

Dynamic adaptation of large-scale brain networks in response to acute stressors

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Stress initiates an intricate response that affects diverse cognitive and affective domains, with the goal of improving survival chances in the light of changing environmental challenges. Here, we bridge animal data at cellular and systems levels with human work on brain-wide networks to propose a framework describing how stress-related neuromodulators trigger dynamic shifts in network balance, enabling an organism to comprehensively reallocate its neural resources according to cognitive demands. We argue that exposure to acute stress prompts a reallocation of resources to a salience network, promoting fear and vigilance, at the cost of an executive control network. After stress subsides, resource allocation to these two networks reverses, which normalizes emotional reactivity and enhances higher-order cognitive processes important for long-term survival.

Stress-induced shifts in neurocognition

Stress is a double-edged sword: it causes us to have difficulty focusing our attention, retrieving information from memory, and making decisions that require complex thought. Extreme and prolonged stress can furthermore have pathological sequelae such as post-traumatic stress disorder and depression. Yet, the acute stress response also enables us to rapidly detect threats, respond adequately, restore homeostasis when threats are no longer present, and better prepare the organism for future challenges [1,2].

Stressors (see Glossary and Box 1) trigger a chain of neuroendocrine reactions throughout the body that is highly preserved across species [3,4]. Animal work at the cellular level has detailed how stress-sensitive neurotransmitters and hormones such as catecholamines and corticosteroids exert modulatory effects on neural excitability and plasticity that are targeted in both space and time [3,5,6]. Spatial specificity allows for selective alterations in widespread

target tissues, whereas temporal specificity allows for time-dependent shifts in these changes. At the systems level, stress-related neuromodulators may therefore trigger coordinated, brain-wide shifts in neural functioning that enable us to reallocate processing resources (Box 2) to meet unstable environmental demands [2,7–9].

Glossary

Attentional blink: impairment in detectability of the second of two targets when presented with a 200 to 500 ms interstimulus interval.

Blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI): neuroimaging technique that uses BOLD contrast to infer changes in neuronal activity from hemodynamic changes.

Catechol-O-methyltransferase (COMT): an enzyme that catabolizes catecholamines. Met-homozygotes have a three- to fourfold lower COMT availability than Val-carriers and therefore have higher basal catecholamine levels.

Catecholamines: class of monoamine neurotransmitters including dopamine and norepinephrine.

Corticosteroids: steroid hormones produced in the adrenal cortex (cortisol in humans, corticosterone in rodents). Corticosteroids bind centrally to MRs and GRs.

Dopamine: catecholamine neurotransmitter produced primarily in the mid-brain ventral tegmental area and substantia nigra.

Endogenous attention: voluntary, internally driven direction of attention.

Executive control network: large-scale network that regulates higher-order cognitive functions such as working memory, goal-directed planning, complex decision making, and endogenous attention.

Exogenous attention: involuntary, reflexive reorienting of attention.

Functional connectivity MRI (fcMRI): application of BOLD-fMRI that quantifies connectivity between regions by temporally correlating BOLD signals measured in different regions.

Glucocorticoid receptor (GR): receptor molecule that binds corticosteroids particularly after stress. The affinity of GR is 10 times lower than that of MR.

Large-scale network: set of brain regions distributed widely across the brain that forms a system of interconnected nodes. Large-scale networks are often identified using functional connectivity MRI.

Locus coeruleus (LC): pontine nucleus that is the primary site of norepinephrine cell bodies.

Mineralocorticoid receptor (MR): receptor molecule that binds corticosteroids with a tenfold higher affinity than GR.

Norepinephrine: catecholamine neurotransmitter enzymatically derived from dopamine and produced centrally primarily in the LC. Also acts peripherally as a hormone.

Pre-pulse inhibition: inhibition of the reaction to a startle stimulus by a weaker preceding stimulus. Often used as a measure of sensory gating.

Salience network: large-scale network that integrates cognitive processing associated with salient stimuli, including exogenous attention.

Sensory gating: the process of filtering out noise from meaningful sensory information.

Stressor: physical or psychological event that threatens an organism's homeostasis (Box 1).

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Box 1. The stress concept

The classic concept of stress, which originates from engineering, refers to forces impinging on a structure that cause a state of deformation ('strain') [123]. By analogy, physical and psychological events that threaten homeostasis in organisms are referred to as 'stressors' [2]. However, there is also a long history in medicine [124] and psychology [1] of referring to the physiological or psychological disturbance that is caused by stressors as 'stress'. Thus, these theorists used the concept of 'stress' to refer to the state of the organism (the 'strain') rather than to the external causes (the 'stressor'). Cognitive psychologists in the 1960s, however, argued against a unified concept of stress and emphasized the mediating role of appraisal, coping, and emotion: depending on the goals, beliefs, and coping strategies of an organism, a stressor may be appraised differently and elicit different affective states and behaviors [125]. Nonetheless, there are striking commonalities between the responses elicited by many types of homeostatic threats, whether physical or psychological in origin. Most importantly, stressors trigger a response that integrates physiological and psychological changes. For instance, bodily changes that support rapid action are accompanied by a strengthening of cognitive functions that support this type of behavior. Autonomic, endocrine, and neuromodulatory systems play key parts in this integration, which is why they have such prominent roles in the stress response.

