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Childhood maltreatment is associated with alteration in global network fiber-tract architecture independent of history of depression and anxiety

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ABSTRACT

Childhood maltreatment is a major risk factor for psychopathology. It is also associated with alterations in the network architecture of the brain, which we hypothesized may play a significant role in the development of psychopathology. In this study, we analyzed the global network architecture of physically healthy unmedicated 18–25 year old subjects (n=262) using diffusion tensor imaging (DTI) MRI and tractography. Anatomical networks were constructed from fiber streams interconnecting 90 cortical or subcortical regions for subjects with no-to-low (n=122) versus moderate-to-high (n=140) exposure to maltreatment. Graph theory analysis revealed lower degree, strength, global efficiency, and maximum Laplacian spectra, higher pathlength, small-worldness and Laplacian skewness, and less deviation from artificial networks in subjects with moderate-to-high exposure to maltreatment. On balance, local clustering was similar in both groups, but the different clusters were more strongly interconnected in the no-to-low exposure group. History of major depression, anxiety and attention deficit hyperactivity disorder did not have a significant impact on global network measures over and above the effect of maltreatment. Maltreatment is an important factor that needs to be taken into account in studies examining the relationship between network differences and psychopathology.

Introduction

Childhood maltreatment is a major risk factor for psychopathology. Maltreatment related adversity has been found to be associated with 33% of the population attributable risk fraction (PARF) for anxiety disorders (Green et al., 2010), 54% of the PARF for depression (Dube et al., 2003b) and 67% of the PARF for suicide attempts (Dube et al., 2001). Similarly, the Adverse Childhood Experience (ACE) study found that childhood adversity accounted for 56%, 64%, and 67% of the PARF for illicit drug use problems, addiction to illicit drugs, and parenteral drug use, respectively (Dube et al., 2003a). Abuse and neglect are also recognized as major risk factors for development of personality disorders (Afifi et al., 2011; Bierer et al., 2003; Cutajar et al., 2010; Gratz et al., 2011; Herman et al., 1989; J. G. Johnson et al., 2001; Lyons-Ruth et al., 2013; McKenzie, 2013; Widom et al., 2009; Zanarini et al., 1997). Maltreatment has even been found to substantially increase risk for psychosis (Alemany et al., 2011; Arseneault et al., 2011; Bebbington et al., 2011; Bendall et al., 2008; Cutajar et al., 2010; Daly, 2011; Fisher et al., 2010; Gaudiano and Zimmerman, 2010; Houston et al., 2011) and to hasten onset and exacerbate course of bipolar disorder (Brown et al., 2005; Daruy-Filho et al., 2011; Etain et al., 2010; Garno et al., 2005; Hyun et al., 2000; Leverich et al., 2002; Lu et al., 2008; McIntyre et al., 2008; Post et al., 2001; Romero et al., 2009). Hence, it is not surprising that exposure to 5 or more forms of maltreatment or household dysfunction was reported to prospectively increase risk of receiving a prescription for an anxiolytic, antidepressant, antipsychotic or mood-stabilizer by 2-, 3-, 10- and 17-fold, respectively (Anda et al., 2007).

Childhood maltreatment is also associated with alterations in brain structure, function and connectivity of regions as well as in the network architecture of the brain (Teicher and Samson, 2016). These alterations may play a significant role in mediating the relationship between exposure to maltreatment and the development of psychopathology. We recently published results on the potential effects of maltreatment on network architecture in 265 subjects using between subject cross correlations in cortical thickness to delineate a 112 node cortical

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network (Teicher et al., 2014a). In this study we found that maltreatment was associated with reduced centrality in anterior cingulate and temporal pole and increased centrality in insula and precuneus. To our knowledge, this is the only study investigating structural network architecture of maltreated individuals using graph theory.

On the other hand, a number of studies have been published in the last few years on the potential effects of maltreatment on network architecture using functional connectivity. One study assessed the effects of maltreatment on the neural network of emotion regulation (Cisler et al., 2013). This study found difference in network topology for individuals resilient versus susceptible to maltreated related depression, though the study was limited to a small number of subjects and to 21 brain regions. Another study calculated a measure, which is equivalent to degree centrality in graph theory and found differences in the whole-brain functional connectivity patterns between MDD subjects with and without a history of childhood maltreatment (L. Wang et al., 2014). Other studies examining functional networks have mainly focused on regional changes. These studies have investigated specific nodes or specific pairings of nodes and have reported which nodes are more or less central or which connections are stronger or weaker compared to individuals not exposed to maltreatment.

Earlier reports found that maltreatment was associated with highly significant reductions in whole-brain white and gray matter volumes (De Bellis et al., 2015) suggesting that the effects of maltreatment may be widespread throughout the brain. This is consistent with findings reporting alterations in prefrontal cortex, limbic system, striatum, temporal lobes, parietal and occipital cortex and cerebellum (Teicher et al., 2016). Therefore it is likely that maltreatment may produce extensive alterations in network architecture that would be discernible in global measures of network structure such as global efficiency, small-worldness and clustering coefficient.

