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Altered amygdala connectivity in urban youth exposed to trauma

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Early life trauma exposure represents a potent risk factor for the development of mental illnesses such as anxiety, depression and post-traumatic stress disorder. Moreover, deleterious consequences of trauma are exacerbated in youth living in impoverished, urban environments. A priori probability maps were used to examine resting-state functional connectivity (FC) of the amygdala in 21 trauma-exposed, and 21 age- and sex-matched urban children and adolescents (youth) without histories of trauma. Intrinsic FC analyses focused on amygdala-medial prefrontal circuitry, a key emotion regulatory pathway in the brain. We discovered reduced negative amygdala-subgenual cingulate connectivity in trauma-exposed youth. Differences between groups were also identified in anterior insula and dorsal anterior cingulate to amygdala connectivity. Overall, results suggest a model in which urban-dwelling trauma-exposed youth lack negative prefrontal to amygdala connectivity that may be critical for regulation of emotional responses. Functional changes in amygdala circuitry might reflect the biological embedding of stress reactivity in early life and mediate enhanced vulnerability to stress-related psychopathology.

Keywords: adolescent; child; maltreatment; resting-state; urban

INTRODUCTION

Estimates regarding rates of exposure to traumatic events in childhood range widely from 15 to 60% (Kessler *et al.*, 1995; Dube *et al.*, 2001; Stein *et al.*, 2010), with strong evidence for the highest incidence occurring in urban, inner city settings (almost 90%; Gillespie *et al.*, 2009; Goldmann *et al.*, 2011). Trauma and stress injure the brain, precipitate cognitive-behavioral, emotional, and somatic problems, and are strong predictors of psychiatric illness (McEwen, 2012). Trauma in early life is especially harmful—associated with ~50% of childhood psychiatric disorders, and 30% of later-onset clinical disorders (Green *et al.*, 2010).

Neurological evaluation of the link between trauma and psychiatric illness converges on amygdala and prefrontal brain regions. The amygdala is essential for the detection of threat and enhancement of vigilance (Zald, 2003) and is a central activator of the physiologic stress response (Dedovic *et al.*, 2009). In contrast, the prefrontal cortex (PFC) is critical for regulation of emotion (Quirk and Beer, 2006). Animals that experience early life adversity show structural and functional changes in both the amygdala (Malter Cohen *et al.*, 2013b for a review) and PFC (review by McEwen and Morrison, 2013). Furthermore, early life adversity may also perturb the direct bidirectional connections between these two regions (review by Tottenham and Sheridan, 2009).

Research in humans and animals consistently demonstrates altered frontoamygdala connectivity is another consequence of early life stress (Gee *et al.*, 2013a; Malter Cohen *et al.*, 2013a; Philip *et al.*, 2013; Grant *et al.*, 2014). Compromised connectivity between the amygdala and PFC has been implicated in the pathophysiology of stress-related disorders. Specifically, altered frontoamygdala connectivity has been observed in anxiety (Kim and Whalen, 2009; Roy *et al.*, 2013), depression (Tang *et al.*, 2013) and post-traumatic stress disorder (PTSD; Edwards *et al.*, 2013, Stevens *et al.*, 2013, Brown *et al.*, 2014). It is possible that altered frontoamygdala connectivity may emerge early in life, proximal to negative traumatic experiences, and that this shift may be formative in determining healthy or deleterious outcomes for the individual. After all, frontoamygdala circuitry undergoes rapid changes across childhood and adolescence (Hare *et al.*, 2008, Gee *et al.*, 2013b, Gabard-Durnam *et al.*, 2014), and thus alterations occurring during this period may have lasting effects.

Although animal research has addressed embedding of stress exposure in frontoamygdala pathways in early life, research in humans is relatively recent. Gee *et al.* (2013a) and Nooner *et al.* (2013) provided the first studies of early life stress and functional connectivity (FC) in children/adolescents. Gee *et al.* examined task-related variation in FC associated with orphanage rearing in 6-17 year olds during a face-processing task, whereas Nooner *et al.* examined how trauma-symptoms in a healthy sample of community youth relate to variations in intrinsic FC during resting-state. Both studies evidenced altered frontoamygdala FC, with orphanage-reared children showing more medial frontal and typically developing youth showing more lateral frontal amygdala FC effects. Frontoamygdala FC alterations have also been shown to relate to trauma, diurnal cortisol and internalizing symptoms in a longitudinal community sample of young adults (18 year olds; Burghy *et al.*, 2012; Herringa *et al.*, 2013). These studies compel the need for more research during formative years, prior to when psychopathology becomes chronic. Research that examines youth at high risk for developing clinical disorders could lead to identification of latent neural risk factors contributing to psychopathology in the aftermath of trauma exposure.

Here, we examine intrinsic resting-state neural FC in urban, low-income, minority trauma-exposed and comparison youth (ages 9-15).

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Past research shows not only that trauma frequency is extreme in African Americans living in impoverished urban areas, but also that negative consequences of trauma in urban, African American communities may be more severe (Alim *et al.*, 2006). For example, while ~20% of trauma-exposed individuals in the general population subsequently develop PTSD, African American urban residents who experience trauma are nearly two times more likely develop PTSD (Goldmann *et al.*, 2011). In addition, lower income is a significant predictor of more severe emotional psychopathology following trauma (Lowe *et al.*, 2014). Thus, additive effects of trauma frequency and stress burden may be particularly deleterious to healthy emotional development. Investigating the correlates of trauma exposure on the developing brain in a low income, African American urban cohort of youth provides an opportunity to identify neurological changes in those who are at highest risk for developing psychopathology.

