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Structural variations in prefrontal cortex mediate the relationship between early childhood stress and spatial working memory

Jamie L. Hanson[1], **Moo K. Chung**[1], **Brian B. Avants**[2], **Karen D. Rudolph**[3], **Elizabeth A. Shirtcliff**[4], **James C. Gee**[1], **Richard J. Davidson**[1], and **Seth D. Pollak**[1]

[1]University of Wisconsin-Madison

[2]University of Pennsylvania

[3]University of Illinois at Urbana-Champaign

[4]University of New Orleans

Abstract

A large corpus of research indicates exposure to stress impairs cognitive abilities, specifically executive functioning dependent on the prefrontal cortex (PFC). We collected structural MRI scans (n=61), well-validated assessments of executive functioning, and detailed interviews assessing stress exposure in humans, to examine whether cumulative life stress affected brain morphometry and one type of executive functioning, spatial working memory, during adolescence —a critical time of brain development and reorganization. Analysis of variations in brain structure revealed that cumulative life stress and spatial working memory were related to smaller volumes in the PFC, specifically prefrontal gray and white matter between the anterior cingulate and the frontal poles. Mediation analyses revealed that individual differences in prefrontal volumes accounted for the association between cumulative life stress and spatial working memory. These results suggest that structural changes in the PFC may serve as a mediating mechanism through which greater cumulative life stress engenders decrements in cognitive functioning.

Keywords

stress; prefrontal cortex; brain development; early life stress; development; neuroimaging; frontal lobe; adolescent development; cognitive neuroscience; chronic stress; spatial working memory; executive functioning; neural plasticity

Introduction

Stress can impact a broad range of social, cognitive, and physiological functions (Arnsten, 2009; Lupien, McEwen, Gunnar, & Heim, 2009; Schwabe, Wolf, & Oitzl, 2010; Tang et al., 2006). These effects appear to be non-linear in nature. Exposure to low amounts of stress, for example, appears to promote beneficial effects such as better emotional and physiological regulation (Boyce & Chesterman 1990), enhanced cognitive functioning (Parker et al., 2005; Schwabe, Wolf, & Oitzl, 2010; Schwabe et al., 2011), and protective neurobiological changes such as larger prefrontal cortices and lower cortisol levels (Lyons et al., 2002; Tang et al., 2006; Tang et al., 2011) after mild stress. More extreme stress has,

Jamie Hanson, Waisman Center and Department of Psychology, University of Wisconsin-Madison, 1500 Highland Ave, Madison, WI, 53705, Telephone: 608-890-2525, Fax: 608-890-2424, jlhanson5@wisc.edu.

conversely, been linked with deleterious effects on cognition, along with alterations in the hippocampus and prefrontal cortex (for review, see Arnsten, 2009; Lupien et al., 2009).

A class of cognitive processes known as “executive functions” appear to be particularly vulnerable top the negative effects of stress. Executive functions encompass facets of high-order cognition, such as inhibitory control, cognitive flexibility, working memory, and sustained attention (Zelazo, Craik, & Booth, 2004). A large body of research in typically-developing individuals, humans who have suffered brain damage, and non-human animal research samples has linked executive functions with the prefrontal cortex (PFC; e.g., Dias, Robbins, & Roberts, 1996; D’Esposito et al., 1995; Owen et al., 1996; Williams & Goldman-Rakic, 1995). But little is currently known about the neurobiological correlates of stress-induced changes in executive functions in the developing organism.

Chronic levels of high stress lead to structural changes of the PFC in rodents, with reduced dendritic arborization and lower spine density (Cook & Wellman, 2004; Holmes & Wellman, 2009; Liston et al., 2006; Radley et al., 2006). Such chronic stress has also been linked with executive function deficits in rodents, non-human primates, and humans (Evans & Schamberg, 2009; Holmes & Wellman, 2009; Murphy et al., 1996; Oei et al., 2006; Sanchez et al., 1998). This previous research has been conducted in adult humans and non-human animals; it is not clear if these patterns would be seen early in development.

