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Childhood Maltreatment is Associated with a Sex-Dependent Functional Reorganization of a Brain Inhibitory Control Network

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Abstract: Childhood adversity represents a major risk factor for drug addiction and other mental disorders. However, the specific mechanisms by which childhood adversity impacts human brain organization to confer greater vulnerability for negative outcomes in adulthood is largely unknown. As an impaired process in drug addiction, inhibitory control of behavior was investigated as a target of childhood maltreatment (abuse and neglect). Forty adults without Axis-I psychiatric disorders (21 females) completed a Childhood Trauma Questionnaire (CTQ) and underwent functional MRI (fMRI) while performing a stop-signal task. A group independent component analysis identified a putative brain inhibitory control network. Graph theoretical analyses and structural equation modeling investigated the impact of childhood maltreatment on the functional organization of this neural processing network. Graph theory outcomes revealed sex differences in the relationship between network functional connectivity and inhibitory control which were dependent on the severity of childhood maltreatment exposure. A network effective connectivity analysis indicated that a maltreatment dose-related negative modulation of dorsal anterior cingulate (dACC) activity by the left inferior frontal cortex (IFC) predicted better response inhibition and lesser attention deficit hyperactivity disorder (ADHD) symptoms in females, but poorer response inhibition and greater ADHD symptoms in males. Less inhibition of the right IFC by dACC in males with higher CTQ scores improved inhibitory control ability. The childhood maltreatment-related reorganization of a brain inhibitory control network provides sex-dependent mechanisms by which childhood adversity may confer greater risk for drug use and related disorders and by which adaptive brain responses protect individuals from this risk factor. *Hum Brain Mapp 35:1654–1667, 2014.* © 2013 Wiley Periodicals, Inc.

Key words: functional brain imaging; sex differences; inhibition; child neglect; child abuse; adult survivors; drug addiction; psychological adaptation

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INTRODUCTION

Childhood adversity represents a major risk factor for the development of drug use disorders [Green et al., 2010; Kessler et al., 1997] and other health risk behaviors and psychopathologies [Green et al., 2010; Heim et al., 2004; Nanni et al., 2012]. Moreover, there exists a dose–effect relationship between childhood traumatic experiences and drug use disorders with greater cumulative [Dube et al., 2003; Turner and Lloyd, 2003] or more severe [Schilling et al., 2008] childhood adversity associated with increased risk for drug use problems. The consistent finding of negative psychiatric outcomes and enormous economic burden associated with childhood adversity has led to a call for public health efforts to develop intervention programs focused on primary prevention [Fang et al., 2012; McLaughlin et al., 2010]. The development of such prevention measures is hindered, however, by a currently limited understanding of the neurodevelopmental outcomes that translate childhood adversity into poor mental health in later life. The premise of the current study is that a characterization of the effects of childhood trauma on neurodevelopmental outcomes is critical to understanding and modifying the relationship of this established risk factor to a multitude of negative health outcomes.

As part of a larger investigation of the mechanisms of risk for drug use disorders, this study sought to specifically investigate the impact of childhood trauma on neurocognitive functions that are impaired in drug abuse and dependence. Chronic drug abuse has been associated with cognitive deficits [Madoz-Gúrpide et al., 2011], particularly for executive functions related to inhibitory behavioral control [Colzato et al., 2007]. These associations are consistent with the diagnostic hallmark of drug addiction pertaining to the inability to control urges for drug use [Everitt and Robbins, 2005; Kalivas and Volkow, 2005] and is supported by neuroimaging findings of alterations in the neural response to demands for response inhibition [Kaufman et al., 2003; Li et al., 2007]. Importantly, neural and behavioral indicators of inhibitory control deficits in adolescence predict later drug use problems [Nigg et al., 2006; Norman et al., 2011; Tarter et al., 2004], indicating the potential value of such measures as markers of risk for drug use disorders. Impairments in behavioral inhibition have likewise been identified in victims of childhood abuse or neglect [Brodsky et al., 2001; Chugani et al., 2001; Grilo et al., 1999; Mueller et al., 2010]. Therefore, this study focused on elucidating the effects of childhood maltreatment on neural and behavioral measures of inhibitory control to identify potential neurocognitive markers of vulnerability for drug addiction associated with this risk factor. Although there is an emerging human functional neuroimaging literature pertaining to childhood adversity [Dannlowski et al., 2012; Dillon et al., 2009; Mueller et al., 2010], knowledge of the underlying neural representation of inhibitory control deficits resulting from childhood trauma remains limited. Inhibitory control is an executive function that develops throughout childhood and adolescence [Cohen et al., 2010; Fair et al., 2007; Rubia et al., 2006]. This study sought to test the hypothesis that a heightened risk for drug use and other disorders associated with childhood adversity is due, at least in part, to neurodevelopmental alterations in the functional organization of neural information processing correlates of inhibitory behavioral control.

Moreover, we hypothesized that the neurodevelopmental effects of childhood maltreatment on inhibitory control processes differ significantly between the sexes. This hypothesis is partly predicated on findings that adult males and females differ in neural processing strategies to exert control over prepotent motor responses [Li et al., 2006, 2009]. Furthermore, there is a developing literature of sex differences in trauma-related outcomes [Campbell-Sills et al., 2009; DeSantis et al., 2011; Everaerd et al., 2012; Felmingham et al., 2010], potentially related to sex differences in neurodevelopmental responses to childhood maltreatment [Christakou et al., 2009, De Bellis et al., 2001; Schmithorst et al., 2008]. In particular, females are more vulnerable to many of the negative psychiatric consequences of childhood adversity [Edwards et al., 2003; Holbrook et al., 2002; Kilpatrick et al., 2003; MacMillan et al., 2001; Scher et al., 2004]. Therefore, we hypothesized that a history of childhood maltreatment would negatively impact behavioral measures of inhibitory control in maltreated individuals, particularly so for females, but that the neural processing correlates of this behavioral deficit would exhibit qualitative sex differences.

