CHAPTER

30

Time-Dependent Shifts in Neural Systems Supporting Decision-Making Under Stress

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Abstract

Acute stress profoundly affects cognitive functions such as decision-making. This promotes rapid decision-making in threatening situations, but impairs flexible and elaborate decisions. Dual-systems models of decision-making propose that these two types of decisions rely on distinct neural systems, but their regulation under stress remains unclear. Here, we integrate existing knowledge of effects of stress at the neuroendocrine, cellular, brain systems, and behavioral levels to describe how stress-related neuromodulators trigger time-dependent shifts in balance between specific large-scale neural systems. We argue that stress triggers a reallocation of neural resources toward a "salience" network, which supports rapid but rigid decisions, at the expense of an "executive control" network, which supports flexible, elaborate decisions. This resource reallocation actively reverses during recovery from stress, presumably to support adjustment of long-term goals. We conclude by showing how this biphasic-reciprocal model elucidates paradoxical findings reported in human studies on stress and cognition.

INTRODUCTION

We make many of our most important decisions under stress. These include complex rational decisions, such as whether to take a mortgage and buy a house, but also split-second decisions, for instance, to dodge a looming object. As most of us have experienced, these two types of decision-making are not equally affected by stress. Acute stress appears to hamper complex types of judgment, but at the same time, it makes us alert and ready to decide promptly and reflexively in acutely threatening situations. A widely held view is therefore that stress triggers a breakdown of neural systems supporting higher-order, goal-directed types of cognition, such that as a consequence, decision-making is relinquished to phylogenetically older neural systems that control reflexive or habitual behavior [1,2]. This apparent shift from a strategic to a tactical mode of decision-making allows us to make rapid, life-saving decisions, but does so without cognitive flexibility or regard for long-term consequences.

The notion of a shutdown of higher-order cognition during acute stress is rooted in dual-systems models of decision-making. Such models distinguish cognitive or neural systems characterized, for instance, as slow versus fast [3], controlled versus automatic [4], reflective versus reflexive [5], or model-based versus model-free [6]. While these distinctions have a long history in psychology and cognitive neuroscience, exactly which "dual systems" are involved in these two types of decision-making, and how these are differentially affected by stress, has remained underspecified and poorly understood.

In this chapter, we describe a model of how acute stress affects two distinct neural systems supporting these different types of decision-making [7]. This model integrates existing data across multiple levels of analysis. We will explain how, at the neuroendocrine level, stressors trigger a precisely timed concatenation of events throughout the body [8,9]. At the cellular level, these reactions can modulate neural excitability and plasticity in a manner that is both regionally and temporally specific [8,10,11]. By considering an emerging

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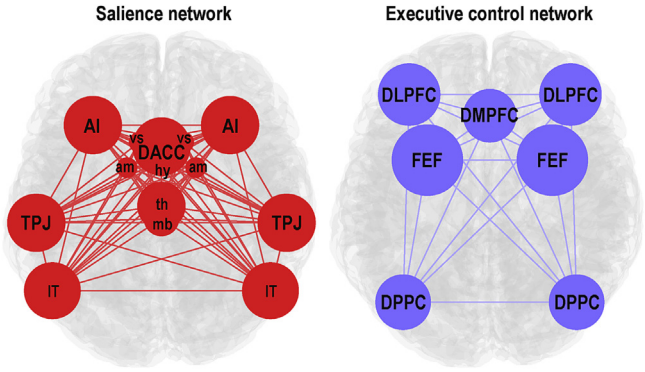

FIGURE 30.1 Anatomical overview of salience network (SN) and executive control network (ECN) nodes. Sphere sizes illustrate relative sizes of the clusters that exhibit functional connectivity with the respective networks. SN nodes: *AI*, anterior insula; *am*, amygdala; *DACC*, dorsal anterior cingulate cortex; *hy*, hypothalamus; *IT*, inferotemporal cortex; *mb*, midbrain; *th*, thalamus; *TPJ*, temporoparietal junction; *vs*, ventral striatum. ECN nodes: *DLPFC*, dorsolateral prefrontal cortex; *DMPFC*, dorsomedial prefrontal cortex; *DPPC*, dorsal posterior parietal cortex; *FEF*, frontal eye fields (precentral/superior frontal sulci). *Adapted from Hermans EJ, Henckens MJAG, Joëls M, Fernández G. Dynamic adaptation of large-scale brain networks in response to acute stressors. Trends Neurosci 2014;37:304–14; Hermans EJ, van Marle HJF, Ossewaarde L, Henckens MJAG, Qin S, van Kesteren MTR, et al. Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. Science 2011;334:1151–3.*

literature on large-scale neurocognitive systems in the brain, we will next explore how such effects can generate coordinated, brain-wide shifts in neural functioning at the brain systems level [12,13]. Finally, we will show how an understanding of the spatiotemporal dynamics of effects of stress on these large-scale neural systems can shed new light on the vast and sometimes paradoxical literature on the effects of acute stress on decision-making at the behavioral level. In the following section, we start by introducing the concept of large-scale neurocognitive systems.

LARGE-SCALE NEUROCOGNITIVE SYSTEMS AND SHIFTS IN RESOURCE ALLOCATION

Recent years have seen a rapid proliferation of research into large-scale neurocognitive systems in the human brain. Whereas human neuroimaging initially focused on mapping specific cognitive functions onto individual brain regions, it turned out that activation, and also deactivation, of certain sets of brain regions is consistently associated with broader cognitive domains [14]. Furthermore, such sets of brain regions not only respond coherently during task execution, but also maintain coherent activity even when not performing any specific task [15,16]. Regions that exhibit such intrinsic functional connectivity also show stronger structural connectivity [17]. These observations have led to the recognition of large-scale neurocognitive systems as an important level of organization within the architectural hierarchy of the human brain [15,18–20], and have caused a paradigm shift in the field of human neuroimaging toward mapping functional connectivity of the human brain [21].

