Archival Report

Triple Network Functional Connectivity During Acute Stress in Adolescents and the Influence of Polyvictimization

Rachel Corr, Sarah Glier, Joshua Bizzell, Andrea Pelletier-Baldelli, Alana Campbell, Candace Killian-Farrell, and Aysenil Belger

ABSTRACT

BACKGROUND: Exposure to both chronic and acute stressors can disrupt functional connectivity (FC) of the default mode network (DMN), salience network (SN), and central executive network (CEN), increasing risk for negative health outcomes. During adolescence, these stress-sensitive triple networks undergo critical neuromaturation that is altered by chronic exposure to general forms of trauma or victimization. However, no work has directly examined how acute stress affects triple network FC in adolescents or whether polyvictimization—exposure to multiple categories/subtypes of victimization—influences adolescent triple network neural acute stress response.

METHODS: This functional magnetic resonance imaging study examined seed-to-voxel FC of the DMN, SN, and CEN during the Montreal Imaging Stress Task. Complete data from 73 participants aged 9 to 16 years (31 female) are reported.

RESULTS: During acute stress, FC was increased between DMN and CEN regions and decreased between the SN and the DMN and CEN. Greater polyvictimization was associated with reduced FC during acute stress exposure between the DMN seed and a cluster containing the left insula of the SN.

CONCLUSIONS: These results indicate that acute stress exposure alters FC between the DMN, SN, and CEN in adolescents. In addition, FC changes during stress between the DMN and SN are further moderated by polyvictimization exposure.

https://doi.org/10.1016/j.bpsc.2022.03.003

Perceiving and responding to stressors are vital for daily functioning, and dysregulated neurobiological acute stress responses (ASRs) are associated with adolescent development of psychiatric disorders (1,2). Characterizing ASRs in adolescents is critical, because they experience increased exposure to intense and novel stressors and brain maturation in stress-sensitive circuits involved in emotional processing and executive control (3–6). Acute stress exposure typically elicits temporary psychological, biological, and behavioral changes through the process of allostasis, which is terminated upon stressor cessation, allowing the body to recover to its homeostatic baseline (7). Chronic stress exposure associated with trauma can lead to allostatic load as the brain adapts to repeated stressors, resulting in blunted or prolonged neurobiological ASRs and increased risk for developing mood and anxiety disorders (8,9). The cumulative burden of exposure to acutely stressful victimization events in different environments is reflected by polyvictimization (PV), defined as experiencing victimization across multiple categories/subtypes, including conventional crimes, child maltreatment, peer/sibling victimization, sexual victimization, and indirect victimization. The allostatic load associated with PV has been hypothesized to lead to long-term neurobiological changes to neural systems critical for regulating adaptive ASRs (8). Yet, little is known about the neurobiological impacts of PV or how PV influences neural network responses to stress in adolescence, especially in the context of the rapid maturation of these networks during this developmental period. This study aims to elucidate these relationships and represents the first analysis of PV’s influence on neural network ASRs in adolescents.

Previous studies of victimization in adolescents using functional magnetic resonance imaging (fMRI) typically only include a single type of victimization [i.e., neighborhood violence (10) or victimization by peers (11)], but studying the isolated influences of specific types of victimization may overestimate the impact of any individual category (12). Findings related to specific trauma subtypes may be confounded by PV, because adolescents experiencing a single victimization incident in one year are 2 to 3 times more likely to experience an additional subtype (13). Furthermore, extant studies of trauma-related neural functional connectivity (FC)—the temporal correlation between activation of different brain regions, indicating their participation in a common network—typically compare binary groups: those with past trauma exposure and control subjects (14,15). Such study designs do not allow for analysis of the cumulative impact of multiple

SEE COMMENTARY ON PAGE 847
forms of trauma exposure. Similarly, using a total victimization measure may conflate the neurobiological effects of exposure to multiple forms of trauma with frequent exposure to one form (16,17). Hickman et al. (16) found that PV independently predicted child posttraumatic stress symptoms and behavioral problems, even when models accounted for total lifetime victimization exposure or frequency of most individual PV categories (16). Analyzing categorically defined PV enables measurement of victimization’s influence across spectra of cumulative burden and subtypes of trauma, rather than binarily analyzing trauma-exposed individuals versus control subjects.

