

Susceptibility or Resilience to Maltreatment Can Be Explained by Specific Differences in Brain Network Architecture

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ABSTRACT

BACKGROUND: Childhood maltreatment is a major risk factor for psychopathology. However, some maltreated individuals appear remarkably resilient to the psychiatric effects while manifesting the same array of brain abnormalities as maltreated individuals with psychopathology. Hence, a critical aim is to identify compensatory brain alterations that enable resilient individuals to maintain mental well-being despite alterations in stress-susceptible regions.

METHODS: Network models were constructed from diffusion tensor imaging and tractography in physically healthy unmedicated 18- to 25-year-old participants ($N = 342$, $n = 192$ maltreated) to develop network-based explanatory models.

RESULTS: First, we determined that susceptible and resilient individuals had the same alterations in global fiber stream network architecture using two different definitions of resilience: 1) no lifetime history of Axis I or II disorders, and 2) no clinically significant symptoms of anxiety, depression, anger-hostility, or somatization. Second, we confirmed an a priori hypothesis that right amygdala nodal efficiency was lower in asymptomatic resilient than in susceptible participants or control subjects. Third, we identified eight other nodes with reduced nodal efficiency in resilient individuals and showed that nodal efficiency moderated the relationship between maltreatment and psychopathology. Fourth, we found that models based on global network architecture and nodal efficiency could delineate group membership (control, susceptible, resilient) with 75%, 82%, and 80% cross-validated accuracy.

CONCLUSIONS: Together these findings suggest that sparse fiber networks with increased small-worldness following maltreatment render individuals vulnerable to psychopathology if abnormalities occur in specific nodes, but that decreased ability of certain nodes to propagate information throughout the network mitigates the effects and leads to resilience.

Keywords: Abuse and neglect, Anxiety, Brain network architecture, Childhood adversity, Depression, Early life stress

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Maltreatment and household dysfunction is a major risk factor for psychopathology associated with 33%, 54%, 64%, and 67% of the population attributable risk for anxiety disorders (1), depression (2), addiction (3), and suicide attempts (4). Abuse and neglect are also recognized as major risk factors for personality and psychotic disorders (5–22) and for hastening onset and exacerbating the course of bipolar disorder (23–32). A critical unanswered question is why some maltreated individuals develop psychopathology whereas others remain resilient.

We have hypothesized that maltreatment increases risk by altering trajectories of brain development. The most consistent findings are smaller midsagittal area (33–37) or decreased fractional anisotropy (38,39) of the corpus callosum and lower hippocampal volume in adults (40–51). Maltreatment is also associated with attenuated development of the anterior cingulate cortex (52–55), orbitofrontal cortex (55–57), and dorsolateral prefrontal cortex (54,58) as well as with enhanced

amygdala response to threat (59,60) and alterations in functional connectivity (61–64).

Maltreatment also appears to affect brain network architecture (65). We recently reported that maltreated individuals had diffusion tensor imaging networks with reduced degree, strength, and global efficiency but increased path length and small-worldness (66). Puetz *et al.* (67) reported similar alteration in maltreated children. We originally presumed that psychiatric and neurobiological susceptibility would align and that brain abnormalities would be detectable in maltreated individuals with psychopathology but not in maltreated individuals without psychopathology. However, that turns out not to be the case. Indeed, studies have reported a compelling set of structural and functional brain differences in maltreated individuals with no history of psychopathology (39,51,52,60,66,68–79). Thus, the relationship between maltreatment, brain changes, and psychopathology remains unclear.

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Two major possibilities arise. First, these alterations may have no relevance to psychopathology, which would call into question numerous circuit-based models. Alternatively, there may be specific neurobiological alterations that enable resilient individuals to effectively compensate for abnormalities in stress-susceptible structures. Hence, we sought to determine if psychiatrically susceptible and resilient subjects had the same overall differences in network architecture and to identify specific differences that may enable resilient individuals to maintain mental well-being.

We theorized that susceptibility and resilience could be explained by integrating the multiple hit concept (80,81) with network architecture. Brain network architecture needs to balance the opposing demands of integration and segregation to combine the presence of functionally specialized and segregated modules with a robust number of connecting links (82). This tradeoff can be seen in network properties such as small-worldness, which reflect the ratio of local clustering coefficients to overall path length. We found that maltreated individuals had slightly sparser networks with increased small-worldness resulting from intact local modular architecture but lower connectivity between modules (66). The weaker degree of integration between clusters in maltreated individuals renders their networks more vulnerable and puts them at increased risk for psychopathology by making it harder to effectively compensate for second-hit abnormalities that might occur within a cluster, community, or node. Until both processes occur, these individuals may appear resilient. True resilience occurs in maltreated individuals with both global network and specific nodal abnormalities but who are effectively compensated, which may result from partially isolating and limiting the impact of problematic nodes. Hence, we tested the hypothesis that susceptible and resilient individuals have comparable abnormalities in global network architecture, but that resilient individuals have a lower degree of right amygdala centrality, as right amygdala hyperreactivity to threatening stimuli is the most consistent functional abnormality in maltreated individuals (59,60). Additionally, we conducted exploratory analyses to identify other nodes with abnormal centrality in resilient individuals.

METHODS AND MATERIALS

Subject Recruitment

The Partners Healthcare Institutional Review Board approved this study, and all subjects provided written informed consent. Recruitment followed previously reported methods (see Supplement) (51,65,66). The sample was enriched to increase the number of participants exposed to three or more types of maltreatment. Subjects were selected based on exposure, not psychiatric history, as selecting subjects for any specific disorder or for none could bias the results by including the most affected or most resilient subjects.

Subject Assessments

Assessment, evaluations, and Structured Clinical Interviews for DSM-IV Axis I and II psychiatric disorders (83) were conducted by mental health professionals blind to the neuroimaging results. The Maltreatment and Abuse Chronology of

Exposure (MACE) scale was used to evaluate type and timing of maltreatment during childhood (84). (See MACE Scale in the Supplement for additional information.)

Current symptoms of depression, anxiety, somatization, and anger-hostility were assessed using Kellner's Symptom Questionnaire (85), which has good psychometric properties and reliably reveals strong associations between self-reported exposure and psychopathology (39,84,86–88). Parental education and perceived financial sufficiency (89) were collected, as these are important risk factors for maltreatment and may have effects on trajectories of brain development.