Here, we integrate animal data at the cellular and systems levels with an emerging human literature on changes in large-scale network properties that subserve adaptive shifts in cognition and behavior [10,11]. We focus our discussion on two such large-scale networks: the

Box 2. Resource allocation

The concept of resources forms an important parameter in any system characterized by dynamic equilibrium. Examples can be found ranging from economics to computer science and biology. A concrete definition of resources can, however, only be formulated with reference to a specific system. In biological systems such as the brain, the main rate-limiting resource is energy. The brain's energy consumption (20% of the body's total usage) is disproportionate to its size (about 2% of body weight) [57], and the brain must compete with other organs for energy resources [126]. The brain can summon additional energy supply in response to stress through sympatho-adrenal activation, limiting insulin secretion and thereby glucose uptake into energy stores [127]. However, such increases are surprisingly moderate. Bioenergetic studies show that in comparison with rest, the brain's glucose use increases only about 5% in response to simple tasks, and up to 12% in conditions of mental stress [128]. Therefore, sudden shifts in cognitive demands may be dealt with more efficiently when resources can also be strategically reallocated within the boundaries of energy supply. Recent studies into the interactions between large-scale connectivity networks shed light on how this may be accomplished. For instance, task-positive and task-negative networks activate reciprocally [96], suggesting that neurocognitive functions subserved by one network can be suspended in favor of another. It is not clear, however, how this competitive allocation of resources [58] is achieved. One possibility is that one system simply uses all its available resources and thereby 'steals' resources from another system. Another scenario is that resource allocation is realized by mechanisms of active suppression [129]. We highlight the potential role of neuromodulatory systems in processes of active reallocation [130], but much remains to be learned about the underlying mechanisms.

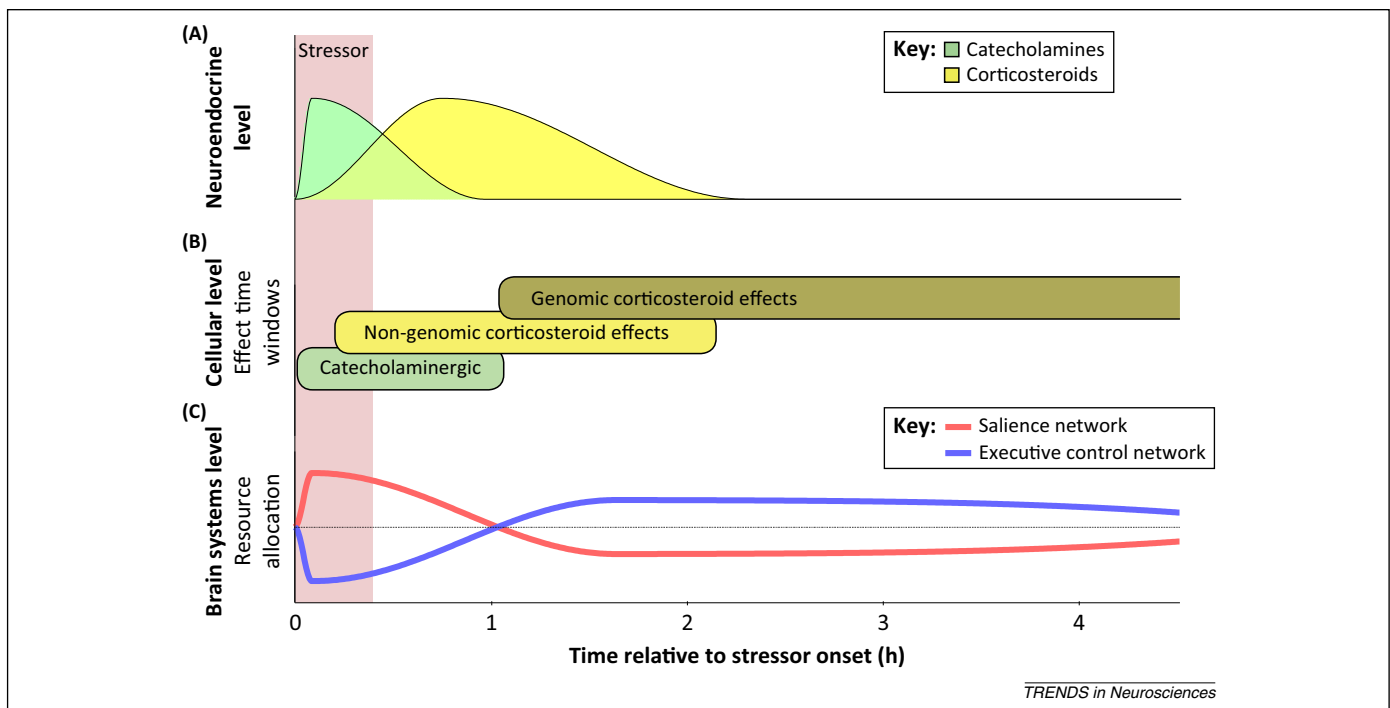


Figure 1. Biphasic-reciprocal model of reallocation of neural resources in response to stress. This figure illustrates the link between effects of stress at neuroendocrine (A), cellular (B), and brain systems (C) levels. (A) Neuroendocrine level: following exposure to a stressor, central levels of catecholamines (e.g., norepinephrine and dopamine) increase promptly and normalize not long after stressor offset. Corticosteroid levels in the brain rise more slowly and remain increased for a longer period. (B) Cellular level: cellular effects occur within distinct effect time windows. Catecholamines primarily exert immediate effects through G protein-coupled receptors. Corticosteroids have rapid non-genomic effects that may overlap and interact with catecholaminergic effects in an early time window, but also exert slower genomic effects. (C) Brain systems level: due to local differences in receptor distribution and signaling cascades, opposite effects occur within different neurocognitive systems. We propose that this causes a dynamic reallocation of neural resources to systems responsible for attentional vigilance (saliency network) and executive control (executive control network; see Figure 2 for an anatomical overview of both networks). Crucially, our model proposes that stress-related hormones and neurotransmitters strengthen saliency-network activity during the acute stress phase at the cost of executive-control-network function, but subsequently contribute actively to the return to homeostasis by reversing this balance (see section on slow effects of corticosteroids for an explanation of underlying cellular mechanisms, and see Figure 3 for empirical evidence at the neural level). By introducing time dependency and cognitive domain dependency as critical factors, our model explains substantial variability observed in effects of stress on cognition at the behavioral level (Box 3).

salience processing network and the executive control network [12,13]. After summarizing empirical evidence, we propose a model (Figure 1) that describes how these two networks are regulated in a biphasic and reciprocal fashion in response to acute stressors.