To test the study hypotheses, 40 adult men and women with a range of exposure to childhood abuse and/or neglect but without drug use or other Axis I disorders underwent functional magnetic resonance imaging (fMRI) while performing a stop-signal task. As a laboratory measure of inhibitory control, stop-signal tasks test an individual's ability to inhibit a prepotent motor response [Logan and Cowan, 1984]. A brain inhibitory control network identified by independent component analysis (ICA) was subjected to graph theoretical and structural equation modeling (SEM) analyses. Stop-signal reaction times and a self-report measure of childhood maltreatment were incorporated into analyses to link maltreatment-related changes in neural processing to the inhibitory control of behavior.

METHODS AND MATERIALS

Subjects

Forty individuals [21 females, 29.6 $\pm$ 7.9 (mean $\pm$ standard deviation) years of age, 38 right-handed] were enrolled in the study. Subjects were recruited from local newspaper advertisements, flyers posted in the community, and advertisements displayed in Little Rock city buses targeting individuals with childhood maltreatment histories and healthy controls. Following a discussion of study procedures, subjects provided informed consent to participate in the study, which was approved by the Institutional

Review Boards at Emory University and the University of Arkansas for Medical Sciences (UAMS).

Inclusion/exclusion criteria

Men and women between the ages of 18 and 45 were included in the study. Subjects were free of psychotropic medication, major medical disorders, and did not have a history of loss of consciousness greater than 10 min. A Masters-level trained clinical interviewer conducted a Structured Clinical Interview for DSM-IV Axis I disorders (SCID) [First et al., 2007]. Participants did not meet criteria for past or current DSM-IV drug abuse or dependence or other Axis I disorders with the exception that past mood disorders were permitted. Urinalyses to detect recent cocaine, methamphetamine, amphetamine, opiate, and cannabis use were conducted on the day of the fMRI scan and corroborated the non-drug abusing status of subjects defined by the SCID.

The specific childhood adversity investigated by this study was childhood maltreatment—specifically forms of abuse and neglect. To assess childhood maltreatment exposure, all subjects completed a 28-item Childhood Trauma Questionnaire [Bernstein et al., 2003], which uses a five-point Likert scale of severity and provides a quantitative measure of childhood physical, emotional, and sexual abuse, and physical and emotional neglect. The CTQ has good internal consistency, classification accuracy, and validity in drug-abusing populations [Bernstein et al., 1997, 2003; Thombs et al., 2007]. Due to the dose-dependent association of exposure to multiple types of trauma with poor health outcomes [Felitti et al., 1998; Huang et al., 2012], and because the CTQ subscales load onto a higher-order factor [Scher et al., 2001], a CTQ total score was calculated as the sum of scores from each maltreatment subtype. Each of the five CTQ subscales has a possible range of 5 to 25. Total CTQ scores range from 25 to 125. Normative data from a community sample calculated 50th percentile CTQ total scores as 28 for females and 29 for males, with means of approximately 32 for both sexes [Scher et al., 2001].

Drug use disorders and ADHD are highly comorbid [Ohlmeier et al., 2008]. The 66-item Conners Adult ADHD Rating Scale–Self-Report: Long Version (CAARS) [Conners et al., 1998] was also administered, and scores corresponding to DSM-IV ADHD inattentive symptoms (nine items, possible range: 0–27), DSM-IV ADHD hyperactive-impulsive symptoms (nine items, possible range: 0–27), and DSM-IV ADHD total symptoms (18 items, possible range: 0–54) were calculated. The CAARS served as a measure of clinically relevant symptoms of impulsivity and inattention and enabled group-matching for subclinical symptoms of ADHD.

fMRI Task

Study subjects underwent fMRI while engaged in a visual, performance-adjusted stop-signal task. Subjects were instructed to press a single button with the index finger of their dominant hand as quickly as possible whenever an alphabetical letter (go stimulus) appeared on the screen but to withhold their response when the stop signal (a white square) appeared around the letter. The inter-trial interval was fixed at 2,000 ms. The stop signal appeared in 75 of the 300 trials (225 go trials) following a short delay. The stop signal delay (SSD) was initially set to 250 ms and increased by 50 ms following a successful stop trial or decreased by 50 ms following an error of commission on a stop trial. This adjusting procedure was designed to obtain a successful stopping rate of approximately 50% [Aron and Poldrack, 2006; Rubia et al., 2003]. Three 20-s rest periods were presented throughout the 16.6 min task scan.

Behavioral Measures

Stop-signal reaction time (SSRT) was calculated by subtracting the mean SSD from the nth percentile largest go-trial reaction time where n is the successful stop rate. Non-responses to the go stimulus can lead to a greater probability of non-responses on stop trials, thereby artificially increasing the rate of successful stops. Due to variability in the go response rate (i.e. errors of omission), the calculation of the successful stop rate was adjusted for the go response rate according to the following algorithm:

$$\text{Successful Stop Rate} = \frac{g \times \text{ss}}{g \times \text{ss} + e,}$$

where g is the go response rate, ss is the number of successful stops on stop trials, and e is the number of errors of commission on stop trials.

Post-error slowing rates were also calculated to further enable group comparisons for stop-signal task performance. Post-error slowing was defined as the percentage reaction time increase for go trials that followed an error of commission on a stop trial relative to the mean reaction time for go trials that did not follow a stop trial.

The relationship of sex and CTQ to SSRT were tested in ordinary least squares (OLS) regression analyses in SAS 9.2.

fMRI Acquisition

Of the 40 subjects, 15 subjects (nine females) were scanned with a Philips Achieva 3T MRI in the Brain Imaging Research Center (BIRC) at UAMS and 25 subjects (12 females) were scanned with a Siemens Trio 3T MRI in the Biomedical Imaging Technology Center (BITC) at Emory University. For each imaging session, 498 functional T2*-weighted echo-planar images (EPIs) were acquired using the following parameters: 3x3x3 mm^3 voxels, TR = 2,000 ms, TE = 30 ms, FOV = 192 × 192 mm^2, flip angle = 90°, matrix = 64 × 64, 34 slices. Although identical scan parameters were used to acquire imaging data at both sites, the alternating slice acquisition sequence differed between the Siemens and Philips scanners.

