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ORIGINAL ARTICLE

Context Matters: Situational Stress Impedes Functional Reorganization of Intrinsic Brain Connectivity during Problem-Solving

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Abstract

Extensive research has established a relationship between individual differences in brain activity in a resting state and individual differences in behavior. Conversely, when individuals are engaged in various tasks, certain task-evoked reorganization occurs in brain functional connectivity, which can consequently influence individuals' performance as well. Here, we show that resting state and task-dependent state brain patterns interact as a function of contexts engendering stress. Findings revealed that when the resting state connectome was examined during performance, the relationship between connectome strength and performance only remained for participants under stress (who also performed worse than all other groups on the math task), suggesting that stress preserved brain patterns indicative of underperformance whereas non-stressed individuals spontaneously transitioned out of these patterns. Results imply that stress may impede the reorganization of a functional network in task-evoked brain states. This hypothesis was subsequently verified using graph theory measurements on a functional network, independent of behavior. For participants under stress, the functional network showed less topological alterations compared to non-stressed individuals during the transition from resting state to task-evoked state. Implications are discussed for network dynamics as a function of context.

Key words: brain state transition, connectome predictive modeling, graph theory, networks, situational stress

Introduction

Intrinsic patterns in functional connectivity predict a variety of meaningful diagnostic and behavioral outcomes (Krienen et al. 2014; Rosenberg, Finn, et al. 2016a; Tavor et al. 2016). At the same time, a host of literature documents that as people engage in cognitively demanding tasks, initial network components reorganize and become more specialized (Hugdahl et al. 2015; Schultz and Cole 2016; Bolt et al. 2017). Yet, to what extent network reorganizations occur from rest to task as a function of context, and the consequences this reorganization (or lack thereof) has for performance on cognitively demanding tasks, remains unclear (Mill et al. 2017). This study investigates how situationally stressful contexts alter the relationship between resting-state and task-dependent brain network dynamics as they relate to performance on cognitively intensive tasks. Examining whole-brain connectivity patterns indicative of underperformance both before and during completion of a problem-solving task in either the presence or absence of stressors, we investigate whether context can dictate the link between specific brain patterns and underperformance by meaningfully altering transitions from rest to task and, in this case, by inhibiting adaptive reconfiguration to task in a manner predictive of success on cognitively demanding tasks.

Resting-State and Task-Dependent Brain Patterns Are Associated with Optimal Cognition

Brain patterns in functional connectivity at rest have been linked to a variety of task-related differences and cognitive performance capabilities, including emotion regulation (Morawetz et al. 2016), attention (Rosenberg, Zhang, et al. 2016b), distractibility (Poole et al. 2016), fluid intelligence (Finn et al. 2015), memory (Wang et al. 2010), and working memory (Magnuson et al. 2015). As such, resting-state networks are thought to reflect an underlying functional architecture that shapes network dynamics during cognitive processing (Wig et al. 2011; Mueller et al. 2013). As the brain undergoes transition from intrinsic to performance-related connectivity, intrinsic networks reorganize by recruiting different or additional regions to assist with specialized, functional processes (Cole et al. 2014). Moreover, the capacity to reorganize efficiently is important for successfully meeting the demands of a given task (Braun et al. 2015). Specifically, the ability to coordinate among process-relevant regions, while excluding noise from irrelevant regions, is ideal (Cole et al. 2013).

Problem-solving is one such specialized functional process that is supported by a variety of functional neural components given its ultimate reliance on different executive processes, including updating or working memory, inhibition, and shifting (Miyake et al. 2000). Thus, it is likely that both initial, intrinsic network properties and the ability to transition into alternate network configurations in response to task demands—configurations that instantiate successful execution of executive processes—collectively bear on successful outcomes (Anderson et al. 2014). For example, problem-solving, intelligence, and visuospatial and working memory are all fortified by greater frontoparietal network (FPN) cohesiveness, both at rest and during performance (Cocchi et al. 2013; Markett et al. 2014). In contrast, intrusion from other components during problem-solving appears to interfere with FPN connectivity, undermining optimal processing. For instance, the activation of networks associated with self-referential and social cognition or emotion processing at times when people are attempting to problem solve and predict worse performance, likely due to competition for limited cognitive and neural resources (Liston et al. 2009; Henckens et al. 2012; van Ast et al. 2016). This perspective is supported by recent findings, indicating that stressed individuals' suboptimal problem-solving performance was characterized by less global neural network stability (Liu, Ein, et al. 2017a; Liu, Amey, et al. 2017b). This suggests that increased interactions between regions integral for emotion processing and regions integral for optimal performance on cognitively demanding tasks ultimately may be bad for performance as a whole.

Context and Intrinsic Properties May Influence the Brain's Ability to Adaptively Transition between States

If intrinsic networks can influence task-related neural responses, then it stands to reason that they do so by either facilitating cognition that is congruent with demands of a task (when the task requires cognitive operations that are similar to what is already more intrinsically connected) or hindering cognition when the demands of a task conflict (e.g., if a performance context requires problem-solving, but also introduces evaluative stress, thus facilitating self, social, or emotion-oriented processes). In the case of the latter—hindered cognition—it is possible that individual predispositions in resting connectivity result in maladaptive neural activation, which acts to reduce the efficiency of adaptation to the ostensible task demands.

Borrowing from clinical literature, past research suggests that neural transition from default mode network (DMN) dominant activity to FPN dominant activity is generally facilitated among depressed and anxious individuals, with the reverse observed among nondepressed individuals (e.g., in depressed individuals, FPN activation couples with more error-related rumination processing compared with DMN activation, and vice versa for nondepressed individuals; Hamilton et al. 2011). Other examples of altered brain patterns persisting from rest to task have been identified in specific cognitive traits (Vidaurre et al. 2017), personality dispositions (Dubois et al. 2018), and additional clinical instances such as autistic spectra disorders (Assaf et al. 2010), bipolar disorder, and schizophrenia (Rashid et al. 2014). These intrinsic brain patterns may be uniquely problematic when situational demands conflict with neural diatheses, that is, in specific contexts, certain individuals may be more prone to exhibit maladaptive brain patterns at rest that persist into a given task. In addition to rumination-based dispositions like depression (e.g., Berman et al. 2011), another interesting alternative factor that may hinder task-oriented reconfiguration is that individuals who experience stress chronically may learn to link stress-oriented memories and emotions with other similar, negative affect-inducing contexts (e.g., via mood congruent memory recall; Smith et al. 2005, 2006; Forbes et al. 2018). In these instances, specific neural responses to situational stressors could become fortified, or more normalized over time, such that affectively congruent contexts spontaneously elicit learned neural stress responses that indirectly interfere with normative network transitions from rest to task (e.g., Gagnon and Wagner 2016).

