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Childhood Maltreatment: Altered Network Centrality of Cingulate, Precuneus, Temporal Pole and Insula

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Abstract

Background—Childhood abuse is a major risk factor for psychopathology. Previous studies have identified brain differences in maltreated individuals but have not focused on potential differences in network architecture.

Methods—High-resolution T1-weighted MRI scans were obtained from 265 unmedicated, right-handed 18-25-year-olds who were classified as maltreated (n=142, 55M/87F) or non-maltreated (n=123, 46M/77F) based on extensive interviews. Cortical thickness was assessed in 112 cortical regions (nodes) and inter-regional partial correlations across subjects were calculated to derive the lowest equivalent cost single-cluster group networks. Permutation tests were used to ascertain whether maltreatment was associated with significant alterations in key centrality measures of these regions and membership in the highly interconnected ‘rich club’.

Results—Marked differences in centrality (connectedness, ‘importance’) were observed in a handful of cortical regions. Left anterior cingulate had the second highest number of connections (degree centrality) and was a component of the ‘rich club’ in the control network but ranked low in connectedness (106th of 112 nodes) in the network derived from maltreated-subjects (p<0.01). Conversely, right precuneus and right anterior insula ranked first and 15th in degree centrality in the maltreated network versus 90th (p=0.01) and 105th (p<0.03) in the control network.

Conclusions—Maltreatment was associated with decreased centrality in regions involved in emotional regulation and ability to accurately attribute thoughts or intentions to others and with enhanced centrality in regions involved in internal emotional perception, self-referential thinking and self-awareness. This may provide a potential mechanism for how maltreatment increases risk for psychopathology.

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Keywords

Childhood abuse; early life stress; network analysis; graph theory; anterior cingulate cortex; precuneus; insula; temporal pole; centrality

Introduction

Exposure to childhood maltreatment has been found in both retrospective and prospective studies to markedly increase risk for major depression (1–4), bipolar disorder (5, 6), anxiety disorders (2, 3, 7), post-traumatic stress disorder (PTSD) (3, 8), substance abuse (2, 9, 10), personality disorders (11–13) and psychoses (14, 15). Maltreatment may increase risk for psychopathology by serving as an early life stressor that induces epigenetic modifications, reprograms stress-response systems and alters trajectories of brain development (16). Overall, a growing body of research has identified maltreatment-related differences in corpus callosum size and integrity (17–23), adult hippocampal volume (20, 24–33) and amygdala reactivity (34–38). Several studies have also reported a diverse array of cortical differences involving dorsolateral, dorsomedial, orbitofrontal, anterior cingulate and sensory cortices (39–46).

While these studies have been influential in shaping our understanding of the impact of maltreatment on the developing brain, there is increasing recognition that the brain is structurally and functionally organized into complex networks and psychopathology may result from alterations in the organization of these networks. Considerable progress has been made in recent years in the analysis of networks using graph theory (47). Briefly, four types of networks have received the most attention: (i) functional connectivity networks discernible in resting state fMRI; (ii) structural connectivity networks based on diffusion tensor imaging of fiber tracts; (iii) structural connectivity networks delineated by between subject intraregional correlations in measures of cortical thickness or gray matter volume (47); and (iv) electrophysiological networks derived from EEG or MEG (48).

The aim of this study was to ascertain whether exposure to maltreatment in the form of physical, sexual or emotional abuse (PA, SA, EA) or physical or emotional neglect (PN, EN) would affect network structure, causing certain regions to serve to a greater or lesser degree as central hubs. In particular, we predicted that cortical regions that appear to be adversely affected by early stress would play a less important role in the cortical network of maltreated subjects. Further, we hypothesized that this approach would identify cortical regions that take on a more influential role in the maltreated subject's network.

Methods and Materials

Subject Recruitment

This study was approved by the McLean Hospital IRB. All subjects provided informed written consent and were screened, recruited and evaluated using previously described methods (33). Our goal was to recruit a sample of subjects from the community that would provide a rigorous test of our hypotheses with as few confounding factors as possible, and without the subjects' awareness of our specific entry criteria. To meet this aim we recruited

unmedicated, right-handed 18–25 years olds through advertisements on mass transit and in newspapers with the tag line “Memories of Childhood”. Subjects were required to be free from neurological disease or head trauma resulting in loss of consciousness for more than 5 minutes, or for any duration if medical evaluation provided evidence of a concussion. Subjects were also excluded who had experienced 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.

