological stressors and this activation seems to be linked with coping behaviors [46]. Afferent regulation of these ORX neurons involves the CeM/BNST, medial amygdala, and C1 adrenergic neurons in the RVLM [47]. Under acute stress, ORX neurons promote adaptive behavior to remain safe, however, in the case of chronic or repeated stress, dysregulation of ORX neurons promote maladaptive behaviors [46,48,49]. While ORX have been shown to promote the HPA axis response it has also been shown that HPA activation induces ORX activity [50].

6. Periaqueductal gray: integration of autonomic, pain modulatory, and motor responses for coping to stress

The PAG consists of different functional columns: dorsal PAG, dorsolateral PAG, lateral PAG and ventrolateral PAG, which participate in different responses to external stressors [51]. The PAG receives input from the medial prefrontal and anterior cingulate cortices, the

amygdala, the hypothalamus and noradrenergic and adrenergic fibers from the medulla [52]. Different responses to stress are mediated by different columns of the PAG, which receive inputs from different forebrain areas. The lateral and dorsolateral PAG are involved in the defense reaction and initiate fight-or-flight responses associated with tachycardia, hypertension, and redistribution of blood flow by activating sympathetic preganglionic neurons controlling cardiovascular effectors (Fig. 1) [52,53]. In contrast, neurons of the ventrolateral PAG column inhibit the sympathoexcitatory neurons of the RVLM and activate the vagal preganglionic neurons, initiating a passive coping response referred to as "playing dead" and characterized by immobility, bradycardia, and hypotension [52]. The autonomic responses to stressors are integrated with pain modulatory and motor responses via the PAG [51]. For example, active coping associated with sympathoexcitation is associated with opioid-independent analgesia and increase motor activity including locomotion; passive coping associated with sympathoinhibition is associated with opioid-mediated analgesia and freezing responses [52]. These pain modulatory effects are mediated by descending input from the PAG to the RVMM, nucleus raphe magnus, and other portions of the pontomedullary reticular formation that send serotonergic, enkephalinergic, GABAergic, or glutamatergic projections to the spinal cord [54,55].

7. Locus coeruleus: behavioral arousal and stress response

The LC-norepinephrine system has a major role in behavioral arousal and stress responses (Fig. 1) [56,57]. The interactions between the LC and CRH neurons of the CeM/BNST constitute a third stress system that may have particular relevance in mechanisms of anxiety [58]. Acute stress increases the level of vigilance and favors emotionally charged responses to salient information and promotes emotional memory consolidation. The LC is a heterogeneous structure containing subsets of neurons that innervate discrete targets and contribute to distinct aspects of behavior [59]. For example, in response to stress LC neurons innervating the CeM become more excitable and promote anxiety-like behavior whereas LC neurons innervating the medial prefrontal cortex become less excitable and appear to promote exploration [59]. CRH neurons in the CeM activate fast tonic activity of LC neurons [60], which release norepinephrine in the amygdala and promote emotional learning via beta-adrenergic receptors [61]. The paraventricular nucleus of the thalamus (PVT) may play a major role in stress-promoted consolidation of emotional memories to guide behavior [62]. Neurons of the PVT receive dopaminergic and noradrenergic inputs from the LC and inputs from ORX neurons. The PVT projects to components of the so-called "brain anxiety network" composed of a number of interconnected cortical regions that detect threats and execute appropriate defensive responses via projections to the shell of the nucleus accumbens, dorsolateral region of the BNST, and lateral region of the central nucleus of the amygdala [62]. The LC may also participate in autonomic responses to stress via its excitatory projections to the RVLM and IML and inhibitory projections to parasympathetic nuclei [63]. The LC also has reciprocal interactions with C1 neurons of the RVLM [64], as neurons in the C1 area send a glutamatergic projection to the LC [65]. As discussed below, C1 neurons constitute a brain "alarm system" that responds to internal homeostatic challenges such as hypoxia and inflammation and triggers sympathoexcitatory cardiovascular responses, arousal and respiration [66].