MATERIALS AND METHODS

Participants

The current study evaluated 42 urban youth, ages 9-15 (mean = 12.6, s.d. = 2.1). Participant ages were selected to align with the emergence of puberty; puberty has been identified as a time when affective disorders frequently manifest (Angold *et al.*, 1998). The majority of participants ($n = 27$) reported annual incomes of <$40 000, and only a small number ($n = 6$) reported incomes>$60 000. Participants were drawn from a larger study, and chosen to represent trauma-exposed ($n = 21$) and comparison ($n = 21$) groups matched on age and sex. Data from 18 participants have been reported previously (Thomason *et al.*, 2013). Participants were recruited through advertisements posted on the Wayne State University website, Craigslist (Detroit), printed flyers, or through Metro Detroit mental health clinics. Exclusionary criteria included: English as a second language, lower than a 2nd grade reading level, history of brain injury, neurological or movement disorders or presence of magnetic resonance imaging (MRI) contraindication. Parental informed written consent and child/adolescent assent were obtained prior to participation. Demographic and behavioral measures were administered during a laboratory visit, and MRI was performed during a subsequent visit (~2 weeks following the laboratory visit). All experimental procedures were approved by the Human Investigation Committee of Wayne State University.

Demographic data analysis

Highest level of parent/caregiver educational attainment and annual household income were coded as ordinal variables and compared between groups using Mann-Whitney U-tests. Independent samples *t*-tests or χ^2 tests were used to test for group differences in age, sex, IQ (derived from the Kaufman Brief Intelligence Test, version 2; Kaufman and Kaufman, 2004), pubertal development (using Tanner staging; Marshall and Tanner, 1968), and parent report of child race/ethnicity. Effects were considered significant at $P \leq 0.05$. Statistical analyses were two-tailed and implemented in IBM statistical package for the social sciences (SPSS) Statistics 21 (SPSS, Inc., Chicago, IL).

Trauma exposure

Utilizing both parent and child endorsements, participants that experienced at least one trauma indicated on the Children's Trauma Assessment Center Screen Checklist were categorized as 'trauma' (source: Michigan Trauma Assessment Center). Forms of trauma included victimization (e.g., physical, psychological, or sexual abuse), neglect, and exposure to violence. Frequently, trauma exposed youth experienced more than one type of trauma. Number and type of endorsed traumas are provided in Table 1.

Self-reported affect measures

Participants completed two validated self-report questionnaires: the 10-item Children's Depression Inventory (CDI; Saylor *et al.*, 1984) and the 41-item Screen for Childhood Anxiety-Related Disorders (SCR; Birmaher *et al.*, 1997). The SCR was administered during the lab visit and again at the MRI visit. Lab and MRI SCR scores were highly correlated, $r(42).0.76$, $P < 0.001$. Thus, average across SCR measurements is reported. A visual analog scale (VAS) was used to obtain

Table 1 Demographic and clinical characteristics by group

Variable	Trauma ($n = 21$)	Comparison ($n = 21$)	Group comparison (*P*-value)
Age, m (s.d.)	12.77 (2.00)	12.32 (2.19)	ns
Pubertal maturation (tanner stage), m (s.d.)	3.75 (0.95)	3.12 (1.38)	ns
Sex (female), *n* (%)	15 (71.43)	14 (66.67)	ns
IQ, m (s.d.)	90.55 (10.9)	109.94 (16.04)	<0.001
Race/ethnicity, *n* (%)			
African American	10 (47.62)	10 (47.62)	ns
Caucasian	4 (19.05)	10 (47.62)	
Hispanic	3 (14.28)	0 (0)	
Not reported	4 (19.05)	1 (4.76)	
Annual household income, *n* (%)			
<$40 000	17 (81)	10 (47.6)	0.018
$40 000 to $60 000	1 (4.8)	7 (33.3)	
$60 000 to $80 000	2 (9.5)	1 (4.8)	
$80 000 to $100 000	0	1 (4.8)	
Over $100 000	0	2 (9.5)	
Not reported	1 (4.8)	0	
Highest level of parental education, *n* (%)			
No GED/no high school diploma	2 (9.5)	1 (4.8)	ns
GED/high school diploma	4 (19)	1 (4.8)	
2-year degree or some college	8 (38.1)	9 (42.9)	
4-year degree	3 (14.3)	7 (33.3)	
Masters	3 (14.3)	2 (9.5)	
Doctorate	0	1 (4.8)	
Not reported	1 (4.8)	0	
Type of trauma endorsed[a], *n* (%)			
Physical abuse	4 (19%)	0	
Neglectful home environment	3 (14%)	0	
Emotional abuse	2 (10%)	0	
Exposure to domestic violence	14 (67%)	0	
Exposure to any other violence not already identified	11 (52%)	0	
Multiple separations from parent or caregiver	4 (19%)	0	
Sexual abuse or exposure	5 (24%)	0	
Anxiety symptoms (SCR)[b], m (s.d.)	22.97 (16.49)	14.23 (11.08)	0.05
Depressive symptoms (CDI)[c], m (s.d.)	4 (5.32)	1.8 (2)	ns
Motion during scan			
Translational max frame-to-frame excursion (s.d.)	0.66 (0.31) mm	0.56 (0.25) mm	ns
Rotational max frame-to-frame excursion (s.d.)	0.59 (0.27)°	0.56 (0.33)°	
Translational mean movement (s.d.)	0.13 (0.08) mm	0.1 (0.6) mm	
Rotational mean movement (s.d.)	0.11 (0.06)°	0.12 (0.08)°	
Translational rms (s.d.)	0.1 (0.05) mm	0.08 (0.02) mm	
Rotational rms (s.d.)	<0.001 (<0.001)°	<0.001 (<0.001)°	

Note. [a]Trauma criteria are from CTA Center Screen Checklist (Item 1) by the Michigan Trauma Assesement Center. [b]SCR, Screen for Child Anxiety-Related Emotional Disorders. [c]CDI, Children's Depression Inventory. All *P*-values derived from *t*-tests with the exception of sex and race/ethnicity comparisons, which used χ^2 tests, and income and parental education, which used Mann-Whitney U-tests. Abbreviations: m, mean; s.d., standard deviation; *n*, number; ns, not significant; max, maximum; rms, root mean squared (head position change during the resting-state scan).

an average rating of fear/anxiety during the MRI visit (repeat measures at 30-min intervals) as previously described (Thomason *et al.*, 2013).