Subjects selected for evaluation either had no history of childhood maltreatment, reported exposure to a specific type of maltreatment (e.g., parental verbal abuse) or had exposure to one or more maltreatment-related events (i.e., PA, SA or witnessing of domestic violence) that fulfilled the DSM-IV A1 and A2 criteria for a traumatic experience. Subjects were selected without regard to psychiatric history, except for high levels of drug or alcohol use, which were grounds for exclusion. Selecting subjects meeting criteria for a specific disorder could bias results by only including the most severely affected subjects. Conversely, selecting subjects without any psychiatric history could bias results in the opposite direction. From a fully assessed sample of 604 individuals a subset of 265 subjects (~ 44%) underwent neuroimaging as per protocol. Neuroimaged subjects used alcohol to only a modest extent (median of 8.6 drinks per month), and degree of use was unrelated to early adversity ($F(1,244) = 0.06, P > 0.8$). Similarly drug use was extremely low (median 0 days per month) and unrelated to early adversity ($P > 0.5$). All subjects tested negative for drug use by urinalysis and for recent alcohol consumption by breath test. Subjects were paid \$20–\$25 for completing the online assessment, \$50 per interview and assessment session (typically two 4-hour sessions) and \$100–150 for the MRI protocol, which lasted up to 2 hours.

Subject Assessments

Structured Clinical Interviews for DSM-IV Axis I and II psychiatric disorders (SCID) were used for diagnoses. Maltreatment was assessed using the 100-item semi-structured Traumatic Antecedents Interview (TAI) (49). This interview evaluates reports of PA, SA, PN, EN, witnessing violence, significant separations or losses, verbal abuse, or parental discord (49). The reliability of TAI variables ranges from acceptable to excellent (median intraclass $R = 0.73$) (49). Subjects were evaluated using both self-report and interview versions of the Conflict-Tactic Scales (50) (CTS), the Childhood Trauma Questionnaire (51) (CTQ), and the Adverse Childhood Experience (1) (ACE) score. Symptom ratings were assessed using Kellner’s Symptom Questionnaire (52), Dissociative Experience Scale (53) and Limbic System Checklist-33 (LSCL-33) (54).

Low income and poverty may be important risk factors. Young adult subjects were often uncertain about parental income while they were growing up. However, 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. Mental health

professionals (psychiatrists, Ph.D. psychologists, clinical nurse specialists) conducted the assessment and evaluation interviews and were blind to the neuroimaging results.

MRI acquisition

High-resolution T1-weighted MRI datasets were acquired on a Trio Scanner (3T; Siemens AG, Siemens Medical Solutions, Erlangen, Germany). The scanner was upgraded during the course of the investigation to Total Imaging Matrix (TIM), with a corresponding switch from an eight-element phased-array RF reception coil (n=192) to a 32-element coil (n=73). The gender distribution (62% and 61% female) and percent of subjects with maltreatment histories (52% and 58%) did not differ significantly between cohorts studied prior to or following the upgrade (Fisher exact $p > 0.8$ and $p > 0.4$, respectively). The GRAPPA acquisition and processing was used to reduce the scan time, with a GRAPPA factor of 2. Scan parameters were: the sagittal plane, TE/TR/TI/flip = 2.74 ms/2.1 s/1.1 s/12 deg; 3D matrix $256 \times 256 \times 128$ on $256 \times 256 \times 170$ mm field of view; bandwidth 48.6 kHz; scan time 4:56.

MRI analysis

Cortical reconstruction and thickness analyses were performed with the Freesurfer image analysis suite (version 5.1), which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications by the developers (55–60). Overall, thickness measures were calculated for 148 regions (using the *aparc.a2009s* template) and combined into 112 cortical regions through weighted averaging of the thickness of smaller adjacent components of the same underlying structure (e.g., right hemisphere orbital sulcus thickness was defined as the volume weighted average of the thickness of the lateral orbital sulcus, medial-olfactory orbital sulcus and H-shaped orbital sulcus).