8. Lower brainstem as effector of the stress response

The cerebral cortex, amygdala, hypothalamus, and PAG largely control the preganglionic sympathetic or parasympathetic output via premotor autonomic neurons located in the medulla and pons. The RVLM contains premotor sympathoexcitatory neurons that project to the IML and have a critical role in control of blood pressure [1]. They include the C1 neurons that also synthesize epinephrine and function as sensors and mediators of responses to internal stressors such as hypoxia and hypoglycemia [66]. These neurons receive excitatory inputs from the PVH and PAG and are inhibited by the baroreflex. The C1 neurons not only activate sympathetic cardiovascular responses via excitatory glutamatergic projections to the IML but also stimulate the HPA axis and the LC, and A5 noradrenergic neurons in the pons, which also have sympathoexcitatory effects [67,68]. C1 neurons also increase breathing and coactivate sympathetic and cardiovagal outflows [69].

The RPa receives excitatory inputs from both the DMH and contains sympathetic premotor neurons that elicit increase in heart rate and contractility in response to external stressors (Fig. 1) [28,70,71]. Neurons of the RPa receiving inputs from the DMH also provide sympathoexcitatory outputs that initiate heat-conservation responses to cold including skin vasoconstriction and thermogenesis through brown fat lipolysis [42]. A glutamatergic input from the dorsal hypothalamus to the RPa triggers stress-induced hyperthermia by activating brown fat thermogenesis but, unlike the heat-conserving response to cold, does not result in skin vasoconstriction but rather vasodilation; this may explain flushing (skin vasodilation) while feeling of being too hot during stressful times [43].

The NTS is the first relay station for cardiovascular, respiratory, and gastrointestinal reflexes, and is a target of inhibition during stress responses resulting in sympathoexcitation. For example, a GABAergic input from the CeM to the NTS inhibits baroreflex responses [24]. Inputs from the dorsolateral PAG also inhibit bradycardic responses to the baroreflex via a relay in the lateral PB (Fig. 1) [72]. Circulating glucocorticoids reduce glutamate release from primary afferents in the NTS via retrograde endocannabinoid signaling [73]. In contrast, activation of the ventrolateral PAG modulates promotes baroreflex responses [74]. The NTS may also participate in the regulation of stress and emotional responses via long GABAergic projections to the PVH and BNST [75]. The dorsal motor nucleus of the vagus provides inputs controlling motility and secretion and may participate in mechanism of stress-induced gastric mucosal lesion [76]. Noradrenergic (A2) as well as adrenergic (C2) neurons in the regions of dorsomedial medulla, send direct projections to CRH neurons of the PVH to activate the HPA axis in responses to acute systemic (but not psychogenic) stressors [77].

9. Conclusion

Areas of the CAN are interconnected and play a critical role in different aspects of the stress response. These responses are not only critical for survival and adaptation to internal or external challenges, but also initiate signals that trigger emotion, affect decision making, and promote social behavior. The insular and anterior cingulate cortices are the two major components of the salience network. This network utilizes relevant information, including homeostatic signals, to exert an executive control of behavior [13–16]. The amygdala provides automatic tagging of the behavioral relevance to innate, conditioned, and environmental stimuli and is a hub for integration of innate survival response, arousal, motivation, decision making, and social recognition, affiliation, or avoidance [18]. The hypothalamus and the PAG serve as a link between forebrain areas involved in cognitive and affective aspects of the stress response and the lower brainstem areas initiating the appropriate autonomic and other effector components of these responses [28]. For example, the PVH via projections to the RVLM/C1 initiate sympathoexcitatory responses required to maintain the internal milieu, the DMH via projections to the RPa initiates responses to external stressor, and the ORX neurons, which are critical for maintenance of the arousal state, are recruited both by psychological and physiological stressors to promote adaptive behavior via projections to multiple targets. The different columns of the PAG initiate specific patters of autonomic, motor and pain modulatory responses that depend on the nature of and ability to cope to the external stressor. The PB and LC have a critical in integration of homeostatic signals, arousal, and autonomic (as well as respiratory) components of the stress response.

The premotor neurons in the lower pons and medulla, via the preganglionic sympathetic and parasympathetic neurons, orchestrate the stress response. The C1 neurons of the RVLM, both via their output to these preganglionic neurons and their interactions with the LC, PB, and hypothalamus provide a prototypical "alarm" system activating autonomic, respiratory, and arousal responses [66]. The combination of increasingly sophisticated experimental methods in animals and functional neuroimaging in humans will continue to provide further insight into the complex and interactive aspects of the responses to stress.

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Declaration of competing interest

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