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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.

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Competing financial interests

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Keywords

Childhood Maltreatment; Abuse and Neglect; Diffusion Tensor Imaging; Brain Networks; Depression; Graph Theory

1. 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; Garo 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 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 maltreatment 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 network 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 network (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 widespread as initially predicted and if they were primarily local (within a given brain division) or long-range (interconnecting different divisions).

2. Methods

2.1. 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 minutes, 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 interviewed pool we selected the neuroimaging sample. The large number of subjects screened was not specifically required to increase the number of participants with moderate-to-high levels of maltreatment. Most online screened subjects were eliminated due to histories of head injury/possible concussion, exposure to multiple types of trauma (e.g., natural disasters, motor vehicle accidents), prematurity or birth complications and binge drinking.

2.2. Subject Assessments

Mental health professionals (psychiatrists, Ph.D. psychologists, clinical nurse specialists) conducted all of the assessment and evaluation interviews and were blind to the neuroimaging results. Structured Clinical Interviews for DSM-IV Axis I and II psychiatric disorders were used for diagnoses (First et al., 1997). The Maltreatment and Abuse Chronology of Exposure (MACE) scale was used to evaluate the type, timing and severity of exposure to maltreatment during childhood (Teicher and Parigger, 2015). The MACE provides ratings on 10 types of maltreatment: (a) sexual abuse; (b) parental verbal abuse; (c) parental non-verbal emotional abuse; (d) parental physical abuse; (e) witnessing interparental violence; (f) witnessing violence towards siblings (Teicher and Vitaliano, 2011); (g) peer emotional bullying; (h) peer physical bullying; (i) emotional neglect and (j) physical neglect. The scale provides excellent overall reliability and good to excellent reliability at each age and to each type of maltreatment as well as to the severity of exposure across each year of childhood.

MACE Severity correlated 0.738 with Childhood Trauma Questionnaire (CTQ) score and MACE Multiplicity correlated 0.698 with the ACE scale scores. However, MACE accounted for 2.00- and 2.07-fold more of the variance, on average, in psychiatric symptom ratings than CTQ or ACE, respectively (n=1051). The MACE was our primary measure of exposure as it provided data on timing of exposure not available in other instrument. Further, each MACE category fits a Rasch Model which means that each category provides a 'fundamental measurement' of exposure in which items are measured on an interval scale with a common unit (Bond et al., 2015; Brogden, 1977). This is a remarkable property, rarely attained in rating scales used in psychiatry, even though we often treat them as interval or ratio measurements. Symptom ratings were assessed using Kellner's Symptom Questionnaire (Kellner, 1987), Dissociative Experience Scale (Bernstein and Putnam, 1986), and Limbic System Checklist-33 (Teicher et al., 1993).

We evaluated financial sufficiency and parental education to collect information on the family's socioeconomic status since this is an important risk factor for maltreatment, and may also have effects on trajectories of brain development. Subjects may not be certain about parental income while they were growing up but they were well aware of the degree of perceived financial sufficiency or stress they experienced during this time. This was rated from 1 (much less than enough money for our needs) to 5 (much more than enough money

for our needs). Perceived financial sufficiency explained a greater share of the variance in symptom ratings than combined family income.

2.3. MRI Data Acquisition

Multiple diffusion-weighted images and high-resolution T1-weighted images were acquired at the Neuroimaging Center at McLean hospital (3T Siemens Trio with 32-channel coil; Siemens AG, Siemens Medical Solutions, Erlangen, Germany). An image analyst with expertise in neuroanatomy observed all scans and sequences with discernible motion artifacts were recollected. Multiple diffusion-weighted images were acquired in 72 directions. Scan parameters were: $b=1000$ sec/mm²; echo time (TE)/repetition time (TR)=81 msec/6sec; matrix=128 × 128 on 240mm × 240mm field of view (FOV); slices 3.5mm without gap, to yield voxel size of 1.8mm × 1.8mm × 3.5mm. Anatomical images were acquired using magnetization prepared rapid gradient echo (MPRAGE) sequence. Scan parameters were as follows: the sagittal plane, echo time/repetition time/inversion time/flip 1/4 2.74 msec/2.1 sec/1.1 sec/121; three-dimensional matrix 256 × 256 × 128 on 256 × 256 × 170 mm field of view; bandwidth of 48.6 kHz; scan time 4:56.