Criteria for Susceptibility or Resilience

Resilience refers to the dynamic process leading to some aspect of positive adaptation (e.g., emotional well-being) in the face of significant adversity (90). We defined resilience in two ways. In both instances, we designated subjects who reported exposure to two or more types of maltreatment as at risk, as this degree of exposure increased odds of lifetime history of major depressive disorder by 4.67-fold (95% confidence interval, 2.68–8.39, $p < 10^{-8}$). One classification was made based on presence or absence of history of major Axis I or II DSM-IV disorders. The second classification was made based on presence or absence of clinically significant symptoms on Kellner's Symptom Questionnaire. Hence, we used both lifetime categorical and current state dimensional definitions.

Magnetic Resonance Imaging Data Acquisition

Magnetic resonance imaging scans were acquired using 3T Siemens TIM Trio scanners (Siemens Healthcare, Erlangen, Germany) using previously reported methods (see MRI Acquisition in the Supplement) (66). Briefly, multiple diffusion-weighted images were acquired in 72 directions. Scan parameters were as follows: $b = 1000$ s/mm²; echo time = 81 ms; repetition time = 6 seconds; matrix = 128 × 128 on 240 mm × 240 mm field of view; slices 3.5 mm without gap.

Magnetic Resonance Imaging Analysis and Network Construction

Diffusion tensor imaging scans were analyzed, and unweighted networks were constructed using previously published methods (see MRI Analysis in the Supplement) (66). Scans were parcellated into 90 regions using the automated anatomical labeling template (91), and the number of fiber streams interconnecting each of these nodal regions was calculated. Fiber streams connecting nodes were defined as edges, which were classified as 0 (no interconnecting fiber streams) or 1. Graph theory was used to calculate global network parameters, including global efficiency, degree, transitivity, vulnerability, and small-worldness. These network parameters have been described in detail previously (R packages *igraph*, *brainGraph*; R Foundation for Statistical Computing, Vienna, Austria) (66,92–98).

Statistical Procedures

Statistical Assessment of Group Differences in Global Network Architecture. An omnibus multivariate analysis of variance test was used to determine if there were significant multivariate group differences in network architecture. Individual analysis of covariance analyses were

performed to delineate which specific global network measures differed between the groups. Tukey post hoc tests were used to determine significance of the contrasts of the two groups within each of the significant main effects. Covariates included age, sex, parental education, and financial sufficiency.

Statistical Assessment of Group Differences in Right Amygdala Centrality. For these analyses, we compared groups based on current symptoms, as this resulted in groupings of similar size that were closely matched for maltreatment history. Multivariate analysis of variance was used to test the hypothesis that the asymptomatic group differed from symptomatic and unexposed control groups. We focused on three a priori measures of nodal centrality: 1) nodal efficiency (N_{eff}), which measures the ability of a node to propagate information with other nodes in the network; 2) degree centrality, which is the number of connecting nodes; and 3) closeness centrality, which is the average distance from a node to all other nodes in the network. Together, these provide a good understanding of the connectivity and influence of a particular node on the network. Age and sex were included as covariates.

Exploratory Identification of Additional Nodes That Differ Between Susceptible and Resilient Participants. The aim was to identify other nodes that differ significantly between susceptible and resilient participants, which is complicated by the number of potential nodal comparisons. To limit this number, we first chose a priori to use N_{eff} as the single measure of centrality. Then we used random forest regression with conditional inference trees (RFR-CIT) and elastic nets to identify a sparse set of nodes that might best predict this group difference (see Identifying Nodal Differences in the [Supplement](#)).

Classifying Susceptible, Resilient, and Unexposed Control Participants Based on Network and Nodal Parameters. RFR-CIT was used in a multiclass prediction model (see Multiclass Prediction in the [Supplement](#)) to assess how well five measures of global network architecture plus N_{eff} values could predict the correct classification of the 310 symptomatic, asymptomatic, and healthy control participants using 10-fold cross-validation. This process was also repeated restricting the number of nodes to only those identified as significant in the prior analysis.

RESULTS

The sample consisted of 342 participants (132 men and 210 women) 21.7 ± 2.5 years of age. Key demographic features are presented in [Supplemental Table S1](#). Of the participants, 56% had moderate to high exposure to maltreatment (mean 4.1 ± 2.1 types), and the remainder were no to low exposure control participants (0.4 ± 0.5 types).

Resilient Versus Susceptible by Lifetime Diagnosis

Clinical and Demographic Characteristics. Based on these criteria, there were 143 (52 men and 91 women) susceptible, 49 (18 men and 31 women) resilient, and 95 (40 men and 55 women) unexposed control participants. There were no

differences between groups in sex ($\chi^2_2 = 0.86, p = .65$), but there was a modest difference in age ([Table 1](#)). [Table 1](#) presents number of types and severity of maltreatment for the different groups. Multivariate analyses indicated marked overall group differences in exposure (Pillai-Barlett trace [PBT] = 0.750, $F_{22,540} = 14.71, p < 10^{-16}$). Susceptible subjects reported greater exposure to all types of maltreatment than control subjects, whereas resilient subjects reported greater exposure to most types. Susceptible subjects reported greater overall exposure than resilient subjects (PBT = 0.217, $F_{11,176} = 4.432, p < 10^{-5}$) and greater exposure to sexual abuse, witnessing violence to siblings, parental verbal abuse, and emotional neglect.

Overall, 60%, 54%, 41%, 24%, 15%, and 4% of susceptible participants had histories of major depression, one or more anxiety disorders, one or more personality disorders, attention-deficit/hyperactivity disorder, eating disorders, or bipolar disorder. By definition, none of the resilient subjects or control subjects had a history of psychopathology.

Network Architecture. There was a significant multivariate group effect on overall network architecture (PBT = 0.088, $F_{10,552} = 2.545, p = .005$), which was not influenced by inclusion of mean fractional anisotropy values (see Between Group Differences in the [Supplement](#)). There were significant network differences between susceptible subjects and control subjects (PBT = 0.069, $F_{5,227} = 3.353, p = .006$) and between resilient subjects and control subjects (PBT = 0.092, $F_{5,133} = 2.688, p = .02$) but not between susceptible subjects and resilient subjects (PBT = 0.023, $F_{5,182} = 0.856, p = .51$). As seen in [Figure 1A](#), there were significant group differences in univariate measures of degree, vulnerability, and small-worldness, with most significant comparisons between unexposed control subjects and resilient participants despite their lower degree of exposure.