A growing number of such large-scale neurocognitive systems have been discovered and described since 2005 [19,22]. The first was a set of midline structures that activates whenever an individual does not direct attention to the outside world. This "default mode," or task-negative, network has been shown to play a role in memory processes and in forms of internally directed cognition such as self-referential processing and mind wandering [14].

Later work revealed two dissociable "task-positive" networks, which activate during externally directed cognition (Fig. 30.1). One of these is the salience network (SN), a network that integrates a variety of neurocognitive functions associated with processing of, and responding to, salient stimuli. These functions include regulation of reflexive and habitual behaviors, exogenous (bottom-up) attention, and regulation of autonomic and neuroendocrine systems [22]. The other task-positive network is referred to as the executive control network (ECN), a large-scale network that regulates high-order cognitive functions such as complex decision-making, endogenous (top-down) attention, and working memory [22–24]. Notably, the alleged functions of the ECN and SN map remarkably well onto the slow and fast, or reflective and reflexive, systems for decision-making, respectively, as mentioned above [3,5].

One explanation for the observed effects of stress on cognitive functioning is therefore that neurotransmitters and hormones released during acute stress somehow trigger a shift of resources from the ECN to the SN. This notion of a "reallocation" of neural resources is consistent with bioenergetic studies, which have shown that the net increase in the brain's energy consumption in response to mental challenges is remarkably small. For instance, glucose consumption increases only a few percent in response to moderately demanding cognitive tasks, and up to 12% during acute stress [25]. One reason for this may be that even at rest, the brain already uses an excessive amount of energy (20%) that is disproportionate to its weight (2%). Furthermore, during acute stress, the brain must compete with other organs for energy resources [26]. The ability to reallocate the brain's energy resources within the boundaries of energy supply may therefore yield a more efficient way of dealing with sudden changes in cognitive demands during challenging situations.

Studies into the interactions between large-scale connectivity networks are beginning to shed light on how such shifts in resource allocation may be accomplished. For instance, task-positive and task-negative networks activate reciprocally, that is, their activity at rest is negatively correlated [23]. Such observations suggest that neurocognitive functions subserved by one network can be suspended in favor of another, and that different large-scale networks may thus compete for limited resources [27]. It remains unclear, however, how such "network switches" are established. It is possible that one system simply uses all its available resources and thereby "steals" resources from another system. Another possibility is that resources are reallocated between large-scale systems partly by active suppression of neural systems that are not currently needed [28].

One way in which an active shift in resource allocation may be achieved is through activation of stress-sensitive neuromodulatory systems, which target neural tissues throughout the brain. Research in animals has demonstrated how acute stressors trigger multiple waves of neurochemical changes. Among the most rapid of these are neuropeptidergic (e.g., corticotropin-releasing factor) and catecholaminergic (e.g., norepinephrine and dopamine) responses [8], which initiate almost immediately and generally subside not long after termination of the stressor. Stressors furthermore increase the release of corticosteroids through activation of the hypothalamic–pituitary–adrenal (HPA) axis. Corticosteroids easily cross the blood–brain barrier, but peak concentrations in the brain are not reached within 20 min after onset of a stressor, and remain elevated longer than catecholaminergic changes, at least in rodents [29]. In addition to temporally specific effects, catecholaminergic and corticosteroid actions can also be spatially specific, owing to, for instance, regional variation in receptor distribution, affinity, and downstream signaling cascades. Thus, as we will detail below, these different classes of stress-sensitive neuromodulators (in particular catecholamines and corticosteroids) may allow for well-timed shifts between distinct neural circuits.

In the remainder of this chapter, we will explain how spatially and temporally specific effects of stress-sensitive hormones and neurotransmitters at the cellular level may dynamically alter the balance between large-scale neurocognitive systems involved in distinct types of decision-making. We will first describe how the SN and ECN are rapidly affected during the immediate phase of acute stress, before turning to slower effects during the phase of recovery from stress, return to homeostasis, and preparation for future challenges.

SALIENCE NETWORK AND ACUTE STRESS

Responding adaptively in threatening circumstances requires the ability to make prompt decisions to change one's current course of action, to reorient attention toward the currently most relevant sensory information, and to free necessary energy reserves to take appropriate action. The SN (see Fig. 30.1) has been proposed as a neurocognitive system that integrates such functions [19,22,30]. It includes regions associated with sensory vigilance and attentional reorienting (amygdala, thalamus, and inferotemporal/temporoparietal regions) [24,31,32], habitual behavior (striatum) [33], autonomic–neuroendocrine control (dorsal anterior cingulate cortex, hypothalamus) [34], visceral perception (anterior insula), and catecholaminergic signaling (brain-stem/midbrain nuclei) [35]. Metaanalyses of human functional neuroimaging studies show that these regions respond consistently to a variety of salient stimuli, including aversive affective material, conditioned stimuli [36], and pain [37]. Thus, SN activity is closely associated with characteristics of stressor-induced arousal, which suggests that neurotransmitters and hormones released during acute stress and emotional arousal may modulate activity within this network.