2.4. MRI Analysis and Network Construction

DTI networks were constructed by the following process for each subject. First, all scans were visually inspected for motion artifacts or incomplete coverage. Second, eddy current corrected DTI data was fit to a diffusion tensor model in order to generate FA images. This was done using FMRIB's Diffusion Toolbox (FDT: FSL FMRIB Software Library) (FMRIB Centre, UK). The parcellation process for each subject was conducted in the DTI native space (G. Gong et al., 2009; Li et al., 2009). In detail, each individual's co-registered structural image was normalized to the template in Montreal Neurological Institute (MNI) space. The resulting inverse transformation was used to transform the AAL template (Tzourio-Mazoyer et al., 2002) from MNI space to the DTI native space. Both the normalization and the inverse transformation were implemented using FSL. Subsequently, diffusion tensor tractography (DTT) was performed on every subject. By this procedure, fiber streams were estimated with the deterministic tractography method implemented in the Diffusion Toolkit and TrackVis (R. Wang et al., 2007).

Each subject's brain was parcellated into 90 regions (45 for each hemisphere with the cerebellum excluded) with the AAL template in individual subject's DTI space. Each brain region (ROI) was defined as nodes (vertices). Voxels were selected within the node regions as seed points when it had an FA value greater than 0.2. The tracking procedure was initiated from the seed points and was terminated at voxels with an FA value of less than 0.15 or when the angle between adjacent steps was greater than 45 degrees. This process was repeated for all the voxels within each node.

Two AAL node regions (ROI) were considered to be connected if the reconstructed fiber streams touch these two regions. Fiber streams connecting nodes were defined as edges. The number of fiber streams interconnecting nodes were used as "weights" for weighted networks. In an unweighted network all possible connections between nodes were designated as 0 (no interconnecting fiber streams) or 1 (1 or more interconnecting streams).

2.5. Graph Theoretical Analyses of the DTI Network

We evaluated the global topological properties of the anatomical network by quantifying the measures using the graph theory. For each individual subject, the DTI network architecture was constructed and the following measures were calculated for the whole brain network: average degree (K), strength (S), shortest path length (L), global efficiency (E_{glob}), local efficiency (E_{loc}), local clustering coefficient (C) and small-worldness (S). Additionally, Laplacian spectrum for individual network was investigated and skewness, maximum Laplacian spectrum, eigenvalue that gives the maximum Laplacian spectrum and the distance of the Laplacian spectrum from the network models were examined (de Lange et al., 2014). A brief definition and the characteristics of the graph measures are as follows. We represented the graph with G , total number of nodes with N , total number of edges with E and index with i and j .

2.5.1. Degree (K)—The degree of a node k_i is the number of direct connections for each node. It characterizes the network activity for node i . The higher the degree the more connected the node is to its neighbors. Degree of the whole network K is the average of k_i for all nodes.

$$K = \frac{1}{N} \sum_{i \in G} k_i \quad (1)$$

2.5.2. Strength (S)—The strength of a node s_i is the sum of the fiber streams that are running from or through the node region. This is the weighted measure of the degree and it also characterizes the connection of the node with its neighbors taking into account the density of the connection. The strength of a network S is the average of the strengths across all of the nodes in the network.

$$S = \frac{1}{N} \sum_{i \in G} s_i \quad (2)$$

2.5.3. Shortest Path Length (L)—Path length is defined as the distance between a pair of nodes. For example to evaluate the path length from node i to node j , we count how many paths (connection between nodes) are required to travel from node i to node j . Shortest path length (L) is the average of the shortest paths for all nodes in the network.

$$L = \frac{1}{N(N-1)} \sum_{i \neq j \in G} L_{ij} \quad (3)$$

2.5.4. Global Efficiency (E_{glob})—This metric represents the parallel information transfer in the network (Latora and Marchiori, 2001) and gives an indication of how efficiently information within one node can get to other nodes in the network. E_i is the inverse of the mean path length connecting node i to each other node in the network. Global efficiency quantifies the global integration of the network as well as the shortest path length, although

the former may be preferable when estimating topological distances in relatively sparse or disconnected graphs (Bullmore and Sporns, 2009) and may be a superior measure of integration (Bullmore et al., 2009).

