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Early adverse life events are associated with altered brain network architecture in a sex- dependent manner

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ABSTRACT

Introduction: Early adverse life events (EALs) increase the risk for chronic medical and psychiatric disorders by altering early neurodevelopment. The aim of this study was to examine associations between EALs and network properties of core brain regions in the emotion regulation and salience networks, and to test the influence of sex on these associations.

Methods: Resting-state functional and diffusion tensor magnetic resonance imaging were obtained in healthy individuals (61 men, 63 women). Functional and anatomical network properties of centrality and segregation were calculated for the core regions of the two networks using graph theory. Moderator analyses were applied to test hypotheses.

Results: The type of adversity experienced influences brain wiring differently, as higher *general* EALs were associated with decreased functional and anatomical *centrality* in salience and emotion regulation regions, while *physical* and *emotional* EALs were associated with increased anatomical *centrality* and *segregation* in emotion regulation regions. Sex moderated the associations between EALs and measures of *centrality*; with decreased *centrality* of salience and emotion regulation regions with increased *general* EALs in females, and increased *centrality* in salience regions with higher physical and emotional EALs in males. Increased *segregation* of salience regions was associated with increased *general* EALs in males. Centrality of the amygdala was associated with physical symptoms, and segregation of salience regions was correlated with higher somatization in men only.

Conclusions: Emotion regulation and salience regions are susceptible to topological brain restructuring associated with EALs. The male and female brains appear to be differently affected by specific types of EALs.

1. Introduction

A history of early adverse life events (EALs) has been linked to an increased risk for the development of chronic psychiatric (Kessler et al., 2010; Green et al., 2010; McGowan and Szyf, 2010; Chu et al., 2013) and medical (Lanius et al., 2010; Bradford et al., 2012; O'Malley et al., 2011; Lackner et al., 2004) conditions, including chronic pain disorders (Bradford et al., 2012; Gupta et al., 2014). EALs can be associated with early epigenetic changes (Cottrell and Seckl, 2009; Bale et al., 2010; Teicher et al., 2002, 2003; Teicher and Samson, 2016), long lasting changes in brain development, and changes in myelination, neurogenesis, and synaptic branching

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Table 1
List of brain regions of interest and their representative Destrieux regions.

Region	Full Destrieux name	Destrieux label
Emotion Arousal Network		
Pregenual Anterior Cingulate (pgACC)	Anterior part of the cingulate gyrus and sulcus	ACgG
Subgenual Anterior Cingulate (sgACC)	Subcallosal area, subcallosal gyrus	SbCag
Amygdala (AMYG)		
Middle Anterior Cingulate (aMCC)	Middle-anterior part of the cingulate gyrus and sulcus	MACgG
Salience Network		
Anterior Insula (aINS)	Anterior segment of the circular sulcus of the insula	ACirIns
Anterior Insula (aINS)	Inferior segment of the circular sulcus of the insula	InfCirIns
Anterior Insula (aINS)	Short insular gyri	ShoInG
Middle Anterior Cingulate (aMCC)	Middle-anterior part of the cingulate gyrus and sulcus	MACgG

(Teicher et al., 2003; Teicher and Samson, 2016). Epigenetic changes in gene expression can influence the responsiveness of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system (Cottrell and Seckl, 2009; Lupien et al., 2009; Miller et al., 2009; Cole et al., 2012; Slavich and Cole, 2013).

Multimodal neuroimaging studies have shown that a history of EALs is associated with alterations in the core regions of the emotion regulation (Table 1, Fig. 1, pregenual anterior cingulate cortex [pgACC], anterior mid-cingulate cortex [aMCC], subgenual cingulate cortex [sgACC], and amygdala) (Teicher and Samson, 2016; McCoy et al., 2016; Pechtel and Pizzagalli, 2011; McCrory et al., 2012; Thomason et al., 2015) and salience (anterior insula [aINS] and anterior mid-cingulate cortex [aMCC]) (Gupta et al., 2014; Teicher and Samson, 2016; Marusak et al., 2015) networks. Alterations in these networks are associated with biased threat appraisal and outcome expectancy (Bangasser and Valentino, 2014), autonomic hyperarousal (Mayer et al., 2015), response inhibition (Brodsky et al., 2001; Grilo et al., 1999; Mueller et al., 2010), abnormal fear extinction, and emotional dysregulation (Herringa et al., 2013a). The neural correlates of these processes differ significantly between the sexes (Ruigrok et al., 2014; Cosgrove et al., 2007; Cahill, 2014; Sacher et al., 2013; Ingalhalikar et al., 2014). The prevalence and vulnerability to different types of EALs (i.e., physical, emotional, sexual, and general) (Gupta et al., 2014; Stevens and Hamann, 2012; Cahill et al., 2001; Wager et al., 2003; Wager and Ochsner, 2005; Lungu et al., 2015; Hamann, 2005; Elton et al., 2014), and the impact of EALs on emotional arousal and fear extinction processes differ significantly between the sexes (Gupta et al., 2014; Brodsky et al., 2001; Stevens and Hamann, 2012; Cahill et al., 2001; Wager and Ochsner, 2005; Lungu et al., 2015; Hamann, 2005; Elton et al., 2014; Wager et al., 2003). In general, emotional regulation regions show a greater response to aversive stimuli in women (Bangasser and Valentino, 2014; Herringa et al., 2013b), whereas males display greater connectivity between two core salience network regions, anterior insula and the anterior mid-cingulate (Elton et al., 2014; Moriguchi et al., 2014). Greater effective connectivity of the core regions of the salience network, the anterior mid-cingulate and the anterior insula during a response inhibition task has been reported in males but not females with a history of severe childhood trauma (Elton et al., 2014). Surprisingly, given the known sexual dimorphism of the brain, few studies examine whether sex moderates the relationship between EALs and the brain.

