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Identifying Features of Resilience to Childhood Maltreatment in Resting-State Connectivity Data From Adults With and Without a History of Mood Disorder

Mindy Westlund Schreiner, Leah R. Thomas, Ha D.H. Le, Myah Pazdera, Daniel A. Feldman, Brian Farstead, Katie L. Bessette, Robert C. Welsh, Sheila E. Crowell, Erin A. Kaufman, Heide Klumpp, and Scott A. Langenecker

ABSTRACT

BACKGROUND: Childhood maltreatment (CM) is associated with negative mental health outcomes. Many studies conceptualize resilience as experiencing CM without developing psychopathology (primary resilience). However, some people may develop subsequent psychopathology but recover and demonstrate higher global functioning (secondary resilience). This study investigated the role of salience and emotion network (SEN) (including the amygdala, subgenual anterior cingulate cortex, and anterior insula) and cognitive control network (CCN) (including the dorsolateral prefrontal cortex, inferior parietal lobule, and thalamus) connectivity in primary and secondary resilience.

METHODS: We examined resting-state functional connectivity in 108 nonclinical control participants and 154 individuals with any mood disorder (AMD). We measured functioning and CM using the Global Assessment of Functioning (GAF) scale and the Childhood Trauma Questionnaire (CTQ), respectively. For primary resilience, we conducted whole-brain analyses of SEN and CCN regions to test for group × CTQ interactions. For secondary resilience, within-AMD group analyses tested for CTQ × GAF interactions.

RESULTS: Group × CTQ interactions revealed that control participants with higher levels of CM showed greater within-SEN and within-CCN connectivity than participants in the AMD group. In the AMD group, participants with higher levels of CM and functioning (secondary resilience) showed greater within-CCN connectivity while participants with higher levels of CM and lower functioning showed greater within-SEN connectivity.

CONCLUSIONS: Greater SEN connectivity appears to play a key role in primary resilience, as observed in the control group, but only within the context of greater CCN connectivity. Future work should explore which cognitive control features are most beneficial and whether targeted interventions help foster resilience to recurrent psychopathology.

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Childhood adversity comprises environmental circumstances that shape human development, including poverty, exposure to violence, and childhood maltreatment/abuse (1,2). Childhood maltreatment (CM) includes physical, sexual, and emotional abuse and neglect, medical/dental neglect, educational neglect, and exposure to violence (3). CM is associated with structural and functional neural differences, highlighting its potential to disrupt typical neurodevelopment (4). Many studies of CM and resilience have focused on primary resilience, wherein individuals experience CM but do not develop psychopathology. However, it is also important to consider secondary resilience, where individuals experience CM and subsequent psychopathology, but demonstrate recovery, including higher levels of functioning.

Studies have investigated the impact of CM on neurobiology among youths and adults. However, it is unclear which neurobiological features contribute to increased psychopathology risk. Some changes may reflect stress adaptations, representing neurobiological indicators of resilience. While a review by Roeckner *et al.* highlights both pre- and posttrauma neurobiological features that predict resilience, most reviewed studies have targeted non-CM–related traumatic experiences (e.g., vehicle accidents, military deployment, and natural disasters), underscoring the gap in our knowledge about the impacts of CM (5).

Resting-state functional neuroimaging studies have identified associations between CM and brain activation and connectivity in the cognitive control network (CCN) and the salience and emotion network (SEN) (6–8). The CCN includes the prefrontal cortex (PFC), parietal cortex, and dorsomedial thalamus. The SEN includes the anterior insula, anterior cingulate cortex (ACC), and amygdala, among others. While individuals may experience the same outcome regardless of exposure to CM (such as major depressive disorder [MDD]),

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they exhibit shared and distinct patterns of functional connectivity (FC). Wang *et al.* (9) demonstrated that regardless of CM history, individuals with MDD showed reduced FC in the ventromedial PFC (vmPFC) and ACC relative to nonclinical control participants (NCCs), potentially contributing to emotional and behavioral difficulties. However, compared with participants with MDD and no CM, participants with MDD and CM showed reduced FC of frontolimbic brain regions negatively associated with emotional neglect (9). CM has also been associated with decreased negative connectivity between the amygdala and occipital cortex and precuneus and decreased positive connectivity between the amygdala and orbitofrontal cortex (OFC), suggesting disruptions in frontolimbic neurocircuitry (10). Furthermore, CM has been associated with decreased negative connectivity between the dorsal ACC (dACC) and precuneus and decreased positive connectivity between the dACC and paracingulate gyrus and frontal pole, indicating SEN connectivity disruptions (11). Our group has indicated a link between CM and diminished cognitive control performance and network connectivity (12,13).

Despite various psychopathological conditions being associated with CM, some individuals demonstrate resilience by adjusting to trauma and challenging situations. An individual's capacity for resilience is determined by a combination of dynamic environmental, social, and biological factors. By examining trajectories and outcomes among individuals who experienced CM, research has found evidence for biologically based underpinnings of resilience. Individuals with CM without subsequent psychopathology show structural and functional neurobiological differences. Individuals who experience CM without developing posttraumatic stress disorder (PTSD) have smaller vmPFC and larger amygdala and hippocampal volumes than individuals who experience CM and develop PTSD (14). Functionally, these individuals demonstrate increased negative connectivity between the dACC and the lingual and occipital fusiform gyri (11).