Even though the impact of PV on FC is unclear, early-life exposure to adverse events is linked with aberrant FC; trauma exposure can have long-lasting effects on adolescent FC both at rest (10,18) and during emotional and cognitive tasks (19). Recent research suggests that trauma exposure causes widespread alterations in broader networks, particularly the default mode network (DMN), salience network (SN), and central executive network (CEN) (14,20–23). The triple network model posits that these networks direct critical cognitive processes, including perception, emotional affect regulation, and social functioning, that are closely associated with areas of impairment often seen in victimized adolescents: the SN enables convergence of sensory and affective inputs; the DMN is responsible for introspection, retrospection, and prospecting; and the CEN drives top-down attentional control and goal-directed behavior (22).

The triple network model of posttraumatic stress disorder (PTSD) suggests that traumatic stress exposure is associated with 1) increased within-network SN FC, resulting in hyperarousal/highened threat detection, and increased FC between the SN and the CEN and DMN, impairing the SN’s ability to modulate between the two networks when switching between task-relevant and task-irrelevant behaviors; 2) reduced within-network DMN FC and between-network connectivity with the CEN, resulting in intrusive symptoms, fear generalization, and an altered sense of self; and 3) reduced within-network CEN FC leading to cognitive deficits (24). Previous work indicates that FC in triple network regions shortly after trauma exposure can predict future development of PTSD symptoms (25). Adolescent resting-state FC (rsFC) studies have revealed that trauma exposure is associated with aberrant rsFC between these networks, particularly between the DMN and SN (15,19).

However, current analyses mainly address trauma’s influence at rest, and less is known about how trauma impacts these networks during stress in adolescents. Analyzing the triple networks during acute stress is particularly important, because increased vulnerability to stress, decreased CEN FC during acute stress, and an absence of decreased DMN FC during stress are found across a wide range of psychiatric disorders (26). Considering that aberrant FC within and between the triple networks is found in many psychiatric disorders (22,23) and that these networks are impacted by both acute (27,28) and chronic (29,30) stress exposure, it is important to elucidate the mechanisms by which PV moderates FC during acute stress yielding more sustained effects on cognition and behavior.

This report examined modulation of FC within and between the triple networks during acute psychosocial stress (the Montreal Imaging Stress Task [MIST]) to determine PV’s influence on neural ASRs. Neural activation during MIST has been previously reported for this adolescent sample, who display a heterogenous range of psychiatric symptoms (17,31). This FC analysis represents a necessary expansion on our prior work to better characterize adolescent neural ASRs. We hypothesized that during stress, adolescents would exhibit increased FC within and between the DMN and SN, as identified by studies of acute stress in healthy adults (27). Prior work has primarily examined the influence of trauma on triple network FC at rest (24), and we expected that stress exposure would further exacerbate previously reported trauma-related differences in triple network FC; we predicted that during acute stress exposure individuals with greater PV history would exhibit higher within-network SN FC, reduced within-network DMN and CEN FC, and higher SN-CEN and SN-DMN between-network FC (24).