Spatially and temporally specific effects of stress-related neuromodulators at the cellular level

Animal work has indicated that acute stressors trigger multiple waves of neurochemical changes (Figure 1A). The earliest responses to acute stressors are mediated by neuropeptides, such as corticotropin-releasing factor, and by catecholamines, such as norepinephrine and dopamine [3]. These changes initiate almost instantly and normalize within 30 to 60 minutes. Stress also triggers activation of the hypothalamic–pituitary–adrenal axis, which leads to a surge of corticosteroid production in the adrenal cortex. Peak concentrations in the brain are not reached within 20 minutes after stressor onset [14], which implies that the role of corticosteroids in the immediate stress response must be limited. As we detail below, these multiple waves of neuromodulatory changes and their interactions allow for intricately timed modulation of distinct neural circuits.

Rapid effects of catecholaminergic activation

Acute stress promptly activates the locus coeruleus (LC), the brain's primary source of norepinephrine [15,16]. Neurocomputational studies in monkeys show that this leads to a shift from a phasic towards a tonic mode of LC activity, which is associated with enhanced scanning of the environment for potentially salient information [15,17]. Central catecholaminergic activation is followed by activation of the peripheral sympatho-adrenomedullary system, which triggers release of epinephrine from the adrenal medulla. Epinephrine further increases norepinephrine release through ascending vagal projections to the nucleus of the solitary tract (NTS) [9]. Noradrenergic projections are widespread and include the entire cerebral cortex, hypothalamus, thalamus, and amygdala [18]. Effects of stress levels of norepinephrine may be regionally specific owing to local differences in receptor distribution. Whereas α 2A-adrenoceptors in the prefrontal cortex (PFC) are occupied at moderate levels of norepinephrine [19], the lower-affinity α 1 adrenoceptors in the PFC, and β 1 adrenoceptors in the amygdala, are engaged at stress levels only [20]. Stress levels of norepinephrine may therefore have opposite effects on neural functioning in PFC and the amygdala [7,8].

The dopaminergic system is also activated by stressors [21,22]. Stress increases extracellular dopamine levels most pronouncedly in PFC, but also in nucleus accumbens and dorsal striatal regions [23], probably through increased tonic firing [24,25]. Although such findings seem to be inconsistent with the known role of dopamine in reward signaling, recent work shows that distinct subpopulations of dopaminergic neurons respond to appetitive versus aversive events [26]. Neurons responsive to aversive stimulation were found in more dorsolateral parts of the midbrain in monkeys [27]. In rats, dopamine release in the dorsal striatum and nucleus accumbens is triggered by aversive stimuli [28]. Aversive stimulation selectively modified synapses on dopaminergic cells that project to

the PFC in mice [29], which may explain the increase in prefrontal dopamine turnover after exposure to stressors. As is the case with norepinephrine, the effects of dopamine on target tissues are regionally specific. In the PFC, moderate stimulation of D1 receptors reduces neural firing to noise stimulation in both rats and monkeys, whereas stress levels of D1 stimulation unselectively suppress all neural firing [30]. Again, this pattern is different in the amygdala, where expression of conditioned fear, for instance, depends on D1 receptor availability [31].

Rapid effects of corticosteroids

Although corticosteroids cross the blood–brain barrier and potentially reach all brain regions equally well, variation in corticosteroid receptor affinity, distribution, and downstream signaling cascades allow for spatially and temporally specific effects of corticosteroids at stress levels. For instance, high-affinity mineralocorticoid receptors (MRs) and low-affinity glucocorticoid receptors (GRs) are co-expressed in the hypothalamic paraventricular nucleus and in limbic regions including amygdala and hippocampus, but GRs dominate in nearly all brain regions (except CA3), including the PFC [2].

In vitro rodent studies have shown that corticosteroids exert effects involving low-affinity membrane-associated GRs and MRs, which initiate rapidly when corticosteroids reach target tissues [32] (Figure 1A). In the paraventricular nucleus of the hypothalamus, corticosteroids rapidly and reversibly decrease neuronal excitability via GRs [33]. Conversely, enhanced neuronal excitability has been reported for hippocampal and amygdala neurons through MRs [32]. In the hippocampus, these rapid effects are readily reversible, but in the basolateral amygdala they last longer [34], perhaps providing a longer time-window for processing salient information following stressful events. Thus, although rapid corticosteroid actions so far have only been examined in a limited number of brain regions, these effects also seem to be regionally specific [4].

Furthermore, corticosteroid actions interact with catecholaminergic activity [9]. Noradrenergic activity is increased through GR activation at the level of the NTS and the LC [35], and corticosteroids increase norepinephrine levels in the amygdala [36]. Corticosteroids also potentiate effects of stress on dopamine release [37] and act within the PFC to regulate dopaminergic projections from the ventral tegmental area [38]. Postsynaptically, corticosteroids may potentiate noradrenergic effects on target cells by enhancing the β -adrenoceptor–cAMP system [39], thus enhancing amygdala function [40,41]. A similar effect was observed in the nucleus accumbens [42]. Contrariwise, corticosteroids potentiate the negative effects of norepinephrine on PFC function [43] through membrane-bound GRs [44].

Slow effects of corticosteroids

Corticosteroid binding also leads to altered gene transcription, a relatively slow process that results in changes in levels of multiple proteins that affect neuronal function [4]. These genomic effects take at least an hour to initiate but can continue for at least several hours (Figure 1A). Profound regional differences have also been described regarding these genomic actions. Notably, such effects may

oppose rapid effects in multiple brain regions. GR-mediated effects 4 hours and more after stress enhance PFC function and facilitate working memory in rats [45] by increasing GR/SGK (serum- and glucocorticoid-inducible kinase)-induced glutamate receptor trafficking [46]. Similar effects were found in the dorsal hippocampus [47]. These effects are opposite to those observed in the ventral hippocampus [48] and (basolateral) amygdala [49]. Genomic actions of corticosteroids may thus provide a mechanism that actively reverses the rapid effects of the various stress mediators described above.