$$E_{glob} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{ij}} \quad (4)$$

2.5.5. Local efficiency (E_{loc})—Global efficiency can be calculated for small subgraphs. Local efficiency calculates the efficiency for a subgraph of each node (G_i), which contains all the neighboring nodes. Local efficiency of a network is the average of the efficiency for all nodes.

$$E_{loc} = \frac{1}{N} \sum_{i \in G} E_{glob}(G_i)$$

2.5.6. Local clustering coefficient (C)—Local clustering coefficient is defined by the ratio of the number of edges. A local clustering coefficient of a node is calculated by dividing the number of edges of a node by the maximal number of edges possible for that node. The clustering coefficient of a graph is the average of the local clustering coefficient for all nodes (Chen et al., 2008).

$$E_{loc} = \frac{1}{N} \sum_{i \in G} \frac{\text{number of edges in } G_i}{k_i(k_i - 1)} \quad (5)$$

2.5.7. Small-worldness (S)—Small-worldness is a measure describing the small-world property in a network (Anderson and Cohen, 2013; Rubinov and Sporns, 2010). Small-world network is characterized by a dense local clustering of connections among the neighboring nodes with relatively few long-range connections (Bassett and Bullmore, 2006) as is familiar to us in our personal experience of social network of family and friends. This structure is advantageous because it is designed to process information both within the segregated regions distributed areas at the same time minimize wiring costs while supporting dynamical complexity.

$$S = \frac{C/C_{rand}}{L/L_{rand}} \quad (6)$$

2.5.8. Laplacian spectrum measures—The Laplacian spectrum is defined as a spectrum of a normalized Laplacian matrix of the network connectivity (de Lange et al., 2014). It demonstrates the relative frequencies of the eigenvalues for a normalized Laplacian matrix and illustrates the characteristics of the network structure at the level of the global system as well as the dynamic interactions among the local network structures (Banerjee, 2012; Banerjee and Jost, 2007). Furthermore, it is suitable for describing the community structure

of the network (Cheng et al., 2015) and has successfully been applied to real world data including biological networks (A. Singh and Humphries, 2015). The spectral plots and the measure derived from the Laplacian spectra were calculated according to de Lange et al (de Lange et al., 2014). Briefly, Laplacian matrix is derived from the adjacency matrix (A) of the network. The adjacency matrix is defined as $n \times n$ matrix, $A=[a_{ij}]$, $a_{ij}=1$ if there is connection between node i and j . Next, when we define the degree matrix (D) as a $n \times n$ diagonal matrix with $D=[d_{ii}]$, $d_{ii}=\text{degree of node } i$, the Laplacian matrix (Lap) is derived by $Lap=D-A$.

2.5.8.1 Maximum Laplacian spectrum and its eigenvalue: Peaks in the Laplacian spectrum occurs when there are recursive manipulations underlying the creation of the network structure. The high multiplicities of certain eigenvalues give the maximum Laplacian spectrum.

2.5.8.2 Skewness: Negative and positive skewness reflect a relative abundance of large and small λ , respectively that characterize the network. This value is influenced by the topological properties of the network such as the community structure and bipartiteness.

2.5.8.3 Distance of the spectra from network models: The Laplacian spectra for each subject were compared to the spectra of network models of Erdős-Rényi (ER), Watts-Strogatz (WS) and the Barabási-Albert (BA) model. Models were created following de Lange (de Lange et al., 2014). Briefly, ER model for random network was created by randomly placing the connections between nodes (Erdős and Rényi, 1959), Watts-Strogatz (WS) model for small-world networks by randomly rewiring 30% of the connections of a lattice ring network node (Watts and Strogatz, 1998) and Barabási-Albert (BA) model (Barabasi and Albert, 1999) for scale-free networks by stochastic growth process starting from a 4 node lattice.