Network Analysis

Cortical morphometric networks were determined following procedures published by He, Chen, Evans and colleagues (47, 61–63), albeit with minor modifications. This approach is based on the observation that certain pairings of cortical regions (e.g., frontal-temporal, frontal-parietal, intrahemispheric) vary in tandem across individuals in thickness or gray matter volume, and that the statistical dependence between distinct brain regions is due to structural or functional associations between these regions (63, 64). This approach has been used to identify the modular and small-world network structure of the cerebral cortex in normal individuals (65, 66) and network abnormalities in Alzheimer's disease (62, 67), schizophrenia (61), epilepsy (68–70), multiple sclerosis (71) and aging (72).

FreeSurfer measures of cortical thickness were adjusted by regression to remove potential influences of gender, parental education, perceived financial stress, race, ethnicity and scanner upgrade. Interregional partial correlation matrices were then derived for each group by calculating partial correlation coefficient for all regional pairings of adjusted thickness measures across group members (R package *ppcor*). The partial correlation between any two cortical regions represents their conditional dependencies after partialling out the effects of the other 110 regions. A threshold was then applied to the matrices to create a graph

representing strong (suprathreshold) partial correlations as connections (edges) between regions (61). Group-specific thresholds were set to ensure that the graphs of both groups had the same number of edges or wiring cost (number of edges divided by maximum possible number of edges) (61).

To determine a meaningful wiring cost for nodal comparisons we calculated the minimum number of edges required to produce fully connected networks. In a connected network there is at least one sequence of paths connecting each node to every other node. The control and maltreated networks did not differ significantly in requisite wiring cost, and we selected the greater of the two costs, which was 14%. He et al.(62) used 13% as an arbitrary cost to help ensure that all nodes were included in the network, while minimizing the number of false positive paths.

Our approach differed from He et al (61, 62) in one significant way as they selected either positive or negative partial correlations that exceeded threshold by using absolute values (62). We only included positive suprathreshold partial correlations in our networks, based on the observation by Gong et al (64) that only positive thickness correlations were mediated by direct fiber pathways.

Centrality Measures—Key centrality measures include: degree centrality (number of directly interconnected nodes); betweenness centrality (frequency with which a node falls between pairs of other nodes on their shortest interconnecting path); closeness centrality (normalized number of steps required to access every other node from a given node in a network) and eigenvector centrality (a spectral centrality measure based on the idea that the importance of a node is recursively related to the importance of the nodes associated with it). Graph theory postulates that nodes with high degree centrality are “in the thick of things”, and serve as focal points of communication. Nodes with high betweenness centrality have the greatest potential to control communication, whereas nodes with high closeness centrality are the most independent and can spread information most quickly throughout the network. Eigenvector centrality is a measure of a node’s overall influence, and is the basis of Google’s PageRank algorithm.

Rich Club

Rich-club’ phenomenon is said to be present when the hubs of a network tend to be more densely connected among themselves than to lower-degree nodes (73). We applied the methodology for rich-club determination as described by van den Heuvel and Sporns (74).

Statistics

Data analyses were conducted in R (packages *sna*, *igraph*, *bootstrap*) using routines written by MHT and KO. We sought to test the hypothesis that childhood maltreatment was associated with alterations in network architecture, in particular with a shift in importance (centrality) of specific hubs. As the between-subject interregional partial correlations technique only delineates a single network for each group we assessed the reliability (SD, 99% confidence interval) of these differences using jackknife resampling (75). Network

delineation from partial correlation coefficients precluded use of bootstrap resampling with replacement.

Although concerns have been raised about biasing effects of volume differences on functional connectivity and fiber networks (76, 77) we found no significant association between volume and centrality measures on these thickness networks.

Permutation testing was used to assess the significance of differences in nodal centrality (62, 78). Briefly, this test ascertains the probability that the degree of difference observed in the entire constellation of non-independent nodal centrality measures between the two groups could have occurred by chance based on 10,000 network comparisons derived by randomly assigning subjects to the two groups. This approach controls for multiple comparisons by assessing differences over and above those occurring by random chance across all of the myriad comparisons. Probability values derived using this method were several orders of magnitude less significant than uncorrected probability values based on individual t-tests from means and SDs. Further, we only considered a node to differ in centrality between the control and maltreated network if permutation-derived p values were ≤ 0.05 on at least two of four centrality measures, reducing the odds of chance occurrence to 1/400.

Jackknife resampling was also used to assess the probability (with 99% confidence interval) that a node was included in the rich club in the maltreated and control network. Permutation testing was used to determine the significance of observed probability differences, and provided a multiplicity-corrected estimate several orders of magnitude less significant than uncorrected p-values.

