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Decreased default network connectivity is associated with early life stress in medication-free healthy adults

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Abstract
Early life stress (ELS) is a significant risk factor for psychopathology, although there are few functional imaging studies investigating its effects. Previous literature suggests that ELS is associated with changes in structure and function in the medial prefrontal cortex (MPFC), which forms the main anterior node of the default network (DN). This study investigated the impact of ELS history on resting state DN connectivity, using seed-based correlation analyses (SCA) involving the posterior cingulate cortex (PCC). Data were analyzed from 22 adult subjects without psychiatric or medical illness (13 with and 9 without ELS); none were taking psychotropic medication. Relative to controls, the ELS group had significant decreases in DN connectivity, observed between the PCC seed and the MPFC and inferior temporal cortex. Further analyses revealed a trend-level increase in connectivity between the amygdala and MPFC associated with ELS history. In conclusion, this study found that subjects with ELS, in the absence of psychiatric illness and medication exposure, demonstrated decreased DN connectivity, and trend-level increases in connectivity between the amygdala and MPFC. These findings suggest that altered resting state connectivity is a correlate of stress exposure, rather than a product of medication or psychiatric morbidity.
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1. Introduction

There is extensive evidence that exposure to early life stress (ELS) confers a significant risk for psychiatric illness. ELS, often defined as childhood maltreatment, abuse, neglect or parental loss, is strongly linked to post-traumatic stress

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disorder (PTSD), major depressive disorder (MDD), bipolar disorder, panic disorder, social phobias and substance abuse (Heim and Nemeroff, 2001; Heim et al., 2010, 2000; Kendler et al., 2004). ELS is associated with poorer response to treatment, increased chronicity of symptoms, and suicide risk (Brown and Moran, 1994; Dube et al., 2001; Zlotnick et al., 2001, 1997). ELS is also highly prevalent: reports indicate that over 6 million children in the United States are abused or neglected every year (US Department of Health and Human Services Aoc, Youth and Families, 2007), and actual numbers are likely to be higher due to under-reporting. For example, Briere and Elliott (2003) found as many as 14.2% of men and 32.3% of women reported a history of childhood sexual abuse, and 22.2% of men and 19.5% of women met criteria for physical abuse. Different kinds of abuse are often comorbid, with nearly 30% of sexually abused girls between the ages of 6 and 16 years also reporting physical abuse (Horowitz et al., 1997).

Magnetic resonance imaging (MRI) studies of samples characterized by a history of significant ELS are one way to evaluate and measure neurobiological correlates of adverse early-life experiences. Structural MRI studies have consistently demonstrated that ELS is associated with changes in specific brain regions, especially the prefrontal cortex (PFC). The PFC is relatively slower to mature than other brain regions, and as such may be more susceptible to impairment incurred during the developing years, possibly mediated by excessive glucocorticoid exposure secondary to severe environmental stressors (Conrad et al., 2007; Patel et al., 2002). ELS is associated with decreased PFC gray matter and volume (De Bellis et al., 1999, 2002), and studies of children with ELS but without PTSD have shown reduced volume in the dorsolateral PFC (DLPFC), medial PFC (MPFC), and orbitofrontal cortex (Hanson et al., 2010). In adults with a history of ELS, reduced volumes in the MPFC and DLPFC have been reported (Andersen et al., 2008). Structural changes in other brain regions have been mixed, but alterations in the hippocampus (Bremner et al., 1997; Carrion et al., 2007; Driessen et al., 2000; Vythilingam et al., 2002), amygdala (Carrion et al., 2001; Mehta et al., 2009), corpus callosum (Andersen et al., 2008; Kitayama et al., 2007), anterior cingulate cortex (Cohen et al., 2006; Hanson et al., 2010; Kitayama et al., 2006; Tomoda et al., 2009; Treadway et al., 2009) and cerebellum (Carrion et al., 2009; De Bellis and Kuchibhatla, 2006) have been described (for a review, see Hart and Rubia, 2012).

In contrast to the number of structural MRI studies, few functional MRI studies have investigated effects of ELS. One area of functional imaging research relevant to ELS is the study of the default network (DN). The MPFC, the main anterior node of the DN, is located within the regions where structural changes are highly associated with ELS. First described in 2001 (Raichle et al., 2001), the DN additionally includes the posterior cingulate cortex/precuneus (PCC), lateral parietal cortices and medial temporal regions. The DN exhibits a high degree of activity during periods of rest (Gusnard and Raichle, 2001), and thus resting state activity of DN was coined the ''default mode'' of brain function, to describe a period when subjects are awake and alert but not involved in a specific task (Raichle et al., 2001). Since DN regions demonstrate high levels of functional connectivity with each other (Greicius et al., 2003), resting state analyses may provide a robust baseline for comparison between samples and for use in clinical applications (Fox and Greicius, 2010).

Abnormalities of DN functional connectivity, and especially the MPFC, have been associated with ELS and PTSD. In the first study of ELS and the DN, Bluhm et al. (2009) measured resting state DN connectivity in 17 women with PTSD from childhood abuse, and compared them with 15 healthy controls. Patients in this study had PTSD defined by the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), in addition to a history of childhood trauma and dissociative symptoms, and were on medications. Using seed-region functional connectivity analysis (SCA) from the PCC, the authors found decreased DN connectivity in PTSD subjects, including between the PCC and MPFC. This important initial study indicated that childhood ELS exposure might be associated with decreased DN connectivity among people who developed PTSD.

Interestingly, resting state DN connectivity has been suggested as a predictor of PTSD symptoms after trauma exposure. Lanius et al. (2010) evaluated 11 subjects (6 women) who had experienced a significant motor vehicle or workplace accident, and followed them for up to 12 weeks. Using SCA, the authors found that the strength of the connectivity between the PCC and MPFC was directly related to PTSD severity immediately after the trauma. Furthermore, when assessing connectivity between the PCC and amygdala, the authors found that the strength of this connectivity at week 6 could predict the severity of PTSD symptoms at week 12. This important study indicated that resting state DN connectivity could be used as a potential prognostic indicator of PTSD. The results suggested that acute effects of trauma may be associated with decreased PCC to MPFC connectivity, but to our knowledge no study to date has investigated longer-term neural network correlates of early life traumatic events.

Other, more traditional task-based functional neuroimaging studies consistently have underscored the importance of the MPFC within the context of the DN and trauma exposure. The MPFC, along with its subcomponent the ventromedial PFC, are implicated in PTSD pathophysiology. The MPFC is a major part of the fear circuitry loop that encompasses the MPFC, hippocampus and amygdala (Shin and Handwerger, 2009) (Bryant et al., 2008). Healthy MPFC activity is required to modulate ascending amygdala activity; activation of the MPFC is required for extinction of fear conditioning in healthy individuals (Milad et al., 2007). This is in contrast to PTSD subjects, who exhibit a relative hypoactivation of MPFC during fear extinction (Rougemont-Bucking et al., 2011). These findings are supported by studies comparing emotional processing in PTSD subjects and controls: when watching fearful faces, those with PTSD demonstrate decreased MPFC activity in the context of increased amygdala activity (Shin et al., 2005). This process may not be permanent, as demonstrated by one study in which recently traumatized police officers received exposure psychotherapy, resulting in increased MPFC activity associated with decreased amygdala activity during traumatic memory retrieval (Peres et al., 2011).

Taken together, these findings indicate an association between trauma exposure and changes in DN resting state connectivity, which may be driven by abnormal MFPC function.