Resilient Versus Susceptible by Current Symptoms

Clinical and Demographic Characteristics. To avoid confusion, we refer to susceptible maltreated subjects with clinically significant symptoms as symptomatic and to resilient maltreated subjects without clinically significant symptoms as asymptomatic. There were 118 (52 men and 66 women) control subjects without symptoms, 86 (36 men and 50 women) asymptomatic maltreated subjects, and 106 (34 men and 72 women) symptomatic maltreated subjects. [Table 2](#) presents current symptoms and exposure history. There were no differences between groups in sex ($\chi^2_2 = 3.68, p = .159$), but there was a modest difference in age ([Table 2](#)).

There were marked group differences in degree of exposure to maltreatment (PBT = 0.716, $F_{22,584} = 14.801, p < 10^{-16}$). Both symptomatic and asymptomatic groups reported greater exposure to all types of maltreatment than the control group. On one hand, there was only a minor multivariate difference in exposure to maltreatment in symptomatic versus asymptomatic subjects (PBT = 0.113, $F_{11,176} = 2.045, p = .03$) with no significant univariate differences in exposure to any of the 10 types of maltreatment. On the other hand, there were marked differences between symptomatic subjects and asymptomatic subjects in symptom scores but no differences between asymptomatic subjects and control subjects on any of the symptom scales ([Table 2](#)). Asymptomatic participants also did

Table 1. Groups Based on Lifetime History of Psychopathology Meeting Axis I or II DSM-IV Criteria

	Control (1)	Resilient (2)	Susceptible (3)	1 vs. 2	1 vs. 3	2 vs. 3	F	p
Age, Years	22.1 ± 2.46	21.7 ± 2.46	21.2 ± 2.46	$p > .60$	$p < .02$	$p > .30$	4.4	$p < .02$
Parental Education, Years	16.6 ± 3.15	14.7 ± 3.15	14.8 ± 3.15	$p < .01$	$p < 10^{-4}$	$p > .90$	10.6	$p < 10^{-4}$
Financial Sufficiency During Childhood	3.36 ± 0.90	2.94 ± 0.90	2.76 ± 0.90	$p < .10$	$p < 10^{-5}$	$p > .40$	13.1	$p < 10^{-5}$
Number of Types of Maltreatment	0.58 ± 1.62	2.96 ± 1.55	4.36 ± 1.59	$p < 10^{-11}$	$p < 10^{-12}$	$p < 10^{-5}$	147.2	$p < 10^{-43}$
Sexual Abuse	0.05 ± 1.78	0.59 ± 1.71	1.87 ± 1.75	$p > 0.4$	$p < 10^{-10}$	$p < 10^{-4}$	30.8	$p < 10^{-12}$
Parental Verbal Abuse	1.92 ± 2.75	5.82 ± 2.63	7.22 ± 2.69	$p < 10^{-11}$	$p < 10^{-12}$	$p < .02$	101.6	$p < 10^{-33}$
Parental Nonverbal Emotional Abuse	2.02 ± 2.04	4.33 ± 1.95	4.98 ± 1.99	$p < 10^{-7}$	$p < 10^{-12}$	$p > .20$	58.3	$p < 10^{-21}$
Parental Physical Abuse	2.14 ± 2.44	4.03 ± 2.33	4.86 ± 2.39	$p < .001$	$p < 10^{-11}$	$p > .10$	34.0	$p < 10^{-13}$
Witnessing Interparental Violence	0.67 ± 2.26	1.34 ± 2.16	1.79 ± 2.21	$p > .30$	$p < .003$	$p > .40$	6.7	$p < .01$
Witnessing Violence Toward Siblings	0.19 ± 1.62	0.74 ± 1.55	1.49 ± 1.58	$p > .20$	$p < 10^{-6}$	$p < .02$	17.9	$p < 10^{-7}$
Peer Emotional Bullying	3.0 ± 2.96	6.60 ± 2.84	7.47 ± 2.90	$p < 10^{-8}$	$p < 10^{-12}$	$p > .20$	63.6	$p < 10^{-22}$
Peer Physical Bullying	0.51 ± 2.44	2.57 ± 2.34	2.49 ± 2.39	$p < 10^{-4}$	$p < 10^{-6}$	$p > .90$	20.3	$p < 10^{-8}$
Emotional Neglect	0.87 ± 2.02	1.88 ± 1.93	3.09 ± 1.97	$p < .05$	$p < 10^{-11}$	$p < .002$	33.7	$p < 10^{-13}$
Physical Neglect	0.44 ± 1.82	0.93 ± 1.74	1.62 ± 1.78	$p > .40$	$p < 10^{-4}$	$p < .07$	11.7	$p < 10^{-4}$

Values are presented as mean ± SD. Exposure to maltreatment was controlled for age, sex, parental education, and financial sufficiency. $df = 2,284$ for Age, Parental Education, and Financial Sufficiency; for all other measures, $df = 2,279$.

not differ from control participants in lifetime prevalence of Axis I or II disorders associated with increased aggression.

Network Architecture. There was a significant multivariate group effect on network architecture (PBT = 0.083, $F_{10,596} = 2.594$, $p = .004$). There were significant differences between symptomatic subjects and control subjects (PBT = 0.061, $F_{5,212} = 2.762$, $p < .02$) and between asymptomatic subjects and control subjects (PBT = 0.093, $F_{5,192} = 3.955$, $p < .002$) but not between symptomatic subjects and asymptomatic subjects (PBT = 0.023, $F_{5,182} = 0.856$, $p > .5$). As seen in Figure 1B, there were group differences in univariate measures of global efficiency, degree, vulnerability, and small-worldness.

Differences in Amygdala Centrality Between Symptomatic and Asymptomatic Maltreated Participants

Multivariate connectivity measures were significantly lower in asymptomatic participants than in symptomatic participants on the right side (PBT = 0.045, $F_{3,186} = 2.94$, $p = .035$). Univariate comparisons indicated that these groups differed in measures of N_{eff} ($F_{1,188} = 5.52$, $p < .02$) and degree centrality ($F_{1,188} = 3.94$, $p < .05$) but not closeness ($F_{1,188} = 3.03$, $p = .083$) (Figure 2). Asymptomatic subjects also showed

multivariate differences from control subjects in right amygdala connectivity (PBT = 0.051, $F_{3,200} = 3.57$, $p = .015$), whereas susceptible subjects did not differ from control subjects (PBT = 0.003, $F_{3,220} = 0.20$, $p = .90$). Asymptomatic subjects had significantly lower N_{eff} ($F_{1,200} = 7.84$, $p < .006$), degree centrality ($F_{1,200} = 7.83$, $p < .006$), and closeness ($F_{1,200} = 4.66$, $p < 0.04$) than control subjects. There was no significant main or interactive effect of sex on right amygdala N_{eff} .