2.6. Statistical Procedures

All measures described were calculated for individual subjects. The first question we sought to address was whether exposure to moderate-to-high versus no-to-low-levels of childhood maltreatment was associated with overall differences in network architecture including covariates for age, gender, parental education and financial sufficiency. Results were adjusted for multiple comparisons using the method of Benjamini and Hochberg (Hochberg and Benjamini, 1990). We also determined whether differences between groups persisted with the inclusion of covariates for subject's years of education, verbal IQ and non-verbal IQ. The second question was whether the differences between no-to-low and moderate-to-high exposure groups persisted when covariates for psychopathology were included, and the percent of variance in the network measures could be attributed to each of the predictors.

Recently, with the progress of statistical techniques, new methods were proposed to evaluate more accurately the relative importance of individual regressors in multiple regression analysis. Conventional methods to assess relative importance in linear models assume that all regressors are uncorrelated. In this special case, each regressor's contribution is their univariate values of r^2 and the full model r^2 value is simply the sum of all the univariate r^2

values. However, with real world observational data this is rarely the case and potential predictor variables are generally cross-correlated. Thus it is no longer accurate to decompose the full model r^2 into individual univariate r^2 regressors (Grömping, 2012). One particularly useful technique to more accurately assess the contribution of independent variables in multiple regression analyses with collinear predictors is a technique for variance decomposition developed by Lindeman, Merenda and Gold (Lindeman et al., 1980). In this method, r^2 is decomposed by calculating the contribution of each regressor by averaging over all possible sequential orderings of variable entries into the regression, taking into account the contribution of the preceding variables (R package relaimpo). This technique is also recommended by Johnson and Lebreton (J. W. Johnson and Lebreton, 2004) and Grömping (Grömping, 2012) and we used it to gauge the relative importance of exposure to maltreatment versus psychopathology on network architecture. Because there are limits to the degree of collinearity that this approach can effectively manage, we assessed the degree of cross-correlation and calculated the variance inflation factor (VIF) for each predictor variable. Typically, VIFs exceeding 4 warrant further investigation, while VIFs exceeding 10 are signs of serious multicollinearity. Hence, we made sure that VIFs were well below 4.

In addition to these network analyses simpler comparisons were made between groups using permutation analysis (10,000 iterations) to better understand whether the potential effects of maltreatment on fiber stream number were global, as we hypothesized, or more regionally specific. For these analyses we assessed group differences in age and gender corrected fiber stream numbers in right and left hemisphere and within and between major brain divisions (i.e., frontal, temporal, parietal, occipital, insula, cingulum, thalamus, limbic system, basal ganglia). Calculations were made of the total number of fiber streams between all nodes in one division and all nodes in another division, or between all nodes in a division or hemisphere. Findings were corrected for number of comparisons.

3. Results

3.1. Subjects

The sample consisted of 262 healthy, unmedicated, right-handed subjects (102M/160F; 18–25 years; 22.4 ± 2.3 years) with complete Maltreatment and Abuse Chronology of Exposure (MACE) scores and high quality DTI images. Seventy-three (27.8%) of these subjects were also included in our previous network analysis paper (Teicher et al., 2014a). Subjects were grouped into those with no-to-low levels of exposure to maltreatment (MACE scores 0–1, $n=122$, $MACE \pm SD = 0.47 \pm 0.50$) or moderate-to-high exposure ($n=140$, $MACE 4.12 \pm 2.12$) to approximately balance group size. Demographic characteristics of subjects in each group are shown in Table 1. Subjects in the moderate-to-high exposure group were slightly younger and were raised in families with lower levels of parental education and financial sufficiency, and these sociodemographic factors were included as covariates in the data analyses. There was no significant difference between groups in level of subject education, however there were slight but significant differences in verbal and non-verbal IQ. As expected, odds ratios for lifetime history of mood disorders and anxiety disorders were substantially higher in subjects with moderate-to-high exposure. There was no significant difference between groups in prevalence of ADHD.

3.2. Group Difference in Fiber Streams

Subjects with moderate-to-high exposure to maltreatment had, on average, 7.1% fewer calculated fiber streams than subjects with no-to-low exposure ($F_{1, 261} = 4.95, p < 0.03$). More specifically there was a 6.9% reduction in the right hemisphere ($F_{1, 261} = 5.62, p < 0.02$) and a 7.2% reduction in the left ($F_{1, 261} = 4.86, p < 0.03$). There was no significant difference between groups in the number of fiber streams interconnecting hemispheres ($F_{1, 261} = 1.15, p = 0.28$).