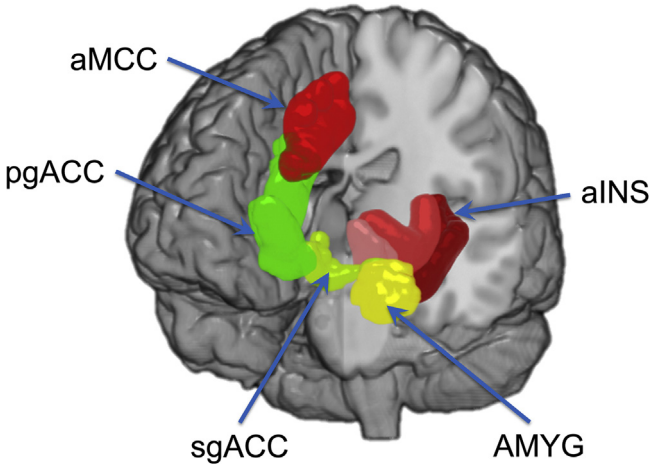

Fig. 1. Regions of interest from the emotion regulation and salience networks. Regions are depicted on an inflated brain in MNI Space.
Emotion Regulation Network [Green]: AMYG, amygdala; sgACCA, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex.
Salience Network [Red]: aINS, anterior insula (includes the following subregions: anterior segment of the circular sulcus of the insula [ACirIns], Inferior segment of the circular sulcus of the insula [InfCirIns], and Short insular gyri [ShoInG]); aMCC, anterior mid cingulate cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Studies have suggested that there is some overlap in the outcomes of different types of EALs, and that early adversity regardless of the type generally activates a stress-response in the brain related to alterations in emotional and cognitive systems (Teicher and Samson, 2016; Singer et al., 2009). A few other studies have shown that type of adversity leads to very specific outcome behavior such as emotional abuse leads to low self-esteem, while physical abuse can lead to dissociation or psychosis (Singer et al., 2009). However, for the most part, studies have failed to adequately address the issue of specificity. While specific types of EALs have been associated with alterations in specific brain regions (Teicher and Samson, 2016), these studies often used psychiatric samples and have not examined the influence of sex (Teicher and Samson, 2016; Herringa et al., 2013b). It is important to investigate different categories of childhood adversity as each may result in specific abnormalities or adaptations in targeted brain regions and pathways during critical and vulnerable times of brain development (Teicher and Samson, 2016).

Network analysis assesses the role of brain regions in the structural integrity and information flow of anatomical or functional brain networks by computing their topological properties using graph theory. Whole brain anatomical and functional connectivity, as defined by density of white matter tracts between regions and regional time series correlations during rest or task-evoked fMRI, are used to represent a large-scale brain network. Both functional and anatomical connectivity are considered different forms of information transfer mechanisms (Rubinov and Sporns, 2010; Bullmore and Sporns, 2009; Sporns, 2013a). Anatomical and functional connections between brain regions shape information flow by: 1) promoting functional integration by

enabling *global* communication between communities through network hubs, and 2) promoting functional segregation through *local* and intrinsically densely connected network communities (Sporns, 2013b). In healthy controls, hub regions marked by alterations in centrality are likely to participate in integrative processing and adaptive behavioral responses, but in neuropsychiatric and chronic pain disorders, hub regions have been found to be most susceptible to nonadaptive alterations in centrality (Crossley et al., 2014; Teicher et al., 2014).

In the current study, graph theory was applied to resting state (RS) and diffusion tensor imaging (DTI) data to compute local weighted network metrics indexing *centrality* and *segregation* (Rubinov and Sporns, 2010; Sporns, 2013a; Opsahl et al., 2008; Opsahl et al., 2010). *Measures of centrality* (strength and betweenness centrality) quantify the importance of a region's influence on communication and information flow in large-scale brain networks. *Strength* represents the sum of connections at a given brain region, factoring in the "weight" of each connection and reflects a brain region's total level of involvement in the network. *Betweenness centrality* describes degree to which a brain region lies on the shortest paths between two other regions. Regions with high betweenness centrality can control communication between other regions. *Measures of functional segregation* (clustering coefficient and local efficiency) reflect the concept that the brain can be decomposed into modules or communities comprised by densely connected groups of regions associated with specialized functional processing (Sporns, 2013b). The *clustering coefficient* of a region quantifies the probability that brain regions in a particular area are also connected to each other indicating how embedded a region is in local communities. *Local efficiency* indicates how effectively information is integrated between the closest neighbors of a given brain region within a community. Higher values reflect greater communication with the other regions within their local community. Overall, the greater responsiveness of emotional regulation and salience network regions to aversive stimuli in women and men with a history of EALs may reflect denser local connectivity between regions within those networks (greater functional segregation) and/or greater influence of those regions on communication and information flow in the brain.

The aim of this study was to identify the association between the centrality and segregation of core salience and emotion regulation regions in anatomical and functional brain networks with specific EALs (general, physical, emotional), and determine the effect of sex on these associations.

We tested the following hypotheses: 1. A stronger history of EALs is associated with higher measures of centrality and segregation for the core regions of the salience and emotion regulation networks, and this effect is moderated by sex. 2. Specific types of EALs will affect the brain differently. 3) EALs will have a greater effect on the network properties of emotion regulation regions in women, and with salience regions in men. Given that EALs are thought to be a risk factor for psychiatric and chronic pain disorders, the relationship between EAL-associated network alterations and measures of enhanced interoception, somatization, and trait anxiety were examined.