Exploratory Differences in Centrality Between Symptomatic and Asymptomatic Maltreated Participants

The elastic net provided a simple five-node model that included right amygdala followed by left frontal inferior pars triangularis, right middle cingulum, right paracentral lobule, and left supplemental motor area (Supplemental Table S2). RFR-CIT provided a nine-node model that independently included all the nodes identified in the elastic net plus left and right olfactory cortex and left and right postcentral gyrus.

As seen in Table 3, the same basic pattern held with lower N_{eff} values for resilient subjects than for susceptible subjects or control subjects for all identified nodes, although not all of these differences were statistically significant. Control subjects and susceptible subjects did not differ on any of these N_{eff}

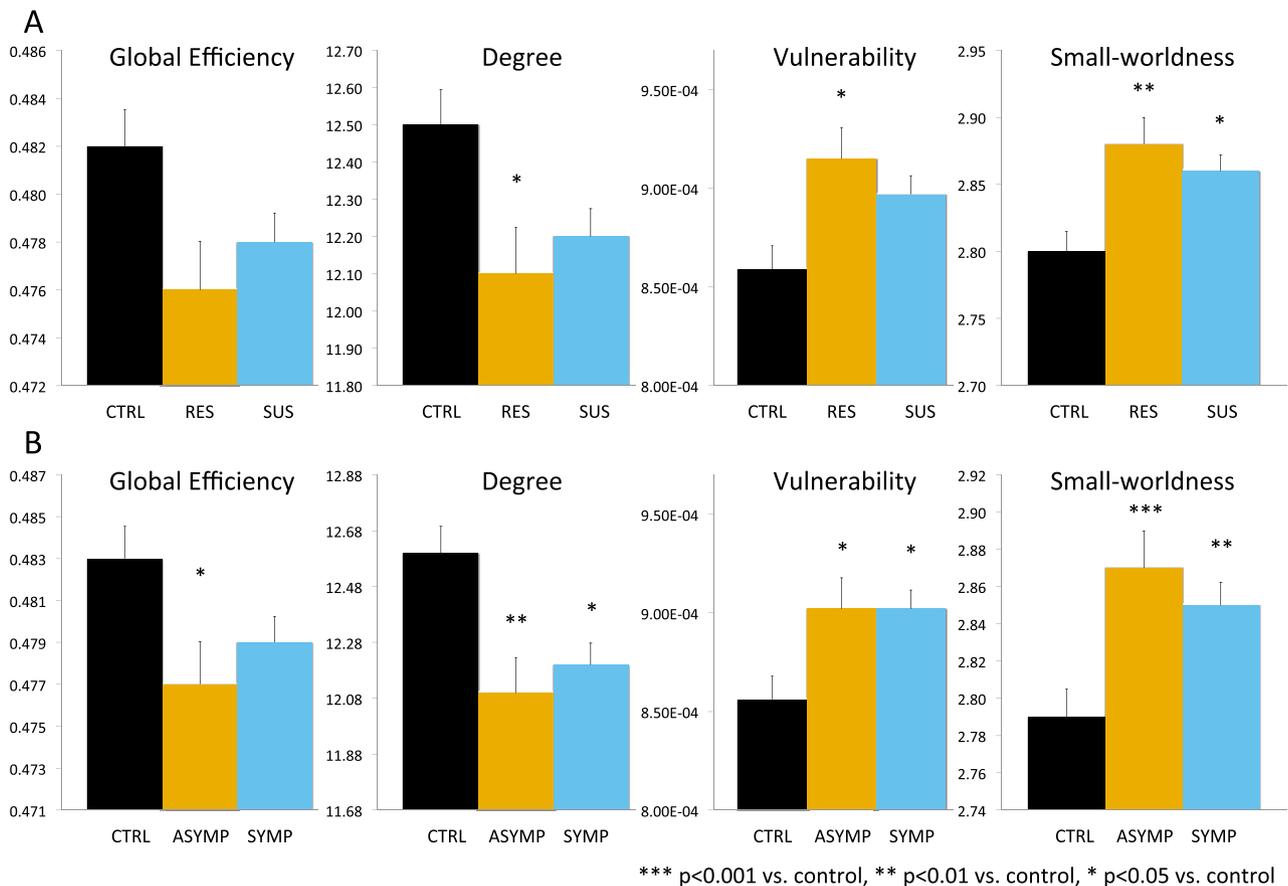


Figure 1. Group differences in global network architecture based on lifetime psychiatric history (A) and current clinically significant symptoms of depression, anxiety, anger-hostility, or somatization (B). CTRL, individuals with no history of maltreatment or Axis I or Axis II DSM-IV disorders; RES, individuals with history of maltreatment but no history of psychopathology; SUS, individuals with history of maltreatment and psychopathology; ASYMP, history of maltreatment but no clinically significant symptoms; SYMP, history of maltreatment and current clinically significant symptoms.

measures. There were no main or interactive effects of sex on N_{eff} in any of these regions.

A key consideration is whether reduced N_{eff} moderates the relationship between maltreatment and psychopathology. Hence, interactive effects of N_{eff} for the nine identified nodes on the association between multiplicity of maltreatment and symptoms of anxiety or depression were assessed using analysis of covariance. As illustrated in Figure 3, there were significant interactive effects such that a strong linear relationship between MACE multiplicity scores and depression or anxiety emerged in individuals with high, but not low, N_{eff} in left frontal inferior pars triangularis. Figure 4 illustrates group differences in primary and secondary network interconnections of the pars triangularis. Similarly, there was a significant interactive effect between N_{eff} in left olfactory area and anxiety ratings ($p < .04$) and left middle cingulum and depression ($p = .05$). These results were not corrected for multiple comparisons owing to the low power of tests for moderation with continuous variables (99). Statistical associations between measures of N_{eff} and scores on Kellner's Symptom Questionnaire are discussed in Correlation Between Measures in the Supplement.

Multiclass Predictive Classification

A key consideration is how well network information can predict class membership. Using RFR-CIT for multiclass classification indicated that measures of global network architecture (i.e., global efficiency, small-worldness, degree, transitivity, and vulnerability) and N_{eff} of 90 nodes were able to correctly categorize control participants, asymptomatic participants, and symptomatic participants in the sample with 97.8% accuracy ($p < 10^{-15}$) and $\kappa = .966$. As seen in Table 4, all groups were identified in the sample with better than 97% balanced accuracy. Cross-validated predictive accuracy was also good with the model identifying the out-of-bag sample with overall accuracy of 71.6% ($p < .02$) and $\kappa = .557$. Balanced accuracy for each class ranged from 79% to 89%.

