Acute stress promotes brain network integration and reduces state transition variability

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Despite the prevalence of stress, how brains reconfigure their multilevel, hierarchical functional organization in response to acute stress remains unclear. We examined changes in brain networks after social stress using whole-brain resting-state functional MRI (fMRI) by extending our recently published nested-spectral partition method, which quantified the functional balance between network segregation and integration. Acute stress was found to shift the brain into a more integrated and less segregated state, especially in frontal-temporal regions. Stress also stabilized brain states by reducing the variability of dynamic transition between segregated and integrated states. Transition frequency was associated with the change of cortisol, and transition variability was correlated with cognitive control. Our results show that brain networks tend to be more integrated and less variable after acute stress, possibly to enable efficient coping.

stress | integration | segregation | state transition

Acute stress profoundly shapes our behavioral responses and brain functions. Although several studies have identified the impact of acute stress on functional connectivity (FC) based on modules at a single level (1), stress-induced functional reconfiguration based on hierarchical modules is yet to be delineated.

Functional segregation (i.e., relatively independent processing in specialized systems) and integration (i.e., global cooperation between different systems) are the two basic features in brain networks (2). To better understand the stressed brain, we used the nested-spectral partition (NSP) method to measure segregation and integration in brain networks (3). Compared to classical measures of segregation and integration (e.g., modularity and participant coefficient) that are based on the modular partition at a single level in brain networks (4), this NSP approach defines segregation and integration across multiple levels (3) and has been found to be more powerful in linking brain networks to cognition (5).

In nonstress conditions, resting brains of healthy young adults are close to a balanced state between hierarchical segregation and integration and operate near a critical state to support switching between network states (5). In stressful situations, stress neuromodulators, such as cortisol and noradrenaline, may interact with neural circuits and reconfigure brain functional networks (6). Early life exposure to cortisol has been linked to reduced network segregation (7). Meanwhile, pharmacological functional MRI (fMRI) research showed that noradrenergic activation results in interconnectivity within a distributed network (8). Hence, we hypothesized that, in response to stress, brain networks would deviate from a balanced state toward a less segregated and more integrated state. Maintaining such a state over time may be vital for sustaining a high vigilance level (9). We expected a less variable dynamic transition between integrated and segregated states in resting brains under stress. Here, we performed a reanalysis of the data from our published studies (1, 10). Thirty individuals were exposed to stress (Trier Social Stress Test [TSST]) and nonstress conditions, at least 30 d apart. The cortisol responses were collected at different experiment time points (Fig. 1A), and the stop-signal reaction time (SSRT) was measured as an index of cognitive control.

Results

Stressors successfully evoked elevated cortisol secretion [paired t test, $t(24) = 2.768$, Cohen's $d = 0.793$, $P = 0.011$] and promoted cognitive control [$t(27) = -2.103$, $d = -0.496$, $P = 0.045$; Fig. 1A]. In the NSP method ($SI\ Appendix$), higher H_B reflects stronger network integration, and smaller H_B indicates stronger segregation. In static FC networks, stress vs. control difference in regional measure H_B^i was significantly distributed toward above-zero values (two-sample Kolmogorov–Smirnov test, $d = 0.109$, $P < 0.001$; Fig. 1B), although the global alteration was nonsignificant [$t(27) = 1.246$, $d = 0.298$, $P = 0.223$]. Group comparison identified sensitive regions
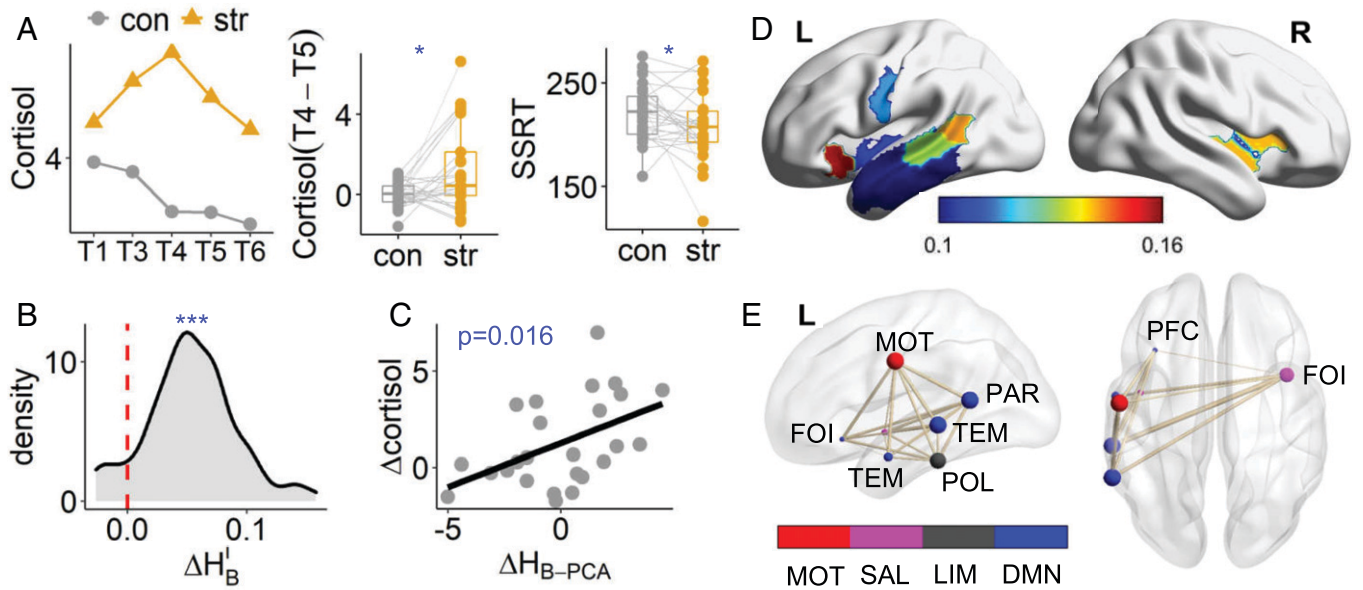
Fig. 1. Static network features. (*A*) Cortisol responses at different experiment time points (T1 to ~T6), cortisol difference (T4 to T5), and SSRT in the stress and control conditions. (*B*) Distribution of stress vs. control ΔH_B^i. (*C*) PCA-obtained overall state alteration predicted the change of cortisol. (*D*) Brain regions with significantly changed H_B^i. (*E*) Visualization of the subnetwork formed by eight regions with significantly alternated H_B^i. The size of nodes represents the change of regional degree (sum of FC). Con, control; DMN, default mode network; FOI, frontal operculum insula; L, left; MOT, somatomotor; PAR, parietal; PFC, prefrontal cortex; POL, temporal pole; R, right; SAL, salience network; str, stress; TEM, temporal. LIM, limbic. *$P < 0.05$; ***$P < 0.001$.