2. Methods and materials

2.1. Subjects

The total sample was comprised of right-handed healthy volunteers (61 men and 63 women). Subjects were screened and classified as healthy if they had no current history of medical conditions, a normal physical examination, and clinical assessment that included a modified Mini-International Neuropsychiatric Interview Plus 5.0 (MINI) (Sheehan et al., 1998). All women were premenopausal and scanned during the follicular phase of their menstrual cycles as determined by self-report of the last day of the menstrual period.

2.2. Behavioral measures

Questionnaires were completed before scanning.

The Early Traumatic Inventory-Self Report (ETI-SR) (Bremner et al., 2005, 2007), a 27-item (total score 0–27) questionnaire was used to access histories of childhood traumatic and adverse life events that occurred before the age of 18 years old and covers four domains: general trauma (11 items), physical punishment (5 items), emotional abuse (5 items), and sexual abuse (6 items). General traumatic events comprise a range of stressful and traumatic events that can be mostly secondary to chance events. Sample items on this scale include death of a parent, discordant relationships or divorce between parents, or death or sickness of a sibling or friend. Physical abuse involves physical contact, constraint, or confinement, with intent to hurt or injure. Sample items on the physical abuse subscale include being spanked by hand or being hit by objects. Emotional abuse is verbal communication with the intention of humiliating or degrading the victim. Sample items on the ETI emotional subscale include the following, "Often put down or ridiculed," or "Often told that one is no good". Sexual abuse is unwanted sexual contact performed solely for the gratification of the perpetrator or for the purposes of dominating or degrading the victim. Sample items on the sexual abuse scale include being forced to pose for suggestive photographs, to perform sexual acts for money, or coercive anal sexual acts against one's will. Each subscale score was calculated based on the number of items receiving a positive response. The ETI-SR was the instrument chosen due to its psychometric properties, ease of administration, time efficient, and ability to measure EALs in multiple domains (Bremner et al., 2007).

The State-Trait Anxiety Inventory (STAI) was used to determine the level of trait anxiety. Somatization was assessed using the Patient Health Questionnaire (PHQ) (Kroenke et al., 2002). The Pennebaker Inventory of Limbic Languidness (PILL), a 54-item scale was used to measure enhanced interoception and the tendency to notice and report a broad array of physical symptoms and sensations (Pennebaker, 1982).

2.3. MRI acquisition, quality control, preprocessing and processing

Whole brain structural functional (resting state) and anatomical (diffusion tensor imaging, DTI) data was acquired using a 3.0T MRI scanner (Siemens Trio; Siemens, Erlangen, Germany). Detailed information on the standardized acquisition protocols, quality control measures, and image preprocessing are provided in previously published studies (Labus et al., 2015; Gupta et al., 2015; Hong et al., 2014; Labus et al., 2016; Irimia and Van Horn, 2012; Irimia et al., 2012; Alger et al., 2016).

2.3.1. Structural gray-matter

Structural T1-image segmentation and regional parcellation were conducted using FreeSurfer (Fischl et al., 2002; Dale et al., 1999) following the nomenclature described in Destrieux et al. (2010). This parcellation results in the labeling of 165 regions, 74 bilateral cortical structures, 7 subcortical structures, the midbrain, and the cerebellum (Irimia and Van Horn, 2012).

2.3.2. Functional network construction

Linear measures of region-to-region functional connectivity were computed using the CONN toolbox (Whitfield-Gabrieli and

Nieto-Castanon, 2012). The connectivity between the 165 brain regions was indexed by a matrix of Fisher z transform correlation coefficients reflecting the association between average temporal BOLD time series signals across all voxels in each brain region. The connectivity matrix was then smoothed with a 4 mm isotropic Gaussian kernel. Functional connections were retained at $z > 0.3$ and all other values were set to 0. The magnitude of the z-score represents the weights in the functional network.

2.3.3. Anatomical network construction

Regional parcellation and tractography results were combined to produce a weighted, unidirected connectivity matrix. White matter connectivity for each subject was estimated between the 165 brain regions using DTI fiber tractography (Irimia and Van Horn, 2012), performed via the Fiber Assignment by Continuous Tracking (FACT) algorithm using TrackVis (http://trackvis.org). The final estimate of white matter connectivity between each of the brain regions was determined based on the number of fiber tracts intersecting each region. Weights of the connections were then expressed as the absolute fiber count divided by the individual volumes of the two interconnected regions (Irimia et al., 2012).

2.3.4. Regions of interest (ROI)

We performed a region of interest analysis. ROIs were restricted to the core regions of the *emotion regulation network* (amygdala, anterior mid cingulate cortex [aMCC], subgenual [sgACC] and pregenual [pgACC] anterior cingulate cortex) as defined by Pezawas et al. (2005); Stein et al. (2007), *the salience network* (anterior insula [aINS], anterior mid cingulate cortex [aMCC]) as defined by Menon and Uddin (2010); Seeley et al. (2007) (See Table 1, Fig. 1). For purposes of simplicity and in order to reduce repetition of the results, the anterior mid-cingulate cortex has been classified under the salience network.

2.3.5. Computing network metrics

The Graph Theory GLM toolbox (GTG) (www.nitrc.org/projects/metalab_gtg) and in-house matlab scripts were applied to the subject-specific anatomical and functional brain networks to compute the strength, betweenness centrality, clustering coefficient, and local efficiency of the ROIs (Rubinov and Sporns, 2010; Sporns, 2013a; Opsahl et al., 2008; Opsahl et al., 2010).