Moreover, contextual factors also exert an influence on network properties throughout the brain in ways that may have downstream consequences for core processes like executive functioning. Contexts that are emotionally or motivationally salient enhance global network connectivity (Kinnison et al. 2012); in particular, stress contexts can facilitate prolonged exchange between networks involved in control and vigilance (Hermans et al. 2011). Importantly, stress during recollection (such as may arise the course of certain performance tasks) encourages greater activation in networks that respond to threat, while discouraging networks that support higher-order, goal-directed thinking (Gagnon and Wagner 2016). This trend serves to mobilize cognitive resources for vigilance and threat responses, but at the expense of deliberative thinking. As stress strengthens connections in the salience network, this directly undermines the cooperation of executive control network regions (Hermans et al. 2014). At the behavioral level, an important consequence of these alterations is poorer recall (Shields et al. 2017), which thwarts optimum performance. Taken together, prior evidence suggests that normative neural transition between brain states is altered in contexts that engender stress and that this trend may be particularly worse for individuals with relevant intrinsic network properties.

The current study aims at examining whether a neural transition tendency from rest to task occurs for individuals differently according to their contexts, which in this case consists of a situation being more or less stressful. If rest-to-task reconfiguration was influenced due to situational stress, this pattern would linger for those under stress but not for their nonstressed counterparts.

To address these premises, it is necessary that participants should not differ across confounding psychological dimensions (e.g., math anxiety) that would be associated with suboptimal cognitive functioning aside from context. One way to randomly select from a sample of cognitively normal individuals, ensure all individuals are exposed to the same stimuli, but place only one group uniquely in a stressful context is to prime stereotype-based stress (SBS) in women. SBS is a robust situational stressor that individuals experience as a result of primed context cues, suggesting they may be negatively evaluated based on their membership in a stigmatized group, not unlike studies on social evaluative threat that utilize the common Trier Social Stress Test (Schmader et al. 2008; Hall et al. 2015; Forbes et al. 2018). Consequently, this form of evaluative threat initiates a persistent cycle of hypervigilance and attempts to regulate accompanying emotions, both of which have been shown to interfere with cognitive capacity that is otherwise needed for optimal performance on cognitively intensive tasks (Schmader et al. 2008). As such, SBS provides a means to place one group under stress while holding other aspects of the situation and individual constant.

Finding Connectivity-Based Neuromarker Associated with Cognition

Taken together, both intrinsic and task-dependent brain states are associated with performance, and stress may alter how intrinsic and task-related brain networks interact. Moreover, people vary in the extent to which they are susceptible to stressors, suggesting performance is affected by individual differences in resting network connectivity interacting with task-related context. Investigating intrinsic networks instantiating multiple psychological processes is inherently complex and thus traditional hypothesis-driven approaches may fail to identify unique patterns characterizing performance outcomes in stressful contexts. One promising approach to addressing this complexity is connectome predictive modeling (CPM)—a completely data-driven approach that treats all possible pairs of brain regions and their associated connectivity values as individual predictors. CPM then constructs a model (the "connectome") that maximally fits behavioral scores (Rosenberg et al. 2017; Shen et al. 2017). As such, CPM is a data-driven, predictive metric, which can be leveraged to identify what aspects of network properties across the whole brain characterize underperformance in individuals. Critically, connectivity provides a window into how different regions are functioning "in relation" to each other. As communication occurs rapidly across multiple timescales during problem-solving, we measured neural activity and connectivity using electroencephalography (EEG), which affords optimal temporal and frequency resolution that would be critical for disambiguating such complex relationships.

Hypotheses

We first collected EEG data from resting state and then placed men and women in contexts that were either stress-free or uniquely stressful to only one group of women. Individuals then completed cognitively intensive, that is, difficult math problems while continuous EEG activity was recorded. We hypothesized that stress would exert an impact on individuals' transition from intrinsic network states at rest to network states more adaptive for cognitively demanding tasks. In particular, using CPM, we investigated whether for women under stress (i.e., women in SBS contexts), network markers of performance at rest would continue to predict performance outcomes when applied to task activity, compared with nonstressed women and all men. This would imply interference with a typical network reconfiguration otherwise normally evident during transitions from rest to problem-solving. Conversely, to the extent the absence of stress allowed for participants to more easily transition from brain states optimal (or suboptimal) for performance at rest to performance during the task, individuals not under stress—and regardless of gender—would exhibit a network of regions predictive of performance "during" the task that differed from the network associated with performance among everyone at rest. Furthermore, we hypothesized that some individuals might be particularly prone to underperforming (or, conversely, to resilience), based on intrinsic network features at rest (e.g., network deviations produced by stress that arise via rumination-based predispositions or that can be learned over time). Statistically speaking, these individuals would make up the bottom and upper percentiles of the population in terms of how strongly or weakly their intrinsic patterns at rest predicted underperformance within the stress context.

Moreover, if stress maintains the predictive power of the intrinsic network markers because it inhibits transition from a default resting state to a task-oriented state in general, we might also expect other, broader brain patterns consistent with this less dynamic response. To provide and index of this, we also examined clustering coefficient and global efficiency, two measures that assess the topography of global functional matrices (local information transfer and information transfer average across all nodes, respectively). It has been well established that the transition of brain networks from rest to task and the ability to accomplish complex cognitive tasks more robustly and efficiently coincide with increases in clustering coefficients and global efficiency (Bullmore and Sporns 2019; Bolt et al. 2017). Thus, if stress interferes with this transition in general, we would expect women in the stress condition to exhibit reduced clustering and global efficiency compared with individuals in all other conditions.

Materials and Methods

Participants

One hundred and fifty-eight white participants (85 females) taken from a larger database (Forbes et al. 2018) completed this study for payment. For the sample size, we aimed for enough numbers of participants to detect a small-to-medium size effect in both the primary regression analyses reported in the studies and the 2 × 2 moderated regression analyses. A sensitivity analysis on G∗ Power revealed that 158 participants would be sufficient to capture a medium size effect (Cohen's $f = 0.22$) for primary regression analyses, with an alpha of 0.05, power of 0.80. Also, 158 participants would be sufficient to capture a medium size effect (Cohen's $f = 0.30$) for 2 × 2 between-subjects group analyses, with an alpha of 0.05, power of 0.80 using 4 groups.

We recruited only participants who were aware of the negative female math stereotype. Specifically, participants needed to score a 3 or lower on the following question during a pre-study screening in order to qualify for the current study: "Regardless of what you think, what is the stereotype that people have about women and men's math ability" (1 = men are better than women; 7 = women are better than men)." Seven participants were excluded in EEG analyses because their EEG data lacked one or more specific cognitive tasks (either resting or math-solving tasks).

Procedure

Upon entering the room, participants were taken to a sound-proofed EEG chamber, seated in front of a computer, and set up for EEG recording. Participants were randomly assigned to either the "stress condition" (i.e., eliciting stereotype threat-based stress for women) or the "control condition." In the stress condition, participants were told that the results of the following tasks would be diagnostic of their math intelligence. In the control condition, participants were told that the results of the following tasks would be diagnostic of the types of problem-solving techniques they prefer (Forbes and Leitner 2014; Forbes et al. 2015). To further prime SBS in the stress condition, participants marked their gender, sessions had a male experimenter present, and all instructions were read via a male experimenter's voice (following protocol of Forbes et al. 2018). Conversely, participants in the control condition did not mark their gender, all sessions had all female experimenters present, and all instructions were read via a female experimenter's voice. Following the instructions, participants completed a math feedback task for 34 min. Participants then answered a series of post-task questionnaires, were debriefed, and were paid for their participation.