In summary, animal research demonstrates that distinct waves of stress-related neurotransmitters and hormones allow for spatially and temporally specific modulation of widely distributed neuronal populations. A recurrent theme throughout these findings is that negative effects on executive control regions such as the PFC are accompanied by positive effects on limbic and subcortical structures such as the amygdala and striatum, and vice versa. These findings strongly suggest that affected brain regions are modulated as part of broader networks [7,50–52], but do not provide a comprehensive account of the architecture and interactions within and between such networks. In the following section, we therefore turn to recent studies in humans of the architecture of large-scale networks involving regions that are differentially modulated by stress-related neuromodulators. We furthermore link these networks to more fine-grained analyses of stress-related changes in cognitive performance (see also Box 3).

Large-scale neurocognitive networks

Research into large-scale neurocognitive networks has developed rapidly over the past decade. Although initial neuroimaging work focused on individual brain regions, it became apparent that specific sets of regions systematically co- or deactivate across wide domains of cognitive tasks [53]. Such sets of regions also exhibit coherent spontaneous activity at rest [54,55], and their topography concurs with

underlying structural connectivity [56]. These observations led to the realization that organization into large-scale neurocognitive networks is a fundamental property of brain architecture [11,13,57].

The first large-scale network identified was the ‘default mode’ network, a set of midline regions that consistently deactivates in response to tasks requiring goal-directed attention [53]. In line with the notion that different large-scale networks may compete for limited resources [58] (Box 2), this network activates reciprocally with two neurocognitive systems that regulate externally directed attention: the salience network, which includes the amygdala, and the executive control network, which involves the PFC [10,12,13,59]. In the following two sections, we detail these two systems and explain how the putative shift in neurocognitive function in response to stressors [7] may be best understood as an altering balance between these two networks.

Effects of stress on the salience network

In potentially or actually unsafe situations, the ability to reorient attention to potential threats, mobilize energy resources, and take rapid unpremeditated action is critical to immediate survival. The salience network (Figure 2) has been proposed as a neurocognitive system that integrates these functions [12,59]. In addition to the amygdala, it consists of regions associated with autonomic-neuroendocrine control (the dorsal anterior cingulate cortex and hypothalamus), visceral perception (the anterior insula), attention (the thalamus and inferotemporal/temporoparietal regions) [59], behavioral reinforcement and habitual behavior (the striatum) [60], and catecholaminergic signaling (the brainstem/midbrain nuclei). Meta-analyses of human functional neuroimaging data show that these regions respond consistently to various salient stimuli, including aversive affective material, conditioned stimuli, and pain [61].

Several authors have noted a striking similarity between the putative roles of cortical components of the

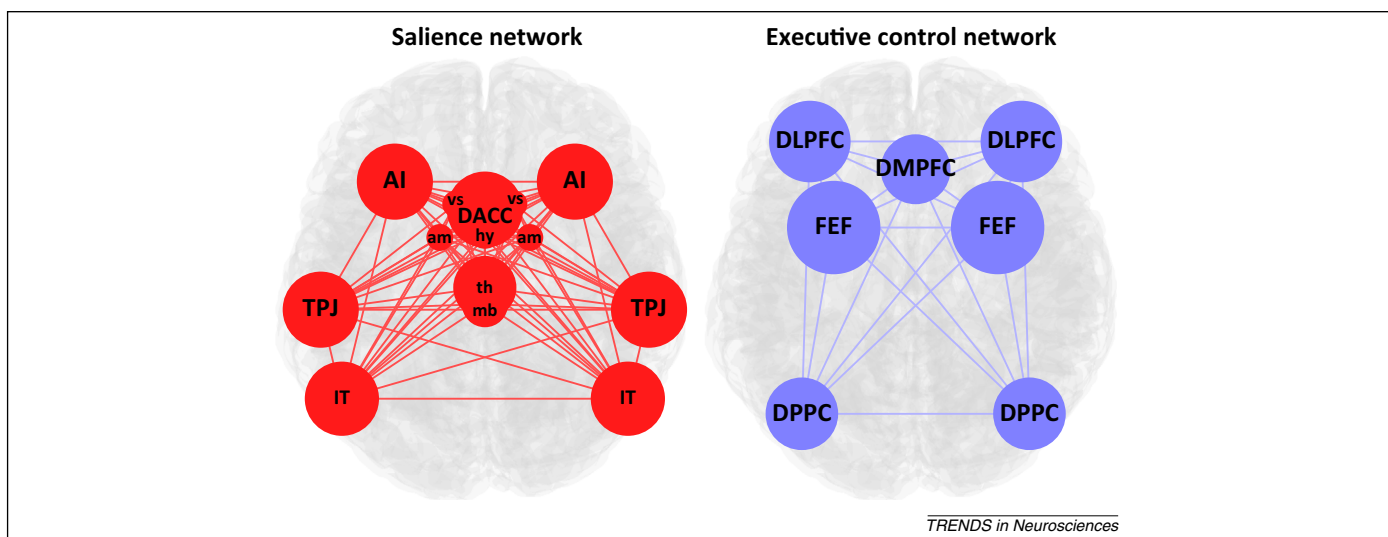


Figure 2. Schematic anatomical overview of salience and executive control networks. The sphere sizes illustrate the relative sizes of the clusters that co-activate with the respective networks. Our model (Figure 1) proposes that these two neurocognitive systems are regulated in a time-dependent and reciprocal fashion by stress-related neuromodulators. Adapted from [10]. Abbreviations: AI, anterior insula; am, amygdala; DACCA, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; DPPC, dorsal posterior parietal cortex; FEF, frontal eye fields (precentral/superior frontal sulci); hy, hypothalamus; IT, inferotemporal cortex; mb, midbrain; Th, thalamus; TPJ, temporoparietal junction; vs, ventral striatum.