Subjects with moderate-to-high exposure had significantly lower total number of fiber streams interconnecting frontal region with basal ganglia ($-13.2\%, p < 0.02$), occipital region ($-34.6\%, p < 0.02$), thalamus ($-27.3\%, p < 0.03$) and insula ($-11.7\%, p < 0.03$) (Fig. 1). Similarly, there were fewer fiber streams interconnecting limbic system with occipital region ($-11.6\%, p < 0.03$) and basal ganglia ($-16.4\%, p < 0.04$), and between occipital region and basal ganglia ($-24.2\%, p < 0.03$). The only division in which there was a significant difference in within regions fiber stream numbers was within the basal ganglia ($-9.6\%, p < 0.03$).

3.3. Effect of Exposure on Global Network

There were marked differences between exposure groups in almost all global network measures (Table 2). The moderate-to-high exposure group had significantly lower degree, strength, global efficiency, and maximum Laplacian spectra and significantly higher pathlength, small-worldness and Laplacian skewness. The moderate-to-high exposure group's network architecture also deviated less from artificial random, small-world and scaling networks than the lower exposure group. Significant differences in network architecture between moderate-high exposure versus no-low exposure persisted even when we added covariates for subject education, verbal and non-verbal IQ.

3.4. Effect of Psychopathology on Global Network

As seen in Table 3, cross-correlation between predictor variables was modest and VIFs for the predictors ranged from 1.03 – 1.28 indicating that multicollinearity was not a concern in these analyses. Maltreatment history, gender, age, parental education and to a lesser degree perceived financial sufficiency accounted for a significant and discernible portion of the overall variance in global network measures (Fig 2). For example, maltreatment history accounted for 3.6% (95% CI 0.64%–8.54%) of the variance in small-worldness. In contrast, history of MDD, anxiety disorders and ADHD did not when maltreatment history and socioeconomic status were taken into account. As seen in Figure 2 disorder histories accounted for much less than 1% of the variance in the global network measures.

4. Discussion

On balance, subjects with moderate-to-high maltreatment had fewer calculated fiber streams in both right and left hemispheres. There were also significant differences in the number of fiber streams interconnecting multiple major brain divisions, particularly those involving frontal cortex, occipital cortex, basal ganglia and limbic system. Hence, reductions in fiber stream numbers in the moderate-to-high maltreatment group were widespread though not

uniform between all divisions. Interestingly, these moderate differences in fiber stream numbers were coupled with more marked between group differences in global measures of network architecture, particularly small-worldness, degree and the extent to which they deviated from artificially constructed network models.

Brain network architecture needs to simultaneously balance the opposing demands of integration and segregation in order to combine the presence of functionally specialized and segregated modules with a robust number of connecting links between the modules (Sporns and Honey, 2006; Tononi et al., 1994). This tradeoff is reflected in the small-worldness properties of the network, which reflect the ratio of the local clustering coefficient to overall pathlength. The greater small-worldness in the moderate-to-high maltreatment versus no-to-lower exposure group makes sense as these subjects had a smaller number of calculated interconnections, reflected in reduced measures of degree and strength, and thus a slightly sparser network (Humphries and Gurney, 2008). The greater small-worldness in the moderate-to-high exposure group is probably a consequence of preserved local modular architecture, as evidenced by comparable between group clustering coefficients, but lower connectivity between modules. The greater small-worldness of the higher exposure group is also consistent with its closer resemblance to a mathematically constructed small-world network. We suspect that the greater number of fiber streams and network strength in the low exposure group may be primarily devoted to enhanced connectivity between modules affording a higher degree of integration, as reflected in greater mean measures of global efficiency. This makes sense, as the most significant between group differences in fiber stream numbers were in the interconnections between regions. There were no significant corrected differences between groups in fiber stream numbers within divisions, except for the basal ganglia.