for stress that had significantly increased H_B^i (*d*'s > 0.493, *P*'s < 0.05, uncorrected; Fig. 1*D*). Within the subnetwork formed by these eight regions (Fig. 1*E*), seven had significantly increased connectivity level under stress (*d*'s > 0.544, *P*'s < 0.05, false discovery rate-corrected), including the left somatomotor cortex, bilateral insula, and left temporal regions. The left-lateralization patterns may reflect increased vulnerability of the left hemisphere to stress (11). These alterations were not detected by classical connectivity analysis (1, 8), showing the added value of the NSP method.

Principal component analysis (PCA) was applied to the H_B^i difference to obtain an overall stress-induced state alteration measure ΔH_{B-PCA}. Larger ΔH_{B-PCA} indicates stronger changes toward integration under stress. ΔH_{B-PCA} was positively correlated with the change of cortisol [linear regression, $F(1,23) = 6.797$, $P = 0.016$; Fig. 1*C*], but not with SSRT [$F(1,26) = 6.797$, $P = 0.441$], indicating that stress-related hormone changes are related to brain-network reorganization.

For dynamic FC networks, the dynamic transition between segregated and integrated states was measured by the time-resolved H_B^i (Fig. 2*A*). We first calculated the transition frequency f between segregated and integrated states (*SI Appendix*). The stress vs. control transition frequency f^i of regions was distributed toward above-zero values ($d = 0.088$, $P < 0.001$; Fig. 2*C*), especially in frontal-temporal regions (*d*'s > 0.411, *P*'s < 0.05, uncorrected; Fig. 2*B*), although the global change was nonsignificant [$t(27) = 1.229$, $d = 0.289$, $P = 0.230$]. The overall change of transition frequency derived from PCA was positively correlated with the change of cortisol [$F(1,23) = 4.611$, $P = 0.042$; Fig. 2*D*], but not with SSRT [$F(1,26) = 0.718$, $P = 0.404$].

We further measured the transition variability F^i, defined as the standard variance of time-resolved H_B^i that is related to the fluctuation range of H_B^i during transition. The stress vs. control regional variability F^i was significantly distributed toward negative values ($d = 0.121$, $P < 0.001$; Fig. 2*F*), and the global-scale variability was decreased [$t(27) = -2.626$, $d = -0.599$, $P = 0.014$]. These changes were prominent in frontal-temporal

regions and occipital pole (Fig. 2*E*; *d*'s < −0.462, *P*'s < 0.05, uncorrected). The PCA-derived overall change of variability was positively correlated with SSRT [$F(1,26) = 6.027$, $P = 0.021$; Fig. 2*G*], but not with the change of cortisol [$F(1,23) = 0.220$, $P = 0.643$].

Discussion

Our study took a hierarchical module approach, which is more effective in revealing the intricate role of segregation and integration than graph-based network analysis at a single level. Our findings delineate stress-induced brain-network reconfiguration in terms of integration, segregation, and state transition and provide a candidate mechanism of stress-related behavioral and physiological changes (10).