Salience Network: Neuroendocrine and Cellular Effects of Acute Stress

Stress-induced arousal is primarily mediated by rapid changes in catecholaminergic signaling. For instance, acute stress almost instantly alters functioning of the locus coeruleus–norepinephrine (LC–NE) system, the primary source of NE (also known as noradrenaline) in the central nervous system [38]. Single-cell recording studies in monkeys have demonstrated that this alteration is best characterized as a shift from phasic activity (i.e., selective responsiveness to sensory stimuli) to tonic activity (increased nonselective background activity) [39]. This centrally mediated activation of the LC–NE system is furthermore accompanied by peripheral activation of the sympathoadrenomedullary system, which triggers the release of epinephrine from the adrenal medulla. In turn, although epinephrine cannot cross the blood–brain barrier, peripheral epinephrine release further increases activity of the LC–NE system through ascending vagal projections to the nucleus of the solitary tract (NTS) [40]. The LC–NE system has wide projections throughout the brain, including the entire cerebral cortex, hypothalamus, thalamus, and amygdala [41]. However, effects of NE can also be regionally specific because of local differences in the

expression of different receptor types, which in turn have different affinities for NE. For instance, whereas α2A-adrenoceptors in the prefrontal cortex (PFC) are occupied at moderate levels of NE [42], the lower-affinity α1-adrenoceptors in the PFC and the β1-adrenoceptors in the amygdala are engaged at stress levels only [43]. Stress levels of NE may therefore have opposing effects on neural functioning in the PFC and the amygdala [12,44], which are critical regions within the ECN and the SN, respectively.

Stressors are also known to potently activate the dopaminergic system [45,46]. This leads to increases in dopamine levels in the PFC, but also in ventral (nucleus accumbens) and dorsal striatal regions [47]. Similar to the LC−NE system, stress mainly increases tonic, rather than phasic, firing in dopaminergic neurons [48,49]. Although dopaminergic activity is often associated mainly with reward processing and appetitive motivation, it has been shown that distinct subpopulations of dopaminergic neurons respond selectively to salient aversive stimuli [50]. For instance, in monkeys, neurons that respond to aversive stimuli have been identified in dorsolateral parts of the midbrain [51]. Furthermore, aversive stimuli trigger dopamine release in the dorsal striatum and nucleus accumbens in rats [52]. Effects of dopaminergic projections are also regionally specific. Whereas moderate stimulation of D1 receptors in the PFC reduced neuronal firing in response to noise stimulation in both rats and monkeys, excessive levels of D1 stimulation reached during acute stress suppress all neuronal firing [53], which explains the known detrimental effects of supranormal D1 stimulation on PFC-dependent functions [54]. This pattern again appears to be different in the amygdala, where the expression of conditioned fear, for instance, has been shown to depend on D1 receptor availability [55].

These findings suggest that both the LC−NE system and the dopamine system contribute to opposing regulation of the SN and the ECN during acute stress, but they may play separate roles. For instance, noradrenergic projections are more widespread and include regions involved in attentional and sensory processes, whereas dopaminergic innervation is more pronounced in the striatum, a region implicated in rigid and habitual behavior [56]. The distinct roles of these two neuromodulatory systems in mediating the central stress response, however, remain to be explored, in particular in humans.

Stress-induced corticosteroid release may also play an important role during the early phase of the stress response by activating rapid, nongenomic pathways. In vitro studies in rodents have shown that corticosteroids exert rapid effects through low-affinity membrane-bound glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs). Such effects can initiate as soon as corticosteroids reach target tissues [57]. In the paraventricular nucleus of the hypothalamus, corticosteroids have been shown to rapidly and reversibly decrease neuronal excitability through GRs, which may contribute to rapid negative feedback of the HPA axis [58]. On the other hand, MR activation has been shown to increase neuronal excitability in the basolateral amygdala [59] and hippocampus [57]. Thus, although these nongenomic pathways are just beginning to be understood and have been examined in only a small number of brain regions, such effects may also be regionally specific and thereby contribute to the regulation of broader neural systems [9].

Corticosteroids may furthermore interact with catecholaminergic activity [40]. For instance, noradrenergic activity has been shown to be amplified by GR activation at the level of the NTS and the LC [60], and NE levels in the amygdala are increased after systemic injections of corticosteroids [61]. Corticosteroids furthermore enhance the effect of acute stress on dopamine release [62], and blockade of GRs within the rat PFC reduces stress-induced dopamine release from the ventral tegmental area [63]. Complex interactions between β-adrenoceptor activation and glucocorticoids also exist regarding synaptic plasticity in the basolateral amygdala [64]. Behaviorally, corticosteroids postsynaptically augment the effects of NE on amygdala function by enhancing the β-adrenoceptor−cAMP system [65−67]. Similar effects have been described in the nucleus accumbens [68]. On the other hand, the negative effects of supraoptimal levels of catecholaminergic activity on PFC function can also be exacerbated by corticosteroids [69] through membrane-bound GRs [70].