Imaging data acquisition

MRI data were acquired using a 3.0 T Siemens Verio scanner. Participants were positioned in a 12-channel transmit-receive head coil and stabilized by padding to reduce motion-related artifacts. Participants were asked to lie quietly in the scanner with their eyes closed for the duration of the 6-min resting-state scan. For functional magnetic resonance imaging (fMRI), a total of 180 T2*-weighted blood oxygenation level-dependent (BOLD) images were acquired (interleaved ascending acquisition) using echo-planar imaging (EPI). The acquisition parameters were: repetition time [TR] = 2000 ms; echo time [TE] = 25 ms; flip angle = 90°; voxel size = 3.44 × 3.44 × 4 mm; matrix = 220 × 220 and 29 slices. Additionally, T1-weighted images were obtained for anatomical reference with the following parameters: TR = 1680 ms; TE = 3.51 ms; flip angle = 9°; voxel size = 0.7 × 0.7 × 1.3 mm; matrix = 256 × 256 and 176 slices.

Image preprocessing

Image preprocessing steps were conducted using SPM8 software (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/). After discarding the first 4 EPI volumes to allow for signal stabilization, images were slice-time corrected, realigned, spatially normalized to the Montreal Neurological Institute (MNI) template, and smoothed using an 8-mm Gaussian kernel. Frame-to-frame excursion, root mean square (rms) and head movement across the scan were calculated and averaged for translational (*x*, *y*, *z*) and rotational (roll, pitch, yaw) movement directions. Motion parameters were compared between groups using two-tailed independent samples *t*-test. Between group motion differences were considered significant at $P < 0.05$.

Seed-based connectivity analysis

Given prior research showing altered intrinsic FC of specific amygdala subregions in adults with PTSD (Brown *et al.*, 2014) and anxiety (Etkin *et al.*, 2009), connectivity of centromedial (CM) and basolateral (BL) amygdala were evaluated separately. Amygdala subregions were the leading choice for seeded ROI analyses because of their unique connectivity profiles. For more detailed discussion of amygdala subregion connectivity in humans, see (Roy *et al.*, 2009). Seed regions were defined for CM and BL amygdala structural subdivisions (Amunts *et al.*, 2005), following prior work (Roy *et al.*, 2009; Qin *et al.*, 2012). In brief, bilateral masks used stereotaxic, probabilistic maps of cytoarchitectonic boundaries defined by SPM Anatomy toolbox (Eickhoff *et al.*, 2005). Cytoarchitectonic maps show high reliability and accuracy for guiding anatomical segmentation of amygdala subregions in children as young as 6 years of age (Kim *et al.*, 2010; Qin *et al.*, 2012). Given that we had no a priori lateralization hypotheses, we averaged signal from right and left amygdala masks. FC of amygdala subregions was determined by semipartial correlation using the Connectivity (CONN) FC Toolbox (ver.12.p; www.nitrc.org/projects/conn). Between group effects were considered within an anatomically defined medial prefrontal region used in prior works (Etkin and Schatzberg, 2011; Marusak *et al.*, 2014). This mask was selected to encompass perigenual (pgACC) and subgenual (sgACC) regions of the anterior cingulate, as these regions suppress limbic reactivity through direct connections to the amygdala. Family wise error (FWE) corrected $P < 0.05$, significance level was used.

Motion poses a significant source of noise in FC analyses. None of the participants included in the present study had motion exceeding 1.5 mm in any direction. We addressed residual motion-related artifacts in three steps. First, Siemens MRI motion correction (MoCo) software was used during image acquisition. This procedure retrospectively measures six parameters of rigid-body translation and rotation and produces a corrected time series using affine transformation. Second, functional image volumes were realigned to the mean image in SPM8. Third, realignment parameters (with another six parameters representing their first order temporal derivatives) were removed with covariate regression analysis before computing amygdala FC. Signals from white matter and cerebral spinal fluid were also regressed out using anatomical component correction (aCompCor; Behzadi *et al.*, 2007; Chai *et al.*, 2012). Low overall movement levels and lack of differences between groups augment confidence that motion did not compromise observed effects.

Secondary whole-brain analyses were performed to comprehensively evaluate connectivity of the amygdala. In addition to CM and BL regions, a superficial (SF) amygdala subregion mask was generated using procedures described earlier, and connectivity from this area was also examined for possible differences between groups. Regions showing altered FC between groups were reported at a threshold of $P < 0.005$, cluster minimum = 10 voxels. This threshold was derived from suggested standards for whole-brain comparisons (Lieberman and Cunningham, 2009). Results that survived multiple comparisons correction for the whole brain (spatial cluster extent threshold; > 158 voxels for $P < 0.05$ FWE corrected) are denoted with an *asterisk in Supplementary Table S1. To plot the direction of trauma-related amygdala connectivity, individual participant beta values were extracted from peaks using 4 mm radius spheres. Pearson correlation was used to test for associations between amygdala FC and anxiety, depressive symptoms, IQ and income. All coordinates are reported in MNI convention.

To further validate our findings, data were re-analyzed using motion 'scrubbing' (Power *et al.*, 2012). Specifically, movement was plotted and visually inspected for each participant using ArtRepair software (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). Through this process we identified four trauma and three comparison participants that required censorship. They were scrubbed, and following this, maximal movement for all individuals in the sample was reduced to 0.171 mm and 0.392°. Major comparisons and study outcomes were evaluated using this alternative analytic scheme, and those data are reported as Supplementary Material.