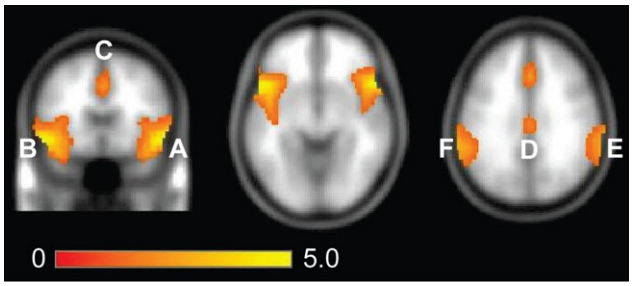
fMRI Data Preprocessing

fMRI data were preprocessed using Statistical Parametric Mapping version 8 software (SPM8; Wellcome Department of Imaging Neuroscience, University College London, UK) in Matlab R2010a software. Preprocessing included slice time correction, motion correction, normalizing to an EPI template in MNI space, and 8 mm full width at half maximum Gaussian smoothing.

Independent Component Analysis (ICA)

The fMRI data analysis involved a step-wise plan of data dimensionality reduction to test the primary study hypothesis that that childhood maltreatment is associated with significant alterations in behavioral and neural processing of inhibitory behavioral control and that these effects differ significantly between the sexes. This approach was selected due to its greater ability to define brain-behavior relationships relative to traditional mass univariate (voxel-wise) analyses [Congdon et al., 2010]. ICA is a data-driven, multivariate statistical technique, which, when applied to fMRI data, can separate out spatial and temporal sources of neural activation. A group ICA on stop-signal task time courses was performed using the Group ICA of fMRI Toolbox version 2 (GIFT) ([Calhoun et al., 2001] implemented in Matlab, solving for 30 components. This technique identified components representing spatially-independent networks of brain activation. For each subject, the modeled blood oxygen level-dependent (BOLD) responses for six trial types [successful stop trials, errors of commission, post-successful stop go trials, post-error go trials, go trials (not following a stop trial), and misses] were used in regression analyses in GIFT as predictors of the time course for each component, controlling for six directions of motion. For this analysis, the canonical hemodynamic response function was convolved with the experimental design (each trial type was modeled as a stick function), and the statistical association of each trial type with each component time course was estimated for each subject. This method is analogous to a general linear model analysis applied in a voxel-wise approach to task-related fMRI data. However, rather than using voxel time courses, component time courses were used, thereby identifying the association of networks rather than individual voxels to each trial type.

We next identified candidate neural processing networks for further investigation of the impact of childhood maltreatment on inhibitory behavioral control. Values for the contrast of successful stop trials minus go trials (not following stop trials) were calculated from the beta estimates for the respective trial types. This trial type-specific contrast was chosen to isolate those neural processes recruited during the inhibition of motor responses, while controlling for those related to sensory and attentional aspects of task performance. A one-sample *t*-test of these contrast values for each of the 30 ICA components identified 11 components that were significantly more active during successful stop versus go trials. Aside from a component attributed to visual processing, the most significantly activated component ($t = 6.18$, $P < 0.001$) represented a network of activation that involved the bilateral inferior frontal cortex (pars orbitalis)/insular cortex, dorsal anterior and middle cingulate cortex, and bilateral inferior parietal cortex/supramarginal gyrus (Fig. 1). This component comprised brain regions identified by the brain-wide analysis of successful stop–go trials (Supporting Information Table I) and was similar spatially to a network previously reported to be negatively correlated with SSRT [Congdon et al., 2010] and was therefore designated as an "inhibitory control network."



Label	Anatomic Region	BA	X	Y	Z
A	R inferior frontal gyrus	47	45	17	-17
B	L inferior frontal gyrus	47	-45	11	-14
C	dorsal anterior cingulate cortex	24	3	17	28
D	middle cingulate cortex	24	3	-25	34
E	R supramarginal gyrus	40	63	-40	28
F	L supramarginal gyrus	40	-57	-46	31

Figure 1.

Illustration (top) and localization (bottom) of brain regions comprising a putative inhibitory control network defined by independent component analysis (ICA). Results displayed as Z-scores with a threshold minimum of 1.0 for visualization purposes. Coordinates correspond with the location of nodes and are reported in MNI standard space. BA, Brodmann area; L, left; R, right.

To investigate the effects of childhood maltreatment on the activation of this functional network during response inhibition, successful stop–go contrast values for the component were used as dependent variables in OLS regression analyses in SAS 9.2 with CTQ total scores, SSRT, and sex as predictors, controlling for age and scan site.

Graph Theory

As an fMRI data analysis approach, graph theory is applied to investigate the spatial organization or topology of functional brain networks and graph indices are calculated based on the correlation matrix of the brain regions (nodes) within a network [Bullmore and Sporns, 2009].

TABLE I. Clinical and stop-signal task performance variables

	Males (19)		Females (21)	
	Mean	SD	Mean	SD
Age (yr)	31.7	7.8	27.6	7.8
Education (yr)	15.7	1.9	15.8	2.1
CTQ Physical Abuse	7.1	3.2	7.5	3.6
CTQ Emotional Abuse	8.6	3.6	9.8	6.0
CTQ Sexual Abuse	6.1	4.6	7.5	5.1
CTQ Physical Neglect	6.6	2.7	6.8	2.4
CTQ Emotional Neglect	8.2	3.8	8.9	4.5
CTQ Total	36.6	13.1	40.4	16.9
DSM-IV Inattentive Symptoms (CAARS E)	5.4	4.7	3.9	2.8
DSM-IV Hyperactive-impulsive Symptoms (CAARS F)	6.9	4.8	5.1	3.6
DSM-IV ADHD Total Symptoms (CAARS G)	12.4	9.1	9.0	5.6
Stop Signal Reaction Time (ms)	197	46	208	55
Average Go Trial Reaction Time (ms)	592	223	690	213
Average Stop Signal Delay (ms)	421	238	521	203
Post-Error Slowing (%)	14	12	15	9
Successful Stop Rate (%)	43	9	46	12
Go Response Rate* (%)	98	2	95	5

Males and females did not differ ($P > 0.05$) on age, education, childhood maltreatment exposure, ADHD symptoms. Males and females differed in go response rate ($P = 0.019$) but no other stop-signal task performance variable.