Salience Network: Behavioral Effects of Acute Stress

Notably, there is substantial overlap between the functions attributed to catecholaminergic, in particular noradrenergic, signaling, on the one hand, and those ascribed to the SN on the other hand. Both systems are strongly implicated in attentional (re)orienting [24,71−73]. Whereas phasic LC−NE signaling is thought to subserve selective processing of stimuli relevant to current task sets, tonically elevated LC activity would lead to enhanced environmental scanning and facilitated reorienting of attention toward unexpected and potentially threatening stimuli [24,39,72,74]. Noradrenergic projections from the LC are further thought to regulate sensory gain to optimize the signal-to-noise ratio (SNR) for sensory gating and sustained attention [39,75,76]. This implies that stress-induced changes in noradrenergic level or activity may amplify sensory information to a supraoptimal level and thereby cause a

decrease in SNR and sensory gating ability due to amplification of sensory noise. Functionally, such a shift in sensory function would benefit attentional vigilance, but at the expense of increased distractibility. In agreement, stimulation of the LC resulted in a suppression of phasic discharge of thalamic and barrel cortex neurons in response to sensory stimuli, which was accompanied by an increase in spontaneous activity [77]. Both stress induction [78] and pharmacological stimulation of the LC [79] in rats have furthermore been shown to impair prepulse inhibition, the phenomenon that a weak preceding stimulus causes an inhibition of the startle reflex in response to a subsequent stronger stimulus, which is seen as an index of sensory gating.

Similar findings have been reported in humans. For instance, oral administration of hydrocortisone rapidly impairs prepulse inhibition [80]. Sensory gating in humans, however, is more commonly investigated using the attentional blink paradigm. The attentional blink refers to the inability to detect the second of two targets when presented with a 200- to 500-ms stimulus onset asynchrony within a rapid serial visual presentation. Computational models of LC–NE function postulate that this attentional blink occurs as a consequence of LC–NE firing in response to the first target. This phasic response would exert a local inhibitory effect on the LC through α2-autoreceptors, thus creating a brief refractory period of suppression of LC responses to subsequent stimuli [81]. If stress shifts the LC from a phasic to a tonic mode of activity [39], one would expect this refractory period to disappear. This "rescue" of the detection of the second target is indeed what is observed, both following administration of the selective NE reuptake inhibitor reboxetine [82] and after stress induction [83], although in the latter study it was not certain that this finding (20 min after stress) was obtained within the time window of elevated catecholaminergic availability. Stress induction has also been shown to selectively modulate distinct components of event-related potentials evoked by sensory stimulation in humans [84–86]. Together, these findings indicate that acute stress induces a hypervigilant state, which is also reflected in the style of decision-making [87], most likely involving tonically elevated LC–NE activity.

As noted above, the SN also comprises striatal regions that are implicated in rigid stimulus-response learning and habitual behaviors [33]. The shift from goal-directed to rigid stimulus-response behavior is a well-documented effect of acute stress in both animals [88,89] and humans [90]. For instance, briefly following corticosterone delivery, rodents exhibit increased persistence in making disadvantageous, high-risk decisions in a rodent model of the Iowa Gambling Task [91], behavior that resembles anxious behavior exhibited by rats in the elevated-plus maze [92]. Such findings concur with clinical observations of stress-related relapse in addiction as well as exacerbation of symptoms in various psychiatric disorders including obsessive–compulsive disorder [2,93]. In humans, there is furthermore experimental evidence that stress enhances simple stimulus-response learning such as classical conditioning using a negative unconditioned stimulus [94].

A number of studies furthermore suggest that there may be sex differences in the rapid effect of stress on decision-making. Stress induction has been shown to increase persistence in making disadvantageous choices in the Iowa Gambling Task in men, but decrease it in women [95–97]. Thus, it appears that, whereas men tend to shift toward a habitual style of decision-making under stress, women may have a stronger tendency to become more inhibited and vigilant [98]. However, what causes this putative sex difference remains unclear [99].

Salience Network: Brain Systems-Level Effects of Acute Stress

Several human neuroimaging studies have reported increased responsiveness of the amygdala, one of the core regions of the SN, during the immediate phase of acute stress following experimental stress induction [100–102]. A number of studies have furthermore shown hyperactivation in limbic and subcortical regions, including the amygdala, after symptom provocation in anxiety disorder patients [103–109]. In line with the notion that such effects are driven by increased noradrenergic activity, pharmacologically increasing central NE levels, through administration of the α2-adrenoreceptor antagonist yohimbine [110] or the selective NE reuptake inhibitor reboxetine [111], mimics these effects, in particular when combined with additional administration of hydrocortisone [112]. Contrariwise, administration of the β-adrenergic receptor blocker propranolol diminishes the amygdala response [113]. It was furthermore shown that carriers of a common functional deletion in the gene coding for the α2B-adrenoreceptor (*ADRA2B*), which reduces the negative feedback function of the noradrenergic system, exhibit stronger stress-induced increases in the phasic amygdala response [102]. Thus, human neuroimaging studies consistently show that NE plays an important role in regulating amygdala responsiveness.

There is also substantial evidence that activity in other regions of the SN increases during acute stress. For instance, activity in the dorsal anterior cingulate cortex and the anterior insula correlates with physiological markers of stress, such as increased heart rate [114], elevated blood pressure [115], and increased cortisol levels [116], and also with reduced heart rate variability

[117], a parasympathetic index of stress [118]. A number of studies furthermore used network-based methods to examine functional connectivity within the entire SN. One early study showed that spontaneous activity within the SN is associated with electroencephalographic signatures of alertness [119]. Furthermore, it was shown that connectivity of the amygdala with a number of SN regions was elevated in the context of stress induction [120]. These regions included a cluster of activation that corresponded with the anatomical location of the LC, although this finding should be interpreted with some caution given the small size of this region [121]. Another study showed that multiple physiological and psychological measures of acute stress, including the cortisol response, changes in α-amylase (a peripheral marker of noradrenergic activity), and subjective mood changes are all associated with increased connectivity within the SN during exposure to a stressor consisting of aversive cinematographic material [122]. Increased interconnectivity within the SN was also found in response to threat of mild electrical shock [123,124]. SN function was furthermore causally linked with noradrenergic activity in a study that showed that administration of the β-adrenergic blocker propranolol diminished connectivity within the SN, whereas blocking endogenous corticosteroid production through administration of metyrapone had no effect [122]. Interconnectivity of the ventral striatum within the SN was finally shown to be increased after administration of L-dopa, which increases dopamine availability [125]. In sum, both the activity of and the interconnectivity of the SN appear to be boosted by catecholaminergic activity during the early phase of the response to acute stressors.