Resilience is often conceptualized as the presence or absence of psychopathology following a stressor. However, this is an inadequate conceptualization. It is important to look at resilience within patient groups. Given varying levels of CM and psychopathology in typical patient samples, having lower severity psychopathology despite high levels of CM also exemplifies resilience. Identifying neurobiological features of this form of resilience may inform strategies to strengthen an individual's capability of resilience, even in the context of a history of CM and existing psychopathology.

We investigated resting-state FC features associated with resilience by examining how they relate to the presence of CM in a large sample of adults with versus without a history of mood disorder(s). While we acknowledge the need for a broader understanding of maltreatment, we narrowly define CM as physical, emotional, and sexual abuse and neglect experienced during childhood. Consistent with reviews by Moreno-Lopez *et al.* (4) and Roeckner *et al.* (5), we hypothesized that resilient adults (NCCs who experienced relatively higher levels of CM or adults with mood disorders who experienced higher levels of CM and had higher levels of functioning) would show greater connectivity within the SEN (particularly connectivity between the amygdala and other regions within the SEN) and between the SEN and limbic/subcortical regions, including the thalamus and primary and secondary visual areas such as the lingual gyrus (11,15,16). We hypothesized a positive association between CM and connectivity within the CCN, including the supramarginal gyrus (17), especially for participants with a history of mood disorder and higher clinician-assessed global levels of functioning (18).

METHODS AND MATERIALS

Participants

We included participants from 3 studies, which have been described elsewhere (18–21). All studies were approved by institutional review boards at the University of Michigan (UM) or the University of Illinois at Chicago (UIC). Participants were recruited from 2011 to 2018. Eligibility criteria included being 18 to 30 years old and having no magnetic resonance imaging (MRI) contraindications. For the any mood disorder (AMD) group, participants were required to have a history of a mood disorder. NCCs met criteria if they had no current or past Axis I DSM-IV-TR diagnosis. Eligible participants were enrolled after providing written informed consent and then completed visits.

Assessment

Staff determined the presence of mood disorder (including MDD, bipolar disorder, and dysthymia) and current state (remitted/euthymic or active) using the Diagnostic Interview for Genetic Studies (22) or the Structural Clinical Interview for DSM-IV (23,24). Diagnostic interviews informed clinician determinations of Global Assessment of Functioning (GAF) scores at the time of the interview. Higher GAF scores reflect higher functioning across psychological, social, and occupational domains (25). These scores were used to operationally define and dimensionally measure resilience in the context of CM. We used the Childhood Trauma Questionnaire (CTQ) total score to estimate CM (26).

Neuroimaging

Acquisition. We acquired data using a 3T GE Signa Excite 2 scanner (n = 33) and a GE Discovery scanner (n = 269) at UM and UIC, respectively. Sites acquired an 8-minute resting-state scan during which participants were instructed to keep their eyes open. UM used a T2*-weighted single-shot reverse spiral sequence with the following parameters: TR = 2000 ms, 240 volumes, flip angle = 90°, FOV = 200 mm, matrix size = 64 × 64, slice thickness = 4 mm, and TE = 30 ms. UIC used parallel imaging with ASSET and T2* gradient echo planar imaging with the following parameters: TR = 2000 ms, 240 volumes, flip angle = 90°, FOV = 220 mm, matrix size = 64 × 64, slice thickness = 3 mm, and TE = 22.2 ms. We acquired high-resolution T1 images for spatial normalization.

Preprocessing and Analysis. Participants were excluded based on movement deviation values (pitch > 0.02, roll > 0.01, and yaw > 0.01), consistent with prior work (27–29). Participants were also excluded following visual inspection of movement time courses for drifting and spikes. We used SPM12 to complete preprocessing, including slice-time correction, motion detection and adjustment, and normalization to Montreal Neurological Institute space. Additional processing was completed using ConnTool [authored by RCW;

(19,30)]. This included cerebrospinal fluid and white matter confound extraction using CompCor (31) and regressions in the order of detrending, 6 motion parameters, cerebrospinal fluid, white matter, and bandpass filtering with a fast Fourier transform filter between 0.01 and 0.10 Hz. We used coordinates of our seeds with a volume of 19 to approximate a sphere. We examined whole-brain connectivity from the SEN and CCN individually. Each network comprised 3 bilateral seeds [6 seeds for each network; see Stange *et al.* (32) for a description and convergence estimates]. The SEN included the amygdala, subgenual ACC (sgACC), and anterior insula. While the dACC is often included as a key node within the SEN, it is not included here due to overlap with other networks (including the CCN), which shifts over the course of development and may be disrupted in the context of psychopathology (8,33–39). The CCN included the dorsolateral PFC (dlPFC), inferior parietal lobule (IPL), and thalamus (Table S1). We applied xDF to estimate the variance of Pearson's correlation coefficients, calculate *z*-statistics maps of FC, and estimate *p* values for correlation coefficients (40).

We used each participant's *z*-statistics map generated using xDF to conduct NCC versus AMD group comparisons in SPM12. We conducted 2 separate whole-brain analyses: one with 6 SEN regions of interest (ROIs) as seeds and another with 6 CCN ROIs as seeds (3 ROIs bilaterally for each network). We examined the interaction between total CTQ scores and group (NCC vs. AMD). We also conducted 2 whole-brain analyses (SEN and CCN) to examine the interaction between total CTQ score (CM) and GAF in the AMD group. Each of these 4 analyses included the standard deviations of 3 motion parameters for each participant as covariates. Results that surpassed an uncorrected $p < .001$ and cluster size (k) of 75 contiguous voxels are reported. This is a more conservative threshold based on prior work, which used AFNI 3dClustSim to determine a threshold of $k > 57$, $p < .005$ based on 1000 Monte Carlo simulations (41). The familywise error (FWE) cluster-level correction embedded within SPM12 is $p < .003$, which provides an overall experimental FWE of 0.012 given 4 models. For brain regions that demonstrated significant associations with ROIs included in these 4 omnibus models, we extracted the values from these clusters for each participant for post hoc analyses, allowing for clarification of which seed ROIs in the models were responsible for the variance and for quantification figures and tables. Using R (42), we enumerated these relationships between each cluster, group, CTQ scores, and the SEN and CCN seeds and visualized the relationships of these connectivity values with CTQ and GAF scores while covarying for site and sex.