*Denotes statistically significant ($P < 0.05$) sex difference.ADHD, attention deficit hyperactivity disorder; CAARS, Conners Adult ADHD Rating Scale; CTQ, Childhood Trauma Questionnaire; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ms, milliseconds; SD, standard deviation.

This approach was applied to explore the impact of childhood maltreatment on inhibitory control network functional connectivity. The nodes of the network were defined by six 6 mm radius spheres drawn in Analysis of Functional Neuroimages (AFNI) software on those peak activations of the inhibitory control network component surviving a *Z*-score threshold of 2.0; coordinates for these network nodes are reported in Figure 1. Singular value decomposition was used to extract the first principle component time course of each node, from which a 6×6 correlation matrix was constructed. From this matrix, strength, a measure of network connectivity, was calculated as the average absolute value of the correlation of each node to every other node in the network.

From the network correlation matrix, an adjacency matrix was calculated, representing the binary connection (or "edge") of each node to every other node in the network. Three graph theoretical measures of network topology—degree, betweenness centrality, and leverage centrality—were calculated from the adjacency matrix [Bullmore and Sporns, 2009]. Degree is defined as the total number of edges that exist between one node and every other node in the network. Betweenness centrality describes the "hub"-like quality of a node and is defined as the number of shortest paths that pass through a given node, relative to all shortest paths between two nodes. Another measure of centrality, leverage centrality [Joyce et al., 2010], describes the influence of a node on all other nodes in the network, and is defined by the degree of one node relative to the degree of all other nodes in the network. In order to compare graph indices between individuals, a consistent network density (or percentage of edges) should exist. The correlation value corresponding to a given density is used as a threshold to compute the adjacency matrix. Degree, betweenness centrality, and leverage centrality were calculated from 14 adjacency matrices created by a range of densities between 0.37 and 0.5 in increments of 0.01 [Lynall et al., 2010] and averaged for each node. We utilized Proc Glimmix of SAS 9.2 with repeated measures over nodes to determine the ability of CTQ total scores, SSRT, and sex and their interactions, controlling for scan site, age, and node, to predict the different graph indices for the network.

An a priori hypothesis of this study was that greater childhood maltreatment exposure would be associated with decreased network connectivity which would result in longer SSRTs (i.e., poorer inhibitory control ability). We further anticipated childhood maltreatment to be associated with sex differences in the specific nodes affected and/or the extent to which network connectivity would be diminished. Unexpectedly, the direction of the effect of childhood maltreatment exposure on the relationship between the graph index of network strength and SSRT was opposite in males (increased) versus females (decreased). This finding prompted an extended investigation of the connectivity of this network to further explore this sex effect.

Structural Equation Modeling (SEM)

In order to investigate a potential mechanism of altered effective connectivity within the inhibitory control network by which CTQ scores, sex, and SSRT interact to predict network strength, network path analyses were performed for male and female participants separately using SAS Proc Tcalis. Structural equation modeling applied to fMRI data describes the functional relationships of brain regions within a network [Caceda et al., 2011; Schlösser et al., 2006]. Path coefficients indicating the strength of the connectivity between brain regions are calculated for each directional path according to the covariance matrix but constrained by the specified anatomical model. In this case, structural equation models were developed using fMRI time courses from the six nodes of the inhibitory control network for each sex. The models were then used in a subgroup analysis to compare network organization in men and women with lower versus higher childhood

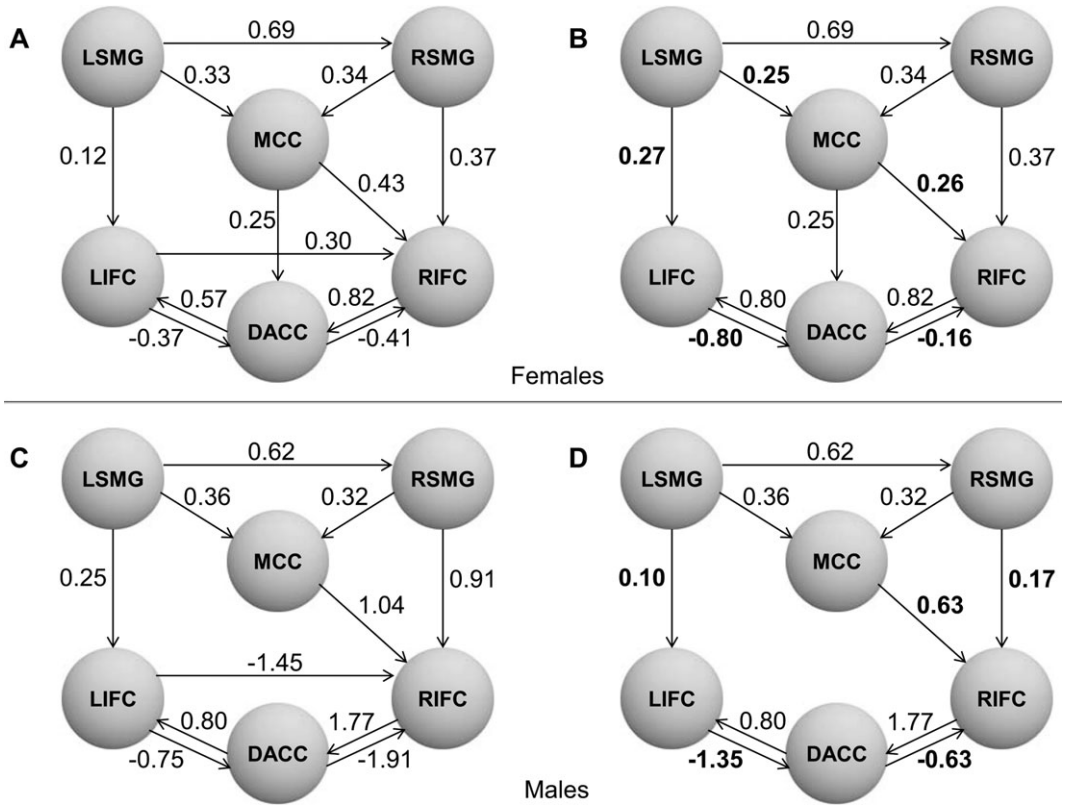


Figure 2.