EXECUTIVE CONTROL NETWORK AND ACUTE STRESS

If a shift toward a hypervigilant and rigid style of decision-making is adaptive in situations of acute stress, it is reasonable to assume that suspending slower and more elaborate types of decision-making also benefits short-term survival [44]. Such goal-directed types of decision-making are thought to be supported by a frontoparietal network involving dorsal frontal (dorsolateral PFC; precentral/superior frontal sulci, or frontal eye fields; and dorsomedial PFC) and dorsal posterior parietal areas [23], which is commonly referred to as the ECN [19] (see Fig. 30.1).

As mentioned earlier, rodent and nonhuman primate work has demonstrated that excessive catecholaminergic activity during acute stress impairs PFC function through occupation of the lower-affinity α1- and β1-adrenoceptors, as well as through supraoptimal dopamine D1 receptor stimulation [2,11]. Inhibitory effects of NE on PFC function are furthermore exacerbated by corticosteroids [70]. A consequence of this supraoptimal catecholaminergic activity is that PFC neurons lose the capacity to maintain persistent patterns of spiking activity, which is seen as an important neurophysiological substrate of working memory maintenance [126].

Executive Control Network: Behavioral Effects of Acute Stress

In humans, a vast majority of studies investigating the effects of acute stress on working memory, one of the cognitive functions supported by the ECN, have found impairments, particularly when testing was performed while catecholaminergic activity was still elevated [94,127–131] (for exceptions see Refs. [132,133]). Consistent with the notion that the ECN supports flexible goal-directed action, stress induction has also been shown to negatively affect task switching [134,135] and cognitive flexibility [136]. In the realm of decision-making, studies have found that acute stress reduces elaboration of alternative problem-solving strategies [137] and more generally impairs strategic decision-making [138–140]. Furthermore, stress increases the subjective valuation of immediate rewards despite negative consequences, as shown, for instance, in increased risky decisions in the Game of Dice Task [141] (but see Refs. [142,143]) and increased rates of delay discounting (i.e., the degree to which one discounts the subjective value of future rewards) [144] (but see Ref. [145]). Finally, also suggesting impaired ability to flexibly adjust one's behavior given changing circumstances, stress has been shown to reduce the sensitivity of instrumental responding to goal devaluation [90,146,147].

Pharmacological studies have provided insight into the mechanisms underlying these effects. One study showed an insensitivity to outcome devaluation similar to what is seen under stress after combined administration of yohimbine and hydrocortisone [148]. Furthermore, stress-induced impairments in cognitive flexibility tasks [149], as well as insensitivity to outcome devaluation [150], are blocked by the β-adrenergic blocker propranolol. Thus, the impairments in goal-directed decision-making seen during acute stress appear to be mediated by rapid catecholaminergic activation, possibly in interaction with corticosteroids.

Executive Control Network: Brain Systems-Level Effects of Acute Stress

Several neuroimaging studies in humans have investigated the effects of stress induction and pharmacological