RESULTS

Participants

Demographics and movement

As shown in Table 1, groups did not differ in age, pubertal maturation, sex, race/ethnicity, parental educational attainment or movement during the resting-state scan. Overall, residual movement was well within accepted standards (< 1.5 mm translational rms; cf. Fair *et al.*, 2012). Relative to comparison youth, trauma-exposed participants reported lower levels of household income and IQ (Table 1), effects that were anticipated based on prior work (e.g., De Bellis, 2001; Lantz *et al.*, 2005). Follow-up analyses controlling for income and IQ were conducted on FC data, as described later. There were significantly more females than males represented across the entire sample, [$\chi^2_{(1)} = 6.1$, $P = 0.014$]. Distribution of participant race/ethnicity across the sample was representative of the study community [Wayne Country, MI; $\chi^2_{(2)} = 4.09$, $P = 0.13$; www.census.gov]. Four participants (three trauma, one comparison) were on psychotropic medications (one on stimulants, one on selective serotonin reuptake inhibitors, two on serotonin-norepinephrine reuptake inhibitors and one on beta-2 adrenergic agonists). Medications were not withheld for

scanning. Follow-up analyses excluding participants on medications yielded no changes to observed effects.

Self-reported affect measures

Although the trauma group was not chosen on the basis of psychopathology, participants with histories of trauma reported higher levels of anxiety (SCR) relative to comparison participants (Table 1). This is consistent with reports that childhood trauma exposure is a strong predictor of emotional psychopathology (Kessler *et al.*, 1997). Follow-up analyses were conducted to account for effects of anxiety on connectivity (see later). Although anxiety scores reported during lab and MRI visits were significantly correlated within subject (see Methods), it is possible that variation across visits differed between groups. We therefore tested for effects of visit on anxiety levels using a Group (trauma, comparison) × Visit (lab, MRI) analysis of variance (ANOVA). Consistent with group differences reported above, a significant main effect of Group emerged, $F(1, 80) = 7.08$, $P < 0.009$. No main effect of Visit, or Group × Visit interaction was observed (P's > 0.4) suggesting that trait anxiety was stable over a period of 2 weeks and variability between visits did not differ between groups. In contrast, average state levels of fear/anxiety during the MRI visit (VAS) did not significantly differ between groups, $t(39) = 0.3$, $P = 0.77$. Given that VAS ratings were previously shown to correlate with cortisol reactivity during the scan (Thomason *et al.*, 2013), this result suggests that connectivity differences are not likely influenced by group differences in biologic stress responsivity during the MRI visit. Groups did not differ on trait levels of depressive symptoms, $P > 0.08$ (Table 1).

Lack of amygdala-sgACC connectivity in trauma-exposed youth

We observed significant group differences in CM amygdala-sgACC connectivity ($x = 8$, $y = 18$, $z = -8$, pFWE $= 0.022$, $Z = 3.80$). Extraction of average connectivity strength within this cluster revealed that the group effect resulted from the predicted negative amygdala-sgACC FC in comparison participants, which was absent in trauma-exposed youth (Figure 1). CM amygdala-sgACC FC was not related to anxiety [SCR, $r(42) = 0.01$, $P = 0.92$] or depressive [CDI, $r(42) = 0.03$, $P = 0.83$] symptoms across the sample, or within the trauma group [SCR, $r(21) = -0.22$, $P = 0.34$; CDI, $r(21) = -0.15$, $P = 0.51$]. Group differences in CM amygdala-sgACC connectivity remained significant when controlling for IQ (peak at $x = -12$, $y = 40$, $z = -4$, pFWE $= 0.025$, $Z = 3.77$) and income (peak at $x = 10$, $y = 22$, $z = -10$, pFWE $= 0.027$, $Z = 3.74$). No significant effects of trauma were observed for BL amygdala-sgACC connectivity at $P < 0.05$ FWE-corrected.

Divergent patterns of amygdala subregion FC across the sample

Secondary whole-brain analyses were performed to examine connectivity of major amygdala subregions. FC maps across the entire sample (Figure 2) revealed unique patterns of connectivity for bilateral CM, BL and SF amygdala subregions that are consistent with previous cytoarchitectonically based amygdala FC studies (e.g., Roy *et al.*, 2009; Brown *et al.*, 2014). Briefly, CM showed that signal covariation with striatal regions, whereas BL showed that signal covariation with temporal and frontal cortical regions. SF signal was strongly correlated with signal in limbic regions.

Trauma effects on amygdala whole-brain connectivity

Extensive differences in amygdala FC were observed between groups (Supplementary Table S1). We also found that in a subset of areas in which groups differed, FC also related to income, IQ, anxiety or depressive symptoms. Thus, not only does amygdala FC vary across brain areas, but this variation relates to symptom severity. Data are summarized in Figure 3 as radar plots. Visual inspection of these plots suggests that, overall, individuals who have experienced trauma demonstrate increased positive connectivity, or lack of negative connectivity, across widespread brain regions. Consistency was observed across amygdala subregions in that frontoamygdala connectivity was negative in the comparison group but not in trauma-exposed youth (Figure 4). This was also true in anterior insula-amygdala connectivity, which was more negative in comparison but not in trauma-exposed participants for the SF subregion. A different effect was observed for the dorsal anterior cingulate (dACC); there, we observed increased positive amygdala connectivity in comparison but not trauma participants (Figure 4).

Replication of results in scrubbed data

Data were reanalyzed utilizing censoring of high-movement frames. Following censoring, average group motion was <0.05 mm and <0.002° rms. As shown in Supplementary Figure S1, main findings of amygdala FC across the sample (Figure 2), and group differences in FC in the sgACC (Figure 1), superior frontal gyrus, dACC and insula (Figure 4) were replicated. However, the group difference in BL amygdala-orbitofrontal cortex connectivity was no longer significant.