RESULTS

Subject Characteristics

The sample consisted of 256 unmedicated, right-handed 18–25 year olds. Overall, 123 (46M/77F) subjects had no exposure to PA, SA, EA, EN or PN and 142 (55M/87F) reported exposure to at least one type of maltreatment based on extensive interviews.

As indicated in Table 1, there were slight but significant differences between groups in degree of parental education and financial sufficiency. As intended, maltreated subjects had substantially greater exposure to early adversity and all forms of maltreatment. Groups differed most in their degree of exposure to emotional abuse and neglect. There were significant mean differences in all psychiatric symptom ratings. Overall, 41%, 35% and 9% of the maltreated subjects had a lifetime history of major depression, anxiety disorders, or PTSD, respectively.

Maltreatment and Node Centrality Measures

Significant group differences in two or more measures of nodal centrality were identified in nine cortical regions. The probability of 9 nodes differing by chance on 2 or more centrality measures was remote ($p < 0.00002$) by Monte-Carlo simulation. Centrality measures were reduced in six nodes and increased in three nodes (Table 2). Measures for all nodes can be found in Appendix Table 1. The most compelling differences were observed in the left

anterior cingulate gyrus and sulcus. Differences in number of first and second-degree nodes associated with the left anterior cingulate are illustrated in Fig. 1. This represented a marked shift as the left anterior cingulate had the 2nd largest degree centrality in the normal network [99% confidence interval 1st – 5th], but ranked only 106th out of 112 nodes in the maltreated network [99% CI 103rd – 109th]. In contrast, the right anterior insula, right precuneus, and right parieto-occipital sulcus had substantially greater centrality in the maltreated network than in the control network. Primary and secondary nodal connections of the right anterior insula and right precuneus, are illustrated in Figure 1.

Maltreatment and network architecture

Differences in centrality were also reflected in the constellation of nodes forming the ‘rich-club’. The pathways linking ‘rich-club’ regions forms a central high-cost, high-capacity backbone for global communication (74). As seen in Figures 2, 3 and Appendix Table 2, a ‘rich-club’ organization is apparent in the network of unexposed subjects for nodes with greater than 15 to greater than 22 direct connections ($k = 15$ to $k = 22$). In the maltreated subject network the ‘rich-club’ phenomenon emerged for nodes with $k = 19$ to $k = 27$ direct connections. Using a $k = 21$ criteria for the unexposed subject network and $k = 19$ for the maltreated network produced equally large rich clubs (22 nodes) that were primarily frontal and temporal in controls and primarily occipital and temporal in the maltreated network. The dice coefficient for the overlap between the unexposed and maltreated rich clubs was only 0.191 [99% CI 0.177 – 0.205]. Just three nodes, the right medial parahippocampal gyrus, left anterior insula, and left superior temporal sulcus had a high probability of membership in both rich clubs. In contrast, the left anterior cingulate had a 95.1% [91.3%–100%] and 0% chance of membership in the unexposed versus maltreated rich clubs (corrected $p < 0.05$), whereas the right precuneus had a 4.1% [0% – 8.7%] and 100% chance of membership in the unexposed versus maltreated rich club ($p < 0.02$). Significant differences in probability of membership were also observed for right middle frontal gyrus (unexposed) and right anterior insula (maltreated).

DISCUSSION

These findings identify compelling differences in the cortical network architecture of young adults with histories of childhood maltreatment. Some of the regions with reduced centrality in the maltreated network were previously found to have reduced gray matter volume (GMV), blood flow or neuronal integrity in maltreated individuals. These include: left anterior cingulate (39, 40, 42, 43); right occipital pole (79); left temporal pole (44); and right medial frontal gyrus (43, 45). Interestingly, the anterior insula, which was a more central component of the maltreated network, displayed enhanced reactivity to emotional stimuli in maltreated children (80). Similarly, right superior temporal gyrus, which had greater degree centrality and was part of the maltreated but not control rich club, was found to have greater than normal GMV in abused children with PTSD (41).

Generally, regions with higher centrality in the unexposed versus maltreated network appear to be involved in emotional regulation, attention and social cognition. The anterior cingulate plays an important role in attention and the regulation of emotions and impulses (81). The

temporal pole is involved in social cognition, particularly theory of mind, in which an individual attributes thought, intentions or beliefs to others (82). Occipital poles subserve visual processing; conveying processed information to visual association cortex, and through reciprocal connections contributing to conscious awareness (83). The middle frontal gyrus plays an important role in working memory and attention. The rostral anterior portion of the middle frontal gyrus is activated by social cognition tasks, which involve self-knowledge, person perception and mentalizing (84).