Resting State

Baseline EEG data were collected before the task began. Participants were asked to sit quietly in the EEG chamber with their feet resting on the ground and their arms on armrests. Participants were asked to keep their eyes open, blinking normally, or closed for 60 s at a time for 5 min (eyes open and eyes closed blocks were counterbalanced across participants).

Math Feedback Task

Participants completed a 34-min math task (Forbes et al. 2018). The task consisted of standard multiplication and division problems (e.g., 7 × 20 =) that initial pilot tests confirmed varied in degree of difficulty (easy, medium, and difficult, ensuring all participants would solve problems correctly and incorrectly). In a given trial, participants were provided with 3 answer options for each problem (A, B, or C), with the answer to each problem randomly placed in 1 of the 3 answer positions. Participants then answered each multiple choice problem using a button box placed on their laps and were not permitted to use scratch paper. After entering their answer, participants received veridical feedback on the accuracy of their answer on their monitor for a duration of 2 s. After the feedback was presented, the next problem was presented on the screen. Each problem was presented for a maximum of 16 s. If participants did not complete a given problem within 16 s, they would receive negative feedback (i.e., that they got the problem wrong). On average, participants completed 83.9 problems, among which around 60% were difficult problems and 40% were easy problems. No participants were excluded due to an insufficient number of EEG trials. Dividing the total number of correct responses by the total number of attempted problems gave us our calculation for math score accuracy for both easy and difficult problems, respectively.

EEG Measurement and Preprocessing

Recording

Continuous EEG activity was recorded using an ActiveTwo head cap with an ActiveTwo Biosemi system (BioSemi, Amsterdam, the Netherlands). Recordings were collected from 128 Ag-AgCl scalp electrodes and bilateral mastoids. Two electrodes were also placed next to each other 1 cm below the right eye to record startle eye-blink responses. A ground electrode was established using BioSemi's Common Mode Sense active electrode and Driven Right Leg passive electrode. EEG activity was digitized with ActiView software (BioSemi) and sampled at 2048 Hz. Data were downsampled post-acquisition and analyzed at 512 Hz.

Preprocessing

For feedback analyses, the EEG signal was epoched and stimulus locked from 500 ms pre-feedback presentation to 2000 ms post-feedback presentation. EEG artifacts were removed following FASTER (Fully Automated Statistical Thresholding for EEG artifact Rejection) (Nolan et al. 2010) preprocessing protocol—an automated approach to cleaning EEG data that is based on multiple iterations of independent component analysis (ICA) and statistical thresholding analyses. In FASTER, EEG trials are filtered by a 0.3- to 55-Hz band-pass FIR filter and baseline-corrected using the time series from 100 ms preceding onset of tasks. First, EEG channels with significant unusual variance (operationalized as activity with an absolute z score larger than 3 SD from the average), average correlation with all other channels, and Hurst exponent were removed and interpolated from neighboring electrodes using spherical spline interpolation function. Second, EEG signals were epoched and baseline-corrected, and epochs with significant unusual amplitude range, variance, and channel deviation were removed. Third, the remaining epochs were transformed through ICA. Independent components with significant unusual correlations with EMG channels, spatial kurtosis, slope in filter band, Hurst exponent, and median gradient were subtracted, and the EEG signal was reconstructed using the remaining independent components. Finally, EEG channels within single epochs that displayed significant unusual variance, median gradient, amplitude range, and channel deviation were removed and interpolated from neighboring electrodes within those same epochs.

Source Localization

Forward and inverse whole-brain models were calculated with an open-access software, MNE-python (Gramfort et al. 2013, 2014). The forward model solutions for all source locations located on the cortical sheet were computed using a 3-layer boundary element model (Hamalainen and Sarvas 1989) constrained by the default average template of anatomical Montreal Neurological Institute magnetic resonance imaging (MRI). Cortical surfaces, extracted with FreeSurfer (Fischl 2012), were subsampled to about 10 240 equally spaced vertices on each hemisphere. The noise covariance matrix for each individual was estimated from the prestimulus EEG recordings after the preprocessing. The forward solution, noise covariance, and source covariance matrices were used to calculate the dynamic statistical parametric mapping (dSPM) estimated (Dale et al. 2000) inverse operator (Dale et al. 1999). Inverse computation was done using a loose orientation constraint

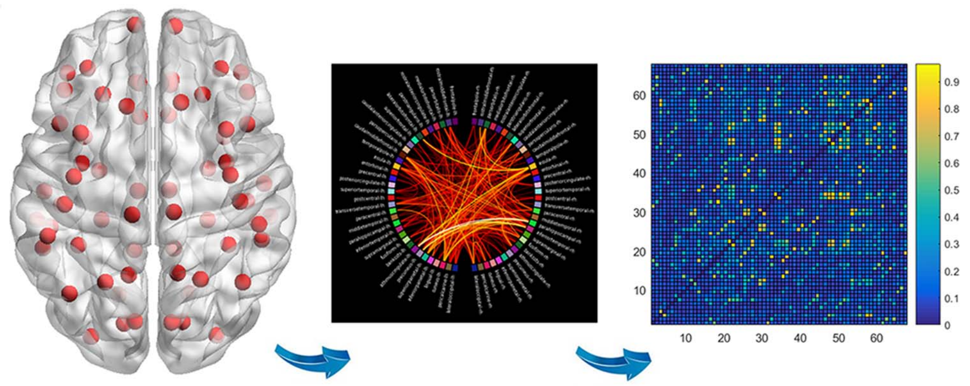

Figure 1. Construction of adjacency matrix. The cortical surface was divided into 68 anatomical regions of interest (ROIs) based on the Desikan–Killiany atlas (Desikan et al. 2006). PLVs were calculated to define the connectivity strength between all possible pairs of nodes. Finally, a symmetric 68 × 68 adjacency matrix was created to record all pairs' connectivity strength.

(loose = 0.11, depth = 0.8) (Lin et al. 2006). The surface was divided into 68 anatomical regions of interest (34 in each hemisphere) based on the Desikan–Killiany atlas (Desikan et al. 2006). For each participant, a time course was calculated for each area/node by averaging the localized EEG signal of all of its constituent voxels at each time point during task performance.

Functional Connectivity Estimation and Network Construction

Frequency coupling was calculated within identical frequency bands (theta: 4–8 Hz; alpha: 8–15 Hz; beta: 15–30 Hz; gamma: 30–55 Hz) and temporal periods between all pairs of nodes. Phase locking values (PLVs) (Lachaux et al. 1999), which measure variability of phase between two signals across trials, were utilized to define connectivity strength. In other words, for every participant, condition, and frequency band, we obtained a symmetric 68 × 68 adjacency matrix, representing all pairs of nodes—or "edges"—in each participant's whole-brain network during a given period (Fig. 1). For the math task period, PLVs were averaged from the first 1000 ms after the math problems appeared, because the first 1000 ms involved a common time interval of all trials for each participant in solving math problems. For the resting-state period, PLVs were averaged from the first 500 ms after the onset of the initial fixation cross.