RESULTS

Of the 282 eligible participants with MRI and CTQ data, 20 (7%) were excluded due to motion. This yielded a final sample of 262 (NCC = 108, AMD = 154). For within-AMD group analyses investigating CTQ and GAF scores, 136 participants had GAF scores. Participant details are shown in Table 1.

NCC Versus AMD Group

Salience and Emotion Network (Analysis 1). Using SEN ROIs of bilateral amygdala, sgACC, and insula as seeds, significant clusters associated with group and CTQ scores included the bilateral insula and left secondary visual cortex. We found significant relationships between connectivity of the left insula cluster with the left amygdala ($F_{5,256} = 5.29$, $p < .001$), right amygdala ($F_{5,256} = 3.18$, $p = .008$), left sgACC ($F_{5,256} = 6.31$, $p < .001$), right sgACC ($F_{5,256} = 4.86$, $p < .001$), left anterior insula ($F_{5,256} = 4.38$, $p < .001$), and right anterior insula ($F_{5,256} = 4.57$, $p < .001$). There was a main effect of CTQ scores on connectivity between the left insula cluster and left amygdala ($p = .003$), right amygdala ($p = .021$), left sgACC ($p = .015$), right sgACC ($p = .008$), left insula ($p = .015$), and right insula ($p = .024$), in which higher CTQ scores were associated with higher connectivity. As hypothesized, there were significant group × CTQ score interactions between left insula cluster connectivity with the left amygdala ($p = .035$) and right sgACC ($p = .041$) seeds. Interactions demonstrated that the effect of the CTQ was greater for NCCs (Figure 1).

Significant relationships emerged between connectivity of the right insula cluster and the left amygdala ($F_{5,256} = 6.34$, $p < .001$), right amygdala ($F_{5,256} = 3.28$, $p = .007$), left sgACC ($F_{5,256} = 6.17$, $p < .001$), right sgACC ($F_{5,256} = 7.02$, $p < .001$), left anterior insula ($F_{5,256} = 3.34$, $p = .006$), and right anterior insula ($F_{5,256} = 7.30$, $p < .001$). There were main effects of CTQ scores on connectivity between the right insula cluster and left amygdala ($p < .001$), right amygdala ($p = .022$), left sgACC ($p = .021$), right sgACC ($p < .001$), left anterior insula ($p = .040$), and right anterior insula ($p < .001$) seeds. Consistent with our hypotheses, significant group × CTQ score interactions emerged between right insula cluster connectivity with the left amygdala ($p = .005$), right sgACC ($p = .009$), and right anterior insula ($p = .032$) seeds. These interactions demonstrated that the effect of CTQ scores was greater for NCCs (Figure 2).

Significant relationships emerged between connectivity of the left secondary visual cortex and the left amygdala ($F_{5,256} = 4.90$, $p < .001$), right sgACC ($F_{5,256} = 4.38$ $p < .001$), and right anterior insula ($F_{5,256} = 2.77$, $p = .019$). There was a main effect of CTQ scores on connectivity between the left secondary visual cortex and right anterior insula ($p = .028$) wherein higher CTQ scores were associated with greater negative connectivity between the left secondary visual cortex and right anterior insula (Table S2).

Cognitive Control Network (Analysis 2). Using the CCN ROIs of left and right dlPFC, dorsomedial thalamus, and IPL as seeds, significant clusters associated with group and CTQ scores included the right thalamus, cerebellum, and superior temporal gyrus. Significant associations emerged between connectivity of the right thalamus cluster with the left dlPFC ($F_{5,256} = 2.95$, $p = .013$), right dorsomedial thalamus ($F_{5,256} = 18.47$, $p < .001$), and left IPL ($F_{5,256} = 16.02$, $p < .001$). There were main effects of CTQ scores on connectivity between the right thalamus cluster and right dorsomedial thalamus ($p = .004$) and left IPL ($p = .007$). As hypothesized, there was a significant group × CTQ score interaction for right thalamus cluster connectivity with the right dorsomedial thalamus ($p = .049$). The effect of CTQ scores was greater for NCCs (Figure 3).