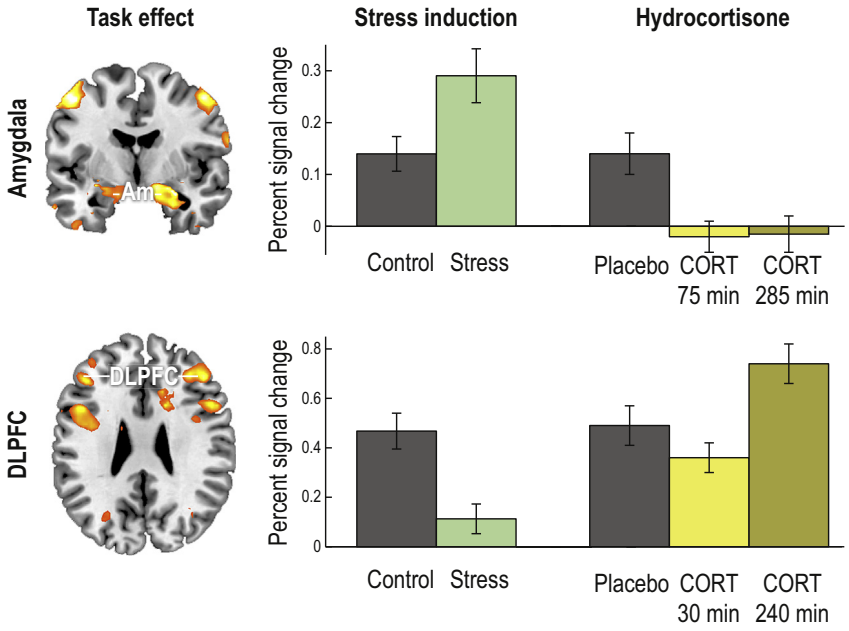

FIGURE 30.2 Opposite effects of stress induction (at short time intervals) and hydrocortisone administration (at different time intervals) on amygdala versus DLPFC. Data from four studies probing amygdala (major node of the salience network) and DLPFC (major node of the executive control network) function are shown. Shortly following stress induction, the amygdala response to salient stimuli increases [100], whereas DLPFC activity related to an executive control task decreases [151]. Contrariwise, administration of hydrocortisone reduces amygdala activity at both 75- and 285-min delays [168] and enhances DLPFC activity only at a 240-min delay [171], which is sufficient to allow genomic effects. For amygdala, bar graphs indicate percentage signal change for emotional facial expressions versus baseline. For DLPFC, bar graphs indicate percentage signal change for a two-back working memory task condition versus a zero-back control. *Am*, amygdala; *CORT*, hydrocortisone; *DLPFC*, dorsolateral prefrontal cortex. *Adapted from Hermans EJ, Henckens MJAG, Joëls M, Fernández G. Dynamic adaptation of large-scale brain networks in response to acute stressors. Trends Neurosci 2014;37:304–14.*

manipulations on neural activity in brain regions within the ECN. One study revealed reduced working memory-related activation in the dorsolateral PFC (DLPFC) immediately after experimental induction of stress [151] (see Fig. 30.2). This negative effect of stress on working memory-related activation of the DLPFC was furthermore shown to be stronger in Met homozygotes for the gene coding catechol-*O*-methyltransferase, who are thought to have higher baseline levels of catecholamines [130]. A similar suppressive effect on PFC activity was found in a task involving reward-related value representation [152], which may explain stress-induced impairments in reward value-based decision-making described in the previous paragraphs. During stress, working memory-related activation of the ECN is further accompanied by a failure to suppress activity in regions that are part of other large-scale networks (e.g., default mode network [151,153]), which is in line with the notion that acute stress impairs selective allocation of processing resources to the ECN. Finally, pharmacological MRI work has shown that combined administration of yohimbine and hydrocortisone was again more effective in reducing PFC activity than either drug alone [110,154]. Thus, human neuroimaging work is in line with animal work [70] and demonstrates that the ECN is suppressed when catecholaminergic effects dominate or coincide with corticosteroid elevation.

SALIENCE NETWORK AND EXECUTIVE CONTROL NETWORK AND RECOVERY FROM STRESS

Excessive and prolonged activation of hormonal responses to stressors exhausts our energy reserves and in the long term results in an increased allostatic load: a failure to maintain homeostatic balance [155]. Therefore, a timely limitation and termination of the stress response is a critical aspect of healthy and adaptive functioning under stress. There is now considerable evidence that corticosteroids play a critical role in this process.

As described before, corticosteroid receptor binding leads to altered gene transcription, a relatively slow process that results in changes in levels of multiple proteins that affect neuronal function [9]. These genomic effects take at least an hour to initiate but can continue for at least several hours. Notably, in many brain regions, such slow genomic effects may oppose the rapid

nongenomic effects described above. GR-mediated effects 4 h and more after stress, for instance, have been shown to enhance PFC neuronal function and facilitate working memory in rats [156], presumably by increasing GR/serum- and glucocorticoid-inducible kinase-induced glutamate receptor trafficking [157]. Similar effects were found in the dorsal hippocampus [158], but these effects are opposite those observed in the ventral hippocampus [159] and (basolateral) amygdala [160]. Thus, like other mechanisms of action, these genomic actions have also been shown to exhibit regional specificity. Genomic actions of corticosteroids may thereby provide a mechanism that actively complements—in an opposite direction—the rapid effects of various stress mediators described above.

Early studies in rodents have indeed shown that administration of corticosteroids can have anxiolytic rather than anxiogenic effects [161]. In agreement with such findings, human studies have demonstrated that hydrocortisone administration at various time intervals before testing reduces emotional interference in cognitive tasks [162,163] and has a protective effect on self-reported mood in stress-induction paradigms [164]. Pharmacological inhibition of cortisol production by means of administration of metyrapone had the opposite effect of increasing sympathetic arousal in response to stressors [165]. Furthermore, hydrocortisone administration in anxiety disorder patients enhances extinction-based psychotherapy [166] and reduces phobic symptoms [167]. Thus, elevation of corticosteroids, in particular at longer delays and when not accompanied by catecholaminergic activation, appears to lead to a suppression of neurocognitive processes supported by the SN.

Recent neuroimaging work in humans has tested whether such slow vigilance-reducing effects of hydrocortisone may indeed be explained by a reduction in responsiveness in SN regions such as the amygdala. Approximately 4–5 h after administration of hydrocortisone, amygdala responsiveness to negative or positive information was reduced [168] (Fig. 30.2). 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 ±2 h before testing reduced functional connectivity between the amygdala and a brain-stem cluster corresponding to the anatomical location of the LC [169], a finding opposite that of the aforementioned study assessing amygdala–LC coupling directly after stress [120]. Effects of hydrocortisone administration on amygdala activity at shorter delays are somewhat less clear, with a reduction at 75 min in a task involving passive viewing of emotional facial expressions [168] and an increased response at 60 min in a task involving emotional distractors [170]. This discrepancy may be explained by different levels of coinciding catecholaminergic activity elicited by these tasks, but also by the critical delay necessary to induce genomic actions, which is approximately 60 min. Nonetheless, hydrocortisone administration studies support the notion that corticosteroids actively contribute to the gradual downregulation of SN regions and thus help in normalizing this aspect of the stress response.