Prediction of Functional Connectivity to Behavior

To assess the relevance of intrinsic functional neural network connections to behavior, math scores (for both easy and difficult problems) were regressed on each of the resting-state network edges for all frequency bands, from $n - 1$ participants. The resulting 2244 × 4 = 8976 *P*-values for each regression were recorded in a 68 × 68 symmetrical matrix from 4 frequency bands, by participant. To identify significant edge associations and to minimize false positives stemming from multiple comparisons, a *P*-value threshold criterion of 0.001 was applied to all matrices. Thus, only pairs whose *P*-values were below 0.001 were retained as part of the network (Fig. 2). The identified network was then utilized for the left-out participant in both rest and task states to test their predictive power to math performance. This procedure repeated n times via a leave-one-out cross-validation.

Graph Theory Analysis of Whole-Brain Functional Networks

Two measures were chosen to explore the topography alteration of the global functional matrices: "clustering coefficient" and "global efficiency." Clustering coefficient measures represent the extent to which nodes in a graph tend to cluster together. This index provides a measure of local information transfer. Global efficiency is a measure of information transfer average across all nodes. Given that the transition of brain networks from rest to task, as well as the ability to optimally perform on complex cognitive tasks, coincides with increases in clustering coefficients and global efficiency (Bolt et al. 2017; Bullmore and Sporns 2009), we would expect global efficiency and clustering measures to show less increase from rest to task among women in the stress condition compared with those in the other conditions. Further information about these metrics can be found elsewhere (Rubinov and Sporns 2010). Graph theory analysis was performed using the Brain Connectivity Toolbox in MATLAB (https://sites.google.com/site/bctnet).

Clustering coefficient and global efficiency were both conducted on binarized graphs. To sparse graphs, the whole-brain functional networks were thresholded using a range of density thresholds with any edge greater than the threshold set to "1" and any edge less than the threshold set to "0." Density thresholds ranged from 5% (the minimum threshold where all graphs were fully connected) to 70% in 5% increments. Using multiple definitions of the graph model ensured that group differences were not dependent on arbitrary factors such as thresholds (Garrison et al. 2015; Kim et al. 2020).

Besides the graph theory measures in binarized graphs, global network strength (by averaging the connectivity values across the whole-brain network) was also explored in weighted graphs for group comparisons.

Results

Manipulation Check: Stress and Math Performance Score

Initial analyses on amygdala activity (assessed via startle probes elicited to positive and negative feedbacks and operationalized as a measure of stress) were conducted in Forbes et al. (2018). These analyses indicated that all participants elicited

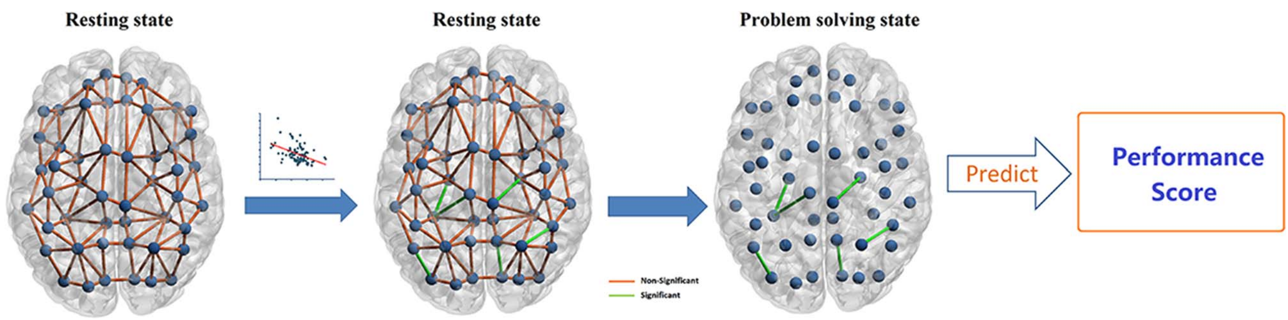

Figure 2. An illustrative example of CPM in our study. Simple linear regressions were conducted for each edge in the (resting state) connectivity matrices and math performance score, producing a matrix of pairs. The matrix was then thresholded based on *P* values, retaining a subset meeting significance criterion (note the green edges in the figure are a hypothetical example—the actual edges resulting from CPM analyses are outlined in the Results section). Linear regression analyses were then likewise conducted for task-related connectivity and problem performance scores in left-out participant.

marginally greater amygdala responses to negative feedback received on the math feedback task compared with positive feedback and women elicited larger amygdala responses to feedback compared with men. However, only women in the stress condition exhibited a unique nonlinear (quadratic) relationship in their amygdala responses to feedback over time, suggesting a unique stress response among individuals experiencing evaluative threat. Women in the stress condition also performed worse on the math task compared with all other conditions, a typical finding in the evaluative threat literature (planned contrast on math test accuracy: $t(1, 156) = 3.17$, $P = 0.002$, $d = 0.51$). These behavioral results overall provide supporting evidence that the evaluative threat and thus stress induction manipulation was successful (see details in Supplementary Results).[1]

Network Prediction of Performance

To clarify relationships between edges and performance (connections that had positive or negative relationships with performance), edges were further grouped into two separate networks by the valence of their *R* values. By averaging all edge's "PLV values" within each of the networks, a summary statistic—"network strength"—characterized each participant's degree of positive and negative connectivity. Math scores were then predicted using the "negative" and "positive" network strength values, respectively, for both easy and difficult problems. Leave-one-out regression showed that the math performances predicted using the "negative" and "positive" network strength were significantly correlated with the observed math performance for both easy and difficult problems (P's < 0.001). These results validated the findings from past literature that intrinsic patterns of functional connectivity at rest were able to predict executive task performance (Reineberg et al. 2018), regardless if the person was in task.

We next sought to determine whether these networks—originally defined from resting period data—remained predictive when applied to task-related activity. Individual's math

1 Overall, these supplementary investigations provided converging evidence from differences in EMG startle responses, to anxiety modulated by stereotype awareness, to quadratic relationships between startle (i.e., amygdala) responses and behavioral measures associated with stress that our stress manipulation was successful and that other potential confounds did not influence the experience of stress among women in the stress condition compared with nonstressed participants.

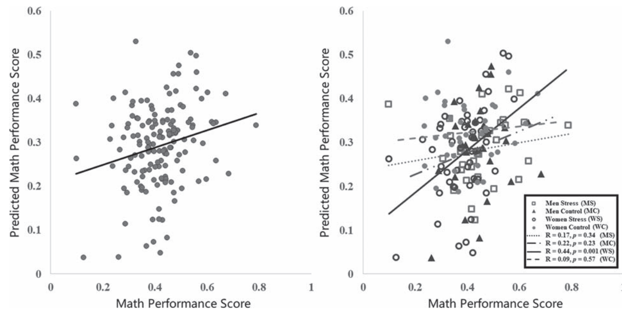

Figure 3. (*A*) The same network identified in resting-state activity, when applied to task-related activity, was also predictive of math performance scores using cross-validation. This effect was significant only for performance on difficult math problems. (*B*) The positive relationship between observed performance and predicted performance was driven by women experiencing situational stress. This effect was not found in any other experimental conditions.

scores on easy and difficult problems were, again, each predicted by the network strength of the same two positive and negative networks (i.e., based on the same edges found at rest) "during the task period" using leave-one-out cross-validation.