Significant associations emerged between connectivity of the right cerebellum cluster with the right dlPFC ($F_{5,256} = 4.82$, $p < .001$), left dorsomedial thalamus ($F_{5,256} = 5.30$, $p < .001$), right dorsomedial thalamus ($F_{5,256} = 8.28$, $p < .001$), left IPL

Table 1. Demographic Characteristics of Study Participants

	Overall, *n* = 262	NCC, *n* = 108	AMD, *n* = 154
Age			
Mean (SD)	22.4 (3.11)	21.9 (2.95)	22.7 (3.18)
Median (minimum–maximum)	22.0 (18.0–30.0)	21.0 (18.0–29.0)	22.0 (18.0–30.0)
Sex, *n* (%)			
Female	170 (64.9%)	62 (57.4%)	108 (70.1%)
Male	92 (35.1%)	46 (42.6%)	46 (29.9%)
CTQ Total			
Mean (SD)	36.3 (13.4)	29.2 (5.88)	41.1 (14.9)
Median (minimum–maximum)	32.0 (25.0–102)	27.0 (25.0–55.0)	37.0 (25.0–102)
Diagnosis, *n* (%)			
Bipolar Disorder	–	–	17 (6.5%)
Dysthymia	–	–	1 (0.4%)
MDD	–	–	136 (51.9%)
GAF, *n* = 136			
Mean (SD)	–	–	77.5 (12.5)
Median (minimum–maximum)	–	–	80 (47–95)

AMD, any mood disorder; CTQ, Childhood Trauma Questionnaire; GAF, Global Assessment of Functioning; MDD, major depressive disorder; NCC, nonclinical control participant.

($F_{5,256}$ = 6.75, $p < .001$), and right IPL ($F_{5,256}$ = 2.51, p = .030). There were main effects of CTQ scores on connectivity between the right cerebellum cluster and right dlPFC (p = .018), left dorsomedial thalamus (p = .008), and right IPL seeds (p = .043). There were no significant main effects or interactions of interest for the right superior temporal gyrus cluster (Table S3).

AMD: Trauma and Level of Functioning (Resilience)

Salience and Emotion Network (Analysis 3). Using the SEN ROIs of the left and right amygdala, sgACC, and anterior insula as seeds, CTQ and GAF scores were associated with SEN connectivity with clusters including 1) the right middle insula and central opercular cortex (right middle insula/prefrontal); 2) the left lingual gyrus, intracalcarine cortex, and occipital pole (left visual cortex); and 3) the left anterior and ventral insula, OFC, frontal operculum cortex, and amygdala (left insula/OFC/amygdala) (Table S4).

Significant positive associations emerged between connectivity of the right middle insula/prefrontal cluster with the left amygdala ($F_{5,130}$ = 4.65, $p < .001$), right amygdala ($F_{5,130}$ = 3.69, p = .004), left sgACC ($F_{5,130}$ = 4.50, $p < .001$), right sgACC ($F_{5,130}$ = 3.98, p = .002), left anterior insula ($F_{5,130}$ = 3.18, p = .001), and right anterior insula ($F_{5,130}$ = 5.00, $p < .001$). There were significant main effects of CTQ scores on connectivity between the right middle insula/prefrontal cluster and the left amygdala ($p < .001$), right amygdala (p = .015), right sgACC (p = .011), and left anterior insula (p = .021). There were significant main effects of GAF scores on connectivity between the right middle insula/central

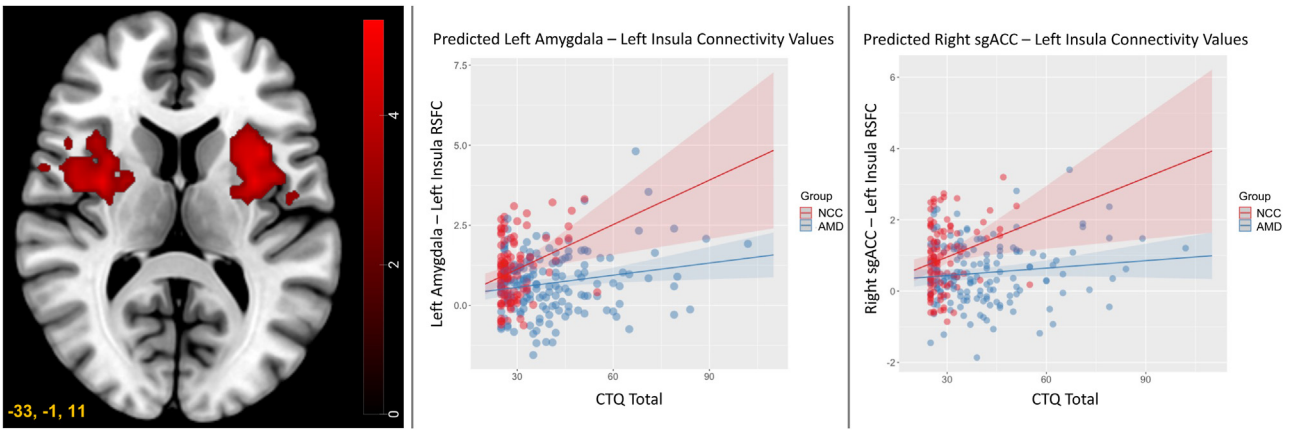

Figure 1. Predicted values for salience and emotion network seed connectivity: left insula. Predicted values for left insula connectivity with left amygdala and right subgenual anterior cingulate cortex (sgACC) seeds. Coordinates in yellow are in Montreal Neurological Institute standard space. AMD, any mood disorder; CTQ, Childhood Trauma Questionnaire; NCC, nonclinical control participant; RSFC, resting-state functional connectivity.