2.4. Data analysis

To determine both the conditional effects of EALs on the strength, betweenness centrality, clustering coefficient, and local efficiency computed for each ROI (see Section 2.3.5), and the potential moderating effects of sex on this relationship, a moderator analysis was performed using an ordinary least squares model within the GTG toolbox. For each ROI ($n = 5$, bilaterally), the network metrics of interest ($n = 4$) were regressed onto sex, ETI-SR subscale score (general, physical, and emotional) and their interaction. As only a few subjects (12(10%) of 124) endorsed items on the ETI-SR sexual subscale score, the subscale was excluded from analyses. Age was included as covariate. A significant interaction between sex and ETI-SR subscale score indicates a moderator effect (Fairchild and MacKinnon, 2009). To aid in the interpretation of the interaction effect, partial correlations between the regional network metric and ETI-SR subscale score were calculated within each sex, controlling for age. We report significant conditional effects for the ETI-SR subscale score only if no significant moderator effect is evident. We did not report the conditional effect of sex on the brain from the model as this is beyond the scope of the hypotheses. To control for Type I error we used a two prong approach: Significance was determined via Freedman & Lane's non-parametric permutation testing strategy and specifying 10,000 permutations (Freedman and Lane, 1983). This method provides good control over type I error rates and is robust to the presence of outliers (Freedman and Lane, 1983; Winkler et al., 2014). In total, 3 emotion-regulation and 2 salience regions were tested. Permuted probability values were further corrected using an FDR adjusted p value, where a FDR $q < 0.05$ was considered significant (Benjamini et al., 2006; Benjamini and Hochberg, 2000). This correction was performed within each subscale analysis by modality (RS, DTI) and within each brain network (emotional, salience), and by laterality.

Group differences in behavioral measure scores were evaluated by applying two-tailed independent T-tests between men and women. Pearson's correlation was used to determine the relationship between properties of brain regions associated with EALs and behavioral variables.

3. Results

3.1. Subject characteristics

Subject characteristics are provided in Table 2. Men were slightly older than women subjects, $d = -0.46$. There were no significant differences between men and women on all the ETI-SR subscale scores except for the ETI-SR physical subscale score, where men had higher scores than the women, $d = -0.41$. On the physical abuse subscale, 33 of the 61 men (54%) and 28 of the 63 women (44%) endorsed a history of physical abuse (score >1), and 19 men (31%) 16 women (25%) endorsed moderate to high levels (score ≥ 3). Emotional abuse was endorsed by 22 of the 61 men (36%) and 17 of the 63 women (27%) Moderate to high levels of emotional abuse was reported by 9 men (15%) and 14 women (22%). Forty men (66%) and 43 women (68%) reported experiencing a general trauma, and 18 men (30%) and 27 women (43%) reported experiencing greater than three traumas (moderate to high levels). Men and women differed on their report of somatization symptoms, with women reporting higher scores than the men, $d = 0.44$. In females, the ETI-SR sexual subscale score was negatively correlated with the PILL ($r = -0.32$, $p = 0.04$) and the ETI-SR emotional subscale score was positively correlated with trait anxiety ($r = 0.20$, $p = 0.03$). In males, the ETI-SR general subscale score was positively correlated with somatic symptoms as measured by the PHQ ($r = 0.36$, $p = 0.01$).

3.2. Centrality of salience regions

Significant results are summarized in Table 3.

3.2.1. Anatomical network centrality in salience regions

Sex moderated the relationship between increased ETI *general* trauma score and decreased centrality of right anterior mid-cingulate (betweenness centrality: $q = 0.004$). While the association of ETI *general* scores with the betweenness centrality of the right anterior mid-cingulate was positive in women ($r_{women} = 0.32$, $p = 0.02$), it was negative in men ($r_{men} = -0.29$, $p = 0.03$). There was no main effect observed for ETI *general* trauma scores and betweenness centrality of the right betweenness centrality.

The anatomical centrality of salience regions was not related to *physical* and *emotional* ETI.

3.2.2. Functional network centrality in salience regions

There was a significant moderating effect of sex, where higher ETI *general* scores were associated with decreased left anterior insula betweenness centrality ($q = 0.004$), which was only significant in women ($r_{women} = 0.52$, $p = 1.6 \times 10^{-4}$) but not in men ($r_{men} = 0.04$, $p = 0.76$). A main effect was observed where higher

Table 2
Demographic and behavioral variables.

N (Total = 124)	Men				Women				Frequency	T-value	p-value	Cohen's d (Effect Size)
	61				63				N/124 (%)			
	Mean	SD	N	Range	Mean	SD	N	Range				
Age	33.51	12.20	61	19–61	28.49	9.75	63	18–52		2.53	0.01	−0.46
State-Trait Anxiety Inventory (STAI)												
STAI Trait Anxiety	44.10	7.78	58	34–67	45.07	9.95	54	33–71		−0.59	0.55	0.11
Early Traumatic Inventory (ETI)												
ETI Total	4.26	4.40	61	0–16	3.51	3.71	63	0–15	54 (44%)	1.04	0.30	−0.19
ETI General	1.71	1.80	61	0–8	1.44	1.41	63	0–6	54 (44%)	0.90	0.37	−0.16
ETI Physical	1.61	1.81	61	0–5	0.95	1.35	63	0–5	43 (35%)	2.29	0.02	−0.41
ETI Sexual	0.13	0.56	61	0–3	0.30	0.83	63	0–4	12 (10%)	−1.21	0.23	0.24
ETI Emotional	0.85	1.47	61	0–5	0.83	1.52	63	0–5	39 (32%)	0.10	0.92	−0.02
Patient Health Questionnaire (PHQ)												
PHQ Overall	1.34	1.78	55	0–9	2.20	2.16	59	0–10		−2.34	0.02	0.44
Pennebaker Inventory of Limbic Languidness (PILL)	3.26	4.12	40	0–20	4.42	4.93	45	0–19		−1.21	0.23	0.26

Questionnaires: State-Trait Anxiety Inventory (STAI), Early Traumatic Inventory (ETI) total scores and ETI subscale scores (general, physical, sexual, emotional), Patient Health Questionnaire (PHQ), Pennebaker Inventory of Limbic Languidness (PILL).
Subject Number (N), Standard Deviation (SD).
Significance = $p < 0.05$.