The negative network remained predictive of performance for difficult problems during task activity ($\beta = 0.25$, $F[1149] = 8.32$, Cohen's f^2=0.09, $P = 0.004$). All other relationships were nonsignificant during task activity (all $Ps > 0.22$; Fig. 3A). That is, brain regions collectively exhibiting an increase in activation were associated with decreased performance on difficult (i.e., the most cognitively intensive) problems specifically.

Contextual Influence

Next, we sought to determine whether context, and thus stress, played a role in the predictive relationship between task-related network strength and performance. Double moderation analyses assessed network strength's predictive relationship with math scores (in the previously identified network from resting state), as a function of condition and gender (i.e., the moderators). These analyses used unstandardized regression coefficients and 95% bias-corrected confidence intervals (CIs) from 10 000 bootstrap estimates (Hayes 2013; model 3). 95% CIs are considered significant if the interval (e.g., [0.3, 0.7]) does not contain zero (Cumming 2008). Results revealed a significant interaction between gender and condition ($P = 0.0384$, 95%, CI = [0.015, 0.52]). Conditional effects identified that, only for women in the stress condition, increased activation of the negative network during solving difficult problems predicted math performance (β = 0.54, $F[1, 47] = 10.48$, Cohen's f^2=0.25, $P = 0.0004$). Conversely, no such relationships were found among control women, as well as men in both conditions (all $Ps > 0.23$), suggesting that the relationship between the negative network during task and performance outcomes, which was initially derived via resting-state analyses, only persisted when women were experiencing stress (Fig. 3B).

Potential Functions of Identified Brain Regions

Having determined that intrinsic neural patterns interacted with context to predict performance, we considered what functional themes might characterize, in particular, worse performance (i.e., the negative network). Assessing the specific functional roles of brain regions identified via data-driven approaches is a frequent challenge in neuroscience, one that is often susceptible to reverse inference biases. To attenuate this as best as possible, we conducted an exploratory meta-analysis using the "Neurosynth" program to outline potential functional roles of the regions identified from CPM analyses (http://neurosynth.org; Yarkoni et al. 2011). Given coordinates of a given brain voxel, Neurosynth provides terms most often associated with the area, ranked by posterior probability (pp) and z scores.

Examining the negative networks from all leave-one-out cycles at rest, activation of 3 edges during the task (identified at rest) was consistently found to predict poorer performance for women in the stress condition (note that these edges were identified among all participants in the cross-validation trials but based on moderated regression analyses, these findings were ultimately driven by women in the stress condition). The first edge consisted of connectivity between right supramarginal gyrus (R-SMG) and right cuneus (R-CUN) in the theta band. The second edge consisted of connectivity between right pars-opercularis (inferior frontal gyrus; R-IFG) and left precentral cortex (L-PreC) in the beta band. The third edge consisted of connectivity between R-SMG and left superior-parietal cortex (L-SPC) in the beta band.

Evaluative threats have been described to undermine performance by initiating a cycle of hypervigilance and negative arousal, which is theorized to detract from requisite executive function resources (Schmader et al. 2008). We found some evidence of correspondence with these general themes in Neurosynth results; nodes of the negative network were associated with terms related to social cognition, emotion, and attention. For instance, R-IFG was strongly associated with "social" and "empathy" across both pp and z scores, as was L-SPC and R-CUN for "spatial attention." Other frequent terms included "TOM" (theory of mind), "intentions," and "mental state," as well as "visual" and "spatial attention." We observed the broad trend that edges appeared to reflect links between functions that revolve around internally oriented processing (self or social cognition; Hoffmann et al. 2016) and those that typically relate to problem-solving (visuospatial attention [VSA], calculation, and responding; Anderson et al. 2014). However, these findings are exploratory in nature, and as such, relationships remain tentative. Some discrepancies existed between pp and z scores as well (e.g., "emotion" and "pain" were evident when examining z scores but not pp). We reserve further consideration about edge relationships, as well as full details regarding both networks, for the Supplementary section.

Independent Replication of Primary Findings

To further validate the generalization of the connectivity markers (the 3 edges found at rest) to math underperformance and the reliability of context influence during the rest–task transition, identical functional connectivity models were applied to an independent data set consisting of EEG data collected from 101 white participants 2 years after Study 1. Results showed that significant negative relationship between summation of negative network strength and performance on the difficult math was found at rest. Furthermore, only women in the stress condition performed worse on difficult math problems to the extent that the negative network (identified originally at rest) was better connected during the solving of difficult math problems, confirming once more that the relationship between the network and performance on difficult math problems was evident only when individuals were experiencing stress. More details can be found in Supplementary Results.

Relevance of Functional Connectivity to Behavior in Nonstressed Groups

If nonstressed individuals can spontaneously transition from intrinsic network properties to more adaptive network properties associated with optimal performance, then the next question is what are these network states? To answer this, we conducted an additional CPM analysis on task-related EEG activity for everyone but women in the stress condition. These analyses yielded positive and negative networks that significantly predicted participant's math performance during the math task (P's < 0.01).

To determine whether these network–behavior relationships—originally defined from task period data—were either evident intrinsically (i.e., remained predictive when applied to resting-state activity) or reorganized during the rest-to-task transition (i.e., were not predictive in resting-state activity), math scores of difficult problems were predicted by the network strength of these edges (i.e., based on the same edges at task) during the rest period. Results revealed that both positive and negative networks were not predictive of performance for difficult problems during resting-state activity (P's > 0.382; Fig. 4). This suggests that edges identified as predictive of performance during the task were the product of functional reorganization from rest to task for nonstressed participants.

Time-Variant Relevance of Functional Connectivity to Behavior

CPM-based analyses suggest that maladaptive relationships between brain-based connectivity and math underperformance remain only among individuals experiencing stress. These findings were specific to the first second of problem-solving process, however. The question then remains as to whether this maladaptive network pattern is more pronounced during a specific period of time during the problem-solving process. Thus, next we explored whether this uninterrupted connectivity–behavior relation was more pronounced during a specific problem-solving period or was a more pronounced phenomena across the entirety of a problem-solving epoch. To do this, a 5000 ms epoch was extracted from each problem-solving interval, and the 5000 ms epoch was spliced into 1000-ms time windows with an overlap of 500 ms. Whole-brain functional networks across frequency bands were established using the time series from 68 brain regions within every single time window.