Path models of the effects of childhood maltreatment and sex on the effective connectivity of a putative inhibitory control network. Structural equation models of network effective connectivity for females with (**A**) lower Childhood Trauma Questionnaire (CTQ) scores and (**B**) higher CTQ scores and males with (**C**) lower CTQ scores and (**D**) higher CTQ scores. Path coefficients that differed ($P < 0.05$) between females with higher versus lower CTQ scores are bolded in B. Path coefficients that differed ($P < 0.05$) between males with higher versus lower CTQ scores are bolded in D. Subsequent analyses focused on three paths connecting LIFC, RIFC, and DACC that differed between models for subgroups with higher versus lower CTQ scores. Accordingly, coefficients for LIFC→DACC, LIFC→RIFC, and DACC→RIFC paths were estimated for each subject. DACC, dorsal anterior cingulate cortex; LIFC, left inferior frontal cortex; LSMG, left supramarginal gyrus; MCC, middle cingulate cortex; RIFC, right inferior frontal cortex; RSMG, right supramarginal gyrus.

maltreatment exposure. A median split analysis fit a model to 11 females with lower CTQ scores (range: 25–33; mean: 27.4) while attempting to fit the same model to 10 females with higher CTQ scores (range: 38–74; mean: 56.7). This same approach was applied to males, generating a model fitting data from 10 males with lower CTQ scores (range: 25–31; mean: 27.7) and 9 males with higher CTQ scores (range: 32–68; mean: 46.4). The CTQ total score median values for this sample of men (median = 31) and women (median = 33) are consistent with values in the 50th to 75th percentile range for a normative sample, and the upper values of the higher CTQ score subgroups for both sexes exceed the 95th percentile [Scher et al., 2001]. Wald statistics identified non-significant paths to be removed from either or both of the subgroup models. Lagrange multiplier indices provided potential paths for which the higher CTQ score group differed from the lower CTQ score group and thus could be freed and estimated independently for each model. This approach to refining anatomical models identified four models, one for each sex and CTQ score subgroup (Fig. 2A–D), with acceptable fit statistics.

For males and females separately, individual subject path coefficients for selected paths that most differed between the two subgroup models for each sex were obtained by individually freeing selected paths to obtain estimates for each subject while fixing the remaining path coefficients to be equal to the sex-specific group estimate. Correlation analyses tested the linear relationship of CTQ scores to each of these paths for males and females. We also tested the correlation of path coefficients with network strength to determine the contribution of individual paths to this affected graph theory index. Linear regression analyses, controlling for scan site, were conducted to test

whether the relationship of path coefficients to SSRT was moderated by sex and CTQ score. To preserve power, the above analyses treated childhood maltreatment exposure as a continuous variable using the CTQ total score; however, we further explored significant path coefficient × CTQ interaction effects with subgroup correlation analyses for males and females, and/or higher and lower CTQ scores (median split). As the purpose of the subgroup correlation analyses was to characterize the directionality of the relationships between the variables for significant three-way interactions, multiple comparison corrections were not performed.

RESULTS

Subject Maltreatment, ADHD Symptoms, Past Depression, and Task Performance Measures

Males and females did not significantly differ in age, education, CTQ total scores or scores for any of the five CTQ subscales, or any of the CAARS subscale scores for ADHD symptoms. For stop-signal task performance, there were also no sex differences ($P > 0.05$) in SSRT, post-error slowing, average go trial reaction time, average SSD or successful stop rate (Table I). A significant sex difference was observed for the go response rate (males: 98 ± 2%; females: 95 ± 5%; $t = 2.50$, $P = 0.019$). There was no significant effect of CTQ or interaction of sex and CTQ on SSRT. These variables are reported by sex and scanner site in Supporting Information Table II. One male and five females met DSM-IV criteria for lifetime major depressive disorder (MDD) but did not meet criteria in the last month. To test the need to control for the dichotomous variable of lifetime MDD in our statistical models, we conducted a bivariate test on each outcome variable and found no significant differences between having and not having a history of MDD. Since the sample size was relatively small and our goal was to achieve the most parsimonious model, we did not control for MDD.

ICA Regression

There was no significant relationship of CTQ scores, SSRT, sex, or their interactions on the activity of the inhibitory control network for the contrast of successful stop–go trials.

Graph Theory

An investigation of interaction effects on the functional connectivity of the inhibitory control network identified a significant three-way interaction of CTQ scores, SSRT, and sex ($t = -4.89$, $P < 0.001$) on the network index of strength. Greater strength of functional connectivity between network nodes was associated with faster SSRTs for females with lower CTQ scores but slower SSRTs in females with higher CTQ scores, whereas an opposite relationship of these variables existed for males. We explored whether any one type of childhood maltreatment accounted for this interaction effect. The interaction of CTQ subscale scores, SSRT, and sex was significant when modeling physical abuse ($t = -4.11$, $P < 0.001$), emotional abuse ($t = -4.23$, $P < 0.001$), and emotional neglect ($t = -3.47$, $P < 0.001$) independently, but not for physical neglect ($t = -0.11$, $P = 0.91$) or sexual abuse ($t = 0.41$, $P = 0.68$). However, no single subscale was a stronger predictor than the CTQ total score representing the cumulative exposure to each of the five types of maltreatment.

There was no significant effect of node on the relationship of the CTQ × SSRT × sex interaction effect on network strength. There was also no significant interaction effect of CTQ scores, SSRT, and sex for the graph indices of network degree, betweenness centrality, or leverage centrality. However, analyses of effects on measures of degree and centrality are most interpretable when identifying effects on specific nodes. A by-node analysis did not identify a significant effect of CTQ score on specific nodes within the network that survived a Bonferroni correction for multiple comparisons.