METHODS AND MATERIALS

Participants

Data from 79 participants aged 9 to 16 years with PV and acute stress FC data were used for analysis from a sample of adolescents we previously studied (17,31). Recruitment aimed to build a sample with a heterogenous range of psychiatric symptomology (see Supplemental Methods). The parent study was approved by the Institutional Review Boards of University of North Carolina at Chapel Hill and Duke University. Participants gave assent and legal guardians provided consent. Exclusionary criteria included MRI contraindications, medical conditions known to impact the stress response or neuroimaging, history of head injury, an IQ two standard deviations below the mean, lifetime or current DSM-IV-TR Axis I psychotic disorder, and current major depressive disorder, bipolar disorder, PTSD, or substance dependence. Trained researchers determined presence of DSM-IV Axis I disorders using an abbreviated form of the Structured Clinical Interview for DSM-IV (32) and when applicable diagnoses were confirmed via electronic health records. Overall, 49% of subjects met diagnostic criteria for a DSM-IV disorder (including attention-deficit/hyperactivity disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive disorder, and adjustment disorder), and 33% were taking psychotropic medications known to impact neural activity (including stimulants, nonstimulant attention-deficit/hyperactivity disorder medication, antidepressants, antipsychotics, and anticonvulsants). Further demographic information can be found in Table 1.

PV and Demographic Measures

Victimization was evaluated using the Juvenile Victimization Questionnaire, a 34-item questionnaire that measures a range of traumatic exposures experienced by children and adolescents over their lifetime (33). Questions fall within five categories/subscales: nine questions about conventional crime, four about child maltreatment, seven about sexual victimization, six about peer or sibling victimization, and eight about indirect/witnessing victimization. As described in our previous work (17), PV was defined as the total number of Juvenile
TABLE 1. Sample Characteristics (N = 79)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%) or Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female</td>
<td>33 (42%)</td>
</tr>
<tr>
<td>Age, Years</td>
<td>12.8 ± 2.2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>White</td>
<td>56 (71%)</td>
</tr>
<tr>
<td>On Medication</td>
<td>26 (33%)</td>
</tr>
<tr>
<td>DSM-IV Diagnosis</td>
<td>39 (49%)</td>
</tr>
<tr>
<td>Polyvictimization</td>
<td>2.5 ± 1.4</td>
</tr>
</tbody>
</table>

Victimization Questionnaire categories/subscales within which subjects endorsed experiencing at least one type of victimization (with possible values ranging from 0 to 5) (16,34). Owing to the negatively skewed distribution of PV values, the PV variable was square root transformed for analysis.

Supplementary analyses examined other variables that may impact PV or acute stress-related FC. Connections were evaluated between PV and sex (Welch’s t test), age (Pearson correlation), psychotropic medication use (Welch’s t test), psychiatric diagnosis (Welch’s t test), parental socioeconomic status (defined using average parental education; Spearman’s correlation), and race (defined categorically as Black, Other, or White; analysis of variance).

Montreal Imaging Stress Task

MIST was conducted similarly to adult studies (35–37) using our published protocol (17,31). In brief, MIST used a block design with three 6-minute runs of the task, each of which included three sets of alternating rest, control, and experimental conditions. During the rest condition, subjects focused on a screen displaying a static task dial image. For the control condition, participants were told their performance was not recorded as they completed math problems, rotating the onscreen dial using a button box to submit their answers. During the experimental/stress condition, researchers instructed participants to complete math problems quickly within the permitted response time window. Between each run, experimenters provided negative feedback telling the participant their experimental condition performance was below average compared with their peers and it was important that they try harder. Further MIST information is available in our prior publication (31) and in the Supplemental Methods.

Assessment of FC

**fMRI Acquisition.** MRI scans were acquired on a 3T GE MR750 scanner with an 8-channel head-coil at the Duke-UNC Brain Imaging and Analysis Center. High-resolution T1-weighted images were collected using a three-dimensional fast spoiled gradient-recalled sequence (repetition time/echo time = 8.2/3.22 ms; fractional anisotropy = 12%; field of view = 240 × 240 × 166 mm³; matrix size = 256 × 256 × 166; slice thickness = 1 mm). Functional images during MIST were acquired using a spiral-in sensitivity encoding interleaved sequence (repetition time/echo time = 2000/30 ms, fractional anisotropy = 60%, field of view = 24 cm, acquisition matrix = 64 × 64, slice thickness = 4 mm, 34 slices) (31).