DISCUSSION

The present study evaluates links between early life trauma and neural circuit organization, within a high sociodemographic risk youth sample. Our results indicate reduced negative amygdala-sgACC FC in trauma-exposed youth, fitting with prior observed associations between disrupted amygdala circuitry and emotional psychopathology. For example, alterations in frontoamygdala circuitry have been

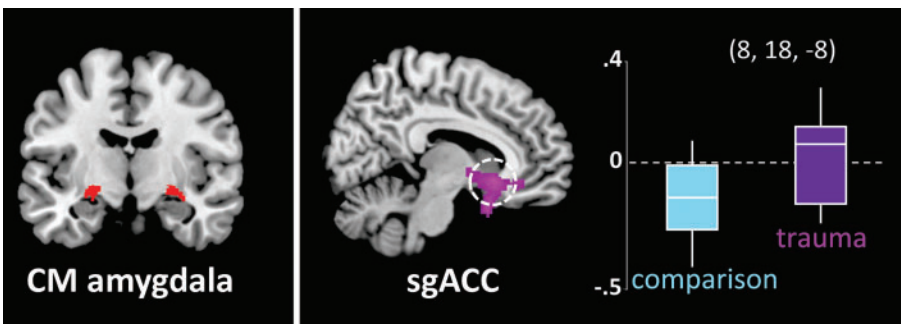

Fig. 1 Absent negative CM amygdala-subgenual cingulate (sgACC) negative connectivity in trauma-exposed youth. Left: Signal was averaged across anatomically defined bilateral CM amygdala source region. Right: Tukey's boxplots depict connectivity values by group centered on the sgACC peak ($x = 8$, $y = 18$, $z = -8$; MNI). The middle line indicates the median, vertical line the range and the limits of the box represent upper and lower quartiles. Results significant at a threshold of $P < 0.05$, FWE-corrected.

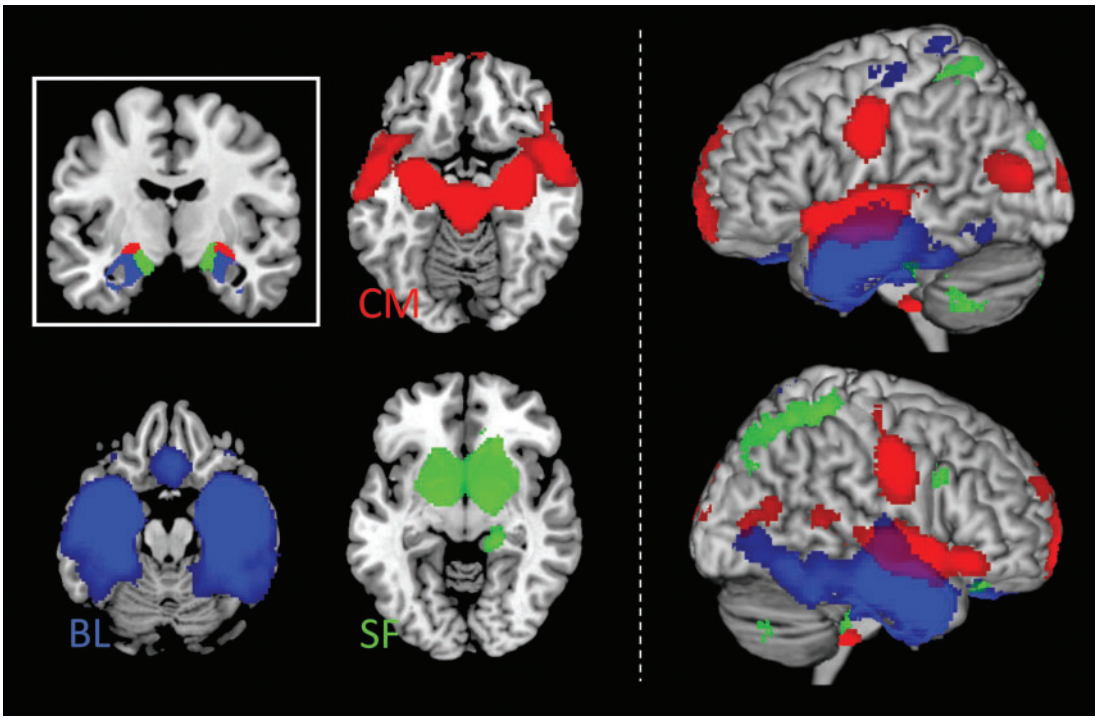

Fig. 2 FC of amygdala subregions across the entire youth sample. Left: Inset shows anatomically defined bilateral amygdala seed regions: CM (CM; red), BL (BL; blue) and SF (SF; green). Axial slices show brain areas positively correlated with amygdala seed regions. Right: Surface renderings are used to depict separation and overlap of amygdala neural networks. Connectivity maps displayed at $P < 0.005$, cluster minimum = 10 voxels.