Restricting the model to five global and nine nodal measures yielded within-sample accuracy of 87.8% and $\kappa = .814$. Cross-validated performance was also highly significant with balanced accuracy for each class ranging from 74.7% to 81.7% versus chance accuracy of 33%. As this approach may lead to overfitting (100) (albeit slight given the sample size), we confirmed the result by dividing the data into balanced training (67% of subjects) and test sets. Selecting the five global

Table 2. Groups Based on Current Symptoms

	Control (1)	Asymptomatic (2)	Symptomatic (3)	1 vs. 2	1 vs. 3	2 vs. 3	F	p
Age, Years	22.0 ± 2.45	21.7 ± 2.45	20.9 ± 2.45	$p < .60$	$p < 10^{-2}$	$p < .08$	5.67	$p < 10^{-2}$
Parental Education, Years	16.6 ± 3.12	14.8 ± 3.12	14.8 ± 3.12	$p < 10^{-3}$	$p < 10^{-4}$	$p > .90$	12.18	$p < 10^{-5}$
Financial Sufficiency During Childhood	3.38 ± 0.85	3.02 ± 0.85	2.62 ± 0.85	$p < .02$	$p < 10^{-9}$	$p < .01$	21.77	$p < 10^{-8}$
Number of Types of Maltreatment	0.34 ± 1.61	3.61 ± 1.60	4.50 ± 1.62	$p < 10^{-11}$	$p < 10^{-11}$	$p < .01$	204.2	$p < 10^{-54}$
Depression	3.23 ± 3.75	4.28 ± 3.72	11.8 ± 3.78	$p < .20$	$p < 10^{-11}$	$p < 10^{-11}$	147.8	$p < 10^{-42}$
Anxiety	4.31 ± 3.43	5.55 ± 3.41	12.7 ± 3.46	$p > .10$	$p < 10^{-11}$	$p < 10^{-11}$	168.8	$p < 10^{-46}$
Somatization	3.77 ± 3.84	4.97 ± 3.81	10.9 ± 3.86	$p > .10$	$p < 10^{-11}$	$p < 10^{-11}$	96.1	$p < 10^{-30}$
Anger-Hostility	3.57 ± 3.49	4.37 ± 3.46	10.2 ± 3.51	$p > .40$	$p < 10^{-11}$	$p < 10^{-11}$	102.3	$p < 10^{-32}$
Sexual Abuse	0.1 ± 1.69	1.21 ± 1.68	1.78 ± 1.70	$p < 10^{-4}$	$p < 10^{-10}$	$p > .10$	28.0	$p < 10^{-10}$
Parental Verbal Abuse	1.43 ± 2.65	6.49 ± 2.63	7.42 ± 2.66	$p < 10^{-11}$	$p < 10^{-11}$	$p > .10$	162.6	$p < 10^{-46}$
Parental Nonverbal Emotional Abuse	1.66 ± 2.00	4.57 ± 1.98	5.25 ± 2.01	$p < 10^{-11}$	$p < 10^{-11}$	$p > .10$	99.8	$p < 10^{-32}$
Parental Physical Abuse	1.92 ± 2.43	4.74 ± 2.41	4.90 ± 2.44	$p < 10^{-11}$	$p < 10^{-11}$	$p > .90$	51.9	$p < 10^{-18}$
Witnessing Interparental Violence	0.23 ± 2.20	1.64 ± 2.18	2.00 ± 2.21	$p < 10^{-4}$	$p < 10^{-6}$	$p > .70$	19.8	$p < 10^{-7}$
Witnessing Violence Toward Siblings	0.03 ± 1.55	1.14 ± 1.54	1.59 ± 1.56	$p < 10^{-5}$	$p < 10^{-10}$	$p > .20$	29.3	$p < 10^{-11}$
Peer Emotional Bullying	3.33 ± 2.84	6.66 ± 2.82	7.59 ± 2.86	$p < 10^{-11}$	$p < 10^{-11}$	$p > .10$	68.2	$p < 10^{-23}$
Peer Physical Bullying	0.54 ± 2.22	2.39 ± 2.21	2.57 ± 2.24	$p < 10^{-7}$	$p < 10^{-8}$	$p > .90$	28.0	$p < 10^{-10}$
Emotional Neglect	0.70 ± 1.98	2.45 ± 1.96	3.18 ± 1.99	$p < 10^{-7}$	$p < 10^{-11}$	$p > .10$	45.6	$p < 10^{-16}$
Physical Neglect	0.19 ± 1.77	1.37 ± 1.76	1.70 ± 1.78	$p < 10^{-4}$	$p < 10^{-7}$	$p > .60$	21.9	$p < 10^{-8}$

Values are presented as mean ± SD. Exposure to maltreatment was controlled for age, sex, parental education, and financial sufficiency. $df = 2,307$ for Age, Parental Education, and Financial Sufficiency. $df = 2,301$ for all other measures.

measures and most important nine nodes that discriminated asymptomatic participants from symptomatic participants in the training set and creating a predictive model on the training set fit the test set with 73%, 79%, and 82% balanced accuracy. See Predictive Multiclass Model in the Supplement for additional information.

DISCUSSION

Susceptible and resilient participants differed markedly from control subjects but not from each other in global network architecture. Hence, maltreatment appears to affect network architecture regardless of psychiatric outcome. Symptomatic participants and asymptomatic participants, however, differed from each other in N_{eff} of the right amygdala and in eight other nodes. Measures of global network architecture and

N_{eff} classified subjects as symptomatic, asymptomatic, or nonmaltreated with good predictive accuracy. Hence, this appears to be a promising approach to understanding neurobiological differences between susceptible and resilient maltreated individuals.

According to this model, both susceptible and resilient individuals have sparse global networks, but resilient individuals differ from susceptible individuals and control subjects in N_{eff} of a small subset of nodes. We propose that one or more of these nodes may function abnormally in susceptible individuals whose sparse network may be unable to compensate for these abnormalities. Alternatively, resilient participants may be able to effectively compensate, as these nodes have a diminished ability to propagate information throughout their network.