**fMRI Preprocessing and Denoising.** The CONN Toolbox (v20.b) (38) was used for preprocessing, denoising, quality assurance, and statistical analysis. Images were processed following the default CONN preprocessing pipeline, including spatial realignment; unwarping; ART-based identification of outlier scans for scrubbing; gray matter, white matter, and cerebrospinal fluid segmentation; Montreal Neurological Institute normalization; and spatial smoothing using a 6-mm full width at half maximum Gaussian kernel. The denoising step used single-subject linear regressions to remove movement artifacts (12 motion parameters; rigid body transformations and their first-order temporal derivatives) and physiological effects (5 parameters each from principal component analysis of white matter and cerebrospinal fluid time courses). The single-subject matrix included regressors for each task condition (rest, control, stress). High-pass filtering (0.008 Hz) was applied after denoising. Visual quality assurance was conducted on structural and functional normalization and registration and after denoising FC value distribution. MIST data from 79 subjects included in our prior PV analysis (17) were initially preprocessed. Subjects with >25% of their volumes scrubbed were removed from analysis (39), resulting in the exclusion of six individuals for a final sample of 73 subjects.

**Generalized Psychophysiological Interaction Analyses.** Generalized psychophysiological interaction analyses were conducted using bivariate regressions (38). Five regions of interest (ROIs) were selected as seeds (Figure 1), matching the 6-mm spherical ROIs used in prior research examining seed-to-voxel FC of these networks (40–42). The DMN hub was the posterior cingulate cortex (PCC) (1, –55, 17), SN hubs were the left and right frontoinsular cortex (IFC) (–32, 26, –14/38, 22, –10), and CEN hubs were the left and right dorsolateral prefrontal cortex (dLPFC) (–42, 34, 20/44, 36, 20). Second-level seed-to-voxel analyses contrasted FC values between stress and control conditions, controlling for sex, age, medication use, and presence/absence of psychiatric diagnosis using a familywise error (FWE) rate-corrected cluster-level threshold p-FWE < .05 after voxelwise height thresholding of p-uncorrected < .005 (43). Separate seed-to-voxel analyses for each ROI examined FC changes associated with acute stress and their relationship with PV. Supplementary seed-to-voxel analyses assessed if there were relationships between stress-related FC from each seed and sex, age, medication use, or psychiatric diagnosis (Tables S1–S4).

RESULTS

**Participant Characteristics**

A total of 73 adolescents were included in the neuroimaging analyses. At least one form of victimization was experienced by 87.7% (n = 64) of subjects, 75.3% (n = 55) reported exposure to two or more categories of victimization, and 28.8% (n = 21) reported exposure to four or more of the five victimization categories. PV was not significantly associated with sex (Welch’s t<sub>57.6</sub> = 1.02, p = .310), psychiatric diagnosis
Stress-Related Triple Network FC and Polyvictimization

(Welch’s $t_{66.0} = -1.57, p = .121$), race ($F_{2,70} = 0.33, p = .717$), or parental socioeconomic status ($t_{66} = -0.079, p = .516$). However, PV was associated with age ($r_{71} = 0.24, p = .042$) and medication use (Welch’s $t_{41.82} = -2.44, p = .019$), with individuals taking medication reporting greater PV.