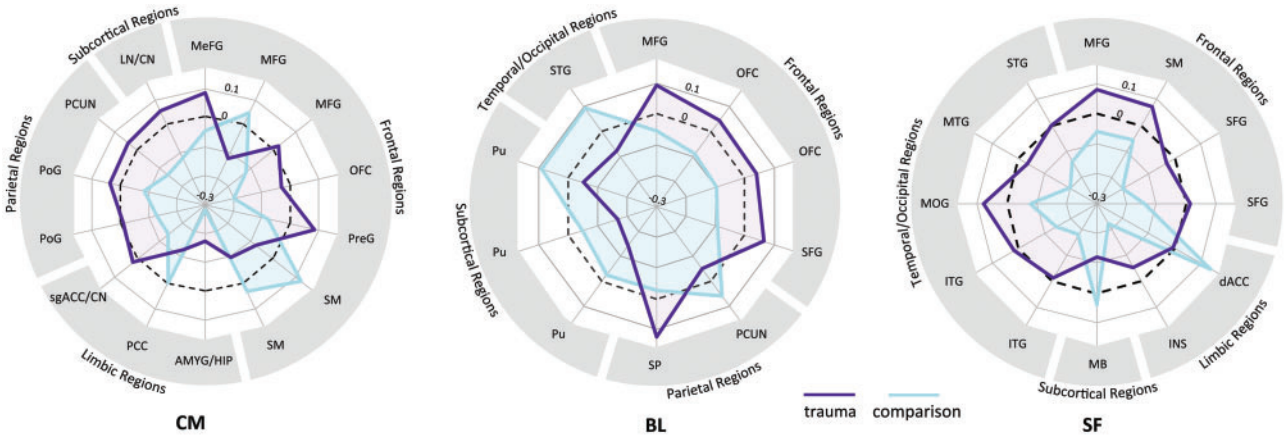

Fig. 3 Differential patterns of amgydala subregion FC across the whole brain in trauma-exposed (purple) and comparison (blue) youth. Numerical values represent the average within-group correlation strength in areas where groups differed, across frontal, limbic, parietal, subcortical and temporal/occipital regions (coordinates are provided in Supplementary Table S1). Wider area on radial plots in trauma-exposed youth suggests a pattern of enhanced positive FC or diminished negative FC of the amygdala to many brain regions, particularly to areas of the frontal cortex. Dashed line indicates zero; the middle of the plot indicates negative values. Abbreviated brain regions are defined in Supplementary Table S1.

reported in adults with PTSD (Brown *et al.*, 2014), and adolescents (Roy *et al.*, 2013) and adults with generalized anxiety disorder (Etkin *et al.*, 2009). We add to this conceptualization by discovering that experience (trauma) is associated with altered intrinsic amygdala FC in formative, developmental years. In particular, trauma-related changes were observed within amygdala-sgACC circuitry, a pathway that is critical for emotion regulation. These findings are in line with our recent study showing a reduced ability to regulate emotional conflict and an absence of negative frontoamygdala connectivity during conflict regulation in trauma-exposed youth (Marusak *et al.*, 2014). The present findings extend this work by demonstrating that deficits in this critical emotion regulatory pathway are present even when individuals are not engaging regulatory control processes.

Four studies most similar to the current investigation are summarized in Supplementary Table S2. The most comparable study, implemented by Gee *et al.*, evaluated FC in orphanage-reared youth during a face processing task (Gee *et al.*, 2013a). Focusing on the same frontoamygdala circuitry emphasized here, they too found abnormalities in neural FC between groups. Interestingly, their effects were related to the type of emotional face being processed. That is, between group

