Stress-Related Noradrenergic Activity Prompts Large-Scale Neural Network Reconfiguration

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Acute stress shifts the brain into a state that fosters rapid defense mechanisms. Stress-related neuromodulators 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.

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cutereporting the release of various hormones and has delineated a chain of neurochemical events in the forebrain (…) –neuropeptide and monamine release plays a key role at shorter time scales (…) –noradrenergic activation during acute stress (HPA) axis, resulting in increased systemic release of corticosteroids, is the hallmark of the stress response. In experiment 1, participants (80 healthy volunteers) also saw a neutral movie matched for audiovisual characteristics (table S1) in a separate counterbalanced session. Physiological and psychological stress measures were obtained around and during scanning. Exposure to the aversive movie triggered elevated salivary cortisol [F(1, 79) = 4.93, P = 0.029, partial eta-squared (η²) = 0.06], salivary alpha amylase [marker of (nor)adrenergic activity; F(1, 79) = 5.61, P = 0.02, η² = 0.07], and heart rate [F(1, 78) = 44.20, P < 0.001, η² = 0.36], and increased subjective negative affect [F(1, 79) = 23.37, P < 0.001, η² = 0.23]. We first identified brain regions that responded preferentially to the aversive movie. Instead of using a pre-specified model that imposes restrictions on the temporal shape of the response that can be detected, we capitalized on the fact that regional activation can be inferred from temporal correlations across participants [fig. S1 (13)].

We observed strong intersubject correlations (ISCs) mainly, but not exclusively, in sensory regions during both movies (Fig. 1, A and B, and

Fig. 1. ISC. Maps are thresholded at P < 0.05, whole-brain FWE-corrected, and overlaid on cortical surface renderings (A and B) and a canonical structural MRI (C). F1, frontoinsular cortex; SMA; supplementary motor area; PCC, posterior cingulate cortex; v(m)PFC, (ventro)mPFC; IFG, inferior frontal gyrus; Th, thalamus; Mb, midbrain; Hy, hypothalamus.
Design and analyses of conventional model-based fMRI studies (15, 16). Among these are regions associated with interoceptive and autonomic-neuroendocrine control [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 (re)orienting [thalamus, and inferotemporal and temporoparietal regions (20)]. A similar set of regions forms an intrinsic connectivity network (ICN) in the resting brain that has been proposed to process salience by integrating affective-homeostatic 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 multisection tensorial probabilistic independent component analysis (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 [see supporting online material (SOM) (22)]. ICA for the aversive condition yielded 18 IC maps (fig. S2), which represent spatially dissociable signal fluctuations originating from separable large-scale neural ensembles (or nuisance sources). Using objective template matching (table S2), we subsequently identified the IC map with the strongest overlap with the ISC contrast map (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 (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 (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 [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 [Spearman’s $\rho(78) = 0.23$, $P = 0.037$], alpha amylase [$\rho(78) = 0.28$, $P = 0.012$], and negative affect change [$\rho(78) = 0.25$, $P = 0.026$], but not heart rate change [$\rho(78) = -0.06$, 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 (23), 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 (experiment 2) implementing a three-armed double-blind between-participants design. Sixty participants received either propranolol (40 mg), a $\beta$-adrenergic receptor blocker; metyrapone (750 mg given twice), a cortisol synthesis blocker; or a placebo (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 (SOM).

We observed robust cortisol responses to stress after the placebo [$F(1, 19) = 8.67$, $P = 0.008$, $P_{\text{adj}} = 0.31$] and propranolol [$F(1, 19) = 11.93$, $P = 0.003$, $P_{\text{adj}} = 0.39$], but not after metyrapone ($F < 1$). Metyrapone lowered cortisol throughout testing [$F(1, 38) = 11.60$, $P = 0.002$, $P_{\text{adj}} = 0.23$]. Conversely, propranolol selectively lowered alpha amylase throughout testing [$F(1, 37) = 9.10$, $P = 0.005$, $P_{\text{adj}} = 0.20$; metyrapone effect: $F < 1$], and lowered heart rate [$F(1, 35) = 29.11$, $P < 0.001$, $P_{\text{adj}} = 0.45$; 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 (peripheral) noradrenergic and glucocorticoid measures, respectively (Fig. 3).

ICA (fig. S4) and template matching of IC maps between experiments 1 and 2 closely reproduced the salience network IC map (Fig. 4A)
and table S5). We investigated drug effects on functional connectivity strength within salience and visual (control) network ICs. (A) Overlap between the IC maps from both experiments (P < 0.001). (B) Functional connectivity strength (±SEM) within both ICs for drug conditions (experiment 2). a.u., arbitrary units.

Fig. 4. Drug effects on functional connectivity within salience and visual (control) network ICs. (A) Experiment 1— Experiment 2

References and Notes

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Supporting Online Material
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Materials and Methods
Figs. S1 to S4
Tables S1 to S5
References
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