salience network and LC activity in attentional reorienting [10,59,62]. Whereas phasic LC signaling is thought to subservise selective processing of stimuli relevant to current task sets, tonically elevated LC activity would lead to enhanced environmental scanning and facilitated reorienting of attention towards unexpected and potentially threatening stimuli [17,59,62]. LC projections are furthermore implicated in regulating gain to attain signal-to-noise ratios that are optimal for sensory gating and sustained attention [17]. This implies that stress levels of noradrenergic activity might increase sensory gain beyond this optimum and cause a drop in signal-to-noise ratio and sensory gating capacity owing to the amplification of sensory noise. Although this would cause distractibility in tasks requiring selective attention, it would benefit the detection of unpredictable stimuli and thereby facilitate attentional vigilance. Indeed, stress [63], as well as pharmacological stimulation of LC activity [64], impairs sensory gating as measured using pre-pulse inhibition in rats. LC stimulation furthermore decreases phasic discharge of thalamic and barrel cortex neurons in response to sensory stimuli, while increasing their spontaneous activity [65].

In humans, administration of hydrocortisone has also been shown to rapidly impair pre-pulse inhibition [66], but sensory gating is more commonly investigated using the attentional blink paradigm, in which participants are instructed to detect serially presented visual targets. Neurocomputational models of LC function postulate that phasic LC firing facilitates processing of the first of two such targets [67]. This phasic LC response is thought to cause the attentional blink (inability to report a second target) through a local inhibitory effect on the LC through $\alpha 2$ autoreceptors, which create a refractory period during which new phasic LC responses are suppressed [67]. If stress shifts the LC from a phasic to a tonic mode of activity [17], one would expect this effect to disappear. Indeed, both administration of the selective norepinephrine reuptake inhibitor reboxetine [68] and stress induction [69] enhance detection of the second target, revealing a mechanism by which acute stress may increase attentional vigilance.

The involvement of striatal regions within the salience network suggests that this network also has a role in rapid unpremeditated action [60]. Both animal [50,52] and human [70] studies show that acute stress is accompanied by a shift from flexible, goal-directed behavior to more rigid stimulus-response behavior. Such findings are consistent with clinical observations of stress-induced relapse in addiction and exacerbation of symptoms in various psychiatric disorders, including obsessive-compulsive disorder [51]. Furthermore, there is evidence that stress enhances simple stimulus-response learning, such as classical conditioning in humans [71]. Thus, the early phase of the acute stress response triggers a sensory hypervigilant state accompanied by an increased reliance on rapid but more rigid stimulus-response behaviors.

Salience network upregulation during acute stress

Neuroimaging experiments in humans [72–74] have shown increased activity in the amygdala, one of the core regions of the salience network, immediately after experimental induction of stress (Figure 3). Hyperactivation in limbic

and subcortical regions, including the amygdala, has frequently been observed after symptom provocation in anxiety disorder patients (e.g., [75]). Pharmacological elevation of norepinephrine levels using reboxetine mimics these effects [76], in particular when accompanied by administration of hydrocortisone [77]. Finally, carriers of a common functional deletion in the gene coding for the presynaptic $\alpha 2b$ -adrenoreceptor (ADRA2B), which reduces negative feedback function of the noradrenergic system, exhibit stronger stress-induced increases in amygdala activity [74].

Activity in other regions of the salience network, including the dorsal anterior cingulate and the anterior insula, has consistently been found to correlate with physiological markers of stress, such as increased heart rate [78], increased blood pressure [79], reduced heart rate variability [80], and increased cortisol levels [81]. Furthermore, a study that used network-based techniques to quantify connectivity within the entire salience network found that its connectivity during acute stress correlated with multiple physiological and psychological measures of stress [10]. A causal role specifically for norepinephrine was suggested by the observation that heightened connectivity was diminished when the β -adrenergic blocker propranolol was administered, whereas inhibition of corticosteroid synthesis using metyrapone had no effect [10]. This finding concurs with a study showing increased functional connectivity between the amygdala and a number of salience network regions directly after exposure to a stressor [82]. These regions included the anatomical location of the LC, although this finding should be considered with caution given the small size of this region [83]. Interconnectivity of the ventral striatum within the salience network was furthermore shown to be increased after administration of L-Dopa, which increases dopamine availability [84]. Thus, catecholaminergic activity seems to potentiate salience network function in the early phase of the stress response.

Salience network downregulation in the aftermath of stress

Another critical feature of an adaptive stress response system is the capacity to limit the consequences of the immediate response, in both duration and amplitude [85]. There is now considerable evidence that the slow actions of corticosteroids described above play a critical part in this process. In line with animal findings showing that corticosteroids reduce anxious behavior [86], studies in humans have demonstrated that hydrocortisone administration at various time intervals before testing reduces emotional interference in cognitive tasks [87,88] and has a protective effect on self-reported mood in stress induction paradigms [89], whereas corticosteroid synthesis inhibition has the opposite effect of increasing sympathetic arousal in response to stressors [90]. Furthermore, hydrocortisone administration in patients with anxiety disorder enhances extinction-based psychotherapy [91] and reduces phobic symptoms [92]. Thus, elevation of corticosteroids, particularly when not accompanied by catecholaminergic activation, seems to lead to a suppression of neurocognitive processes supported by the salience network.