During childhood and adolescence, the PFC has a protracted course of brain development with alterations seen until the second decade of life (Lenroot & Giedd, 2006), making it potentially vulnerable to the effects of chronic early-life stress. Chronic stress, especially very high levels, may affect cognitive functions linked to this region. This study examined whether individual differences in the PFC mediated the effects of cumulative life stress on executive functioning during development.

To probe these questions, we utilized detailed interview metrics of cumulative life stress, well-validated assessments of executive functioning, and neuroimaging methodology appropriate for use with children. Using these tools, we aimed to further elucidate whether (a) cumulative life stress affected working memory (one executive function), and (b) the extent to which individual differences in PFC morphometry mediated this effect.

Methods

Participants

Sixty-one children (32 Males, 29 Females; Mean Age= 142.35 months +/− 21.12 months) completed the Youth Life stress interview (YLSI) and MRI scanning (for additional demographic information, see Table 1). Maternal education was used as an index of socioeconomic status in this study because this measure is strongly associated with child health, household income, and stimulation in the environment (Haveman & Wolfe, 1995; Waldfogel, Han, & Brooks-Gunn, 2002). Children were recruited from the Madison, WI community by posting fliers. Participants were given $60 for a 4-hour visit to the lab. Such recruitment procedures were similar to the large body of normative pediatric brain imaging studies (e.g., Asato, Terwilliger, Woo, & Luna, 2010; Guyer et al., 2011).

To rule out physical abuse or other forms of child maltreatment, parents completed the Parent–Child Conflict Tactics Scale (PC-CTS; Straus, Hamby, Finkelhor, Moore, & Runyan, 1998) and local Department of Human Services records were examined. The PC-CTS is a 20-item measure of the frequency with which a parent has carried out specific acts of physical aggression toward the child. Parents who scored at least 20 on the physical abuse subscale on the PC-CTS and/or had substantiated cases of physical abuse on record with the

Dane County Department of Human Services were excluded from all analyses. Maltreatment was specifically ruled out due to potential unique alteration in brain and behavior stemming from this early adversity (Hanson et al., 2010).

Measurements of Puberty

Cumulative life stress may affect pubertal maturation (Ellis, 2004), which may have direct or indirect influences on brain development. To control for the influence of puberty, pediatric nurse practitioners completed Tanner staging on the children using a physical exam (see Shirtcliff, Dahl, & Pollak, 2009). This involved brief breast palpation for girls, and visual inspection of breast and pubic hair development. An orchidometer was used to measure testicular size in boys, along with visual inspection of genitals and pubic hair. Puberty scores ranged from 1 (no development) to 5 (adult development).

Executive Functioning Assessment

To examine executive functioning, we employed the Spatial Working Memory (SWM) subtest of the Cambridge Neuropsychological Test Automated Battery (Cambridge Cognition, Cambridge, United Kingdom). The CANTAB has been used extensively with children and adolescents (Luciana & Nelson, 2002) and has proved sensitive in discriminating various clinical populations from typically developing children. The CANTAB is computerized for standardized administration- the stimuli cannot be verbalized and the subtasks require non-verbal responses, thus performance is not confounded with subjects' verbal skills. CANTAB data for the Spatial Working Memory (SWM) subtest was available for 44 participants (see Table 1). The SWM subtest involves touching boxes on a screen to find a token. Participants must, through a process of elimination, find one blue "token" in one of the boxes presented. This portion of the CANTAB reflects an individual's visuo-spatial working memory. A participant's score is based upon total errors (touching boxes that have already been found to be empty and revisiting boxes that have already been revealed to contain a token). Raw performance data is z-transformed based on age-based neurocognitive norms for each subject's age and gender. Higher z-scores indicate better performance on this task and a lower number of total errors.