ETI *general* scores were associated with decreased right anterior insula betweenness centrality ($q = 0.01$).

Sex moderated the association between increased ETI *physical score* and increased strength of the right anterior mid-cingulate ($q = 0.01$), with men showing a significant positive relationship ($r_{men} = 0.30$, $p = 0.02$), and women showing a non-significant negative relationship ($r_{women} = -0.23$, $p = 0.07$). There was no main effect observed for ETI *physical* scores and strength of the

Table 3
Anatomical and functional measures of centrality in salience brain regions having a significant association with ETI subscale scores or its interaction with sex.

Anatomical network metric properties of centrality								
Salience network								
ETI general								
Region of interest	Variable	Network metric	T-value	p-value	q -value	β value	Correlation men (p-value)	Correlation women (p-value)
R aMCC	ETI General * Sex	Betweenness Centrality	−3.429	0.001	0.004	−129.131	−0.290 (0.029)*	0.315 (0.018)*
ETI physical								
none								
ETI emotional								
none								
Functional network metric properties of centrality								
Salience network								
ETI general								
Region of interest	**Variable**	**Network metric**	**T-value**	**p-value**	**q -value**	**β value**	**Correlation men (p-value)**	**Correlation women (p-value)**
R aINS (ACirIns)	ETI General	Betweenness Centrality	−3.132	0.003	0.012	−15.821		
L aINS (InfCirIns)	ETI General * Sex	Betweenness Centrality	−3.344	0.001	0.004	−57.310	0.040 (0.758)	0.520 (1.6×10^{-4})**
ETI physical								
Region of interest	**Variable**	**Network metric**	**T-value**	**p-value**	**q -value**	**β value**	**Correlation men (p-value)**	**Correlation women (p-value)**
R aMCC	ETI Physical * Sex	Strength	2.944	0.003	0.012	2.909	0.304 (0.018)*	−0.233 (0.068)
ETI Emotional								
Region of interest	**Variable**	**Network metric**	**T-value**	**p-value**	**q -value**	**β value**	**Correlation men (p-value)**	**Correlation women (p-value)**
R aMCC	ETI Emotional * Sex	Strength	2.645	0.011	0.044	2.844	0.287 (0.026)*	−0.108 (0.403)

Salience Regions of Interest: aINS, anterior insula (includes the following subregions: anterior segment of the circular sulcus of the insula [ACirIns], Inferior segment of the circular sulcus of the insula [InfCirIns], and Short insular gyri [ShoInG]); aMCC, anterior mid cingulate cortex.
Abbreviations: L, left; R, Right; ETI: Early Traumatic Inventory; ROI, region of interest.
Significance = $p < 0.05$; q-value FDR corrected for multiple comparisons $q < 0.05$.

right anterior mid-cingulate.

A moderation effect was observed, where increased ETI *emotional* scores were associated with increased right anterior mid-cingulate strength (q = 0.04) in men only (r_{men} = 0.29, p = 0.03) and this was negative in women (r_{women} = -0.11, p = 0.40). There was no main effect observed for ETI *emotional* scores and strength of the right anterior mid-cingulate.

3.3. Centrality of emotion regulation regions

Significant results are summarized in Table 4.

3.3.1. Anatomical centrality of emotion regulation regions

Increased ETI *general* score was associated with lower betweenness centrality for the left subgenual anterior cingulate cortex (q = 0.03), but there was no moderating effect for ETI *general* scores and betweenness centrality of the left subgenual anterior cingulate cortex. Higher ETI general scores and decreased right pregenual anterior cingulate cortex betweenness centrality (q = 0.003) was only significant in women (r_{women} = 0.42, p = 0.001), and not in men (r_{men} = -0.10, p = 0.49). There was no main effect for ETI *general* scores and the betweenness centrality of the right pregenual anterior cingulate cortex.

Sex significantly moderated the relationship between increased ETI *physical* score and increased strength of the right pregenual anterior cingulate cortex, (q = 0.02), with only women showing a significant positive association (r_{women} = 0.35, p = 0.008, r_{men} = -0.09, p = 0.52). There was no main effect for ETI *physical* scores and the strength of the right pregenual anterior cingulate cortex. Main effects were observed with increased ETI *physical* scores being associated with increased centrality of emotion regulation regions (strength for left amygdala: q = 0.02, and left pregenual anterior cingulate cortex: q = 0.03).

ETI *emotional* scores were not associated with anatomical measures of centrality.

3.3.2. Functional centrality of emotion regulation regions

There were no significant associations between any ETI subscale scores and functional measures of centrality.

3.4. Segregation in salience regions

Significant results are summarized in Table 5.

3.4.1. Anatomical segregation of salience regions

Sex significantly moderated the relationship between higher ETI *general* scores and increased measures of segregation in the left anterior insula in men only (clustering coefficient: q = 0.04, r_{men} = 0.33, p = 0.01; local efficiency: q = 0.04, r_{men} = 0.35, p = 0.009). This relationship was negative but not significant in women (clustering coefficient: r_{women} = -0.15, p = 0.27; local efficiency: r_{women} = -0.15, p = 0.28). No significant main effects were observed for ETI *general* scores and measures of segregation for the anterior insula.