Both static and dynamic network analyses show that acute stress shifts the brain into a state that fosters integration in frontal-temporal regions. In concert with meta-analysis findings showing that stress induces concordant regional activity in the inferior frontal region and insula (12), our results suggest that stress may coordinate activity between otherwise-segregated circuits and integrate information exchange among frontal-temporal regions. As subcortical structures are underrepresented in standard MRI atlases, how other stress-sensitive regions (12), such as the amygdala and hippocampus, contribute to network organization needs to be studied by using a unified whole-brain-network partition. Cortisol plays a critical role in metabolism by mobilizing energy resources and has acute, nongenomic effects on regional brain activity (13). Future pharmacological fMRI research may further examine the causal links between changes in hormones and enhanced stress-related network integration (8).

Our work suggests that stress may reduce the range of dynamic transition between brain states to keep the brain network in a less-segregated state, while still permitting a relatively high rate of state transition. Fast transition indicates high network flexibility, which is needed to enable readiness for swift responses. The correlation between cortisol and transition
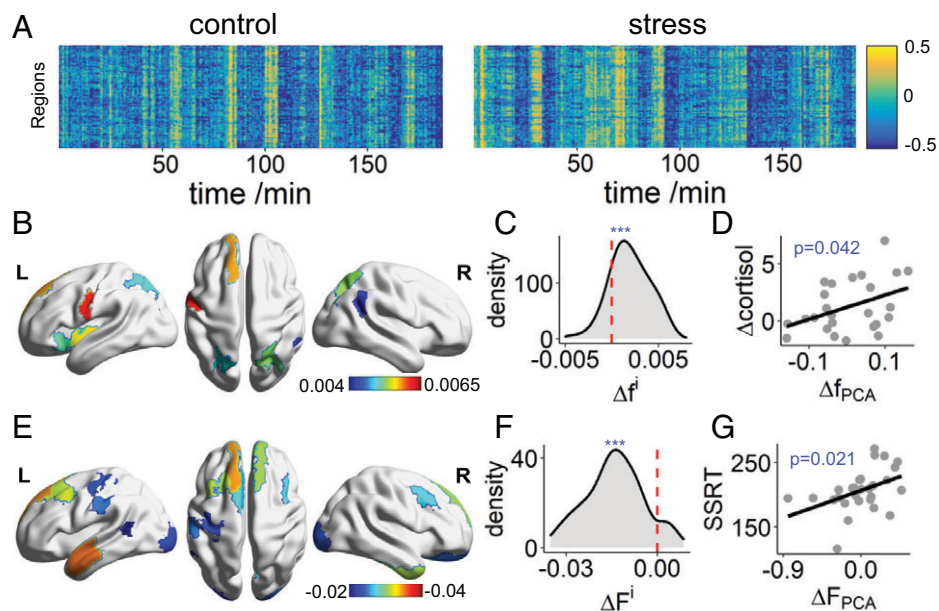
Fig. 2. Network dynamic transitions. (*A*) Dynamic transitions between segregated and integrated states concatenated across participants. Color represents regional H_B^i. (*B*) Regions with significantly increased transition frequency. (*C*) Distributions of stress vs. control difference in transition frequency. (*D*) PCA-obtained overall change of transition frequency and the change of cortisol. (*E*) Regions with significantly decreased transition variability. (*F*) Distributions of stress vs. control difference in transition variability. (*G*) PCA-obtained overall change of transition variability and SSRT at stress. L, left; R, right. ********P* < 0.001.

frequency suggests that cortisol may support stress-related vigilance. High state-transition variability, however, may momentarily deviate the brain toward a segregated state, which may lead to attentional lapses (14). Research showed that dynamic FC variability in the default network relates to ongoing mind-wandering, and attention fluctuations are predicted by sustained attention-network strength (9, 15). By inhibiting state-transition variability, stressed brains may support high levels of vigilance and volitional control (10). The significant correlation between reduced network variability and better cognitive control further supports this notion.

Our research sheds light on stress-induced brain reorganization by demonstrating that acute stress promotes brain integration and reduces state-transition variability. A more integrated and less variable brain network may help orchestrate adaptive responses to stressful challenges. These network features may be useful for clinical diagnosis of stress-related disorders and for pharmacological or behavioral interventions to improve stress management. Our findings hold the potential to inform system-wide models of the neural bases of stress-induced behavioral changes and represent an important step forward in linking brain architecture to atypical mental states.

Materials and Methods

The study was conducted by using a within-subject design, in which one session included an acute stress manipulation (TSST) and one included a control condition. Participants underwent a resting-state fMRI scan and three runs of the stop-signal task. Saliva samples and affect ratings were collected at six time points. All participants provided written informed consent, and the study was approved by the South China Normal University Institutional Review Board. Details are provided in *SI Appendix*.

Data Availability. All data are available on the Open Science Framework (https://osf.io/swdjb/).

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