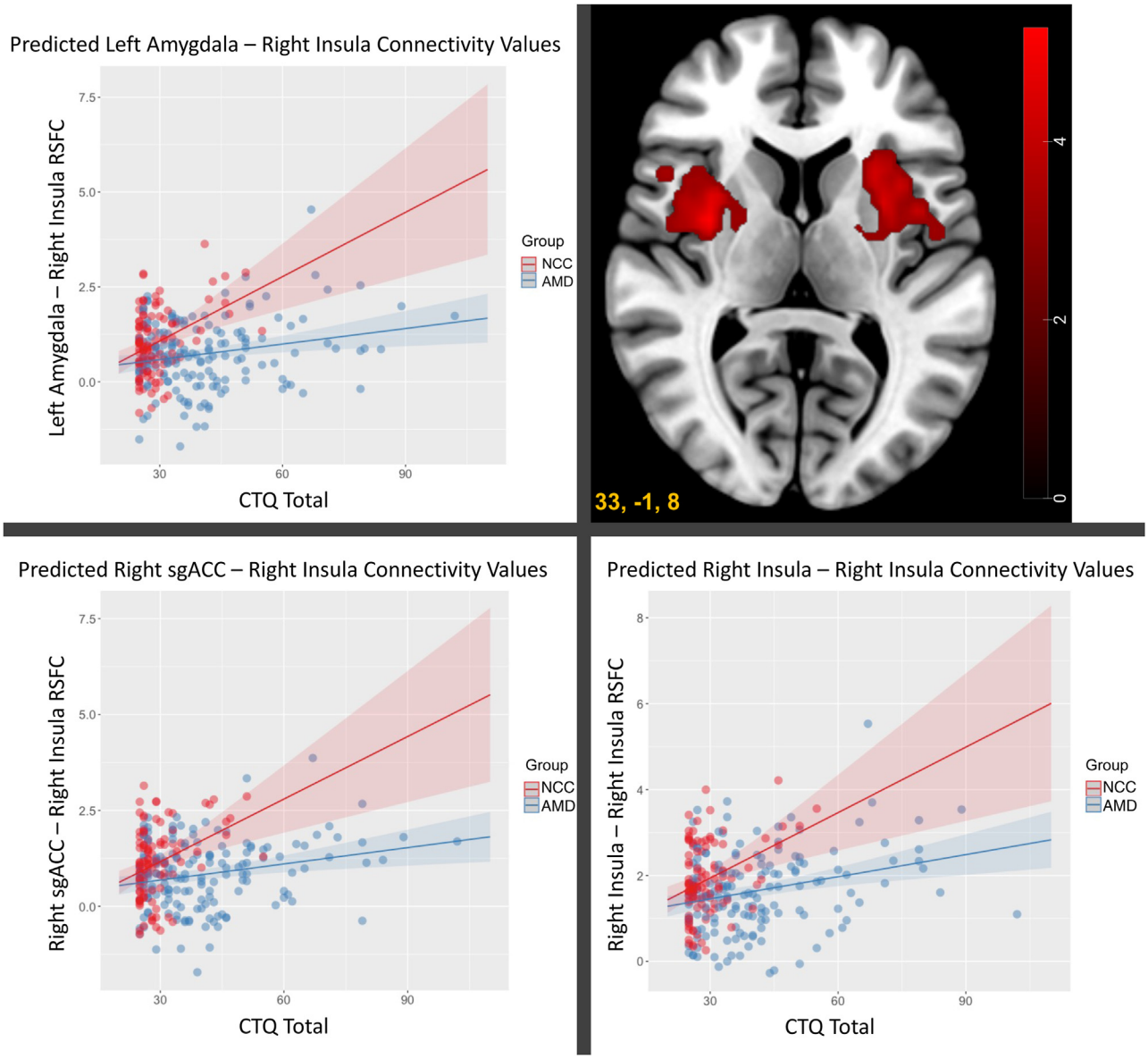

Figure 2. Predicted values for salience and emotion network seed connectivity: right insula. Predicted values for right insula connectivity with left amygdala and right subgenual anterior cingulate cortex (sgACC) and insula seeds. Coordinates in yellow are in Montreal Neurological Institute standard space. AMD, any mood disorder; CTQ, Childhood Trauma Questionnaire; NCC, nonclinical control participant; RSFC, resting-state functional connectivity.

opercular cluster and the left amygdala (p = .004) and right sgACC (p = .021). There were significant CTQ × GAF interactions on connectivity between the right middle insula/prefrontal cluster and the left (p = .003) and right (p = .039) amygdala, inconsistent with our hypotheses. There were also significant CTQ × GAF interactions on connectivity between the right middle insula/prefrontal cluster and the right sgACC (p = .038) and left anterior insula (p = .048), which followed a pattern similar to the interaction with the left amygdala (Figure 4).

A significant association emerged between connectivity of the left visual cortex cluster (left lingual gyrus, intracalcarine cortex, and occipital pole) and left sgACC ($F_{5,130}$ = 3.02, p = .013), in which there was a main effect of CTQ (p = .037). Significant associations emerged between connectivity of the left insula/OFC/amygdala cluster (left insula, OFC, frontal operculum cortex, and amygdala) and the left amygdala ($F_{5,130}$ = 5.66, $p < .001$), left sgACC ($F_{5,130}$ = 10.5, $p < .001$), and right sgACC ($F_{5,130}$ = 3.87, p = .003). There were significant main effects of CTQ scores on connectivity between the left insula/OFC/amygdala cluster and the left amygdala (p = .005), left sgACC (p = .006), and right sgACC (p = .016). There were significant CTQ × GAF interactions with connectivity between the left insula/OFC/amygdala cluster and the left amygdala (p = .016) (Figure 4), contrary to our hypotheses. There were also significant interactions with the