Interestingly, histories of MDD, anxiety disorders or ADHD did not account for a significant percentage of the variance in global network measures in the current study. Similarly, subject specific demographics including education level, verbal and non-verbal IQ also did not account for a significant percentage of variance. A few studies have reported significant alterations in global network architecture measures in individuals with various psychiatric disorders, particularly MDD. For example, lower small-worldness and clustering coefficient measures have been reported in MDD (Long et al., 2015; T. Wang et al., 2016). Increased global efficiency was reported in treatment naïve subjects with MDD (Long et al., 2015), whereas decreased global efficiency was reported in remitted geriatric patients with MDD and mild cognitive impairments (Bai et al., 2012). None of these studies however, took into account histories of childhood maltreatment.

A number of studies have also failed to find any global network differences in MDD. Although, Korgaonkar et al. (Korgaonkar et al., 2014) reported lower structural connectivity values for two specific networks (default mode, frontal-caudate-thalamus) they did not find any correlation between global network parameters and history, severity or duration of MDD using DTI. Singh et al. (M. K. Singh et al., 2013) reported a difference in normalized clustering, but no difference in small-worldness or pathlength based on structural connectivity as inferred from between subject correlations in gray matter volume. Lim et al. (Lim et al., 2013) and Qin et al. (Qin et al., 2014) reported no differences in clustering

coefficient and small-worldness in subjects with late life depression and inpatients with MDD, respectively. Overall, these findings are consistent with our observation that MDD was not significantly associated with alterations in these global measures of network architecture. As childhood maltreatment had significant effects on these measures it would be critical to take maltreatment history into account before attributing observed network differences to psychiatric disorders.

The key strengths of the study include a large sample of unmedicated emerging adults recruited from the community that were selected to provide an increased percentage of individuals with moderate-to-severe exposure to maltreatment, as well as entry criteria that include both psychiatrically susceptible and resilient individuals. Another strength was the comprehensive way that maltreatment was assessed, including use of the MACE, which also assesses exposure to types of maltreatment not included in prior instruments (e.g., CTQ, ACE score). These include peer emotional and physical abuse and witnessing violence to siblings that also increase risk for psychopathology and are associated with differences in brain structure (Khan et al., 2015; Teicher et al., 2014b; Teicher and Vitaliano, 2011).

Key limitations include use of retrospective evaluation of maltreatment that may be subject to recall bias and cross-sectional analysis of cohorts. Hence, the study can only show associations. Though it is likely that exposure to early stress affects global network architecture we cannot rule out the possibility that preexisting differences in network architecture increased risk of being abused, or that network architecture abnormalities run in families and increase risk of abusive behavior by family members. The observation that parallel neurobiological abnormalities, such as reduced hippocampal or corpus callosum volume, have frequently been observed in translational studies of early life stress, where extent of exposure can be experimentally manipulated, and the emergence of comparable neuroimaging findings in an increasing number of longitudinal investigations, lends credence to the prospect that maltreatment is a causal agent (Teicher et al., 2016).

Given that maltreatment is a major risk factor for psychopathology it may be worth speculating how alterations in global network architecture could contribute to risk. One possibility is that a weaker degree of integration between clusters may make it harder to effectively compensate for any abnormalities that might occur within a cluster, community or functional network. This fits with the idea that psychopathology arises from multiple 'hits' (Bale, 2014; Bayer et al., 1999). These hits could be genetic predisposition, prenatal risk factors, or exposure to stressors during different stages of development. The waxing and waning of symptoms within different disorders may then reflect efforts of a less integrated network to compensate, shifting between periods of pathology and health as quasi-stable states. Analysis of functional network architecture during periods of relapse and recovery in maltreated individuals may provide a test of this hypothesis.

5. Conclusions

There were significant differences in multiple measures of global network architecture in subjects reporting exposure to moderate-to-high levels of maltreatment versus subject reporting no-to-low exposure. There was no significant association between global network

architecture and histories of MDD, anxiety or ADHD once maltreatment was accounted for. The nature of the network differences suggests that there may be reduced interconnects between clusters or communities within the network of maltreated individuals.

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Highlights

- Childhood maltreatment was associated with global network architecture abnormalities
- Abnormalities included increased small-worldness and decreased degree and efficiency
- Mood, anxiety and ADHD didn't account for network differences related to maltreatment
- Fiber stream numbers were reduced bilaterally especially frontal to basal ganglia

Figure 1.