Identified nodes have interesting associations with psychopathology. The anterior portion of the middle cingulate cortex

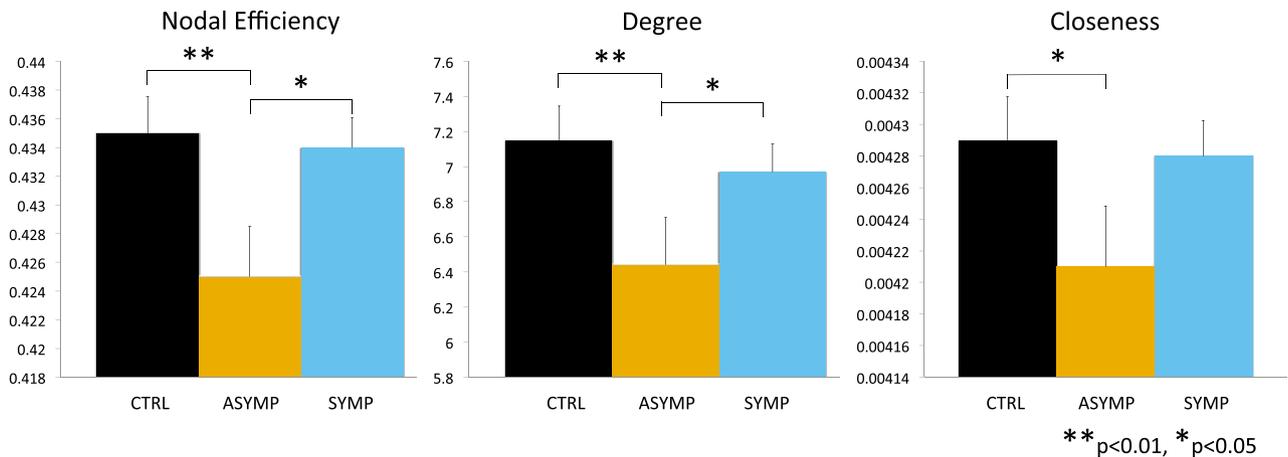


Figure 2. Group differences in centrality of right amygdala based on history of maltreatment and current clinically significant symptoms of depression, anxiety, anger-hostility or somatization. ASYMP, history of maltreatment but no clinically significant symptoms; CTRL, individuals with no history of maltreatment or Axis I or Axis II DSM-IV disorders; SYMP, history of maltreatment and current clinically significant symptoms.

(also known as dorsal anterior cingulate cortex) is the component of the cingulate cortex selectively activated by pain (101) and by stimuli that elicit fear (102) and may be vulnerable to chronic pain and stress syndromes (102). The supplementary motor area is strongly interconnected with the anterior mid-cingulate cortex (103) and plays a critical role in planning and sequencing of movements through its connection to motor cortex. This node, which also contains the pre-supplementary motor area, interconnects with caudate and putamen (104) and appears to be involved in aspects of depression, such as psychomotor retardation (105). Antidepressant response to ketamine is specifically associated with increased blood flow in supplementary motor area and dorsal anterior cingulate cortex (106). The olfactory cortex in the automated anatomical labeling

template corresponds most closely to subcallosal gyrus in the Harvard-Oxford Maximum Probability Atlas and contains portions of Brodmann area 25, which is strongly implicated in the neurobiology of refractory depression (107). Thickness of the pars triangularis correlates with severity ratings in patients with panic disorder (108). Further, the pars triangularis contains a portion of Broca area and could potentially play a role in the self-castigating voices that maltreated individuals often perceive. Reducing N_{eff} of this region may enable maltreated individuals to more effectively compensate by helping to quiet this internal voice. The paracentral lobule is associated with control of urination and defecation, which can be compromised by stress or anxiety. Higher levels of trait anxiety have been associated with stronger interconnections between amygdala and paracentral

Table 3. Group Differences in Nodal Efficiency of Nodes Identified by Random Forest Regression

	Control (1)	Resilient (2)	Susceptible (3)	1 vs. 2	1 vs. 3	2 vs. 3	F	p
Olfactory (R): MNI (x, y, z) = 10, 16, -11	0.491 ± 0.046	0.472 ± 0.046	0.483 ± 0.046	p < .01	p > .10	p > .10	4.64	p < .02
Amygdala (R): MNI (x, y, z) = 27, 1, -18	0.434 ± 0.025	0.425 ± 0.025	0.435 ± 0.025	p < .02	p > .80	p < .01	4.33	p < .02
Frontal Inferior Triangularis (L): MNI (x, y, z) = -46, 30, 14	0.443 ± 0.030	0.434 ± 0.030	0.445 ± 0.030	p < .02	p > .60	p < .01	3.64	p < .03
Postcentral Gyrus (L): MNI (x, y, z) = -42, -23, 49	0.505 ± 0.028	0.495 ± 0.028	0.501 ± 0.028	p < .02	p > .20	p > .10	3.41	p < .04
Olfactory (L): MNI (x, y, z) = -8, 15, -11	0.482 ± 0.047	0.467 ± 0.047	0.479 ± 0.047	p < .03	p > .50	p < .08	2.95	p < .06
Midcingulate Area (R): MNI (x, y, z) = 8, -9, 40	0.513 ± 0.032	0.504 ± 0.032	0.514 ± 0.032	p < .06	p > .80	p < .02	2.74	p < .07
Paracentral Lobule (R): MNI (x, y, z) = 7, -32, 68	0.424 ± 0.017	0.421 ± 0.017	0.426 ± 0.017	p > .10	p > .30	p < .04	2.34	p < .10
Supplementary Motor Area (L): MNI (x, y, z) = -5, 5, 61	0.428 ± 0.030	0.423 ± 0.030	0.432 ± 0.030	p > .20	p > .30	p < .04	2.28	p < .10
Postcentral Gyrus (R): MNI (x, y, z) = 41, -25, 53	0.499 ± 0.025	0.495 ± 0.025	0.501 ± 0.025	p > .30	p > .40	p > .10	1.41	p > .20

Values are presented as mean ± SD, which have been adjusted to remove variance attributable to age and sex. *df* = 2,301 for all analyses. L, left; MNI, Montreal Neurological Institute; R, right.

