Acute stress shifts the brain into a state that fosters rapid defense mechanisms. Stress-related neuropeptides are thought to trigger this change by altering properties of large-scale neuronal populations throughout the brain. We investigated this brain-state shift in humans. During exposure to a fear-related acute stressor, responsiveness and interconnectivity within a network including cortical (frontoinsular, dorsal anterior cingulate, inferotemporal, and temporoparietal) and subcortical (amygdala, thalamus, hypothalamus, and midbrain) regions increased as a function of stress response magnitudes. β-adrenergic receptor blockade, but not cortisol synthesis inhibition, diminished this increase. Thus, our findings reveal that noradrenergic activation during acute stress results in prolonged coupling within a distributed network that integrates information exchange between regions involved in autonomic-neuroendocrine control and vigilant attentional reorienting.

Fig. 1. ISC maps are thresholded at $P < 0.05$, whole-brain FWE-corrected, and overlaid onto cortical surface renderings (A and B) and a canonical structural MRI (C). FI, frontoinsular cortex; SMA, supplemental motor area; PCC, posterior cingulate cortex; (v)mPFC, (ventro)ventral mPFC; IFG, inferior frontal gyrus; Th, thalamus; Mb, midbrain; Hy, hypothalamus.
A contrast between both conditions’ ISC maps produced by nonparametric permutation tests \( P < 0.05 \), whole-brain family-wise error (FWE)-corrected \((14)\) revealed relatively few ISC differences in early visual regions. However, we found increased ISC for the aversive movie in regions (table S3 and Fig. 1C) shown to respond consistently to salient stimuli in meta-analyses of conventional model-based fMRI studies \((15, 16)\). Among these are regions associated with interoception and autonomic-neuroendocrine control \(\text{frontoinsular cortex, dorsal anterior cingulate cortex (dACC), medial prefrontal cortex (mPFC), and amygdala (17–19)}\), peripheral stress effector systems and catecholaminergic signaling \[midbrain and hypothalamic regions (8, 15)\], and sensory and attentional \(\text{re}orienting \[\text{thalamus, and inferotemporal and temporoparietal regions (20)\}]. A similar set of regions forms an intrinsic connectivity network \(\text{(ICN)}\) in the resting brain that has been proposed to process salience by integrating affective-homoeostatic with sensory-attentional information \((21)\). The temporal correlations across participants found here, however, provide no information about functional connectivity, because different regions may respond to different aspects of the movie and therefore display uncorrelated time courses. To test for functional connectivity, we used multisession tensorial probabilistic independent component analysis \(\text{(ICA)}\). We decomposed fMRI data into time courses, spatial maps, and subject modes, which represent signal variation of each IC over time, space, and participants, respectively \[\text{see supporting online material (SOM) (22)}\]. ICA for the aversive condition yielded 18 IC maps \(\text{(fig. S2)}\), which represent spatially dissociable signal fluctuations originating from separable large-scale neural ensembles \(\text{(or nuisance sources)}\). Using objective template matching \(\text{(table S2)}\), we subsequently identified the IC map with the strongest overlap with the ISC contrast map \(\text{(aversive > control; Fig. 2 and fig. S3)}\). The thereby selected IC map for the aversive condition contained all regions mentioned in the previous paragraph except the mPFC \(\text{(see Fig. 2 and table S4 for all coactivated regions)}\). Furthermore, template matching onto a map of the aforementioned salience-processing ICN, kindly provided by the authors of \((21)\), yielded the same IC map \(\text{(table S5)}\). In the remainder, we therefore refer to the selected IC map as the salience network \((21)\). The mPFC appears in another IC map alongside the posterior cingulate cortex, suggesting that these regions form part of another neural system \[\text{the default mode network (12)}\].

To investigate whether functional connectivity strength within the salience network was associated with stress measures, we used compound measures resulting from ICA decomposition \((22)\). Network strength correlated positively with cortisol \[\text{Spearman’s } r (78) = 0.23, P = 0.037\], alpha amylase \[\text{mean } \mu (78) = 0.28, P = 0.012\], and negative affect change \[\text{mean } \mu (78) = 0.25, P = 0.026\], but not heart rate change \[\text{mean } \mu (78) = 0.06, n.s.\].