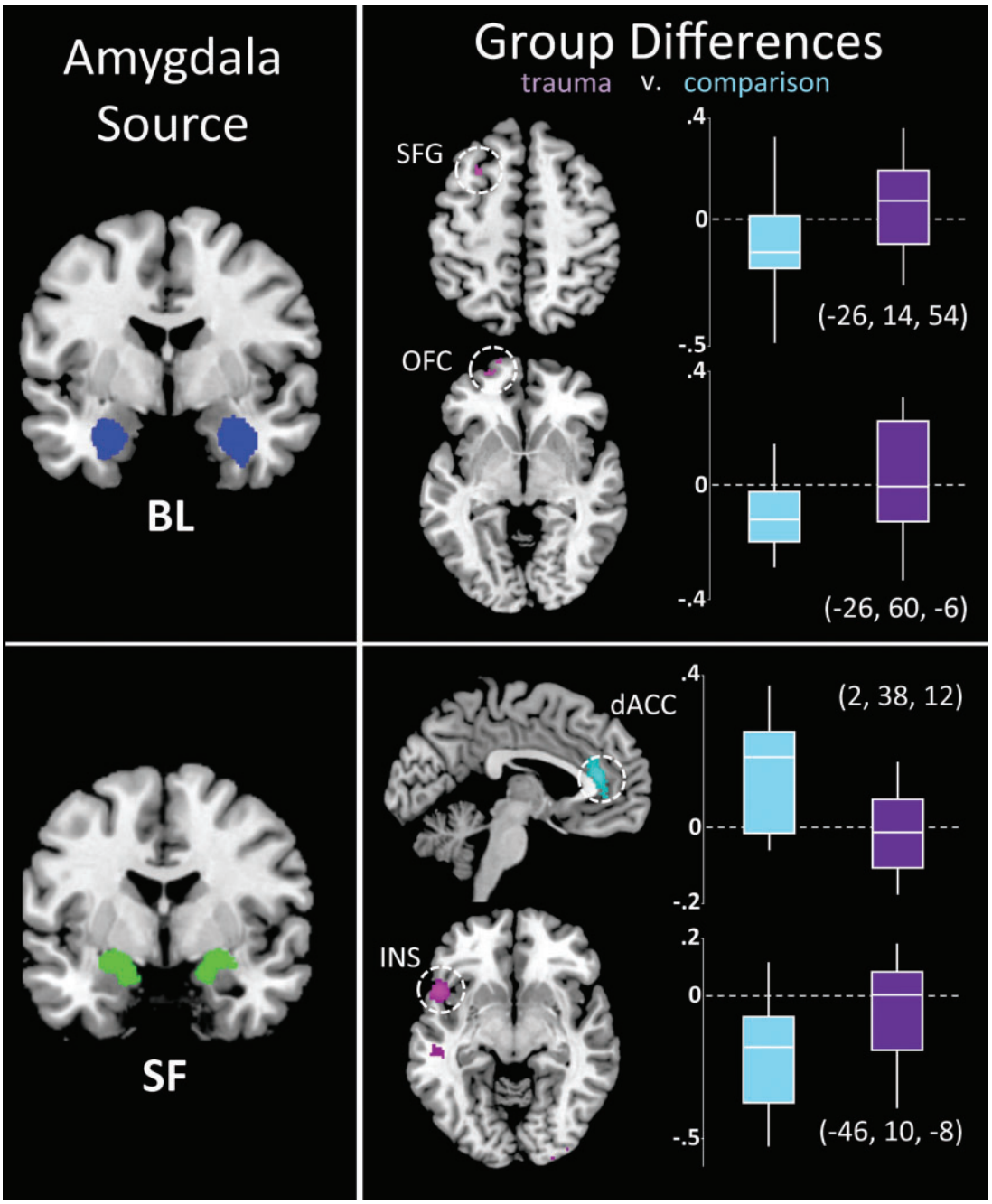

Fig. 4 Regions showing group differences (trauma, purple; comparison: blue) in FC with BL and SF amygdala. Right: Tukey's boxplots depict connectivity values by group. The middle line indicates the median, vertical line the range and the limits of the box represent upper and lower quartiles. Corresponding MNI coordinates of peak group difference (Supplementary Table S1) are indicated adjacent to each boxplot. Results are shown at $P < 0.005$, cluster minimum = 10 voxels, for display purposes.

differences were noted during the processing of fear faces, but the direction of effects differed during processing of happy faces. This result, paired with data presented here about intrinsic FC during resting-state suggests that dynamics in frontoamygdala circuits in trauma-exposed youth may relate to processing demands, and results obtained should be considered in that light. Gee *et al.* also provide evidence that the age of participants being examined may interact with observed effects. They found that comparison and orphanage-reared participants exhibited different patterns of age-related change in frontoamygdala FC to fear faces. Specifically, between group differences appear to have been significant in children but not adolescents. This could be interpreted as a reduction in differences between groups with age. Though the cross-sectional nature of this sample precludes direct evaluation of this possibility, this observation can be regarded in consideration of current theory that principals of neural connectivity at one point in life may be adaptive, while at another may confer risk (Tottenham, 2013).

We interrogated amygdala FC from three amygdala subregions. CM amygdala is involved in allocating attention to relevant stimuli (Davis and Whalen, 2001) and mediating increased vigilance (Dringenberg and Vanderwolf, 1996). In contrast, BL amygdala has been linked to associative learning processes, and the SF amygdala has been implicated in social/affective processing (LeDoux, 2003; Phelps and LeDoux, 2005; Goossens *et al.*, 2009). Given that amygdala subregions exhibit

unique developmental patterns of FC across childhood and adolescence (Gabard-Durnam *et al.*, 2014), it is likely that trauma impacts these circuits in different ways. We support this supposition by having attained commonalities and discrepancies in effects across subregions. Commonalities were observed across amygdala subregions such that youth that endured traumatic experiences tended to have diminished frontoamygdala connectivity. Discrepancies were noted for regions of the striatum, parietal regions and regions comprising the default mode brain network (e.g., precuneus and posterior cingulate). For these areas, CM and BL showed trauma-related FC effects but SF did not. In contrast, analysis of SF connectivity revealed trauma effects in regions that comprise the salience network of the brain, the insula and dACC, whereas other subregions did not. Thus, amygdala subregions critical for learning and attention and for social/affective processing demonstrate overlapping, but also distinct trauma-related alterations in connectivity.

Our results support a model of reduced emotion regulatory control in urban youth with histories of trauma. Amygdala-medial prefrontal correlations are negative at rest (Gee *et al.*, 2013b) and during the regulation of emotional responding (Hare *et al.*, 2008), a pattern of connectivity thought to index top-down regulatory control. Behaviorally, loss of inhibitory affective control has been associated with exposure to trauma (Pechtel and Pizzagalli, 2011) as well as presence of clinical mood disorders (Etkin *et al.*, 2013). Prior research has also described negative attention bias and augmented vigilance in those with histories of early life trauma exposure (Pollak, 2008). Furthermore, studies using task-based fMRI show hyperactivity of the amygdala and/or hypoactivity of medial prefrontal regions in individuals with anxiety (McClure *et al.*, 2007), PTSD (Etkin and Wager, 2007), and in children with histories of early adversity (Tottenham *et al.*, 2011; McCrory *et al.*, 2013), which may reflect failure of prefrontal regions to regulate amygdala reactivity. The direction of our effects (more negative frontoamygdala FC in comparison participants) suggests reduced top-down control via frontoamygdala neurocircuitry may be a consequence of early traumatic experiences.

Whole-brain exploratory analyses identified stronger amygdala-anterior insula connectivity in trauma-exposed youth. Increased FC indicates greater signal covariance between regions that detect threat and generate fear responses (i.e., amygdala; LeDoux, 2003) and process meaning and prediction of aversive bodily states (i.e., insula; Craig, 2011). Stronger amygdala-insula FC has also been reported in adults with PTSD (Rabinak *et al.*, 2011) and adolescents with generalized anxiety disorder (GAD) (Roy *et al.*, 2013), highlighting the relevance of this pathway for clinical disorders. Moreover, task-based fMRI studies have demonstrated increased amygdala and insula reactivity in children exposed to violence (McCrory *et al.*, 2011) and soldiers that endure combat stress (Van Wingen *et al.*, 2011). Increased functional covariance in the amygdala and insula at rest suggests they may be primed for rapid co-activation, or that functions subserved by these regions tend to be more coordinated.

Our results indicate significantly reduced (positive) amygdala-dACC connectivity in trauma-exposed youth. Whereas ventral aspects of the ACC (e.g., perigenual and subgenual regions) are implicated in emotion regulation, dACC is associated with the expression of fear (Etkin *et al.*, 2011). Evidence suggests that top-down (i.e., dACC/lateral prefrontal-based) forms of emotion regulation work by recruiting the ventral ACC (vACC), which dampens limbic reactivity directly (Etkin *et al.*, 2011). Fitting with this conceptualization, our data show congruent between group effects in dACC and sgACC. Dorsal aspects of the ACC are also implicated in sympathetic nervous arousal (Critchley, 2005). Thus, our altered amygdala-dACC FC results may reflect aberrant modulation of autonomic nervous system function. This is consistent with reports of increased arousal and fear in trauma-exposed youth, which may contribute to the development of clinical disorders (e.g., anxiety; Glaser, 2000).