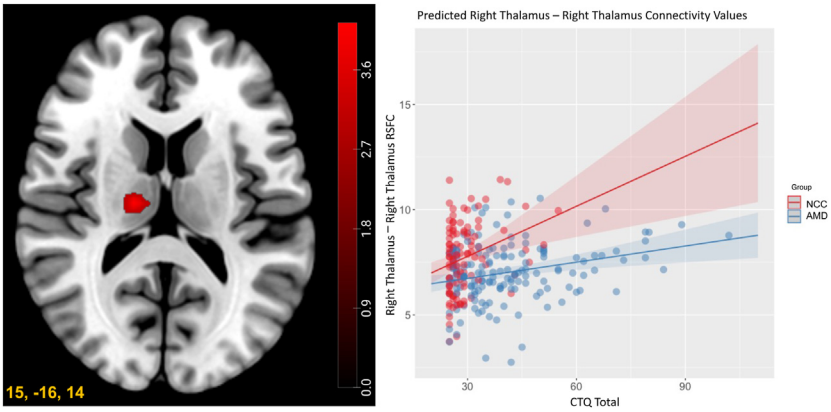

Figure 3. Predicted values for right thalamus connectivity with the right dorsomedial thalamus seed. Coordinates in yellow are in Montreal Neurological Institute standard space. AMD, any mood disorder; CTQ, Childhood Trauma Questionnaire; NCC, nonclinical control participant; RSFC, resting-state functional connectivity.

left (p = .027) and right (p = .040) sgACC, following a similar pattern as the left amygdala.

Cognitive Control Network (Analysis 4). Using the CCN ROIs of the left and right dlPFC, dorsomedial thalamus, and IPL as seeds, one significant cluster was associated with CTQ and GAF scores, which included the bilateral thalamus. A significant association emerged between the connectivity of this cluster and the left dlPFC, $F_{5,130}$ = 4.20, p = .001, in which there was a significant CTQ × GAF interaction for connectivity between the bilateral thalamus and left dlPFC (p = .027) (Figure 5), consistent with our hypothesis of greater within-CCN connectivity among individuals with high GAF and CTQ scores in the AMD group (Table S5).

DISCUSSION

This megastudy provides information regarding potential biomarkers of primary and secondary resilience in the context of CM specifically as it relates to physical, emotional, and sexual abuse and neglect. Consistent with our hypotheses and previous work, regions of the SEN and CCN were associated with differential patterns of connectivity in relation to CM in the NCC and AMD groups. For SEN analyses, our hypotheses were partially supported because we observed a pattern wherein the NCC group with higher levels of CM demonstrated a stronger positive association with connectivity between clusters including the bilateral insula and left amygdala, right sgACC, and right insula seeds. Contrary to our hypotheses, we found a different pattern in our within-AMD group analyses examining CM and functioning; participants with lower functioning and higher levels of CM demonstrated greater amygdala-insula connectivity. However, for NCC-related findings, our interpretations are tempered due to the restricted range of CTQ scores relative to the AMD group.

Our hypotheses for our CCN analyses were supported because the NCC group with higher levels of CM demonstrated a positive association with connectivity between a right thalamus cluster and our right dorsomedial thalamus seed. Within-AMD analyses showed that participants with higher functioning and CM demonstrated greater connectivity between the dlPFC and thalamus. These findings support our hypothesis that resilience is associated with higher within-CCN connectivity. Future studies could align this increased connectivity with associated domains of executive functioning such as inhibitory control, set-shifting, or working memory (32).

Our results showed that insula connectivity with other SEN regions (the amygdala and sgACC) may play an important role in the neural underpinnings of resilience in the context of mood disorders. During an aversive interoceptive processing task, individuals with lower levels of resilience showed greater insula activation in response to the aversive stimulus (43). Furthermore, individuals with higher levels of resilience showed a greater decrease in connectivity between the insula and sgACC following a stress-induction paradigm (44). Increased connectivity between the insula and other SEN regions during rest, as demonstrated in our NCC group with higher CTQ scores, may allow for greater variability in responding to potential threat. However, we did not find this pattern of increased insula connectivity with other SEN regions among individuals with AMD and high CM and functioning. It is possible that individuals who have developed mood disorders and experienced higher levels of CM may not demonstrate the same level of variability when confronted with stressors, potentially due to an allostatic shift. This would be similar to prior research on the impact of chronic stress on the hypothalamic-pituitary-adrenal axis response to acute stressors (45).

Findings of a greater positive association between CM and CCN connectivity in the NCC group suggest that individuals who experience relatively higher levels of CM and do not develop psychopathology may demonstrate a compensatory response. However, our cross-sectional design prevents us from making this determination. The presence of this same pattern among individuals with AMD, high CM, and lower functioning suggests that this relationship is more complicated. Moreover, the range of CTQ scores in the NCC group is restricted, limiting a way to fully model whether the interaction is nonlinear. Given the role of the CCN in executive functioning (46–48), greater within-CCN connectivity may impact whether this greater SEN connectivity is adaptive or maladaptive. Specifically, lower within-CCN connectivity seen among individuals with AMD, high CTQ scores, and low GAF scores