Abnormalities in global network architecture in brain structure have been reported in several disorders including: depression (Ajilore et al., 2014; Bai et al., 2012; Fang et al., 2012; Q. Gong and He, 2015; Korgaonkar et al., 2014; Lim et al., 2013; Long et al., 2015; Qin et al., 2014; M. K. Singh et al., 2013; Tadayonnejad and Ajilore, 2014); schizophrenia (Bassett et al., 2008; Q. Wang et al., 2012); Post-Traumatic Stress Disorder (PTSD) (Long et al., 2013); Alzheimer's disease (Lo et al., 2010); autism (Rudie et al., 2012); irritable bowel syndrome (Labus et al., 2014) and multiple sclerosis (Shu et al., 2011). More studies have found alteration in the functional connectivity networks (Mears and Pollard, 2016). It is likely that maltreatment may also affect global network architecture and may have been an unrecognized confounding factor as it is a major risk factor for depression, schizophrenia and PTSD.

Studies on the association between maltreatment, brain changes and psychopathology have produced some surprising results. We initially thought that brain changes and psychopathology would go hand-in-hand so that individuals who were susceptible and manifest psychopathology would show brain changes whereas individuals who were psychiatrically resilient would not. This however turns out to be more complicated as several studies have now reported comparable brain changes in maltreated individuals without a history of psychopathology and who are essentially asymptomatic (Teicher et al., 2016). This indicates that there is not necessarily a one-to-one correspondence between brain changes and psychopathology. What is particularly clear is that psychopathology does not always mediate the association between maltreatment and brain changes. Further, maltreatment has been an unrecognized associated factor in studies on the neurobiological basis of psychopathology as individuals with psychiatric disorders typically have a substantially higher prevalence of maltreatment than healthy controls. Consequently, inconsistent results between studies may be due to unrecognized differences in degree of exposure to maltreatment in each group. Also, maltreatment is one thing that individuals with different psychiatric disorders often have in common and we do not know whether the fact that the same constellation of brain differences (e.g., in hippocampus, anterior cingulate, ventromedial prefrontal cortex, amygdala) emerges repeatedly across different disorders reflect overlapping neurobiological mechanisms, problems in diagnostic classification, or the specific influence of early life stress on development of stress-susceptible brain regions.

The key question we are asking is whether childhood maltreatment has an effect on the global network architecture of brain structure. In this study, we used diffusion tensor imaging and tractography to probe the structural connectivity network. This goes beyond our prior study that focused exclusively on cortical network architecture (Teicher et al., 2014a). By using DTI instead of thickness measures we were able to evaluate a more complete network consisting of cortical and subcortical nodes. Further we were also able to obtain network measures for each individual rather than on entire groups, enabling us to also assess the contribution of psychopathology. Thus the second question we sought to address is how does the potential effects of maltreatment on network architecture compare to the influence of various forms of psychopathology on network architecture looking particularly at the disorders that are most prevalent in a community sample of maltreated individuals which include depression and anxiety disorders. The third aim of the study was to assess whether group differences in fiber stream numbers were as widespread as initially predicted and if they were primarily local (within a given brain division) or long-range (interconnecting different divisions).

Methods

Subject recruitment

This study was approved by the McLean Hospital institutional review board. Advertisements had the tagline “Memories of Childhood” and were posted on mass transit and newspapers for recruitment. All subjects responding to the advertisement were screened over the phone to be medically healthy, right handed, unmedicated and between 18–25 years of age. Those who met the criteria were recruited and evaluated following methods previously described (Teicher et al., 2014a; 2012). Briefly, they were invited to log onto a HIPAA-compliant online enrollment system to provide detailed information on demographics, medical and psychiatric history, developmental history, life experiences, psychiatric symptomatology and history of childhood maltreatment. Subsequently, those that appeared to meet criteria were invited to the laboratory for further evaluation. All subjects signed informed written consent. Exclusion criteria were as follows; current or prior history of neurologic disease, experienced concussion or head trauma resulting in loss of consciousness for more than 5 min, multiple unrelated forms of adversity including natural disaster, motor vehicle accidents, animal attack, near drowning, house fire, mugging, witnessing or experiencing war, gang violence or murder, riot, or assault with a weapon. Additionally, high levels of drug or alcohol use were grounds for exclusion.

There were no specific inclusion criteria other than 18–25 years of age, medically healthy, right handed, unmedicated and fluent in English. However, the sample was enriched to increase the number of participants exposed to three or more types of childhood maltreatment, so that potential volunteers reporting exposure to multiple types of maltreatment were more likely to be enrolled. Psychiatric history of the subject were not included in the criteria since selecting subjects for any specific psychiatric disorder or for none could bias the results by including the most affected or resilient subjects. Subjects who were not exposed to any form of maltreatment were selected using the same criteria. Subjects received $25 for completing the online assessment, $100 per interview and assessment session (typically one 4-hour sessions) and $100 for a one hour MRI protocol.

Overall, 1526 subjects provided complete on-line information. From this group we interviewed 520 subjects, and from this inter-