**Table 2. Stress Effects on Triple Network Seed Functional Connectivity**

<table>
<thead>
<tr>
<th>Seed</th>
<th>MNI</th>
<th>Direction</th>
<th>Region</th>
<th>Network</th>
<th>k</th>
<th>p-FWE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Default Mode Network: Posterior Cingulate Cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-16 -50 52</td>
<td>‖</td>
<td>L precentral gyrus</td>
<td>Motor</td>
<td>1516</td>
<td>&lt;.000001</td>
<td></td>
</tr>
<tr>
<td>-26 -62 42</td>
<td>‖</td>
<td>L superior lateral occipital cortex</td>
<td>sLOC</td>
<td>794</td>
<td>&lt;.000001</td>
<td></td>
</tr>
<tr>
<td>-46 22 32</td>
<td>‖</td>
<td>L middle frontal gyrus</td>
<td>CEN</td>
<td>790</td>
<td>&lt;.000001</td>
<td></td>
</tr>
<tr>
<td>0 22 44</td>
<td>‖</td>
<td>L paracingulate</td>
<td>PaCi</td>
<td>458</td>
<td>.000105</td>
<td></td>
</tr>
<tr>
<td>42 28 30</td>
<td>‖</td>
<td>R middle frontal gyrus</td>
<td>CEN</td>
<td>274</td>
<td>.005876</td>
<td></td>
</tr>
<tr>
<td>58 -26 28</td>
<td>‖</td>
<td>R frontal pole</td>
<td>CEN</td>
<td>1256</td>
<td>&lt;.000001</td>
<td></td>
</tr>
<tr>
<td><strong>Salience Network: L Insular Cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-8 -52 30</td>
<td>‖</td>
<td>Precuneus</td>
<td>DMN</td>
<td>917</td>
<td>&lt;.000001</td>
<td></td>
</tr>
<tr>
<td>-50 -60 20</td>
<td>‖</td>
<td>L angular gyrus</td>
<td>DMN</td>
<td>312</td>
<td>.001998</td>
<td></td>
</tr>
<tr>
<td>-26 58 -8</td>
<td>‖</td>
<td>L frontal pole</td>
<td>CEN</td>
<td>265</td>
<td>.006185</td>
<td></td>
</tr>
<tr>
<td>-4 50 36</td>
<td>‖</td>
<td>L superior frontal gyrus</td>
<td>CEN</td>
<td>202</td>
<td>.031172</td>
<td></td>
</tr>
<tr>
<td><strong>Salience Network: R Insular Cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 32 -16</td>
<td>‖</td>
<td>R paracingulate</td>
<td>PaCi</td>
<td>201</td>
<td>.027587</td>
<td></td>
</tr>
<tr>
<td>-20 -46 64</td>
<td>‖</td>
<td>L superior parietal lobule</td>
<td>DAN</td>
<td>184</td>
<td>.044158</td>
<td></td>
</tr>
<tr>
<td><strong>Central Executive Network: L Dorsolateral Prefrontal Cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-34 -10 68</td>
<td>‖</td>
<td>L postcentral gyrus</td>
<td>Motor</td>
<td>380</td>
<td>.000464</td>
<td></td>
</tr>
<tr>
<td>-4 -88 -8</td>
<td>‖</td>
<td>L lingual gyrus</td>
<td>Visual</td>
<td>313</td>
<td>.02094</td>
<td></td>
</tr>
<tr>
<td><strong>Central Executive Network: R Dorsolateral Prefrontal Cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10 -66 22</td>
<td>‖</td>
<td>Precuneus</td>
<td>DMN</td>
<td>979</td>
<td>&lt;.000001</td>
<td></td>
</tr>
<tr>
<td>0 56 -12</td>
<td>‖</td>
<td>Medial frontal cortex</td>
<td>DMN</td>
<td>328</td>
<td>.01613</td>
<td></td>
</tr>
</tbody>
</table>

Voxel threshold $p$-uncorrected $<.005$ and cluster size $p$-FWE $<.05$. Region labels and network membership were defined using the CONN Atlas, which provides network grouping based on resting-state analysis of the Cambridge 1000-connectomes dataset using 132 regions from a combination of the Harvard-Oxford cortical and subcortical atlases and the AAL atlas cerebellar parcellation (38). For clusters with multiple corresponding regions, only regions containing $\geq 25\%$ of the cluster volume are listed.

aSMG, anterior supramarginal gyrus; CEN, central executive network; DAN, dorsal attention network; DMN, default mode network; FWE, familywise error; L, left; MNI, Montreal Neurological Institute; PaCi, paracingulate; R, right; sLOC, superior lateral occipital cortex.
exhibit relationships with triple network regions during stress. However, the right FIC seed did demonstrate stress-related FC increases with the right paracingulate and decreases with the left superior parietal lobule of the DAN (Figure 2C), and FC increased between the left dlPFC seed and visual and motor regions (Figure 2D). The CEN right dlPFC seed exhibited increased stress-related FC with DMN clusters, including the precuneus, PCC, and medial PFC (Figure 2E). Supplementary seed-to-voxel analyses revealed no significant relationships between seed FC with triple network regions during acute stress and sex, age, medication use, or psychiatric diagnosis (p-FWE $\leq .05$) (Tables S1–S4), with one exception; females exhibited greater stress-related FC than males within the DMN ($t_{68} > 2.90$, p-FWE = .005).