Schematic illustration showing interconnections between major brain division in which the total number of interconnecting fiber streams between nodes in these regions differed significantly between the no-to-low versus moderate-to-high exposure groups. Thickness of the arrows indicates degree of difference in number of fiber streams and color represents actual (uncorrected) p values.

Figure 2.

Relative importance of history of maltreatment, history of psychopathology, gender, age and socioeconomic factors as predictors of the global network measures: Asterisks indicate significance levels from multiple regression, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 1Demographic Characteristics between Groups. Numerical data are shown as mean $\pm$ SD.

	Moderate-High Exposure	No-Low Exposure	GLM or Odds ratio [95% CI]	P value
AGE (years)	22.0 $\pm$ 2.39	22.8 $\pm$ 2.11	$t_{259.9} = 2.73$	< 0.007
Gender (N)	140 (51M/89F)	122 (51M/71F)	Fisher exact	0.38
Number of Types of Maltreatment (N)	4.12 $\pm$ 2.12	0.47 $\pm$ 0.50	$t_{156.6} = -19.7$	< 10^{-15}
Financial Sufficiency (score 1 to 5)	2.74 $\pm$ 0.94	3.30 $\pm$ 0.79	$t_{259.7} = 5.17$	< 10^{-6}
Parental Education (years)	14.7 $\pm$ 3.13	16.6 $\pm$ 2.73	$t_{260} = 5.15$	< 10^{-6}
Subject Education (years)	15.08 $\pm$ 1.34	15.38 $\pm$ 1.34	$F_{1,258} = 3.21^*$	0.08
Verbal IQ	115 $\pm$ 16	120 $\pm$ 18	$t_{254} = 2.23$	< 0.03
Non-verbal IQ	113 $\pm$ 12	116 $\pm$ 12	$t_{254} = 2.03$	< 0.05
MOOD DO (N, %)	68 (49.6%)	24 (20.2%)	3.88 [2.16–7.14]	< 10^{-5}
ANXIETY DO (N, %)	64 (46.7%)	31 (26.1%)	2.48 [1.42–4.39]	<0.0008
ADHD (N, %)	25 (18.2%)	13 (10.9%)	1.82 [0.84–4.08]	<0.12

* Adjusted for age and gender. Abbreviation: DO - Disorder

Table 2

Network differences between groups.

Network Measures	Moderate-High Exposure	No-Low Exposure	F-Value	P-Value	P-Value (adjusted) *
Degree	12.1 ± 0.90	12.5 ± 0.97	6.95	0.0089	0.021
Strength	850 ± 213	924 ± 260	4.97	0.027	0.041
Path Length	2.48 ± 0.09	2.46 ± 0.10	3.91	0.049	0.059
Global Efficiency	0.476 ± 0.015	0.481 ± 0.016	5.04	0.026	0.0405
Clustering Coefficient	0.473 ± 0.014	0.477 ± 0.015	1.77	0.18	0.20
Small-worldness	2.88 ± 0.15	2.81 ± 0.15	8.20	0.0045	0.021
Laplacian:					
Skewness	-1.35 ± 0.096	-1.39 ± 0.093	6.06	0.014	0.028
Max Laplacian	2.19 ± 0.16	2.24 ± 0.17			
Spectra			4.25	0.040	0.053
Eigenvalue of Max	1.10 ± 0.047	1.09 ± 0.048	1.12	0.29	0.20
ER model distance	27.5 ± 1.1	28.0 ± 1.0	7.11	0.0079	0.021
WS model distance	25.1 ± 1.4	25.7 ± 1.3	7.16	0.0079	0.021
BA model distance	24.7 ± 1.4	25.3 ± 1.3	7.41	0.0069	0.021

* Adjusted using method of Benjamini and Hochberg.

Table 3

Cross-correlation between predictor variables

	Subject Education	Parental Education	Financial Sufficiency	History of MDD	Anxiety DO History	History of ADHD
Maltreatment History	-0.197	-0.302	-0.302	0.286	0.213	0.103
Subject Education	-	0.106	0.130	-0.069	-0.174	-0.086
Parental Education	-	-	0.389	-0.036	-0.057	-0.030
Financial Sufficiency	-	-	-	-0.141	-0.148	-0.111
History of MDD	-	-	-	-	0.327	0.212
Anxiety DO History	-	-	-	-	-	0.122