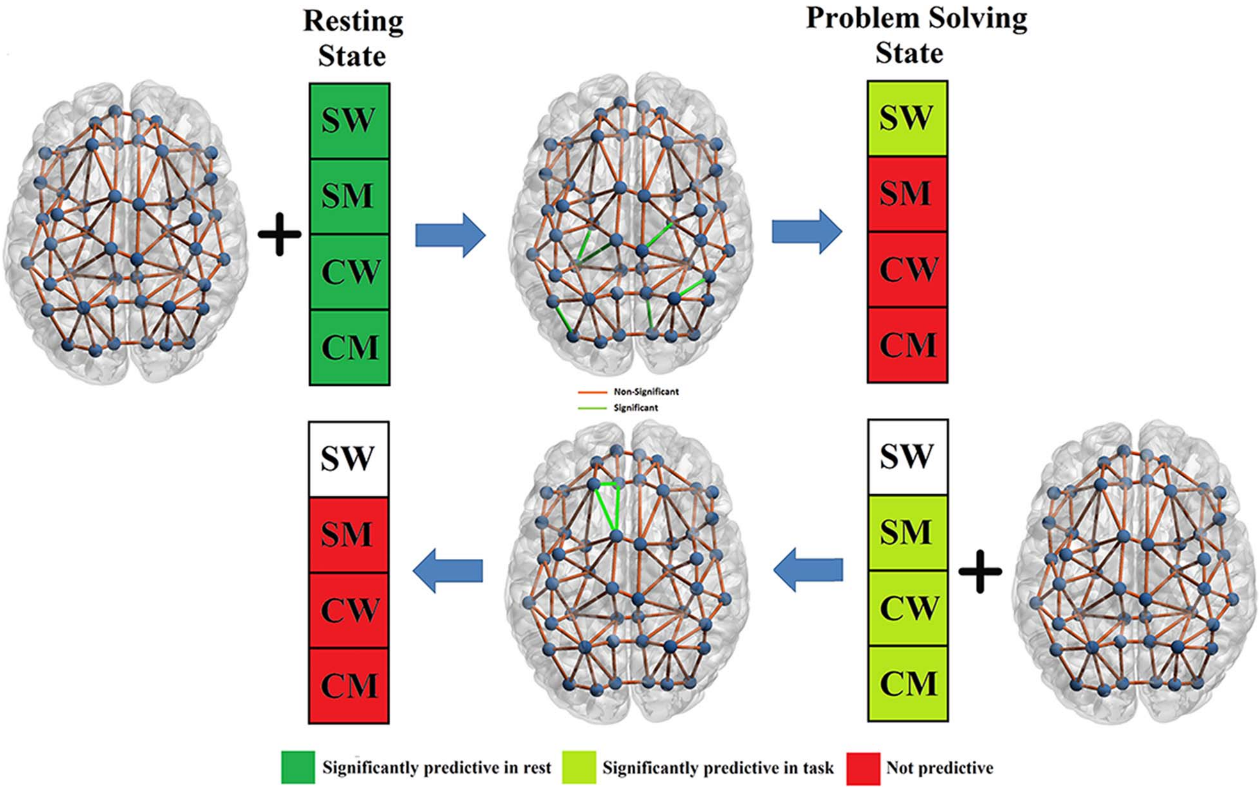

Figure 4. Predicting underperformance across experimental cells: At rest, the "maladaptive" pattern is predictive of underperformance to varying degrees across all individuals. Still at rest, subdividing individuals by experimental cell, we observe the same pattern. During the task, however, the maladaptive pattern remains predictive (i.e., relevant to performance) only for individuals in the cell comprising women in the stress condition. For nonstressed participants, that is, control condition participants and men in the diagnostic math test condition, functional connectivity patterns predictive of success were identified during problem-solving epochs. These connectivity patterns were not found to be predictive of performance in rest epochs. This suggests that nonstressed participants exhibited a functional state transition associated with optimal problem-solving.

Functional connectivity predicting math underperformance (identified by CPM) at rest was applied in networks from every single time window to predict individual's math performance using cross-validation. Given that there is only minor difference between 3 nonstressed groups (see Fig. 3*B*), we collapsed across participants from the 3 nonstressed groups. Linear regression was conducted on observed math performance and predicted math performance and was compared between women in the stress condition and nonstressed participants. Significant effects were found between 0 and 2500 ms (P's < 0.043, after false discovery rate or FDR corrections) for women under stress (Fig. 5*A*,*B*) only. No significant effects were found for other groups across the epoch (P's > 0.29). These findings indicated that the maladaptive state (i.e., where functional connectivity predicted underperformance) only emerged during the first 2.5 s of the problem-solving process. The time course of R values across groups is plotted in Figure 5C.

Direct Comparison of Functional Connectivity Organization Alterations between Stressed versus Nonstressed Groups

We have provided evidence that the predictive power of intrinsic brain connectivity patterns to math underperformance only remains in stress, which is possible because typical network reconfiguration during the rest–task transition was impeded. To verify this hypothesis, we next examined the alterations of functional network organization independent of behaviors. Specifically, we investigated alterations in global efficiency, clustering coefficients (the two graph theory variables), and network strength for whole brain functional network, from resting state to the problem-solving state (i.e., during the problem-solving task) for women in the stress condition and other nonstressed groups. The alterations were measured by subtracting metric values (i.e., global efficiency, clustering coefficient, and network strength) in rest network from the metric values in task network, from each individual. Figure 6 represents the comparison between women in the stress condition and other nonstressed groups in these alterations. Given that the networks identified via CPM were specific to connectivity within theta and beta frequency bands, we yoked analyses involving global efficiency, clustering coefficients, and global network strength to these two frequency bands as well.

Two-way two-sample t-tests were conducted on global network strength, global efficiency, and clustering coefficient between women in the stress condition and participants collapsed from all other 3 nonstressed groups. Results revealed that in the theta band, women in the stress condition exhibited significantly less enhanced global network strength compared with the other groups ($P = 0.022$). In addition, after FDR correction, women in the stress condition exhibited less enhanced clustering coefficient averaged across all nodes in the graph, as well as less enhanced global efficiency, compared with other groups at several density thresholds for the binary graph

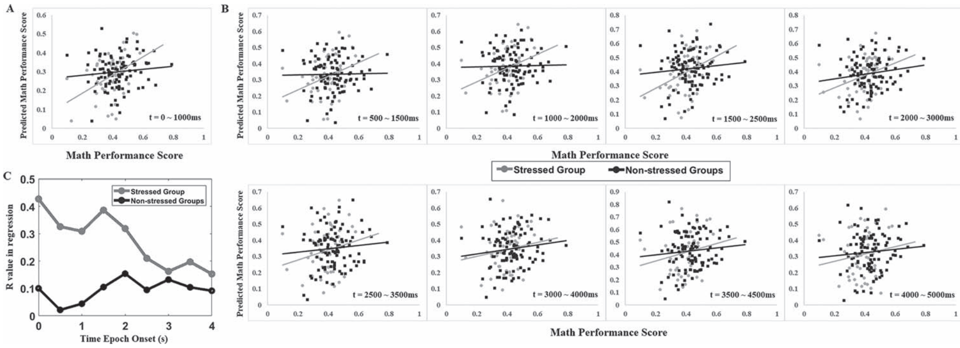

Figure 5. CPM analyses were extended up to 5000 ms during math problem-solving using a sliding window strategy, with a window length of 1 s and a moving step of 500 ms. (*A*) Math performance prediction using cross-validation based on functional network connectivity found during the resting state (gray: women in the stress condition; black: nonstressed participants). (*B*) Math performance prediction within 1000 ms window sliding from 500 to 5000 ms. (*C*) Track of *R* values of regression curves for all of the sliding windows; *x* axis represents the start time for the sliding window. Significant effects for women under stress were found in the first 4 sliding windows (0–2500 ms).