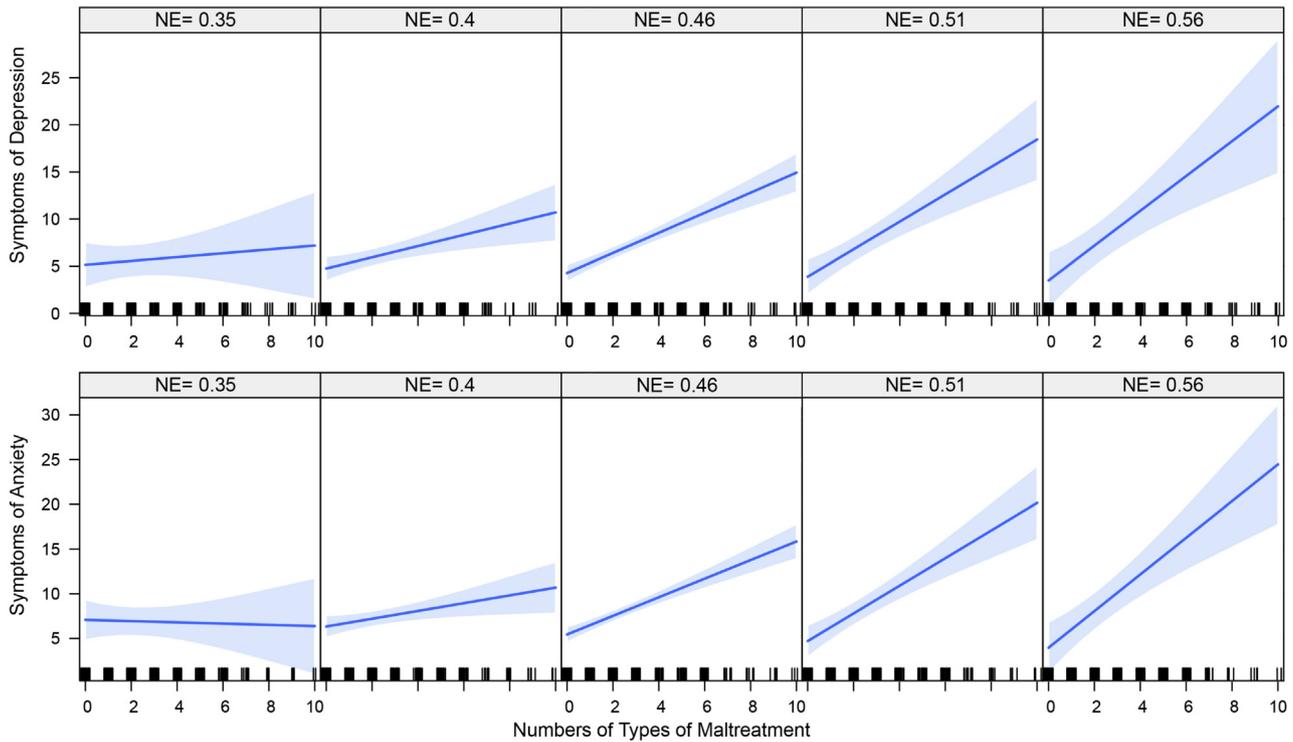


Figure 3. Moderating influence of nodal efficiency (NE) of left inferior triangularis on relationship between multiplicity of exposure to maltreatment and current symptoms of depression ($F_{1,317} = 4.45, p < .04$) and anxiety ($F_{1,317} = 8.30, p = .004$) on Kellner's Symptom Questionnaire. The plots derive from the analysis of covariance model and show the slope of the relationship between Maltreatment and Abuse Chronology of Exposure score and symptom ratings with nodal efficiency fixed at values ranging from lowest to highest at equally spaced intervals.

lobule and between amygdala and dorsal anterior cingulate cortex (109).

We do not know if reduced N_{eff} was a compensatory adaptation that enabled some individuals to regain mental

well-being following exposure to maltreatment or if low N_{eff} was a preexisting protective factor. Longitudinal studies have identified different trajectories of recovery in trauma-exposed individuals. Bonanno and Diminich (110) identified two

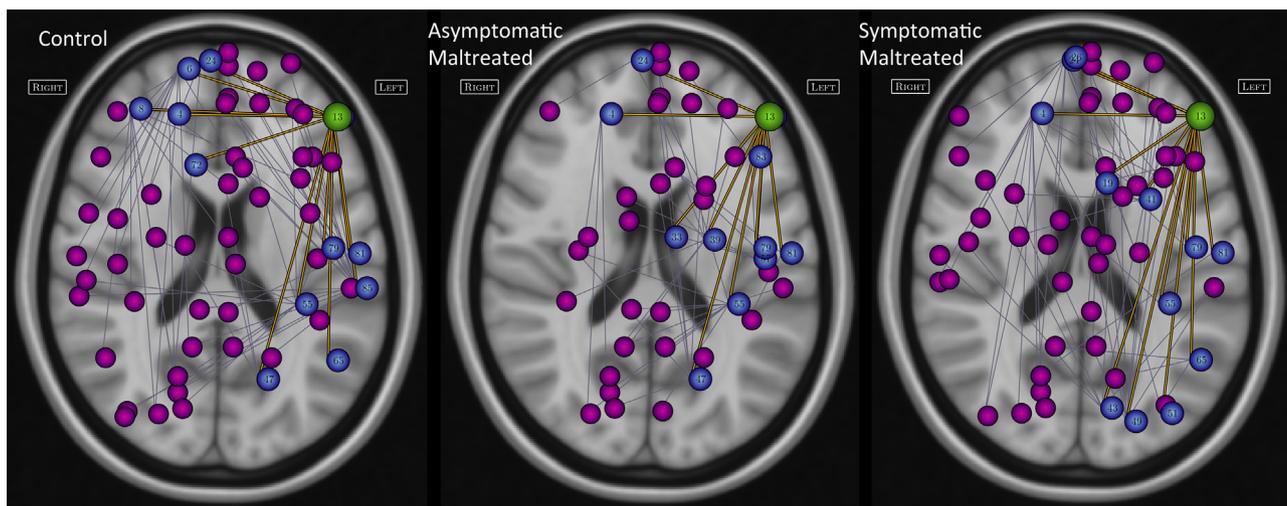


Figure 4. Differences in primary and secondary nodal interconnections of the left inferior frontal gyrus pars triangularis in control, asymptomatic maltreated, and symptomatic maltreated groups. Pars triangularis is illustrated, as this node emerged as the most significant moderator of the relationship between exposure to maltreatment (number of different types) and current symptoms of depression and anxiety. Green circle identifies the location of the pars triangularis, blue circles indicate primary interconnections, and magenta circles indicate secondary interconnections. Region name corresponding to nodal numbers can be found in the automated anatomical labeling system (91).