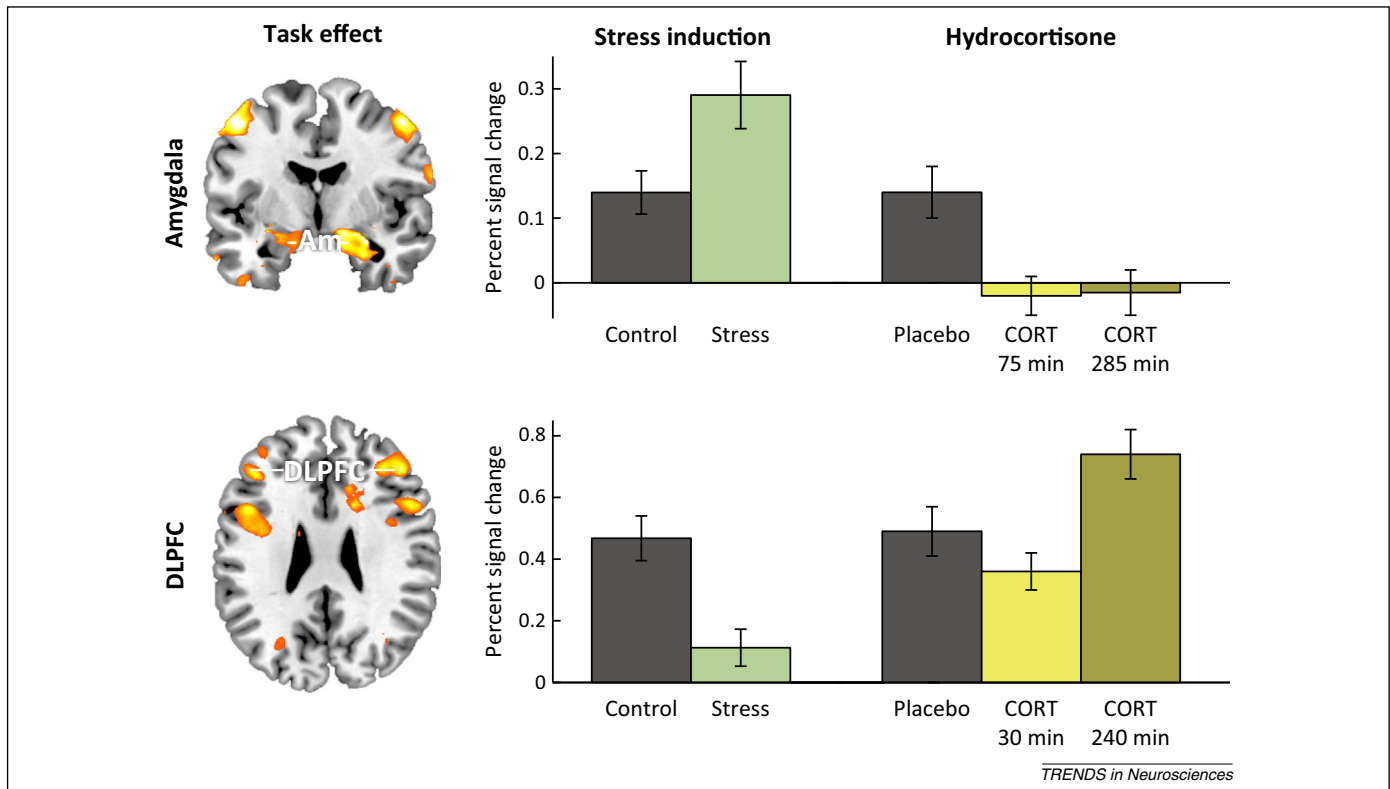


Figure 3. Opposite effects of stress induction (at short time intervals) and hydrocortisone administration (at different time intervals) on amygdala versus dorsolateral prefrontal cortex (DLPFC). This figure shows data from four studies probing the function of the amygdala (a major node of the salience network) and the DLPFC (a major node of the executive control network). Shortly following stress induction, when both catecholaminergic and corticosteroid levels are elevated, the amygdala response to salient stimuli increases [72], whereas DLPFC activity related to an executive control task decreases [114]. Contrariwise, administration of hydrocortisone reduces amygdala activity at both 75 and 285 minute delays [93], and enhances DLPFC activity only at a 240 minute delay [119], which is sufficient to allow genomic effects. For the amygdala, bar graphs indicate percentage signal change for emotional facial expressions versus baseline. For the DLPFC, bar graphs indicate percentage signal change for a two-back working memory task condition versus a zero-back control. The two stress-induction papers [72,114] report data from a single sample of participants. The two hydrocortisone-administration papers [93,119] report data obtained from a second sample. Abbreviations: Am, amygdala; CORT, hydrocortisone.

Recent neuroimaging work in humans has tested whether such anxiolytic-like effects of hydrocortisone may indeed be explained by a reduction in responsiveness in salience network regions such as the amygdala. Approximately 4–5 hours after administration of hydrocortisone, amygdala responsiveness was found to be reduced [93] (Figure 3). Importantly, salivary cortisol levels at this time point had already returned to baseline, strongly suggesting that these effects specifically involve slow genomic actions. Furthermore, hydrocortisone administration approximately 2 hours before testing reduced functional connectivity between the amygdala and a brainstem cluster corresponding with the anatomical location of the LC [94], a finding opposite to the aforementioned study assessing amygdala–LC coupling during acute stress [82]. Effects of hydrocortisone administration on amygdala activity at shorter delays are somewhat less clear, with a reduction at 75 minutes in a task involving passive viewing of emotional facial expressions [93] and an increased response at 60 minutes in a task involving emotional distractors [95]. This discrepancy may be explained by different levels of coinciding catecholaminergic activity elicited by these tasks, but also by the crucial delay that is necessary to induce genomic actions, which is approximately 60 minutes. Nonetheless, hydrocortisone-administration studies support the notion that corticosteroids actively contribute to the gradual downregulation of

salience network regions and thus help to normalize the system.

Effects of stress on the executive control network

If situations of acute threat require attentional vigilance and rapid unpremeditated action, it is conceivable that a shift of neural resources away from regions involved in endogenous attention and higher-order cognition may be beneficial for short-term survival [8]. Such executive control functions are supported by a fronto-parietal network involving dorsal frontal areas (the dorsolateral PFC, precentral/superior frontal sulci, or frontal eye fields, and the dorsomedial PFC) and dorsal posterior parietal areas [96] (Figure 2). As explained above, rodent and non-human primate work has shown that stress levels of catecholamines impair PFC function through the lower-affinity $\alpha 1$ and $\beta 1$ adrenoceptors and excessive dopamine D1 receptor stimulation [6,51], and detrimental effects of norepinephrine are further increased by corticosteroids [44]. Supraoptimal catecholaminergic activity in the PFC impairs the capacity of neurons to maintain persistent patterns of spiking activity, which is a putative neurophysiological substrate of working memory maintenance [97].