ETI *physical* and *emotional* scores were not significantly associated with segregation of salience regions.

3.4.2. Functional segregation of salience network regions

ETI subscale scores were not significantly associated with functional segregation of salience regions.

3.5. Segregation of emotion regulation regions

Significant findings are summarized in Table 6.

3.5.1. Anatomical segregation of emotion regulation regions

No moderation effects were observed, but a main effect was observed, where in both men and women, increased ETI emotional

Table 4
Anatomical and functional measures of centrality in emotion regulation brain regions having a significant association with ETI subscale scores or its interaction with sex.

Anatomical network metric properties of centrality								
Emotion regulation network								
ETI general								
Region of interest	Variable	Network metric	T-value	p-value	q -value	β value	Correlation men (p-value)	Correlation women (p-value)
L sgACC	ETI General	Betweenness Centrality	−2.622	0.010	0.030	−81.541		
R pgACC	ETI General * Sex	Betweenness Centrality	−3.319	0.001	0.003	−259.034	−0.095 (0.485)	0.418 (0.001)**
ETI physical								
Region of interest	**Variable**	**Network metric**	**T-value**	**p-value**	**q -value**	**β value**	**Correlation men (p-value)**	**Correlation women (p-value)**
L AMYG	ETI Physical	Strength	2.777	0.008	0.024	0.003		
L pgACC	ETI Physical	Strength	2.525	0.018	0.027	0.003		
R pgACC	ETI Physical * Sex	Strength	2.812	0.006	0.018	0.007	−0.086 (0.524)	0.351 (0.008)*
ETI emotional								
none								
Functional network metric properties of centrality								
Emotion regulation network								
none								

Emotional Regulation Regions of Interest: AMYG, amygdala, sgACC, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex.
Abbreviations: L, left; R, Right; ETI: Early Traumatic Inventory; ROI, region of interest.
Significance = p < 0.05; q-value FDR corrected for multiple comparisons q < 0.05.

Table 5
Anatomical and functional measures of segregation in salience brain regions having a significant association with ETI subscale scores or its interaction with sex.

Anatomical network metric properties of segregation								
Salience network								
ETI general								
Region of interest	Variable	Network metric	T-value	p-value	q -value	β value	Correlation men (p-value)	Correlation women (p-value)
L aINS (InfCirIns)	ETI General * Sex	Clustering Coefficient	2.651	0.010	0.040	1.0×10^{-4}	0.328 (0.013)*	−0.151 (0.265)
L aINS (InfCirIns)	ETI General * Sex	Local Efficiency	2.644	0.009	0.036	2.0×10^{-4}	0.345 (0.009)**	−0.147 (0.281)
ETI physical								
none								
ETI emotional								
none								
Functional network metric properties of segregation								
Salience network								
none								

Salience Regions of Interest: aINS, anterior insula (includes the following subregions: anterior segment of the circular sulcus of the insula [ACirIns], Inferior segment of the circular sulcus of the insula [InfCirIns], and Short insular gyri [ShoInG]); aMCC, anterior mid cingulate cortex.
Abbreviations: L, left; R, Right; ETI: Early Traumatic Inventory; ROI, region of interest.
Significance = $p < 0.05$; q-value FDR corrected for multiple comparisons $q < 0.05$.

scores were associated with increased local efficiency of the right subgenual anterior cingulate cortex ($q = 0.03$).

ETI *general*, and *physical* scores with were not significantly associated with measures of segregation.

3.5.2. Functional segregation of emotion regulation regions

There were also no significant associations between ETI subscale scores with functional measures of centrality of emotion regulation regions.

3.6. Correlations of network metrics with behavioral variables

In men only, increased anatomical segregation of the left anterior insula (associated with increased EAL general scores) was correlated with increased somatization, (clustering coefficient, $r(59) = 0.46$, $p = 5.00 \times 10^{-4}$ and local efficiency ($r(59) = 0.43$, $p = 0.001$)). In both men and women, the anatomical strength of the left amygdala strength (related to higher *physical* EAL scores) was moderately correlated with higher tendency to notice physical symptoms and sensations ($r(122) = 0.30$, $p = 0.009$). No significant relationships between the ETI-associated network metrics and trait anxiety were observed.

4. Discussion

In general, the findings indicate that the structure (centrality, segregation) of functional and anatomical networks are differentially associated with specific EALs (general, physical, emotional), and often these association are moderated by sex. 1. A history of EALs in healthy individuals was predominantly associated with anatomical network structure. A history of EALs was associated with the functional and anatomical global connectedness

Table 6
Anatomical and functional measures of segregation in emotion regulation brain regions having a significant association with ETI subscale scores or its interaction with sex.

Anatomical network metric properties of segregation								
Emotion regulation network								
ETI general								
none								
ETI physical								
none								
ETI emotional								
Region of interest	**Variable**	**Network metric**	**T-value**	**p-value**	**q -value**	**β value**	**Correlation men (p-value)**	**Correlation women (p-value)**
R sgACC	ETI Emotional	Local Efficiency	2.778	0.009	0.027	2.0×10^{-4}		
Functional network metric properties of segregation								
Emotion regulation network								
none								

Emotional Regulation Regions of Interest: AMYG, amygdala, sgACC, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex.
Abbreviations: L, left; R, Right; ETI: Early Traumatic Inventory; ROI, region of interest.
Significance = $p < 0.05$; q-value FDR corrected for multiple comparisons $q < 0.05$.