Figure 2. Results from the seed-to-voxel analyses examining triple network connectivity during acute stress from the posterior cingulate cortex (A) representing the default mode network, left (B) and right (C) frontoinsular cortex representing the salience network, and left (D) and right (E) dorsolateral prefrontal cortex representing the central executive network. Statistical maps represent region $t$ scores (voxel threshold $p$-uncorrected $< .005$ and cluster size $p$-familywise error $< .05$).

PV Is Associated With Reduced DMN-SN Stress-Related FC
Greater PV was associated with reduced stress-related FC between the DMN PCC seed and a cluster containing the left insula of the SN ($-42, -2, 2; t_{67} > 2.90$, p-FWE = .023, $k = 218$) (Figure 3). This pattern was also seen between the PCC and right insula, although it did not survive multiple-comparison corrections ($38, -16, 10; t_{67} > 2.90$, $p$-uncorrected = .002, $p$-FWE = .167, $k = 144$) There were no significant relationships between PV and SN or CEN seed-to-voxel FC during stress ($p$-FWE $\geq .518$).

DISCUSSION
This is the first study to directly examine changes in triple network FC during acute stress in an adolescent population and probe how PV may influence stress-related FC in these networks. Acute stress was associated with increased DMN-CEN FC and decreased FC between the SN and the CEN and DMN. Greater PV exposure predicted lower acute stress-related DMN-SN FC, specifically reduced FC between the DMN PCC hub and the left insula of the SN. Dysfunctional triple network FC is associated with a wide range of psychiatric symptoms (22,23), and elucidating how PV influences these circuits and their ability to adapt under stressful conditions is critical for understanding how PV can contribute to long-term negative health outcomes.

Triple Network Connectivity During Acute Stress
The insula is a critical hub of the SN and functions as a switch between the DMN and the CEN during different task demands, typically activating the CEN and suppressing the DMN during cognitive tasks (22). While DMN and CEN regions generally exhibit opposing activation patterns as mediated by the SN, increased DMN-CEN coupling is associated with internally directed attentional processes (22,44). In this study, increased DMN-CEN FC may arise from subjects’ increased self-focus and judgment due to poor achievement and negative feedback on MIST (45). Negative FC between the SN and the DMN and CEN may reflect
impairment in switching between these networks during stress (46).

The relationship between the SN and the DMN and CEN varies across psychological conditions, and notably a large portion of stress-related FC studies focus on changes in rsFC before and after stress rather than FC during a stress task (27). Our SN between-network FC results are in line with some of these studies showing that after acute stress exposure, the SN exhibits decreased rsFC with the dIPFC of the CEN (47), and reduced SN-DMN rsFC after stress exposure predicts longitudinal increases in perceived stress levels (48). Contrary to our results, Vaisvaser et al. (49) reported increased DMN-SN and decreased DMN-CEN FC during stress. However, their analysis used a ventromedial PFC seed to represent the DMN (49), and differences in ventral and dorsal DMN connectivity patterns may explain these discrepant findings (50). Temporal FC analyses during a cognitive task revealed increased FC between the PCC and SN at the beginning of the task, followed by increased FC between the PCC and CEN regions as the task progressed (44). Between-network FC may shift during the MIST, and, in addition to exploring other triple network regions, future analyses should explore changes in MIST FC over progression of the task.