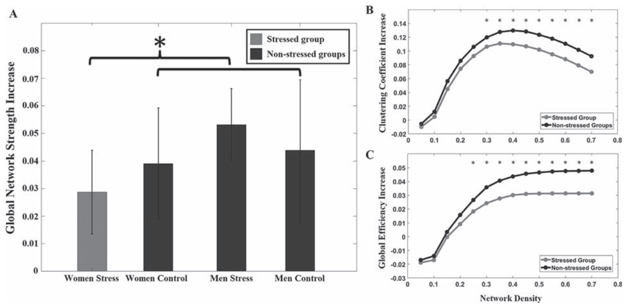

Figure 6. Functional network reorganization comparison between the stressed group (women in the stress condition) and nonstressed group (the other 3 groups) in the theta band. (*A*) Women in the stress condition exhibited reduced global network strength compared with the nonstressed group. (*B*) Women in the stress condition also exhibited reduced clustering coefficient, as well as reduced global efficiency, compared with other groups. Asterisks indicate group differences observed at $P < 0.05$ using two-way two-sample *t*-test.

(corrected *P*'s < 0.05). Similar relationships were not evident in the beta band (*P*'s > 0.18; Supplementary Fig. S2). These findings suggest that functional connectivity alteration and functional network reorganization appeared to be attenuated by stress in general, which may impede the adaptation of brain network for solving math problems.

Discussion

Using a completely data-driven approach, findings from these studies 1) identify intrinsic neural connectivity patterns that modulate problem-solving performance, but linger only in contexts facilitating evaluative stress; 2) identify neural connectivity markers that predict performance among nonstressed individuals during a task but not at rest. Specifically, initially across all participants at rest, connectivity in 3 network edges was found to have a negative relationship with performance on difficult (i.e., more cognitively demanding) math problems: R-SMG and L-SPC, R-IFG and L-PreC, and R-SMG and L-SPC. During task-related activity, these connections remained predictive for underperformance only for those in a stressful context (i.e., women primed with gender-salient, evaluative threat cues) solving difficult, cognitively intensive problems. Conversely, during the task, all other participants exhibited different neural connectivity patterns predictive of performance (Arsalidou et al. 2018), suggesting these individuals transitioned into different brain states during the task. This supports the possibility that appropriate task reconfiguration necessary for optimal performance may be hindered by context, where in this case the experience of stress preserves maladaptive connectivity to modulate performance accordingly (as opposed to initiating different, deviant patterns of activity).

Examining regions associated with underperformance on the problem-solving task further, 3 regions—L-PreC, R-CUN, and L-SPC—also play integral roles within networks known to modulate performance on cognitively intensive tasks: the FP executive and VSA networks (Klingberg et al. 2002; Chambers and Prescott 2010). On the other hand, R-SMG and R-IFG are implicated in internally oriented processes, like self and other cognitions or emotion regulation, which often detract from performance (Hoffmann et al. 2016).

One interpretation of these findings is that these general patterns could reflect a predisposition toward integration of these processes that, when cued by the context, would be inherently antagonistic for optimal math performance (van Ast et al. 2016). An inherent nuance of this predisposition is reflected in the correlational nature of these analyses. Indeed, while some individuals in the stress condition appeared more susceptible to the stress manipulation, performing particularly poor to the extent they exhibited increased connectivity between the negative network edges identified (i.e., those individuals performing worse on the math task on average compared with other groups), others exhibited more resilience under stress and actually performed better to the extent identified negative edges exhibited reduced connectivity (i.e., those individuals performing comparable to or better than others on the math task). Alternatively, another interpretation of the patterns found is that they could represent a particular configuration within the whole-brain network at rest, which individuals formally transition away from, to math-solving-related states, but failed to do successfully in stressful contexts that require greater emotion regulation. These two explanations do not necessarily conflict. Future studies ideally would test which hypothesis most realistically reflects the mechanism underlying current findings.

Regardless of mechanism, the present findings are nonetheless reliable (we replicate our primary finding in an independent dataset) and intriguing. Past research demonstrated that intrinsic network states (Mennes et al. 2011; Zou et al. 2013; Rosenberg, Finn, et al. 2016a) and functional task reconfiguration (Schultz and Cole 2016) play integral roles in cognition and behavior. The present studies suggest that the role of these factors is dependent, to an extent, on the context in which these phenomena transpire. In other words, context may function to regulate certain neural adaptations or selectively facilitate/impede "aspects" of adaptation. As such, the "bad" pattern could be regarded as a unique form diathesis that would otherwise not manifest when not elicited by these unique situational characteristics. The interpretation that stress hindered transition to more appropriate task configurations is further supported by examining what everyone other than women in the stress condition transitioned to—presumably, connectivity facilitating better math performance via engaging appropriate network dynamics. Indeed, in all experimental cells except the stressed group, greater FP and visual–spatial (externally oriented) connectivity and less internally oriented connectivity predicted better performance (see Supplementary Material), which is consistent with a number of past studies (Gerlach et al. 2014).

To further understand how the transition of brain–behavior relationship would be impacted by stress from rest to task, indices of functional network structures, independent of behavior, were also evaluated. Results revealed that stressed individuals exhibited significantly less global network strength between brain regions compared with nonstressed individuals, who collectively exhibited increases in global connectivity across the problem-solving task. This is in contrast to past research that fails to consistently find evidence for global increases or decreases in functional connectivity from rest to task (Lynch et al. 2018). It may depend on tasks and even frequency bands (Ghaderi et al. 2019). Although functional connectivity during task cannot be regarded as the simple summation of functional connectivity at rest and task-evoked activity (He 2013; Mastrovito 2013; Lynch et al. 2018), from a graph theoretical perspective, enhanced global network strength may suggest an overall increased interconnection among the brain's "hubs" (Scheinost et al. 2017). More integration of these hubs could thus support efficient communication between specialized regions across the brain in the service of better performance. Less enhanced global network strength under conditions of stress may therefore reflect poorer network reorganization, or more dependent on intrinsic patterns, to meet task demands.

Additional evidence of a disruption in functional reorganization was also obtained from graph theory analyses, where stressed individuals displayed less global efficiency and smaller clustering coefficients than nonstressed individuals. Generally, neural networks are expected to reconfigure from a modular, baseline topology at rest to a more efficient but costly topology during task (Meunier et al. 2010). That is, temporarily stronger direct connections between specialized nodes required for the task facilitate more efficient signal transmission. Thus, networks with higher cluster coefficients and global efficiency are advantageous to information processing during task (i.e., they reflect a "small-world" architecture; Bassett and Bullmore 2006). All nonstressed participants exhibited increased global efficiency and clustering coefficients, suggesting a network reorganization due to task demands. However, the display of lower enhanced global efficiency and clustering exhibited by individuals experiencing greater stress supports the conjecture that network transition was indeed impeded or tempered in this context.