In contrast, regions with higher centrality in the maltreated network appear to be involved in self-awareness. For example, the precuneus is a major component of the default mode network and is involved in self-referential thinking and self-centered mental imagery (85). The anterior insula contains an interoceptive representation that provides the basis for all subjective feelings from the body (86). The anterior insula is often activated in conjunction with the anterior cingulate and together seem to function as limbic sensory and motor cortices that respectively engender the feelings (insula) and the motivations (cingulate) that constitute any emotion (86). Craig has argued that the anterior insula provides a critical substrate for self-awareness (86).

A key limitation of this study is that thickness networks apply to groups rather than individuals. Hence, this technique produced two networks for comparison rather than 265 individual networks. Fortunately, differences between these two networks can be assessed for statistical significance through resampling and permutation testing. However, differences between subjects in symptoms, diagnoses, or exposure histories cannot be tied back to differences in their individual networks.

Second, thickness analysis is limited to the assessment of cortical networks. While this provides a useful perspective, a more complete description will also need to include subcortical regions.

Finally, this method is the least intuitive of the available techniques for assessing brain networks. Delineation of network structure based on diffusion tensor imaging (DTI) and tractography makes anatomical sense, whereas correlations and anticorrelations in resting state blood-oxygen level dependent (BOLD) fluctuations make physiological sense. Networks delineated by these techniques however may show more differences than similarities in nodal centrality measures. For example, Brown et al (87) recently compared resting-state and DTI-based network structure in 60 healthy adults and found only a modest edge weight correlation of 0.39 and almost no significant correlations in nodal measure. This may be due to the inherent limitations in conventional DTI tractography in resolving crossed paths, or in identifying sparse long-range connections, and to limitations in resting-state functional connectivity in controlling for artifacts related to non-brain sources of variation (87). It may also be the case that brain structure and function are not entirely isomorphic (88).

The mechanisms generating between subject correlations in thickness are not fully understood, but likely reflect a coordinated developmental process brought about through anatomical and functional interconnections between regions (64). For example, certain

regions may covary in volume or thickness as a consequence of mutual trophic effects mediated by direct axonal connections (89). This technique predominantly identifies positive thickness correlations between associated intrahemispheric regions (e.g., Broca and Wernicke's area (63)) and between homologous right and left hemisphere regions (64). However, it also identifies long-range connections from regions that appear to be central hubs. Approximately 60% of positive thickness connections have matching diffusion connections across a large range of wiring costs (8% – 26%) (64). It is possible that positive thickness connections that do not appear to have matching diffusion connections are driven by stable long-range functional connections between regions, but this remains to be determined.

Overall, this technique appears to delineate a network structure that blends features of the fiber-tract and resting-state networks. The major cortical hubs identified in the positive thickness networks overlap extensively with major cortical hubs delineated through functional connectivity analysis (87).

Two recent studies assessed network architecture in individuals exposed to early life stress. Cisler et al (90) compared 22-hub cortical/subcortical resting-state functional connectivity networks in seven resilient subjects with early life stress (ELS), 19 susceptible subjects with ELS and 12 healthy controls. Their key findings were decreased local network connectivity for the dorsal anterior cingulate cortex (dACC) among resilient individuals and decreased hub-like properties of the dACC and decreased local connectivity of the left ventrolateral prefrontal cortex in susceptible individuals. Hence, our findings are similar to theirs though the network we assessed differed markedly in number and location of nodes.

Wang et al (91) conducted a functional connectivity study in 18 medicated patients with major depression and childhood neglect, 20 medicated patients with major depression without neglect and 20 healthy controls. Although they did not conduct a formal graph analysis, they presented degree centrality measures showing widespread reduction in ventral anterior cingulate and other prefrontal regions in subjects with major depression and neglect versus healthy controls. They also found marked differences between major depression with versus without neglect, providing further support for the hypothesis that these are neurobiologically distinct variants (92).