(centrality) of salience regions, but for emotional regulation regions only measures of anatomical centrality were associated with EALs. Anatomical not functional local network connections (segregation) in both salience and emotion regulation brain regions were associated with a history of EALs. 2. Type of adversity experienced influenced brain network structure differently. General EALs were associated with *decreased* centrality in salience and emotion arousal (subgenual anterior cingulate cortex) regions, but Physical and Emotional EALs were associated with *increases* in centrality and segregation in emotion regulation regions (amygdala, subgenula and pregenual anterior cingulate cortex). 3. The hypothesis that EALs would have greater effects on emotional regulation regions in females and salience regions in men was only partially confirmed. Moderator analysis indicated that association between the anatomical centrality of the pregenual anterior cingulate cortex was related to EALs in women only. Although EAL-associated anatomical alterations in the anatomical and functional centrality salience regions were observed for both men and women, EAL-associate alterations in anatomical segregation in the left anterior insula was observed in men only. Overall, these findings indicate that EALs are key predictors of wiring in the healthy adult brain and sex often moderates this association.

4.1. Association of EALs with the centrality of salience network regions

Regions with high centrality promote communication and control information flow in the brain (Rubinov and Sporns, 2010; Bullmore and Sporns, 2009). The salience network consists of the anterior insula and anterior mid-cingulate cortex, core regions that are not only connected to other regions of the salience network, but to those of executive control and emotion regulation networks as well (Seeley et al., 2007; Taylor et al., 2009). These brain regions are responsible for integrating information from both the internal and external environment and coordinating responses, especially during threat and pain, and making necessary behavioral adjustments (Mayer et al., 2015; McCrory et al., 2011). The anterior insula and anterior mid-cingulate cortex are also thought to generate predictions about future body sensations based on past and present signals (Mayer et al., 2015). These regions are integral for the interaction between perceived threats and corresponding body arousal responses, which in turn predict emotion regulation or pain experiences (Mayer et al., 2015; Seeley et al., 2007; Singer et al., 2009).

Previous research has demonstrated decreased gyrification and volume of the anterior insula and anterior mid-cingulate cortex in both adults (Dannlowski et al., 2012) and in children who have experienced early adversity (McCrory et al., 2012; Edmiston et al., 2011). Children with histories of family violence have also shown increased reactivity of the anterior insula in response to threatening or angry faces (McCrory et al., 2011). Recently, using cortical thickness measures, Teicher et al. (2014) also reported enhanced centrality of the anterior insula in healthy individuals with history of early maltreatment compared to those without (Teicher et al., 2014).

4.1.1. Type of adversity matters

In this study higher *general* EALs were associated with reduced centrality in the right anterior insula for functional networks. Since general types of EALs are mostly related to the experience of accidents and natural disasters, and are not a direct result of abuse such as physical assault, it has been suggested that the associated brain changes may be adaptive in nature (Teicher et al., 2002, 2003; Teicher and Samson, 2016). Compared to more specific forms of EALs that address some aspect of interpersonal victimization (such as physical, sexual, or emotional abuse), general EALs may facilitate neurological responses that help with growth and survival (Teicher et al., 2002, 2003; Teicher and Samson, 2016).

4.1.2. Sex matters

In this study, distinct sex dependent increases in the anatomical centrality of salience regions (anterior insula and anterior mid-cingulate cortex) with a history of EALs were observed and these were unique to specific types of adversity. For women, decreased anatomical centrality of the salience regions was associated with increased ETI *general* scores. In men, increased anatomical centrality in the right anterior mid-cingulate cortex was associated with increased *physical* and *emotional* EALs.

Studies have shown that women are more likely to report global or more general childhood adversities and men tend to report higher prevalence of adversity related to physical and emotional abuse (Curran et al., 2016). Although animal models indicate that males and females respond in different ways to different types of adversity, women tend to report higher levels of social support and resource utilization in order to cope with the adversity (Gayer-Anderson et al., 2015). When viewed together with earlier reports, our findings demonstrate that the experience of early EALs not only affects the structure and function of core regions of the brain's salience network, but that such a history also changes their anatomical network centrality in a sex-specific manner, with effects seen mainly in men for more direct forms of EALs (physical and emotional), and in women for general EALs in more resilient ways.

4.2. Association of EALs with centrality of emotion regulation network regions

Regions of the emotion regulation network (amygdala, subgenual and pregenual anterior cingulate cortex) are activated during real or perceived perturbations of homeostasis (Wager et al., 2003; Stein et al., 2007; Cisler et al., 2013a). A history of exposure to adversity has been related to compromised cortical inhibition of the amygdala (Mayer et al., 2015). The pregenual anterior cingulate cortex receives inputs from the prefrontal cortex and plays a primary role modulating activity in the amygdala during emotional processing (Etkin et al., 2006). Individuals with PTSD and traumatized individuals have identical morphological alterations mainly in the amygdala and anterior cingulate cortex consistent with similar characteristics of hypervigilance, acquisition of fearful memories, and difficulties in emotional regulation (O'Doherty et al., 2015; Cisler et al., 2013b).