In humans, stress induction generally leads to working memory impairments when testing is performed within or close to the time window of catecholaminergic effects [71,98–102] (but see [103,104]). In agreement with the

notion that this system supports flexible goal-directed action, stress induction has also been shown to negatively affect task switching [105,106], cognitive flexibility [107], and rational decision making [108]. Moreover, stress induction was shown to render instrumental responding insensitive to devaluation of goals [70,109,110]. A pharmacological study showed similar insensitivity to outcome devaluation after combined administration of hydrocortisone and the $\alpha 2$ antagonist yohimbine, which increases central norepinephrine levels [111]. Furthermore, stress-induced impairments in cognitive flexibility tasks [112] as well as selective outcome devaluation [113] were found to be blocked by the β -adrenergic blocker propranolol.

Executive control network downregulation during acute stress

Neuroimaging work has demonstrated that acute stress negatively affects working memory-related activation of the dorsolateral PFC, one of the major executive control

network regions [114] (Figure 3). This effect is stronger in Met-homozygotes for the gene coding catechol-O-methyltransferase [101], who have higher basal catecholamine levels. In line with stress-related insensitivity to outcome devaluation [70], reduced PFC activation after stress induction was also observed in a task involving reward-related value representation [115]. Working memory-related executive control network activation under stress has been shown to be accompanied by a failure to suppress activity in default mode network regions [114,116], suggesting that acute stress indeed limits selective allocation of processing resources to the executive control network (Box 2). Finally, combined administration of yohimbine and hydrocortisone was more effective in reducing PFC activity than either drug alone [117,118]. Thus, in line with rodent data [44], human studies support the hypothesis that the executive control network is suppressed during the early phase of the stress response when catecholaminergic effects dominate or coincide with corticosteroid elevation.

Box 3. Overview of behavioral studies into stress effects on network function over time

Effects of stress on cognitive functioning in humans have been studied extensively over the past decades. This research has led to standardized protocols for induction of acute stress (e.g., the Trier Social Stress Test) and pharmacological manipulation using administration of stress hormones (e.g., hydrocortisone; synthetic cortisol), as well as for physiological measurement of their effectiveness (e.g., cortisol in saliva). Effects of stress on cognition, however, have been measured using a plethora of cognitive tasks, and the factor of timing with respect to stressor onset has often been ignored or not studied systematically. In Figure 1, we summarize findings from 29 empirical research articles (yielding 35 observations) cited in the main text of this article. All of these studies involved either controlled induction of stress (mainly through psychological manipulations) or administration of hydrocortisone [note that hydrocortisone administration differs from natural stress induction in a lack of activation of other neuroendocrine systems, but also in increased suppression of hypothalamic corticotropin-releasing hormone/arginine vasopressin (CRH/AVP) and adrenocorticotropic hormone (ACTH) release]. As can be seen in panel A, when all cognitive tasks are put together, the effect sizes (Cohen's d ; standardized mean differences) associated

with stress induction or hydrocortisone administration reveal no systematic bias towards better or worse performance. Similarly, when data points are split for tasks tapping into executive control functions (EC; i.e., digit span [98,102–104], reading span [71], n-back [99,101,114,119], Sternberg [100] with emotional distractors [88], dual task performance, task shifting, selective attention, and cognitive flexibility [105–107,112], rational decision making [108], and instrumental learning and extinction [109–111,113,117]) or attentional vigilance-related functions (AV; i.e., attentional blink [69], prepulse inhibition [66], emotional interference [73,87,95], and subjective measures of negative mood [89] and fear [91,92]), no clear bias is visible. Adding the timing factor (panel B), it becomes apparent that two different systems are modulated in a reciprocal manner over time, with a negative rank order correlation over time for attentional vigilance functions [$\rho(8) = -0.72$, $P = 0.019$], a marginally significant positive correlation for executive control functions [$\rho(23) = 0.38$, $P = 0.06$], and a significant difference between these two correlations ($Z = 3.01$, $P = 0.003$). In agreement with our model, trend lines cross after approximately 1 hour when genomic effects of corticosteroids start to develop.

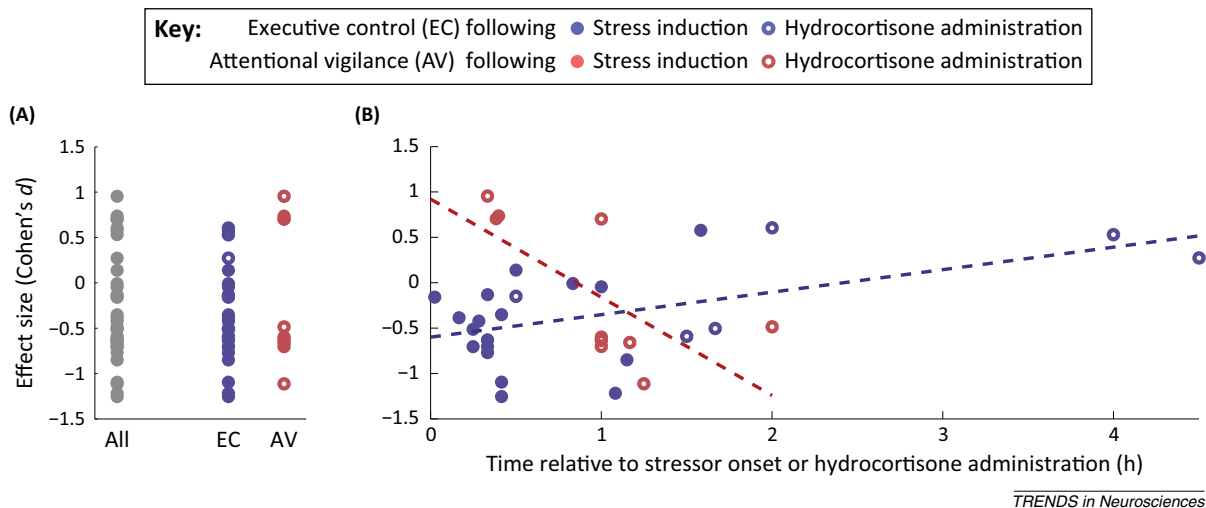


Figure 1. Effect sizes (Cohen's d) of stress induction or hydrocortisone administration (A) overall and sorted by neurocognitive function, and (B) plotted as a function of the time-point at which measurement of cognitive performance started relative to stressor onset or administration. Timing information was obtained from descriptions of the experimental procedures in the respective papers. Broken lines indicate trends over time for each neurocognitive function.