A limitation of the present study, and almost all studies assessing the enduring neurobiological consequences of childhood abuse into adulthood, is our reliance on retrospective assessment of maltreatment based on self-report and interview. Some critics have raised concern about false or 'recovered' memories and recall bias, suggesting that subjects in emotional distress will describe their childhood as more stressful or abusive. Consequently, one might expect high false positive rates for adult reports of childhood abuse. The opposite is true – adults under-report their degree of exposure (93, 94). Individuals reporting abuse retrospectively were those who typically endured the most severe abuse on prospective assessment (94). This fits with other studies showing that adult reports of abuse are verifiable (95). Exposure to childhood maltreatment in this study was assessed remotely through online report, through in-office self-report and through an extensive semi-structured traumatic antecedents interview. Subjects reporting maltreatment were consistent across measures and had persistent (not 'recovered') memories of the

experience. Test-retest evaluation of severity of maltreatment assessed in 60 participants showed that their responses were stable and reliable ($r = 0.894$).

In summary, maltreatment is associated with a marked change in centrality of a relatively small number of cortical regions, which provides a theoretical mechanism through which maltreatment may act to increase risk for substance abuse and mental illness. Taken *in toto* the cortical network organization of maltreated individuals may result in a diminished capacity to: (i) regulate impulses and emotions; (ii) accurately attribute thought, intentions or beliefs to others, and (iii) be mindful of oneself in a social context. On the other hand, this network structure may lead to: (i) the heightened experience of internal emotions and cravings; and (ii) a greater tendency to think about oneself and to engage in self-centered mental imagery. This certainly fits with the knowledge that psychotherapies have been designed to enhance emotional regulation (96), to correct misconceptions about self and others (97), to diminish focus on internal feelings (98) and to decenter from harmful self-centered thinking (99).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Components of the cortical structural connectivity network in healthy unexposed controls and young adults with maltreatment histories. The panels show the primary nodal connections (in purple) with either the left anterior cingulate, right anterior insula or right precuneus (green) along with their second degree nodal connections (in blue). Region names corresponding to nodal numbers can be found in Appendix Table 1.

Figure 2.

Line graphs showing the emergence of 'rich-club' phenomenon in networks for unexposed controls and individuals with maltreatment histories based on the analysis of nodes with more than k degrees. The rich-club coefficient is defined as the ratio of the existing number of edges, over the maximum possible number of edges between nodes with greater than k degrees. Rich-club values (blue) are normalized (red) relatively to a set of comparable random networks (gray). The shaded area shows the existence, and requisite k criteria, for rich-club organization, which occurs at k levels where connectivity in the network exceeds that of the random models as indicated by normalized coefficient with values greater than 1.

Figure 3. 'Rich club' networks in healthy unexposed controls and individuals with maltreatment histories. The maltreated 'rich clubs' were selected to contrast with the control network in either minimum number of required direct connections ($k=21$) or number of total nodes ($k=19$). Node size was scaled by eigenvector centrality. See Appendix Table 2 for region names.

Table 1

Group differences in socioeconomic factors, exposure history and psychiatric symptom scores.

Measures*	Unexposed Controls**	Maltreated	ANCOVA F	probability
Age (yrs)	22.4 (22.0–22.8)	22.2 (21.9–22.6)	0.35	NS
Subjects' Ed. (yrs)	14.8 (14.5–15.0)	14.6 (14.4–14.8)	0.89	NS
Parental Ed. (yrs)	16.1 (15.6–16.5)	15.2 (14.8–15.7)	6.84	p<0.01
Financial Sufficiency	3.46 (3.33–3.60)	2.94 (2.82–3.07)	29.62	p<10 ⁻⁶
ACE Score	0.18 (0.00–0.38)	1.99 (1.80–2.17)	171.49	p<10 ⁻²⁹
CTQ Emotional Abuse [†]	6.28 (5.63–6.92)	11.5 (10.9–12.1)	132.24	p<10 ⁻²⁴
CTQ Physical Abuse	5.75 (5.27–6.22)	7.54 (7.07–8.00)	27.89	p<10 ⁻⁶
CTQ Sexual Abuse	5.08 (4.60–5.55)	6.43 (5.97–6.90)	15.99	p<10 ⁻⁴
CTQ Emotional Neglect	7.31 (6.58–8.03)	11.7 (11.0–12.4)	73.18	p<10 ⁻¹⁴
CTQ Physical Neglect	5.79 (5.34–6.24)	7.56 (7.12–8.01)	30.54	p<10 ⁻⁷
CTQ sum score	30.2 (28.2–32.2)	44.8 (42.8–46.8)	102.93	p<10 ⁻¹⁹
SQ Anxiety	4.85 (4.11–5.59)	7.26 (6.58–7.95)	22.36	p<10 ⁻⁵
SQ Depression	3.92 (3.12–4.72)	6.49 (5.75–7.23)	21.79	p<10 ⁻⁵
SQ Somatization	3.97 (3.25–4.69)	6.23 (5.56–6.90)	20.61	p<10 ⁻⁵
SQ Anger-Hostility	4.20 (3.50–4.90)	5.64 (4.99–6.30)	8.73	p<0.004
Dissociation (DES)	5.82 (4.47–7.18)	9.07 (7.80–10.3)	11.83	p<0.0007
Limbic Irritability (LSCL)	12.2 (10.2–14.4)	21.3 (19.3–23.3)	35.89	p<10 ⁻⁸