There is also considerable evidence of an effect in the opposite direction on ECN functioning several hours after stress. As mentioned earlier, rodent findings show that stress potentiates excitatory neurotransmission through a slow GR-dependent mechanism in the PFC. This effect was accompanied by improved working memory performance 4 h after stress [156], a delay that is long enough to allow genomic effects to develop [9]. A human study administered hydrocortisone at different time intervals to subjects before they performed a working memory task [171] (Fig. 30.2). Hydrocortisone administered 4 h before testing positively affected working memory performance and DLPFC activation, whereas hydrocortisone administered 30 min before testing did not have such an effect. These findings thus suggest that several hours after stress, genomic actions of corticosteroids can complement—in an opposite direction—the stress-induced impairment in executive control functioning seen directly after stress, which may serve to support flexible decision-making and the adjustment of long-term goals. Of note, these slow and presumably gene-mediated effects after stress have as of this writing not specifically been tested with regard to decision-making.

SUMMARY AND CONCLUSION

Dual-systems models of decision-making have long assumed that acute stress induces a shift from slow to fast [3], or reflective to reflexive [5], systems for decision-making. In the previous sections, we attempted to provide a neural basis for these notions by integrating the relevant existing knowledge at multiple levels of analysis. We have summarized rodent data showing that distinct waves of stress-related hormones and neurotransmitters exert specific effects in widely distributed brain regions. A recurrent finding within this literature is that effects in regions such as the PFC are accompanied by opposing effects in limbic and subcortical structures such as amygdala and striatum. This suggests that such brain regions are differentially regulated as part of multiple large-scale functional networks [2,12].

A comprehensive account of the architecture and interactions within and between such networks can be obtained only by investigating the resulting changes at the

brain systems level. We therefore attempted to integrate these findings with an emerging literature in the field of functional connectivity network modeling in humans, which is beginning to reveal how regions shown to be differentially affected by stress play a role in distinct large-scale neural systems. We have argued that the SN and ECN [19] are the most critical neurocognitive systems targeted by such effects. However, as the network architecture of the human brain is parsed in more and more detail [16], it appears likely that a more complex picture will emerge in the future. Nonetheless, taking these networks and the putative roles they play in different types of decision-making as a starting point, we argue that a classification into broad cognitive domains supported by the SN and the ECN is a critical factor in understanding how stress may affect decision-making.

A second critical factor is timing: as we explained earlier, the effects of stress on the SN and the ECN appear to be opposite during the acute phase compared to the slow phase. In this chapter, we have shown how these two phases can be linked to dominating catecholaminergic and corticosteroid actions, respectively. However, future research will probably reveal more complexity also in this domain, for instance, by revealing how neurotransmitters and hormones act outside of their typical temporal domain [8], or by elaborating the roles of, for instance, serotonin and neuropeptides in the central stress response [11], which have received relatively little attention in human research.

Nonetheless, an initial classification across the two factors of network and timing creates order in an otherwise confusing and paradoxical body of empirical research on the effects of stress on human cognition. Fig. 30.3 visualizes the findings from 38 empirical research articles cited in this chapter. All these studies involved either controlled induction of stress (mainly through psychological manipulations) or administration of hydrocortisone. As can be seen in Fig. 30.3A, when all cognitive tasks are taken together, the effect sizes (Cohen's *d*; standardized mean differences) associated with stress induction or hydrocortisone administration reveal no systematic bias toward better or worse performance. Similarly, when data points are split for tasks tapping into ECN functions and SN functions, no clear bias is visible. Adding the timing factor (Fig. 30.3B), it becomes apparent that the two different systems are modulated in a reciprocal manner over time, with trend lines that cross after approximately 1 h, when genomic effects of corticosteroids start to develop.

In Fig. 30.4, we summarize all the literature reviewed in this chapter within a biphasic-reciprocal model of stress-induced reallocation of neural resources. While this heuristic model integrates all the relevant data to the best of our knowledge, many open questions remain.