Our findings agree with theories that postulate a dual architecture of cortical attentional control networks. In addition to a dorsal frontoparietal network involved in regulating attention in focal tasks \((25)\), these theories implicate a ventral attention network that differs little in topology from the network identified here in reorienting attention away from focal tasks \((20)\) and the maintenance of tonic alertness \((24)\). Spontaneous activity in this network has moreover been associated with electroencephalographic signatures of alertness \((25)\). A pivotal question following from these observations is to what extent stress-related neuromodulators such as noradrenaline and cortisol drive this network reorganization. To address this, we performed a pharmacological experiment \(\text{(experiment 2)}\) implementing a three-armed double-blind between-participants design. Sixty participants received either propranolol \((40 \text{ mg})\), a \(\alpha\)-adrenergic receptor blocker; metyrapone \((750 \text{ mg given twice})\), a cortisol synthesis blocker; or a placebo \(\text{(Fig. 3)}\). Stress induction procedures were extended with a threat of mild electrical shock to increase effectiveness in raising cortisol but were otherwise identical to experiment 1 \(\text{(SOM)}\).

We observed robust cortisol responses to stress after the placebo \[F(1, 19) = 8.67, P = 0.008, P_{\text{FWE}} = 0.31\] and propranolol \[F(1, 19) = 11.93, P = 0.003, P_{\text{FWE}} = 0.39\], but not after metyrapone \(F < 1\). Metyrapone lowered cortisol throughout testing \[F(1, 38) = 11.60, P = 0.002, P_{\text{FWE}} = 0.23\]. Conversely, propranolol selectively lowered alpha amylase throughout testing \[F(1, 37) = 9.10, P = 0.005, P_{\text{FWE}} = 0.20\]; metyrapone effect: \(F < 1\), and lowered heart rate \[F(1, 35) = 29.11, P < 0.001, P_{\text{FWE}} = 0.45\]; metyrapone effect: \(F(1, 36) = 1.7, n.s.\). Neither drug affected subjective negative affect \(F < 1\). Thus, as intended, propranolol and metyrapone selectively affected \(\text{peripheral noradrenergic and glucocorticoid measures, respectively (Fig. 3).} \)

ICA \(\text{(fig. S4)}\) and template matching of IC maps between experiments 1 and 2 closely reproduced the salience network IC map \(\text{(Fig. 4A}\).
and table S5). We investigated drug effects on functional connectivity strength within this network in comparison with a visual network as a control for specificity. A 3 (drug) × 2 (IC) analysis of variance yielded a drug-by-IC interaction \(F(2, 57) = 3.46, P = 0.038, \eta^2 = 0.11\). Further testing revealed a drug main effect on the salience \(F(2, 57) = 3.19, P = 0.049, \eta^2 = 0.10\) but not the visual \((F < 1, \text{n.s.})\) network. A planned contrast showed that this effect was carried by a reduction in the propranolol group as compared to the other groups \((F(1, 57) = 5.61, P = 0.021, \eta^2 = 0.09\). Finally, directed one-tailed \(t\) tests demonstrated that propranolol reduced network strength relative to both the placebo \([t(38) = 1.64, P = 0.054]\) and metyrapone \([t(38) = 2.41, P = 0.011]\) groups.

This finding concurs with theoretical frameworks of LC function, which ascribe attentional reorienting functions to cortical noradrenergic projections that parallel those proposed for cortical components of the salience network (20). Animal studies have shown that LC neurons exhibit two distinct functional modes for regulating sensory gain (26). In mildly aroused states that are optimal for focal task performance, the LC responds phasically to task-relevant stimuli (9), engaging \(\alpha-2A\) receptors that strengthen top-down dorsolateral PFC regulation of attention (7). Under stress, however, LC neurons shift to tonically elevated firing rates associated with distractibility and hypervigilance (10). High tonic firing releases large concentrations of norepinephrine, which engages lower-affinity \(\beta\)-adrenergic receptors that impair top-down attentional control but enhance thalamic and sensory functions (7). Thus, besides effects on memory (3, 4), a putative function of these neuromodulatory signals is to send interrupt signals to active functional networks (27), causing disengagement from current task sets (9) and promoting fast adaptation by rearranging network activity (11). Our findings establish a causal link between stress-induced noradrenergic activity and activation of the salience network (20).

Although functional connectivity within the salience network correlated with cortisol increases (experiment 1), our finding that cortisol blockade had no effect suggests that cortisol elevation is not necessary for this network reorganization to occur. It has been suggested that corticosteroids act through mineralocorticoid receptors to promote vigilance in immediate response to stress (11). Nonetheless, we cannot exclude the possibility that with different timing or stronger elevations of cortisol, interactive or additive effects may occur (4).

We have shown that noradrenergic neuronal-modulatory activity in the early phase of the stress response drives a reallocation of neural resources toward a distributed network of regions involved in attentional reorienting, vigilant perceptual intake, and autonomic-neuroendocrine control.

References and Notes


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Supporting Online Material

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References

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