* Covaried by age and gender

** Mean (95% confidence intervals)

[†] CTQ category scores range from 5–25.

ACE - Adverse Childhood Experience, CTQ - Childhood Trauma Questionnaire, DES – Dissociative Experience Scale, LSCL - Limbic System Checklist-33, SQ - Kellner Symptom Questionnaire

Table 2

Regions showing significant differences (corrected probability) in two or more centrality measures in the networks derived from subjects exposed to childhood maltreatment versus unexposed control subjects.

REGIONS	DEGREE CENTRALITY			BETWEENNESS CENTRALITY		
	Unexposed*	Maltreated	prob	Unexposed	Maltreated	prob
54 L anterior cingulate gyrus & sulcus	28 (2 nd)	7 (106 th)	0.008	142 (8 th)	9 (109 th)	0.03
75 L inferior temporal gyrus	24 (8 th)	8 (102 nd)	0.04	159 (3 rd)	6 (111 th)	0.02
78 L temporal pole	24 (7 th)	7 (106 th)	0.04	199 (1 st)	9 (107 th)	0.007
29 R occipital pole	21 (23 rd)	5 (112 th)	0.05	156 (5 th)	6 (112 th)	0.02
16 R anterior insular gyrus	6 (104 th)	23 (15 th)	0.03	4 (107 th)	102 (18 th)	0.04
24 R precuneus gyrus	10 (90 th)	30 (1 st)	0.01	77 (39 th)	156 (2 nd)	0.08
71 L superior parietal gyrus	21 (25 th)	6 (110 th)	0.06	127 (11 th)	10 (104 th)	0.05
13 R middle frontal gyrus	29 (1 st)	13 (74 th)	0.04	159 (4 th)	60 (48 th)	0.08
103 R precentral gyrus & sulcus	25 (6 th)	13 (73 rd)	NS	160 (2 nd)	41 (69 th)	0.05

REGIONS	CLOSENESS CENTRALITY			EIGENVECTOR CENTRALITY		
	Unexposed	Maltreated	prob	Unexposed	Maltreated	prob
54 L anterior cingulate gyrus & sulcus	0.531 (1 st)	0.419 (109 th)	0.007	1.00 (1 st)	0.17 (99 th)	0.001
75 L inferior temporal gyrus	0.526 (3 rd)	0.429 (106 th)	0.01	0.60 (30 th)	0.21 (85 th)	NS
78 L temporal pole	0.526 (4 th)	0.427 (107 th)	0.01	0.65 (24 th)	0.16 (101 st)	0.08
29 R occipital pole	0.505 (17 th)	0.401 (112 th)	0.01	0.59 (32 nd)	0.07 (111 th)	0.06
16 R anterior insular gyrus	0.378 (109 th)	0.536 (12 th)	NS	0.16 (103 rd)	0.55 (15 th)	NS
24 R precuneus gyrus	0.448 (78 th)	0.563 (1 st)	NS	0.17 (100 th)	1.00 (1 st)	0.008
71 L superior parietal gyrus	0.519 (7 th)	0.416 (110 th)	0.01	0.53 (40 th)	0.09 (110 th)	0.09
13 R middle frontal gyrus	0.521 (6 th)	0.491 (54 th)	0.10	0.96 (2 nd)	0.17 (95 th)	0.005
103 R precentral gyrus & sulcus	0.524 (5 th)	0.487 (59 th)	0.09	0.92 (4 th)	0.24 (78 th)	0.02

* mean (rank), L – left, R – right

See Appendix Table 1 for confidence limits on values and ranks