Table 4. Multiclass Classification Within Actual Sample and Within Cross-Validated Out-of-Bag Samples

	Class: Control	Class: Resilient	Class: Susceptible	Overall Measures
Global Measures Plus 90 Nodes				
Within sample				
Sensitivity	0.947 ± 0.009	0.996 ± 0.006	1.000 ± 0.000	Accuracy: 0.978 ± 0.004
Specificity	0.998 ± 0.003	0.978 ± 0.004	0.993 ± 0.004	<i>p</i> value: < 10 ⁻¹⁵
Balanced accuracy	0.973 ± 0.005	0.987 ± 0.003	0.996 ± 0.002	κ : .966 ± .006
Cross-validated (OOB)				
Sensitivity	0.601 ± 0.018	0.978 ± 0.016	0.884 ± 0.031	Accuracy: 0.716 ± 0.019
Specificity	0.985 ± 0.009	0.803 ± 0.008	0.861 ± 0.018	<i>p</i> value: .018 ± .062
Balanced accuracy	0.793 ± 0.011	0.891 ± 0.009	0.873 ± 0.02	κ : .557 ± .03
Global Measures Plus 9 Nodes				
Within sample				
Sensitivity	0.876 ± 0.012	0.935 ± 0.012	0.848 ± 0.012	Accuracy: 0.878 ± 0.007
Specificity	0.94 ± 0.007	0.909 ± 0.007	0.976 ± 0.005	<i>p</i> value: < 10 ⁻¹⁵
Balanced accuracy	0.908 ± 0.007	0.922 ± 0.007	0.912 ± 0.007	κ : .814 ± .011
Cross-validated (OOB)				
Sensitivity	0.623 ± 0.012	0.793 ± 0.041	0.749 ± 0.018	Accuracy: 0.69 ± 0.01
Specificity	0.871 ± 0.011	0.801 ± 0.004	0.884 ± 0.01	<i>p</i> value: < 10 ⁻⁷
Balanced accuracy	0.747 ± 0.009	0.797 ± 0.022	0.817 ± 0.011	κ : .521 ± .015

Values are presented as mean ± SD.
OOB, out-of-bag.

resilience patterns—minimal impact and emergent resilience. Low N_{eff} in specific nodes before acute exposure may predispose individuals to show a minimal impact resilience pattern. In contrast, adaptive changes in N_{eff} over time may be more characteristic of individuals following an emergent resilience pattern with gradual abatement of symptoms following exposure.

Interestingly, Kozisek *et al.* (111) postulated that antidepressants work by increasing brain-derived neurotrophic factor, which enhances neural plasticity, thus allowing for therapeutic alterations in network connections. Our findings suggest that diminishing N_{eff} in these specific nodes may be a potentially beneficial neuroplastic change. It would be important to ascertain if this occurs following successful treatment.

A few prior studies have identified neurobiological differences between susceptible and resilient maltreated participants. De Bellis *et al.* (112) and Morey *et al.* (113) compared maltreated children with and without posttraumatic stress disorder (PTSD) and found that children with PTSD had decreased right ventromedial prefrontal, posterior cerebral, and cerebellar gray matter volumes. In contrast, children without PTSD had larger left amygdala and right hippocampal volumes. Herringa *et al.* (114) found that relatively resilient maltreated youths (fewer internalizing symptoms) had greater prefrontal-amygdala interconnectivity to negative images than more susceptible maltreated youths or control subjects. This finding suggests that reducing amygdaloid influence on the global network and enhancing top-down regulation of the amygdala each may lead to symptom attenuation. These findings are consistent with our observation that susceptible and resilient individuals differ in a small number of regions or pathways that may facilitate compensation.

Our theoretical model posits that psychopathology emerges from the two-hit combination of vulnerable network architecture and abnormal nodal function. A key question is which hit

comes first. We have previously reported that right amygdala volume was most significantly affected by exposure to maltreatment at 10 to 11 years of age (115). We also reported that fiber tracts that differed most strongly between maltreated individuals and control subjects were primarily association and corticolimbic pathways (66) that continue to actively myelinate during adolescence and early adulthood and may be particularly vulnerable at that time (116,117). Hence, it may be the case that nodal abnormalities precede a developmental change in global network architecture that occurs during adolescence or early adulthood and may help explain the marked increase in prevalence of certain psychiatric disorders that occurs during this time (118).

Strengths of this study include a large sample of carefully assessed and unmedicated participants who were recruited from the community and who underwent imaging on the same scanner. Another strength is the comprehensive assessment of maltreatment using MACE, which assesses exposure to types of maltreatment not included in prior instruments.

A common limitation in resilience research is that resilient individuals are often exposed to lower levels of adversity than susceptible individuals (119), and this was a problem using criterion 1. Criterion 2 identified subjects who were resilient by criterion 1 but also included participants who experienced a diagnosable disorder but were now recovered. Interestingly, the key concern in having a resilient group with a lower degree of exposure than the susceptible group is that weaker effects in the resilient group may be secondary to their weaker degree of exposure. This was not a concern, as the resilient group had abnormalities in global network architecture that were at least as strong as abnormalities seen in the susceptible group. Further, the asymptomatic participants had much greater alterations in N_{eff} in key nodes than symptomatic participants despite their slightly lower degree of exposure to adversity. Our susceptible/symptomatic and resilient/asymptomatic groups

were heterogeneous in lifetime diagnoses, and participants within each group varied in exposure histories. More nuanced group differences may be discernible in studies that focus on circumscribed categories, such as trauma-exposed children with and without PTSD (113). Another limitation is reliance on retrospective self-report, which theoretically could be affected by memory impairment associated with psychopathology and mood-congruent memory biases. In a detailed review, Brewin *et al.* (120) found little evidence to support these criticisms. Retrospective reports of abuse are verifiable (121), and modern instruments for assessing maltreatment all show impressive test-retest reliability [e.g., Childhood Trauma Questionnaire, $r = .88$ (122); MACE, $r = .91$ (84)].

In conclusion, the finding that maltreated individuals without psychopathology have basically the same array of neuroimaging abnormalities as maltreated individuals with psychopathology has been perplexing (123). The present findings provide a potential answer to the puzzle by identifying additional abnormalities in resilient individuals that may enable them to effectively compensate. This is novel and important information, as it suggests that efforts to treat maltreated individuals with psychopathology do not have to focus on reversing maltreatment-related alterations, but may instead foster specific nodal changes that bring the circuitry of these individuals more into line with the circuitry of resilient individuals.

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