Executive control network upregulation in the aftermath of stress

Recovery of higher-order cognitive functioning in the aftermath of a stressful experience may support cognitive flexibility and the adjustment of long-term goals. As explained above, recent rodent findings show that acute stress potentiates excitatory neurotransmission through GRs in the PFC. This effect was accompanied by improved working memory performance 4 hours after stress [45], a delay that is long enough to allow genomic effects to develop [4]. A recent human study administered hydrocortisone at different time intervals before performing a working memory task [119] (Figure 3). Hydrocortisone administered 4 hours before testing positively affected working memory performance and dorsolateral PFC activation, whereas hydrocortisone administered 30 minutes before testing did not have such an effect. Thus, these findings suggest that the stress-induced impairment in executive functioning is actively reversed in the aftermath of stress, probably through genomic actions of corticosteroids.

Integration and conclusion

Rodent data show that different waves of stress-related neurotransmitters and hormones have distinct effects in widely distributed brain regions. Although this suggests differential regulation of multiple functional networks [7,50–52], a comprehensive account of such networks and their interactions is currently lacking. Developments in functional connectivity network modeling in humans are beginning to reveal how regions that have been shown to be differentially affected by stress-related neuromodulation are part of distinct large-scale networks. The salience network and executive control network [13] (Figure 2) appear to be important neurocognitive systems targeted by these effects, but further parcellation of the architecture of such networks [55] is likely to yield a more complex picture in the future (Box 4). Taking these networks and the neurocognitive functions they support as a starting point, we argue that a classification into cognitive domains supported by the salience network and executive control network is a crucial factor in understanding how stress affects cognition.

A second crucial factor is the delay between stressor onset and task performance: in the acute phase, neural resources are allocated towards the salience network whereas the executive control network is actively suppressed. In the recovery phase, this effect is reversed by allocating resources to the executive control network and suppressing the salience network (Figure 1). We have associated these two phases primarily with catecholamines and corticosteroids, respectively, but it is already clear that these neurotransmitters and hormones also act outside their typical domain [3]. Future research will further detail and extend our knowledge of neurochemical changes during these two phases. For instance, the roles of dopamine, serotonin, and neuropeptides in the central stress response have been investigated thoroughly in animal models [6], but have received relatively little attention in human research. Nonetheless, an initial classification across the two factors of network and timing creates order

Box 4. Outstanding questions

- If large-scale networks activate reciprocally with respect to one another (see Figure 1 in the main text), how are these network switches generated? What is the involvement of excitatory and inhibitory neurotransmitters in this process?
- How do actions of dopamine during acute stress differ from those of norepinephrine? Given its prominent projections to striatal regions, does the dopamine system have a role in rigid stimulus-response behavior during acute stress?
- How do basal and stress-induced levels of corticosteroids interact in regulating the balance between the salience network and executive control network?
- How does information exchange between nodes within the salience network and executive control network alter under stress? Because these phenomena occur at timescales of milliseconds, answering this question requires *in vivo* electrophysiological experiments in rodents, perhaps combined with interventions offered by optogenetic techniques.
- What is the starting point of the neural events observed in response to stress? For instance, does amygdala activation trigger prefrontal cortex (PFC) dysfunction, or vice versa?
- Are individual differences in salience network or executive control network connectivity, or the balance between these, related to anxious traits, genetic background, (early) life history, and vulnerability for the development of stress-related psychopathology?
- Given that chronic stress causes dendritic and spine loss in the ventromedial PFC, whereas it has the opposite effect on dendrites in the amygdala [51], does it chronically alter the balance and switching between executive control and salience networks?
- Does a network-based approach for identifying biomarkers of stress-related psychopathology have more potential than the traditional approach of locating focal abnormalities such as amygdala hyperreactivity?
- Given the unavoidable side effects of pharmacological manipulations of corticosteroids, can studies into the effects of hydrocortisone administration be cross-validated using different types of manipulations?

in an otherwise confusing body of empirical research on the effects of stress on cognition (Boxes 3 and 4).

The evolutionary benefits conveyed by these finely tuned defense mechanisms, which were alluded to above, are not difficult to envision. A perhaps more captivating question is how the same mechanisms can lead to maladaptation. Why does stress have pathological consequences in some individuals? A suggestion that follows from our model is that maladaptation may result from an inability to contain sympathetic activation by subsequently released corticosteroids, a situation that may occur in individuals with post-traumatic stress disorder [120,121] and burnout [122]. Our model would predict that in such conditions the salience network is strongly activated while later counter-activation of the executive control network is inadequate, potentially impairing an individual's ability to exert cognitive control over the emotional aspects of the stressful event.

In conclusion, in this article we integrate analyses at the neuroendocrine, cellular, brain systems, and behavioral levels to propose a framework describing global and dynamic shifts in network resource allocation in response to acute stressors. Our framework aligns with an ongoing paradigm shift within neuropsychiatry from identifying foci of abnormality towards developing a global understanding of aberrations at the level of large-scale networks [13]. Because acute stress is the most important factor in

development, maintenance, and re-emergence of psychiatric symptoms, improving our understanding of how acute stress changes brain function is critical for advancing our understanding of a wide range of psychiatric conditions.

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