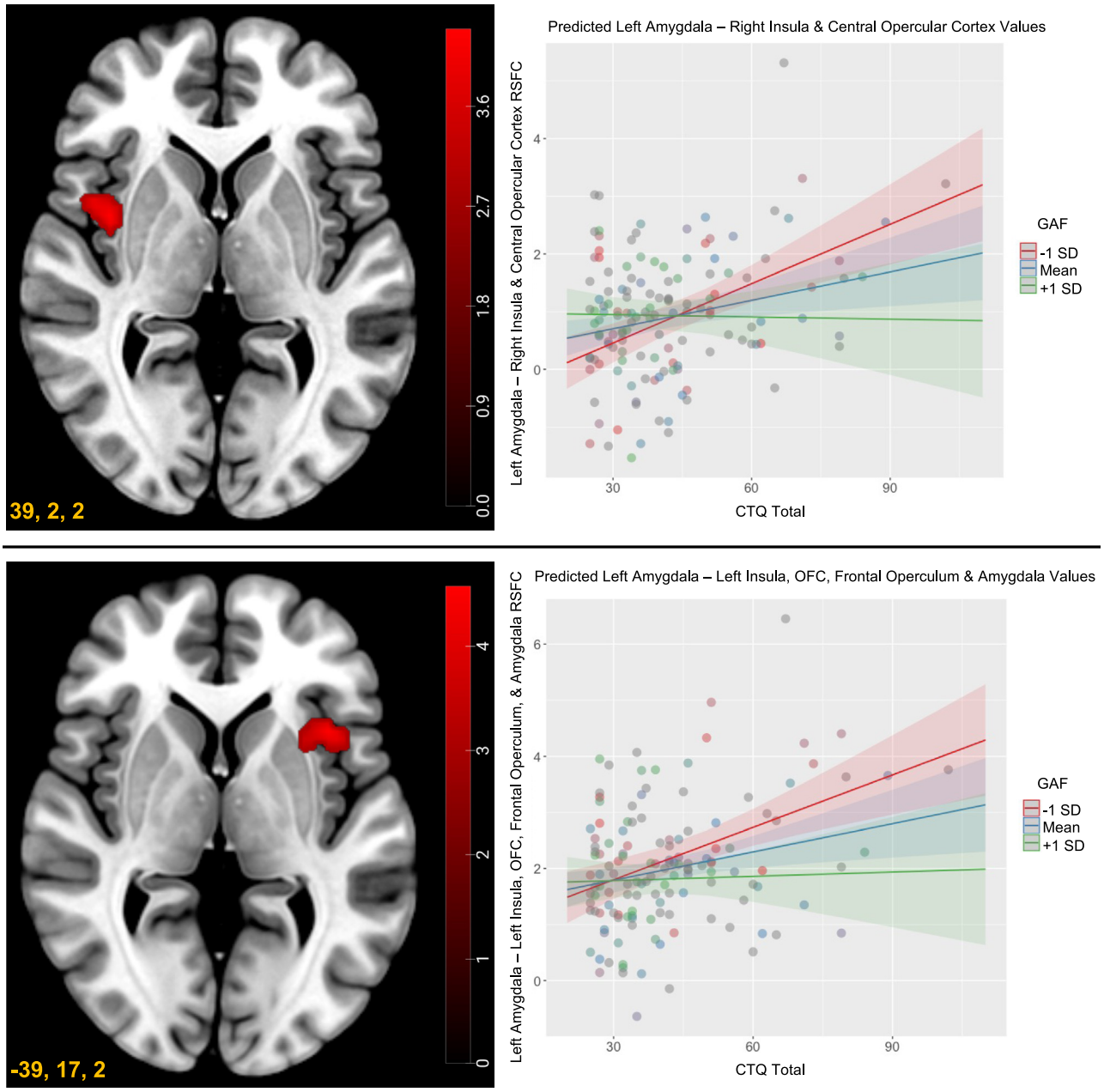

Figure 4. Predicted values for salience and emotion network seed connectivity. Top: Predicted values for left amygdala seed connectivity with the right insula and central opercular cortex. Bottom: Predicted values for left amygdala seed connectivity with the left insula, orbitofrontal cortex (OFC), frontal operculum, and amygdala. Coordinates in yellow are in Montreal Neurological Institute standard space. CTQ, Childhood Trauma Questionnaire; GAF, Global Assessment of Functioning; RSFC, resting-state functional connectivity.

may lead to disruptions in effectively managing and regulating emotional information. While NCCs with higher levels of CM show this higher within-SEN connectivity, the potentially adverse effects may be mitigated by heightened coherence of CCN regions.

Our findings of positive associations between medial thalamic connectivity and CM in the NCC group are consistent with prior work (16). Increased thalamic connectivity suggests increased engagement of thalamic gating and/or integration of incoming stimuli, and increased thalamic activation has been associated with greater resilience among individuals who recently experienced a traumatic event (49,50). Although our findings demonstrate increased connectivity, this may also indicate appropriate facilitation and attendance to incoming stimuli and avoiding trauma-associated symptoms such as fear generalization (51).