We observed that differences in neuroconnectivity between trauma-exposed and control groups were associated with depression or anxiety symptomology only in select regions, including the sensorimotor cortex, middle temporal gyrus and superior parietal cortex. This is highly consistent with the observation that trauma exposure does not precisely predict emergence of psychopathology. Considerable data has shown that outcomes resulting from trauma exposure vary greatly across individuals (Cicchetti and Rogosch, 1996, Felitti *et al.*, 1998; Tottenham and Sheridan, 2009). Thus, one would not expect that the relationship between brain measures and previously experienced trauma would be ubiquitously significantly correlated. These variables are neither orthogonal, nor perfectly correlated. Thus, having observed some but not complete overlap in significance could have been predicted. Similar consideration could explain observed associations in income and IQ, all of which are presented in superscript in Supplementary Table S1.

Given increased awareness that motion confounds interpretation of fMRI data and the resulting shift toward rigorous approaches to dealing with motion in resting-state data, we reanalyzed all data using an alternative scrubbing approach (Deen and Pelphrey, 2012; Van Dijk *et al.*, 2012; Power *et al.*, 2015). We saw that observed main effects were consistent, with the exception of a group difference in the orbitofrontal cortex that did not hold after scrubbing. It is possible this result did not replicate because the group difference covered a smaller territory to begin with (15 voxels), and because clusters smaller than 10 contiguous voxels are not reported as significant. The reason that in large part we saw consistent effects in scrubbed and non-scrubbed data may be due to the low overall movement profile of participants in the original analyses.

Our results underscore that traumatic stress may alter limbic circuitry in the immature brain and this may precede the onset of clinically significant conditions. There is evidence suggesting that changes in frontoamygdala circuits persist even decades later into adulthood (Dannlowski *et al.*, 2012), emphasizing the relevance of early life exposures for lifelong socioemotional functioning. Although altered amygdala connectivity may reflect ontogenetic adaptation to an unsafe rearing environment, it is possible that these neural changes confer elevated threat vigilance, which may be detrimental to healthy emotional development. For instance, it has been suggested that increased amygdala-insula coupling mediates anxious anticipation of negative events (Carlson *et al.*, 2011). Recalibration of neural connectivity in limbic circuitry in early life may be detrimental to evaluation of threat and safety, and compromise a child's ability to master age-appropriate skills in social and cognitive domains. For example, altered connectivity may reflect changes in synaptic function within this emotion regulatory network or reduced priming of network components that allow for rapid control of emotional responding.

Our findings should be considered in light of limitations. First, we were not sufficiently powered to differentiate results based on onset (age) or type of trauma. Although retrospective analysis shows that trauma onset and trauma type relate to distinctive patterns of emotional functioning (English *et al.*, 2005), prior studies also document non-specific effects of trauma type on outcomes (Arata *et al.*, 2007; Collishaw *et al.*, 2007) and some suggest that disentangling unique effects may result in overly narrow interpretations (Green *et al.*, 2010). Next, participants were drawn from a larger study and were not selected on the basis of IQ or income. As a result, groups were not matched on these variables. This is not surprising given the strong association between these variables and trauma prevalence (De Bellis, 2001), but also not ideal for disentangling connectivity effects. However, the alternative is to select matched samples that may not

convey the natural conditions present in trauma exposed individuals, and this could in turn impact observations about neural connectivity. Moreover, we are assured by the consistency of our findings with both animal and human research (Gee *et al.*, 2013a; Malter Cohen *et al.*, 2013a; Brown *et al.*, 2014), and because follow-up analyses indicated that amygdala-sgACC results held when controlling for income and IQ. In addition, we demarcate FC effects that showed correspondence with other risk factors (i.e., poverty, IQ, anxiety, depression). Interactions between these variables are areas for future research. Although we did not find an association between frontoamygdala connectivity and anxiety or depressive symptoms, it is possible that additional symptom-brain associations would be detected with a larger sample. Along this line, an additional consideration is the sample size is relatively small ($n = 42$), and findings are correlational in nature—thus precluding ability to make causal attributions about changes in frontoamygdala connectivity and the experience of childhood trauma. Future longitudinal examinations of amygdala connectivity in larger samples will be necessary to better understand mechanisms contributing to neural circuit reorganization following early life stress. Finally, poor spatial resolution of standard fMRI acquisitions and susceptibility of the amygdala to EPI image distortions and draining vein effects (Merboldt *et al.*, 2001) may lead to spatial localization errors. Furthermore, use of an 8 mm smoothing kernel to investigate small volumes such as amygdala subregions is not an optimal design. Despite these considerations, cytoarchitechtonically based amygdala FC analyses have yielded consistent, replicated delineation of differential connectivity of major amygdala subregions (Etkin *et al.*, 2009; Roy *et al.*, 2009; Roy *et al.*, 2013; Brown *et al.*, 2014). Also, the fact that patterns observed here replicate prior neuroimaging and anatomical work in animals affords further confidence in the approach.

CONCLUSIONS

Reduced negative amygdala-sgACC connectivity was observed in a sociodemographic risk sample of youth exposed to severe trauma. Isolation of these effects augments prior studies in adults obtaining similar results by evaluating intrinsic connectivity in formative years (e.g., childhood) and by measuring change in a sample at substantially increased risk for developing clinical syndromes (i.e., urban, low income, minority). Our results support the supposition that the biological embedding of adversity in early life may include changes in neural connectivity, which in turn may alter interactions with the world and susceptibility to disease.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

Conflict of Interest

None declared.

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