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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.

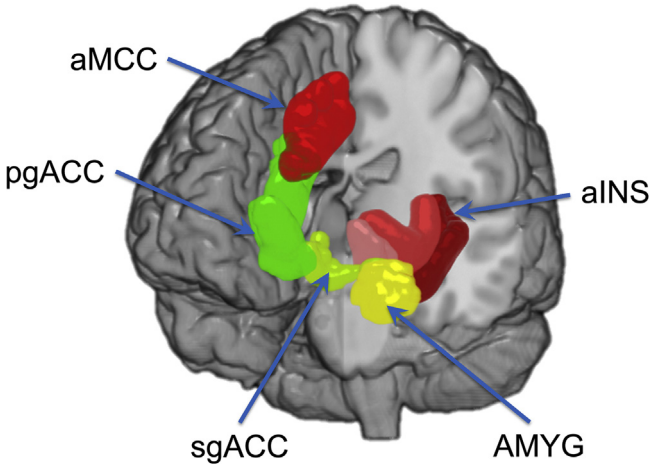

Fig. 1. Regions of interest from the emotion regulation and salience networks. Regions are depicted on an inflated brain in MNI Space.
Emotion Regulation Network [Green]: AMYG, amygdala; sgACCA, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex.
Salience Network [Red]: aINS, 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