Structural Equation Modeling (SEM)

The inhibitory control network model that fit the subgroup of females with lower CTQ scores is illustrated in Figure 2A. Relative to the model for the lower CTQ score subgroup, the model fit was significantly improved for females with higher CTQ scores (Fig. 2B) by freeing path estimates from the LIFC to the dACC, the dACC to the LIFC, the dACC to the RIFC, the left SMG to the LIFC, the left SMG to the MCC, and the MCC to the RIFC. The network model that fit the subgroup of males with lower CTQ scores is illustrated in Figure 2C. For males with higher CTQ scores (Fig. 2D), the model fit was significantly improved by freeing path estimates from the LIFC to the dACC, the dACC to the RIFC, the left SMG to the LIFC, the right SMG to the MCC, and the MCC to the RIFC. Removing the LIFC to RIFC path improved the model fit for both women and men with higher CTQ scores.

We selected those network paths most affected by childhood maltreatment in both men and women (i.e. LIFC-dACC, LIFC-RIFC, and dACC-RIFC) for further analysis to determine which paths accounted for the graph analysis finding of a sex-dependent interaction effect of CTQ scores and SSRT on network strength.

LIFC→dACC path

The LIFC-dACC path coefficient was significantly negatively correlated with CTQ scores for both males ($r = -0.49$, $P = 0.038$) and females ($r = -0.47$, $P = 0.033$). A three-way interaction between path coefficients, CTQ scores, and sex significantly predicted SSRT in the forty subject sample (Fig. 3; $t = 3.24$, $P = 0.003$; r^2 adjusted = 0.19). Subgroup analyses exploring this interaction indicated that

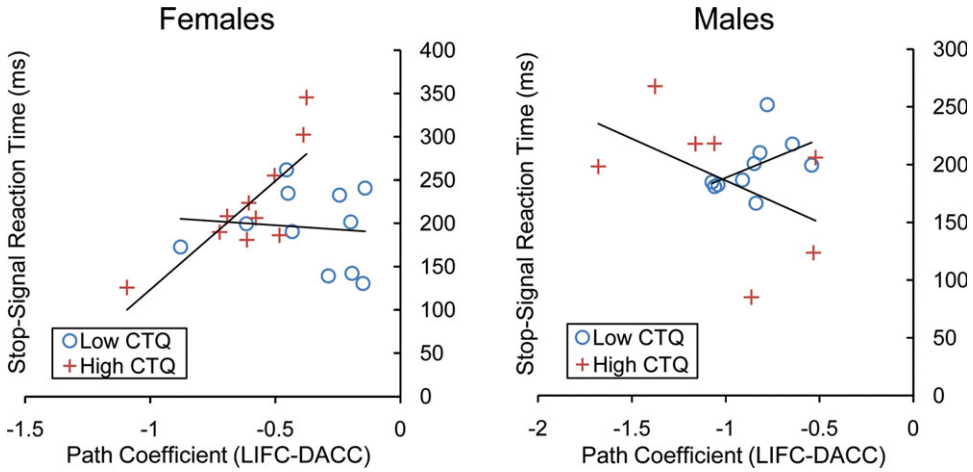


Figure 3.

Sex differences in the influence of childhood maltreatment on the relationship between LIFC→DACC path coefficients for a putative inhibitory control network and inhibitory control ability. Stop-signal reaction times were predicted by the three-way interaction of sex, LIFC→DACC path coefficients, and Childhood Trauma Questionnaire total scores (displayed as a median split for ease of visualization). CTQ, Childhood Trauma Questionnaire.ms, milliseconds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

more negative path coefficients for LIFC-dACC connectivity were related to faster SSRTs in females with higher CTQ scores ($r = 0.82$, $P = 0.0041$), although the correlation of path coefficients with SSRT were not significant for females with lower CTQ scores ($r = -0.10$, $P = 0.77$), males with lower CTQ scores ($r = 0.49$, $P = 0.15$) or males with higher CTQ scores ($r = -0.48$, $P = 0.22$). For females, these path connectivity coefficients were significantly correlated with the graph theory index of network strength ($r = 0.39$, $P < 0.001$), accounting for 15% of the variance in that measure; this path was not significantly correlated with network strength for male subjects ($r = 0.07$, $P = 0.49$).

LIFC→RIFC path

Path coefficients for individual subjects for the LIFC-RIFC pathway were correlated with network strength for males ($r = 0.29$, $P = 0.004$) and females ($r = 0.54$, $P < 0.001$), but were significantly correlated with CTQ scores only for females ($r = -0.47$, $P < 0.001$). However, neither coefficients for this path, CTQ scores, nor sex were significant predictors of SSRT.

dACC→RIFC path

dACC-RIFC path coefficients accounted for 39% of the variance in network strength for males ($r = 0.62$, $P < 0.001$) and 11% for females ($r = 0.34$, $P < 0.001$). The correlation of CTQ scores with this path was not significant for males ($r = -0.16$, $P = 0.56$) or females ($r = -0.14$, $P = 0.56$). However, for male subjects, linear regression determined that SSRT was predicted by the interaction of dACC-RIFC path coefficients and CTQ scores ($t = -2.52$, $P = 0.030$; r^2 adjusted = 0.33). Subgroup correlation analyses exploring this interaction determined that faster SSRTs were correlated with more negative path coefficients ($r = 0.76$, $P = 0.049$) for males with lower CTQ scores, whereas less negative path coefficients predicted faster SSRTs in males with higher CTQ scores ($r = -0.87$, $P = 0.005$). These variables did not significantly predict SSRT in female subjects.

Network Functional Connectivity Predicts ADHD Symptoms

To explore the potential role of the LIFC-dACC path for protection against behaviors related to clinical symptoms of impulsivity, we tested in a linear regression model whether the interaction of sex, LIFC-dACC path coefficients and CTQ scores predicted CAARS DSM-IV total symptom scores for this subclinical sample. The results indicated that for females with higher CTQ scores, negative coupling of the LIFC and dACC was associated with fewer total ADHD symptoms, whereas negative path coefficients resulted in greater ADHD symptoms for males with higher CTQ scores; the opposite relationship existed for the male and female subgroups with lower CTQ scores ($t = 2.56$, $P = 0.016$). This sex-specific association was evident for CAARS hyperactive-impulsive symptoms ($t = 2.58$, $P = 0.015$) as well as inattentive symptoms ($t = 2.16$, $P = 0.039$).