Another interesting consideration is whether the observed deficit of functional reorganization for stressed participants was stable across the entire problem-solving process or was more of a transient state. Our time-variant analyses (Fig. 5) revealed that the maladaptive patterns only predominated in the beginning of the problem-solving process. That is to say, individuals may be more likely to transition out of this counterproductive state as time goes on. However, considering that stressed individuals solved math problems less accurately than other groups, it indicates that stress nevertheless exerts a more deleterious influence on problem-solving abilities several seconds later and in the aggregate. For instance, evaluative stress may evoke additional processes that would be counterproductive to problem-solving, for example, emotion regulation or attempts to discount perceived critical feedback, and indeed past research suggests quadratic relationships between performance and neural correlates of emotion and arousal (e.g., amygdala activity) (Forbes et al. 2018). Future studies are needed, however, to further assess the precise nature of stressed participants' performance in relation to brain states at various time points during rest and problem-solving.

In order to hold all aspects of the context and individual constant while placing one group in an evaluatively stressful context, we employed a SBS paradigm to evoke evaluative threat and thus stress in female subjects. Stress is a subjectively negative experience, accompanied by a cascade of neural and chemical reactions that can adversely affect performance. In evaluative stress paradigms (e.g., the Trier stress test and the SBS paradigm used in this study), stress elicits a host of maladaptive symptoms: increases in cortisol, alpha amylase, increased blood pressure and skin conductance, increased vACC and amygdala activity in response to stressors (e.g., negative task-specific feedback), and accompanying negative perceptions (Allen et al. 2014). While SBS is unique in that only a derogated, socially devalued group experiences the evaluative stress (Schmader et al. 2008), the symptoms associated with it are synonymous with those associated with more domain-general stressors like TST-based evaluative threats. That is to say, stress is ultimately stress as far as the brain and body are concerned, and many different contexts and situations are ripe with the ingredients necessary to evoke that stereotypic brain and body response (at least with respect to rapid responses to immediate stressors) (Hariri and Holmes 2015; Godoy et al. 2018). Furthermore, while some argue that stress is experienced differently by men and women, the evidence for this is mixed at best. For instance, while some evidence finds that men may experience higher cortisol in stress paradigms (Burke et al. 2005), other work have argued women may be more prone to math-related anxiety and stress (Maloney et al. 2012). Importantly, in the present study, stress-based effects were specific to women who were exposed to the SBS manipulation; women in the control condition exhibited comparable patterns, both neurally and behaviorally, to men in either condition. Therefore, we find it reasonable to expect that findings from the present paradigm would generalize to other populations for whom an evaluative threat is salient or use other stress paradigms in general.

Several findings were difficult to interpret definitively in the current study and remain open questions for future studies. For instance, it is unclear why the link between intrinsic connectivity patterns and underperformance in stressful contexts was specific to difficult math problems and not easy math problems. One possible explanation for these findings stems from past evaluative threat-oriented research. Past work on evaluative threat/SBS clearly demonstrates that threat-based underperformance is typically most pronounced on the most cognitively intensive tasks. In fact, when individuals experiencing SBS complete easier problems or specific types of tasks where success is dependent on prepotent responses, their performance is often facilitated (Jamieson and Harkins 2007; Spencer et al. 1999). This suggests that contexts need to be more stressful to preserve intrinsic network properties' influence during performance or keep individuals "stuck" in a maladaptive network state; however, future research would be necessary to validate this theory.

Future work will enhance our understanding of the present phenomena in several ways. The CPM approach employed in this study (by virtue of our research question) identified key network markers, derived from phase locking averaged across time and trials during two temporally generalized events: rest and performance. Further research should clarify how these features realistically interact with other key regions and normal brain states, as parts of process-relevant networks. This would be particularly helpful for understanding the full picture of the rest–task brain network reorganization.

Moreover, this novel CPM approach could be applied to additional contexts, where a similar relational perspective stands to provide insight. Aside from stress, other contexts likely elicit unique reorganization from intrinsic networks to task activation—for example, situations requiring multitasking may favor intrinsic markers that either downplay conflicts or aid in supporting simultaneous/parallel processes or the integration of various processes. Hence, the ability to compare predictive markers across various states and contexts could provide a means to obtain greater dimensionality in functional themes.

While the EEG-based approach utilized in these studies provided high-quality temporal resolution to capture these phenomena, a measure of caution is warranted when interpreting activation as regionally specific, due to the inherent spatial limitations of the methodology. By using a high-density electrode array, adopting advanced Bayesian source localization (incorporating inverse dSPM operators), and engendering a more conservative estimation of neural activity by constraining to regions in proximity of the brain surface using MNE, it is possible to make better inferences about the roles of specific brain regions (Cohen 2014). However, due to lack of precise individual-level brain forward modeling and individual structural MRI scans, EEG source localization may only be accurate to the precision of centimeters (Cohen 2014). Hence the functional interpretation of the mechanism behind our findings remains tentative. Future research should complement these findings by applying spatially attuned, functional MRI—particularly given the importance of amygdala and medial temporal regions in arousal and self-referential processes (Forbes et al. 2018).

Another limitation of these studies is that the number of participants in each group is slightly smaller than would be ideal. While sensitivity analyses in Study 1 indicated that the sample size was sufficient for detecting the effects needed, the sample size for the replication study was slightly lower than required to capture an identical effect size evident in Study 1 (see Supplementary Results for more details). This may result in a reduced chance of detecting a true effect and can increase the false-positive rate (Yarkoni 2009; Button et al. 2013). Thus, although our findings in Study 2 replicated data-driven conclusions drawn from Study 1 and satisfied recent best practices outlined for neuroscience studies (https://www.jneurosci.org/content/40/21/4076), due to marginal sample size limitations, results should be interpreted with caution. Future efforts employing larger sample sizes will be necessary to draw more definitive conclusions.

Conclusion

Employing a CPM approach to characterize markers of cognitive performance and manipulating evaluative stress across contexts, findings across two independent datasets revealed that contexts can modulate optimal or suboptimal neural reconfigurations from rest to task. Stress rendered predisposed individuals "stuck" in maladaptive patterns, whereas nonstressed individuals tended to transition into brain states associated with optimal performance, illustrating one way in which task-evoked adaptation is contingent on contextual demands. This predisposition was reflected on cognitively intensive problems in particular. By illustrating how unique network characteristics provide a means for individuals to thrive (or falter) in specific contexts, these findings draw closer to more ecologically valid models of cognition—and, hopefully, more fruitful, brain-based stress interventions moving forward.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

Conflict of Interest: All authors report no competing interests.

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Author Contributions

M.L.: Designed and conceptualized study, analyzed the data, interpreted the data, and drafted the manuscript. R.A.B.: Interpreted the data and drafted the manuscript for intellectual content. R.C.A.: Conducted manipulation test and drafted the introduction. E.E.S.: Interpreted the data and drafted the introduction. A.M.: Collected data and drafted the introduction. C.E.F.: Designed and conceptualized study, interpreted the data, and revised the manuscript for intellectual content.

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