Contrary to our hypotheses, acute stress was not associated with FC within any network, as has been identified in adult studies (27). Within-network correlations may not have been found in our sample because the DMN, SN, and CEN are less cohesive in adolescents and typically become more defined and segregated with maturation (51) or because network hubs can shift throughout adolescence (52). Although our analysis did not reveal significant differences in triple network FC associated with age, a longitudinal study is necessary to explore whether neurodevelopment during adolescence increases within-network FC during acute stress. Furthermore, while not the primary focus of this analysis, it is important to note that triple network hubs exhibited varied FC with regions outside the triple networks. During stress, the PCC DMN seed also displayed decreased FC with visual and motor network regions and the anterior supramarginal gyrus and increased FC with DAN regions, the superior lateral occipital cortex, and the paracingulate. The right FIC SN seed showed stress-related increases in FC with the paracingulate and decreases with the superior parietal lobule of the DAN, and the left dIPFC exhibited increased FC with visual and motor network regions. The DAN is important for goal-directed control of visuospatial attention (53), which may be important for success on MIST. While the DAN has not been well characterized during stress, it has been implicated in recovery after stress exposure (54). Future work should examine if alterations in DAN and motor and visual network FC are a specific artifact of MIST or are more broadly relevant to ASRs.

**PV and Stress-Related FC**

During acute stress, adolescents with greater PV exposure exhibited reduced FC between the DMN PCC hub and the left insula of the SN. There is limited research examining the relationship between forms of chronic stress exposure and stress-related FC, although some rsFC studies have examined trauma’s impact on these networks. In a healthy sample characterized as experiencing mild levels of childhood trauma, greater early-life stress was associated with greater reductions in rsFC between SN and DMN regions after acute stress exposure, but no prestress differences (55). However, lower DMN-SN rsFC was found at rest, without the influence of acute stress, in an adolescent sample with more severe trauma experiences (19). In the light of this literature, this study’s findings—that acute stress elicits reduced DMN-SN FC, which is further reduced in individuals with PV—suggest that greater DMN-SN reductions may represent PV-induced neural adaptations that impact ability to respond to stress. Polyvictimized individuals have experienced exposure to stressors across different contexts, and repeated trauma exposure is known to alter neurobiological ASRs (8,9). Therefore, the allostatic load associated with PV may lead to increased DMN-SN reactivity to stress. It is important to note that our findings should be considered preliminary, because PV results (p-FWE = .023) would not reach statistical significance if additional corrections were included to adjust for the five ROIs tested. Future analyses should explore if PV similarly impacts DMN-SN FC at rest or if PV is linked to reduced FC between these networks only when they are perturbed by acute stress exposure.

**Limitations and Future Directions**

We identified seeds following several previous triple network studies (40–42,56–58). However, other triple network research has used ROI-to-ROI analytic techniques with predefined nodes for each network (59,60) or identified networks based on independent component analyses of resting-state data (28,61). Our seed-to-voxel analyses allowed for exploration of interactions between critical nodes of the triple network and all brain regions, but the stricter statistical threshold used for
whole-brain analysis may have reduced our ability to detect meaningful within-network FC. Within-network connectivity may have been absent because these networks are less functionally segregated in adolescents (51). Furthermore, even though prior adolescent work has used these seeds (42,62,63), coordinates were based on adult research, and ROIs derived specifically from adolescent studies may yield different results (6-4). Future work should examine triple network connectivity through other FC methods to explore if within-network connectivity is altered during acute stress, in addition to using longitudinal methods to test if within-network FC increases with neurodevelopment.

One strength of our heterogenous sample of adolescents is that they exhibited a range of PV values, enabling a dimensional analysis. However, to enable this PV variability, subjects taking psychotropic medications known to impact neural activation were included (65). While we found greater PV in individuals on medication, all analyses did control for medication status, and supplementary analyses indicated that medication was not significantly associated with triple network FC. Future analyses in a medication-naive population or examining the interactions between PV, stress-related FC, and specific medications would be necessary to ensure that medications did not influence results.