DISCUSSION

We observed sex-dependent effects of childhood maltreatment on the functional organization of a putative brain inhibitory control network in young adults.

Investigation of network effective connectivity revealed childhood maltreatment-related changes in the functional interactions within the network with marked differences between the sexes in the behavioral correlates of these network alterations. Contrary to the expectation that childhood maltreatment would be exclusively associated with functional deficits in the neural processing of inhibitory control, effective connectivity of the IFC and dACC encoded apparent sex-specific adaptive responses of inhibitory control mechanisms to childhood maltreatment. The study findings support the hypothesis that childhood maltreatment alters the functional neurodevelopment of inhibitory behavioral control and suggest mechanisms by which early life adversity confers risk for drug use and other disorders in susceptible individuals and resilience in others.

A series of data reduction steps achieved an increasingly resolved model of the effects of childhood adversity on functional brain organization related to inhibitory control. An ICA of fMRI time courses identified 30 spatially-independent networks of coactivated brain regions, of which an inferior frontal-cingulate-parietal component was chosen for further analysis as a putative inhibitory control network based on empirical and theoretical factors. Subsequent graph analyses attempted to identify the effects of childhood maltreatment on indices of functional connectivity for the brain regions (nodes) comprising the network. Observing a significant effect of childhood maltreatment on the graph index of strength, SEM was then employed to understand how childhood maltreatment specifically affects functional interactions between regions and how this in turn accounts for the effects on global network connectivity observed in the graph analyses.

Despite non-significant effects of childhood maltreatment on the extent of network activation during response inhibition, significant effects of maltreatment on functional and effective network connectivity were observed. There are several possible reasons for this dissociation. Network connectivity approaches measure the functional relationships between brain regions, rather than independently measuring activity across different brain regions. This difference may be of particular significance when exploring neurodevelopmental effects of childhood maltreatment, as childhood trauma affects the morphometry and integrity of white matter tracts [Choi et al., 2009; De Bellis et al., 1999; Paul et al., 2008; Teicher et al., 2004]. The normative development of brain functional connectivity [Dosenbach et al., 2010; Fair et al., 2007, 2008] may similarly be altered or impaired by exposure to childhood adversity. Also, although we selected a component based on its association with successful stopping, connectivity analyses utilized time courses representing activity of nodes across the entire task and thus accounted for connectivity across all task conditions; the relevance of connectivity to inhibitory control ability was tested by the inclusion of SSRT as a predictor in statistical models.

The marked effects of sex and childhood maltreatment on the functional strength and organization of a neural network related to inhibitory behavioral control suggest that there are fundamental differences between the sexes in neurodevelopmental outcomes following early life adversity. These findings are consistent with those of previous studies demonstrating sex × childhood trauma interaction effects on neuroendocrine functioning [DeSantis et al., 2011] and a sex × genotype × trauma effect on brain morphometry [Everaerd et al., 2012]. The sex differences in the current study are not likely explained by differences in type or severity of childhood maltreatment exposure, as males and females did not differ on any of the five CTQ subscales. Moreover, sex differences in trauma-related risk for certain psychiatric disorders are not fully accounted for by differences in exposure rates to specific types of traumas [McCutcheon et al., 2009; Tolin and Foa, 2006], but may instead be due to differences in developmental timing of the exposure [Andersen and Teicher, 2008; McCutcheon et al., 2009] and biological differences between the sexes [Slopen et al., 2011]. Sex hormone-dependent and -independent differences in brain development, including age-dependent sex differences in myelination and synaptic pruning during childhood [De Bellis et al., 2001; Schmithorst et al., 2008] may contribute to different negative and/or compensatory effects in males and females following exposure to childhood adversity. Such disruptions in the development of inhibitory control networks early in life may impair executive abilities in adolescence and adulthood, serving as a risk factor for later life drug use and other disorders. The differential effects of childhood maltreatment on inhibitory control network connectivity in females and males identified in the current study parallel sex differences in the prevalence, course and outcome of stress-related psychiatric disorders like drug addiction, depression, and post-traumatic stress disorder. For example, women exhibit greater vulnerability to the development and negative outcomes of drug dependence [Brady and Randall, 1999; Cotto et al., 2010; Najavits and Lester, 2008; Terry-McElrath et al., 2009; Westermeyer and Boedicker, 2000].

The graph theory analysis finding of differential effects of CTQ and SSRT on network strength for males versus females was further investigated with SEM of network effective connectivity. These analyses identified sex-specific adaptive reorganization within the inhibitory control network. Faster SSRTs in females with greater maltreatment histories were achieved by increasing the negative influence of the LIFC on dACC activity whereas greater stopping ability in males with greater childhood maltreatment histories required a reduction of the negative influence of the dACC on RIFC activity. As each of these paths significantly accounted for network strength, when considered together these path influences provide a more detailed understanding of the graph theory finding of the relationship of network strength to the three-way interaction of sex, childhood maltreatment, and response inhibition.

Preserved response inhibition ability represents a protective factor against drug use problems in at-risk individuals [Nigg et al., 2006]. Although childhood maltreatment was associated with more negative coupling of the LIFC-dACC path for both sexes, the association of this path with SSRT and CAARS scores suggests that this particular response is adaptive only in females. However, both males and females exhibited a range in the extent to which exposure to childhood maltreatment resulted in this path modification. Accordingly, females with higher exposure to childhood maltreatment but *less* negative LIFC-dACC connectivity exhibited poorer inhibitory control and greater symptoms of impulsivity and inattention. Thus, the association of a more negative influence of the LIFC on dACC function with better inhibitory control ability as well as lesser ADHD symptoms in females with significant maltreatment histories is consistent with an adaptive or compensatory response of the LIFC-dACC pathway in conferring protection from negative effects of childhood adversity for at least some forms of cognitive functioning (i.e. inhibitory control, attention, impulsivity). It could be speculated that this "cognitive resilience" serves as a broader mechanism of protection against poor mental health outcomes, although this theory remains to be formally tested by comparison to a non-resilient psychiatric population. As a possible mechanism of resilience among women, an adaptive increase in left hemisphere engagement may serve to enhance cognitive control mechanisms related to the regulation of emotion [Ochsner and Gross, 2005; Wager et al., 2008]. In fact, lesion studies support the importance of left hemispheric cortical regions in the regulation of emotions in females [Tranel et al., 2005], as well as protection against depression [Jorge et al., 2004; Starkstein et al., 1987]. Functionally, the maltreatment-related negative modulatory influence of the LIFC on dACC activity could serve to dampen the hyperresponsivity of the dACC associated with familial risk for trauma-related disorders such as PTSD [Shin et al., 2011]. Furthermore, the observed changes in LIFC connectivity associated with maltreatment-related functional reorganization may adaptively compensate for deficits in RIFC structural connectivity representing markers of familial risk for drug dependence [Ersche et al., 2012].