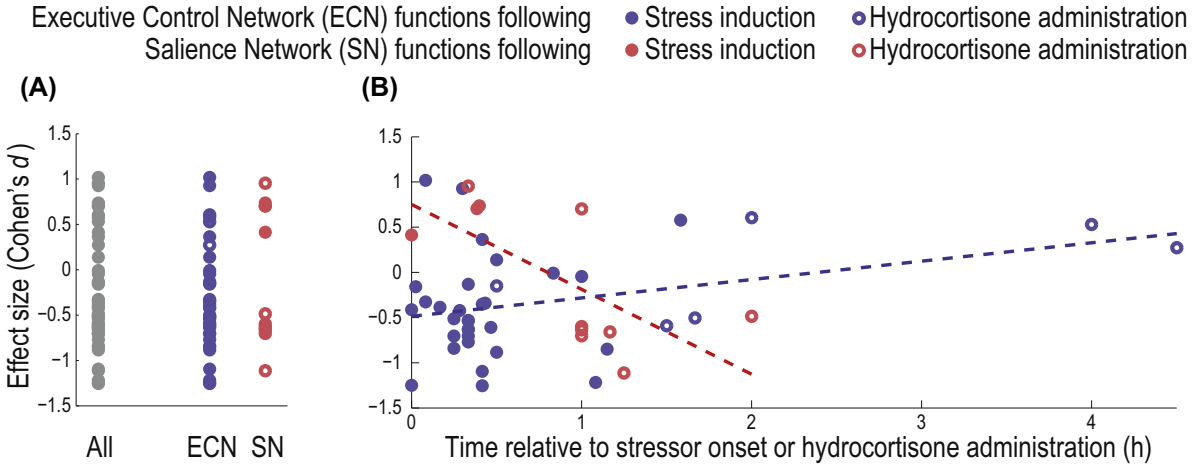

FIGURE 30.3 Effect sizes (Cohen's *d*) of stress induction or hydrocortisone administration (A) overall and sorted by cognitive functions supported by the executive control network (ECN) versus the salience network (SN) and (B) plotted as a function of the time point at which measurement of cognitive performance started relative to stressor onset or administration. Timing information was obtained from descriptions of the experimental procedures in the respective papers. *Dashed lines* indicate trends over time for each neurocognitive function. Data points taken from studies tapping into ECN-dependent functions are plotted in blue (digit span [127,131–133]; reading span [94]; *n*-back [128,130,151,171]; Sternberg [129] with emotional distractors [163]; dual task performance, task shifting, selective attention, and cognitive flexibility [134–136,149]; delay discounting [144]; rational and strategic decision-making [137–140]; risky decision-making [141–143,174]; and instrumental learning and extinction [146–148,150,154]). In red are shown SN-dependent functions (attentional blink [83], prepulse inhibition [80], emotional interference [101,162,170], subjective measures of negative mood [164] and fear [166,167], and hypervigilant style of decision-making [87]). *Adapted and extended from Hermans EJ, Henckens MJAG, Joëls M, Fernández G. Dynamic adaptation of large-scale brain networks in response to acute stressors. Trends Neurosci 2014;37:304–14.*

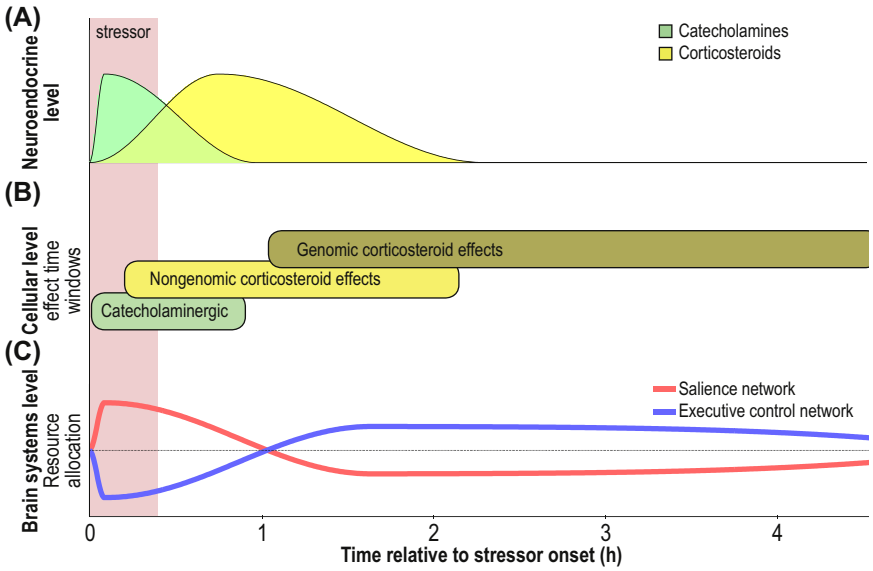

FIGURE 30.4 Biphasic-reciprocal model of reallocation of neural resources in response to stress. The links between effects of stress at (A) neuroendocrine, (B) cellular, and (C) brain systems levels are illustrated. (A) Neuroendocrine level: following exposure to a stressor, central levels of catecholamines (norepinephrine, dopamine) increase promptly and normalize not long after stressor offset. Corticosteroid levels in the brain rise more slowly and remain elevated 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 nongenomic effects that may overlap and interact with catecholaminergic effects in an early time window, but also exert slower genomic effects. (C) Brain systems level: owing 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 (*SN*, salience network) and executive control (*ECN*, executive control network; see Fig. 30.1 for an anatomical overview of both networks). Critically, our model proposes that stress-related hormones and neurotransmitters strengthen SN activity during the acute stress phase at the cost of ECN function, but subsequently contribute actively to the return to homeostasis by reversing this balance (see "Salience Network and Executive Control Network and Recovery From Stress" section on slow effects of corticosteroids for an explanation of underlying cellular mechanisms, and see Fig. 30.2 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 the effects of stress on cognition at the behavioral level. *Adapted from Hermans EJ, Henckens MJAG, Joëls M, Fernández G. Dynamic adaptation of large-scale brain networks in response to acute stressors. Trends Neurosci 2014;37:304–14.*

Most importantly, how and why do individuals differ in their sensitivity to stressors, and why does stress have pathological consequences in some individuals? A suggestion that follows from our model is that individual differences, and ultimately maladaptation, may result from an inability to constrain sympathetic activation by subsequently released corticosteroids, a problem that may occur in posttraumatic stress disorder [172,173]. Our model would predict that in such conditions the SN is strongly activated, whereas later complementary action of the ECN is inadequate, potentially impairing an individual's ability to exert cognitive control over the emotional aspects of the stressful event. Our framework thus aligns with an ongoing paradigm shift within neuropsychiatry from identifying foci of abnormality toward developing a global understanding of aberrations at the level of large-scale networks [19].

In conclusion, in this chapter we integrated neuroendocrine, cellular, brain systems, and behavioral levels of analysis to propose a framework describing global and dynamic shifts in network resource allocation in response to acute stressors. We believe that this framework provides an initial neural foundation for understanding shifts between strategic and tactical modes of decision-making observed under stress.

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