Furthermore, while participants did exhibit a range of PV exposures, participants were excluded from the parent study if they had a PTSD diagnosis. This reduces the generalizability of our findings to individuals with PTSD, and future PV studies should include these individuals to examine if the relationship between PV and triple network FC predicts development of posttraumatic stress symptoms. Analyses did control for psychiatric diagnostic status, and no significant relationship was found between diagnostic status and acute stress-related FC. However, participants exhibited a range of different anxiety and attention-deficit/hyperactivity disorder diagnoses and symptom loads, often having comorbid conditions, and examining binary presence/absence of diagnostic status collapsed variation across mental illnesses. A larger sample with subjects experiencing specific psychiatric disorders, including PTSD, is needed to more comprehensively understand how different psychopathologies may uniquely impact triple network ASRs.

In addition, while analyses controlled for sex and age, owing to sex-dependent differential neural and psychological development that occurs during puberty, future analysis should directly explore interactions between PV, stress-related FC, pubertal development, and sex hormone levels, especially given the fluidity of functional hub roles through adolescence (52). PV was associated with age, with older individuals reporting greater PV—an unsurprising finding given that older adolescents have had more opportunities to be exposed to victimization. In addition to subject age, the age and developmental stage during which an individual was exposed to PV impacts their likelihood of exhibiting psychiatric symptoms (66). Future studies examining the frequency, duration, and developmental timing of PV events are necessary to further elucidate the varying impacts of PV exposure on neurodevelopment and psychopathology.

This PV analysis focused on the cumulative burden of experiencing multiple forms of victimization, but it is possible that specific victimization types have a stronger influence on stress-related FC than others. Structural equation modeling or similar analysis techniques could be used to test the relative influence of different forms of victimization exposure on stress-related FC. Future work should also explore if altered DMN-SN FC mediates the well-documented relationship between PV and psychiatric symptoms (12).

Conclusions
This study demonstrates that during acute stress exposure, adolescents exhibit changes in FC between regions of the triple network; acute stress is associated with increased DMN-CEN FC and decreased connectivity between the SN and the DMN and CEN. Adolescents with greater PV exposure exhibited further reduced stress-related FC between the DMN and SN, possibly reflecting the neural impacts of the cumulative burden of exposure to different forms of victimization. Understanding the relationship between PV and triple network FC during acute stress is important for understanding how PV impacts the adolescent brain and elucidating the neurobiological pathways through which PV leads to negative health outcomes.

ACKNOWLEDGMENTS AND DISCLOSURES
This work was supported by the National Institutes of Mental Health (Grant No. R01MH103790-01A1 [to AB]), Child Health and Human Development (Grant Nos. T32HD040127 [to AP-B] and T32HD007376 [to RC]), and Neurologic Disorders and Stroke (Grant No. T32NS007431 [to RC and SG]). We thank Dr. Jens Pruessner for providing the MiST program, Dr. Joe Schaffner for adapting the MiST for adolescents and for our operating system, and Erik Savereide for proofreading and editing. We also would like to acknowledge project contributions from former lab members, including Mae Nicopolis Yefimov, Ashley Williams, Hannah Waltz, Louis Murphy, Carina Guerra, and Kathryn Scott. The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION
From the Department of Psychiatry (RC, SG, JB, AP-B, AC, AB), Carolina Institute for Developmental Disabilities (JB, AC, AB), and Frank Porter Graham Child Development Institute (JB, AB), University of North Carolina at Chapel Hill, Chapel Hill, Duke-UNC Brain Imaging and Analysis Center (RC, SG, JB, AP-B, AC), Duke University Medical Center, Durham, North Carolina; and the Department of Child and Adolescent Psychiatry & Behavioral Health Sciences (CK-F), Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania.

Address correspondence to Rachel Corr, Ph.D., at rachel.corr@unc.edu. Received Nov 24, 2021; revised Feb 28, 2022; accepted Mar 2, 2022. Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2022.03.003.

REFERENCES
Stress-Related Triple Network FC and Polyvictimization