Contrary to females, a more negative LIFC-dACC path associated with childhood maltreatment in males was not adaptive, as evidenced by increased SSRTs and greater ADHD symptoms. Instead, less inhibition of the RIFC by the dACC enabled males with higher maltreatment histories to successfully countermand motor responses during the stop-signal task. This is in opposition to males with less exposure to childhood maltreatment, in which greater inhibitory influence of the dACC on the RIFC was associated with better response inhibition. The RIFC has been identified as critical for response inhibition [Aron et al., 2003; Chambers et al., 2006]. The apparent dissociation of the dACC-RIFC path for response inhibition in males with lesser versus greater histories of childhood maltreatment exposure could represent a shift from efficient negative-feedback modulation of RIFC activity by the dACC to an adaptive enhancement of RIFC activity by down-regulating its negative modulation as a form of resilience to experiences of child abuse or neglect. Although these inferences are speculative, the observations support marked differences between the sexes in the neural and behavioral responses to childhood maltreatment during childhood. These findings are also consistent with a previous fMRI study of males with childhood abuse histories performing a verbal working memory task [Raine et al., 2001]. In that study, childhood physical abuse was associated with reduced left hemispheric activity, but physical abuse was only associated with reduced right hemispheric activation in the subgroup of men who were violent offenders, suggesting that preserved functioning of the right hemisphere is protective against this negative consequence of childhood maltreatment [Ersche et al., 2012].

Limitations

While the results of this study support significant effects of childhood maltreatment on neural processing related to inhibitory behavioral control, the study had several limitations that weaken the strength of its inferences. A prominent, though small, relevant literature of research findings precluded the development of detailed hypotheses regarding the impact of childhood maltreatment on network functional organization. Therefore, the study had hypothesis-generating as well hypothesis-testing goals. Attempts to replicate the observed network effects are clearly needed. The lack of comparison to a drug-addicted or other psychiatric sample in this study limits the interpretability of the identified neural network alterations as risk or protective factors for drug use or other disorders. However, the observed impact of childhood maltreatment on a neural network associated with response inhibition has relevance for those disorders of inhibitory control for which childhood adversity serves as a risk factor. Although the association of childhood maltreatment with later psychopathology persists throughout the life cycle [Clark et al., 2010; McLaughlin et al., 2010], the age of enrolled participants corresponded to early adulthood to minimize the confound posed by a largely resilient sample. However, the study findings are consistent with a distribution of brain responses that, on one end of the spectrum, may impart resilience to childhood adversity as a risk factor. It is also possible that a recall bias effect for self-reported histories of childhood maltreatment, in which memory of traumatic events may be inaccurate, may have contributed to or diminished the findings; however, the more likely consequence of this effect is decreased significance of the outcomes [Scott et al., 2010] or type-II error. While the CTQ represents a reliable, valid and often used instrument for retrospective characterization of childhood maltreatment, its exclusive use in this study negates an

understanding of the impact of other types (e.g., accidents, bullying) of trauma and other development periods of trauma exposure (e.g., adolescence, adulthood) on brain network organization. Finally, the accurate definition of an absence of psychopathology to substantiate the claim of clinical resilience is a challenge to such research. This study relied on a thorough structural clinical interview based on DSM-IV Axis I diagnostic criteria, but did not assess Axis II disorders. Therefore, given that childhood trauma [Johnson et al., 1999], drug use disorders [Grant et al., 2004], and ADHD [Jacob et al., 2007] are associated with personality disorders, we cannot exclude the possibility that the study findings were influenced by this variable.

While the goal of the fMRI data analysis approach was to achieve step-wise data dimensionality reduction, there are several limitations arising from these methods. First, the stop signal task engages multiple processes related to response execution, response inhibition, attention, and error processing. This study investigated only a single neural processing network related to the process of motor inhibition that was represented by a six node model to enable SEM analysis of the impact of childhood maltreatment on its effective connectivity. Certainly other task-related networks (e.g., error processing) or the inclusion or substitution of other inhibitory control-related nodes (e.g., pre-supplementary motor area, subthalamic nucleus) in the SEM analysis would most probably generate other representations of the effects of maltreatment on the organization of neural processing networks. Further investigation of the effects of exposure to childhood adversity on additional networks mediating various cognitive and affective processes may reveal other neural mechanisms of risk and resilience to psychopathologies. In addition, response inhibition was modeled by the contrast of successful stop minus go trials. This measure of inhibitory control has been questioned both in terms of the role of alternative explanations such as the odd ball effect [Rubia et al., 2005], and the functions attributed to observed neural activations [Lenartowicz et al., 2011; Zhang and Li, 2012] to define components related to response inhibition does not control for visual and attentional processes that are elicited by the presence of the stop signal, regardless of successful inhibition. Finally, the four structural equation models were estimated from subgroups that ranged in size from 9 to 11. Although the group comparison feature of Proc Tcalis utilizes data from both groups to estimate path coefficients that do not differ between groups, subgroup-specific estimates may be less reliable.

CONCLUSIONS

Childhood maltreatment is associated with enduring and sex-dependent changes in the functional organization of a neural network mediating inhibitory control of behavior. Compensatory mechanisms that affect neural network connectivity and organization allow individuals to maintain response inhibitory performance despite significant histories of adversity. In the absence of such adaptive changes, symptoms of impulsivity, inattention, and diminished inhibitory control—and potentially risk for drug use and other disorders—may be increased.

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