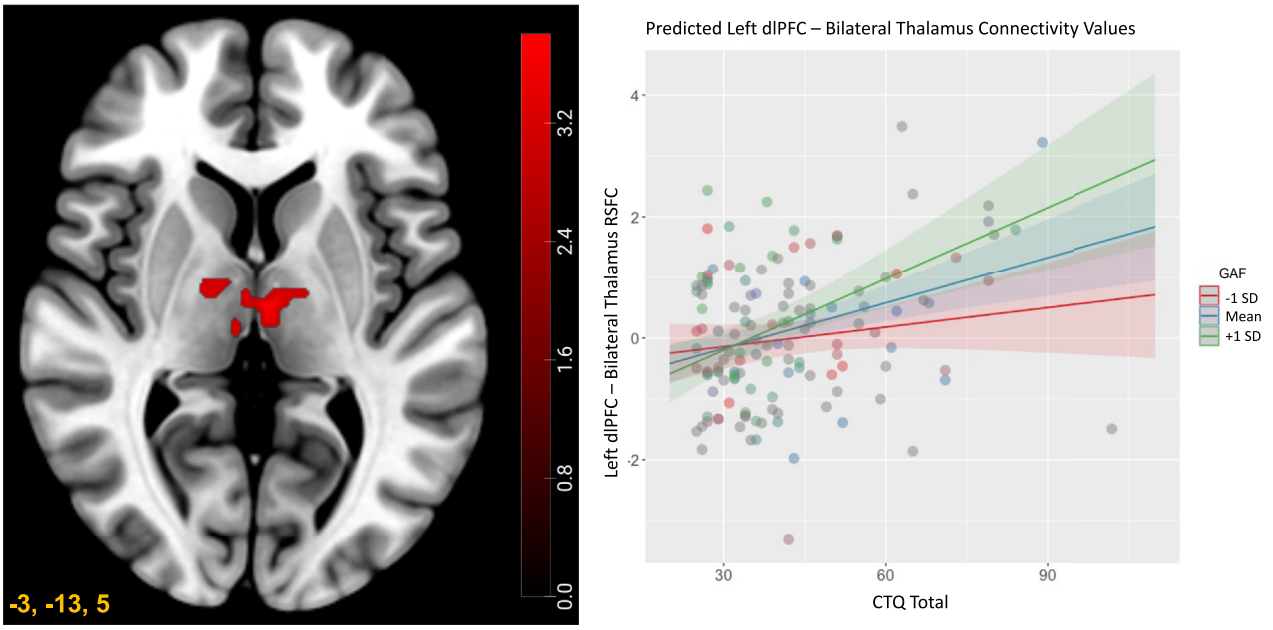

Figure 5. Predicted values for left dorsolateral prefrontal cortex (dlPFC) seed connectivity with the right and left thalamus. Coordinates in yellow are in Montreal Neurological Institute standard space. CTQ, Childhood Trauma Questionnaire; GAF, Global Assessment of Functioning; RSFC, resting-state functional connectivity.

Limitations

Strengths of this megastudy include a large sample size, data-driven hypotheses with empirically derived networks and hubs, and a significant research question. There are also noteworthy limitations. Our results and interpretations are limited by using a cross-sectional design and samples of convenience. The CTQ is a simple and limited retrospective account of specific types of CM, although recent research has demonstrated that such recall in adults is stable over time and not affected by symptom fluctuations (52). Nevertheless, CM is complex and heterogeneous. There may be variability by CM type, the developmental period during which CM occurred, severity, and chronicity. Future research would benefit from more nuanced measures of CM that include adverse life experiences beyond those measured by the CTQ, such as medical and educational neglect and a violent environment. Different CM types may have unique effects on the brain and development and the progression of mood disorders. Our study is also limited by the restricted range of CTQ scores in our NCC group, which highlights the importance of more targeted recruitment of resilient NCC individuals with high CM.

Another important limitation is that our understanding of trauma, resilience, and mental health must extend beyond biological and functional frameworks. Social and structural inequities/equities dampen/facilitate mental wellness. Perceived discrimination, which was not assessed in this study, has been shown to be significantly associated with depression, suicidal ideation, and capability for suicide in Black and African American adults (53) as well as among LGBTQ+ individuals (54,55). Other studies have shown that mental health among youths was directly associated with socioeconomic status, as well as with parental education and employment (56–58). These studies demonstrate that challenging contextual, cultural, and social factors can lead to adverse mental health outcomes, particularly in disadvantaged communities. Future research and treatment must reconsider current approaches that frame resiliency and trauma as individual issues and integrate the impact of systemic factors on mental health.

Conclusions

The current study highlights potential neurobiological features of risk and resilience in the presence of mood disorders and in relation to functional impairment. Individuals who experience moderate levels of CM and do not develop psychopathology may demonstrate increased FC between regions implicated in interoceptive awareness and emotional experience. However, that pattern may only be adaptive in the context of also having increased connectivity between regions involved in cognitive control, such as the integration and regulation of incoming stimuli. These findings highlight the potential for targeted interventions for individuals who have experienced high versus low CM levels. Interventions may be most effective when targeting aspects of cognitive control related to cognitive processing therapy and trauma-focused cognitive behavioral therapy. While we were unable to test the developmental context, there is precedent for examining the acquisition of resilience in relation to CM, which may unfold differently for primary versus secondary resilience. Future work that examines the role of psychosocial interventions in the treatment of individuals with CM and psychopathology may help validate whether these are key factors in fostering resilience.

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ARTICLE INFORMATION

From the Department of Behavioral Health, Nationwide Children's Hospital, Columbus, Ohio (MWS); Department of Psychiatry and Behavioral Health, The Ohio State University, Columbus, Ohio (MWS, LRT, SAL); Department of Psychology and Child Development, California Polytechnic State University, San Luis Obispo, California (LRT); Department of Pediatrics, University of California San Francisco, San Francisco, California (HDHL); Department of Psychiatry, Huntsman Mental Health Institute, University of Utah, Salt Lake City, Utah (MP, DAF, EAK); Department of Biomedical Engineering, University of Utah, Salt Lake City, Utah (DAF); Department of Psychology, University of Southern Mississippi, Hattiesburg, Mississippi (BF); Department of Psychiatry and Biobehavioral Sciences and Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, California (KLB, RCW); Department of Psychology, University of Oregon, Eugene, Oregon (SEC); and Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois (HK).

Address correspondence to Mindy Westlund Schreiner, Ph.D., at mindy.westlundschreiner@nationwidechildrens.org.

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