4.2.1. Type of adversity matters

In this study, *general* EALs were associated with *decreased* anatomical centrality in the left subgenual anterior cingulate cortex, while greater *physical* EALs were associated with *greater* anatomical centrality of the left amygdala and left pregenual anterior cingulate cortex. Similar to the findings in the salience network, *general* EALs may have a more adaptive function (Teicher et al., 2002, 2003; Teicher and Samson, 2016). This is because general types of EALs may not be as severe or personal in nature, and hence are less likely to be internalized as some of the other types of EALs such as physical, sexual, or emotional abuse. The observed increase in the anatomical centrality of core emotion regulation regions with increased physical EALs is consistent with the increased emotional responsiveness of the brain seen in other studies neuroimaging studies (Graham et al., 2015; Baker et al., 2013; Eluvathingal et al., 2006; Choi et al., 2009). This alteration is likely to play a role in the higher susceptibility of individuals with a history of physical early adversity to develop stress-sensitive

disorders. The difference in our results from the Teicher et al. (2014), where decreased centrality was observed in regions of the emotion regulation network could be attributed to the absence of the investigation of EAL subscale scores.

4.2.2. Sex matters

In women but not men, decreased centrality of the right pregenual anterior cingulate cortex was associated with *general* EALs but greater centrality of the right pregenual anterior cingulate cortex was associated with *physical* EALs. The observed sex related differences in the alteration of emotional regulation regions with EALs are consistent with the observation that women with a history of EALs may engage maladaptive emotional coping strategies to a greater degree than men, as previously suggested (Bangasser and Valentino, 2014). Our results also demonstrate that specific types of stressors lead to specific abnormalities or adaptations in targeted brain regions and pathways differently in males and females (Teicher and Samson, 2016).

4.3. Association of EALs with altered anatomical segregation of salience and emotion regulation network regions

High functional segregation indicates a brain region is participating in a local community of densely interconnected network of regions, and has the ability to efficiently transmit information within this local network (Wang et al., 2010). In this study, greater *emotional* EALs were associated with greater anatomical segregation of the right subgenual anterior cingulate cortex (emotional regulation region). Sex dependent findings were also observed in the salience network, with higher *general* EALs being associated with greater anatomical segregation in the left anterior insula in men only. These results are consistent in highlighting the role EALs play in the development of the infrastructure underlying salience and emotion regulation networks. High segregation could also indicate longer connection distances in communicating with regions from other networks, suggesting that a higher biological cost is involved (van den Heuvel and Sporns, 2011). This would suggest that experiences of early adversity could be associated with less efficient long projections through the edges to modules in the periphery, but also increase chances for disruptions in the topology of these brain regions and thereby increase vulnerability to disease, especially in males.

4.4. Alterations in anatomical network measures associated with behavioral measures

In both men and women, higher scores of *physical* EALs were associated with greater centrality of the left amygdala, and this was correlated with higher physical symptoms and sensations. In men, higher scores for *general* EALs were associated with greater anatomical measures of segregation in the left anterior insula, which in turn was correlated with high somatic symptoms. These findings, when viewed in the context of the close interactions between emotion regulation and salience network regions suggest that early adversity may lead to brain alterations associated with greater emotional distress to somatization in both men and women.

4.5. Limitations

In this study we did not observe a strong correspondence between the observed anatomical and functional network alterations. Ultimately, a task may be required to observe analogous functional alterations. It is also plausible anatomical rewiring of these regions has not yet impacted function but instead could be a predisposing vulnerability factor in these healthy subjects. Female sex hormones were not measured in this study and therefore their influence on the current findings cannot be determined. Measures such as the ETI-SR are based on subjective recall, and could therefore be influenced by reporting bias. However, previous studies have demonstrated that the ETI has acceptable psychometric properties and has been validated against more extensive interview measures of EALs. The findings are also limited in that the ETI does not capture severity (Elton et al., 2014) or specific time of exposure to adversity (Andersen and Teicher, 2008), which would be important to assess in future studies. The ETI-SR does not provide a comprehensive assessment of neglect, another form of maltreatment (Teicher and Samson, 2016), but rather focuses on abuse and other trauma (Bremner et al., 2000, 2007). More research is necessary to determine if physical and emotional neglect may similarly impact the brain. Since the current healthy sample subjects did not report any current psychiatric disorders, future studies will be needed in order to better determine the relationship between childhood adversity as a risk factor and psychiatric disorders. Finally, although we have a fairly large sample and use a two-fold approach to controlling type 1 error rate, replication studies will be required to ultimately assess the reliability of the results.

4.6. Conclusions and clinical implications

When viewed together with previous reports, our results are consistent with the concept that exposure to childhood adversity can result in remodeling of the brain, resulting in alterations in functional and anatomical network properties (Elton et al., 2014; Choi et al., 2009; Paul et al., 2008). The observation that many of the brain changes were specific for certain types of EALs is consistent with a previous report, showing that childhood maltreatment (physical, emotional or sexual abuse) is associated with altered *centrality* of regions involved in emotion regulation and salience (Teicher et al., 2014). This has implications of childhood adversity as a risk factor for the development of non-adaptive alterations in key hub regions of the emotional arousal and salience networks, which could lead to the development of psychiatric disorders later in life. On the other hand, the exposure to general types of childhood adversity highlights adaptive responses associated with the more effective modulation of brain circuits involved in emotion and fear, which are characteristic of highly resilient individuals. These results suggest that compared to more interpersonal types of early adversity, general childhood adversity could actually play an important role in decreasing the vulnerability to illness. The influence of specific EALs on the architecture of emotion regulation and salience regions depended on sex suggesting different susceptibility to specific types of EALs in men and women. The observed sex related differences may be related to differences in hormonal effects on brain development resulting in differences in myelination and synaptic pruning (De Bellis et al., 2001; Schmithorst et al., 2008). Alternatively, the impact of cultural gender roles and the availability of social support may interact to influence how stress sensitization to EALs differently impact men and women and dictates coping abilities.

Disclosures

No conflicts of interest exist.

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