Assessment of Cumulative Life Stress

To assess cumulative life stress, interviewers administered the lifetime adversity section of the Youth Life Stress Interview (YLSI; Rudolph & Flynn, 2007; Rudolph & Hammen, 1999) separately to children and their parents. Postdoctoral fellows, advanced graduate students, and Postbaccalaureate staff conducted all interviews. Interviewers received intensive training and ongoing consultation from the developers of the YLSI at the University of Illinois at Urbana-Champaign. This interview assessed children's exposure to severe negative life events and circumstances across their lifetime, excluding events within one year to distinguish recent life stressors. General and specific probes were employed to assess a child's exposure to particularly stressful events and circumstances (e.g., death of a close family member or friend, exposure to severe marital conflict, and severe chronic illness of a close family member or friend). Semi-structured follow-up questions were then asked to assess the event's context (e.g., timing, duration, objective consequences).

Integrating across parent and child reports, an independent rating team of 3–7 members provided a consensual rating on a 10-point scale that reflected the overall level of cumulative life stress. This coding of the YLSI incorporates a detailed consideration of the context of events and the impact on an individual child's life, rather than simply reflecting the sum of the number of stressors. For example, a parent's loss of employment receives a uniform score within many stress checklist approaches, but the YLSI differentiates a parent leaving an unsatisfying job because of lack of financial need, from being fired following

numerous years of fulfilling and dedicated service (Wethington, Brown & Kessler, 1995). To detail specific examples from our study, a score of a 1 was given to a child whose pet was hit by a car, but was not seriously injured. A score of a 5 was given to a child who was in foster care early in life, had multiple moves, and also had one of their parents die early in life. A score of a 7.5 was given to a child whose parent had serious chronic medical issues that also caused instability in employment. Also reflected in this score were the facts that this child's sibling had serious medical and mental health issues, there was serious marital conflict in the family,resulting in parental separation, and one of the child's parents was incarcerated extensively. A score of a 10 was given to a child who was homeless, had several close family members die unexpectedly, and whose parents had a highly conflictual relationship that resulted in separation. A key point is that the scores not only reflect the objective stressors, but also the subjective impact of these events as perceived by the child. This rating system has high reliability and validity (Rudolph & Flynn, 2007; intraclass correlation coefficient = .99;).

Assessment of secondary psychopathology

To assess child psychopathology, parents completed the computerized Diagnostic Inventory for Children and Adolescents (Reich, 2000) regarding their child. Responses were used to generate specific DSM diagnoses. Three children were diagnosed with Attention-Deficit Hyperactivity Disorder; our results are not changed by removal of these subjects.

MRI Acquisition

All children completed one MRI scan. High-resolution anatomical MRI images were obtained using a 3-Tesla GE SIGNA (General Electric Medical Systems, Waukesha, WI) scanner with a quadrature head RF coil. A three-dimensional, inversion recovery (IR) pulse sequence was used to generate T1-weighted images with the following parameters: TR/TE = 21/8 ms, flip angle = 308, 240 mm field of view, 256-192 in-plane acquisition matrix (interpolated on the scanner to 256-256), and 128 axial slices (1.2 mm thick) covering the whole brain. Before MRI scanning, participants were oriented to the MRI through the use of a mock-MRI simulator. During MRI acquisition, participants were instructed to stay as still as possible and were able to watch a movie of their choosing.

Diffeomorphic image normalization, Template Creation, & Tensor-based morphometry

T1-weighted images were corrected for field inhomogeneity and masked to exclude all extraneous aspects of the brain (e.g., dura matter, skull) were excluded in these masks. These masked images were then used in template creation. After going through a 6-parameter rigid-body transformation, each individual brain was registered to our template using Symmetric Normalization (SyN). This algorithm allows for large deformations, but also constrains the deformations to be physically reasonable. The nonlinear transformations resulting from the SyN algorithm also provide deformation tensor fields, defined in the optimal template space, that describe the voxel-wise shape change from the template to each subject's brain. Jacobian determinants of the deformation field indicate the fractional volume expansion and contraction at each voxel, quantifying the magnitude of regional volume alterations required to match the template. Before the statistical testing, this adjusted Jacobian map was subjected to a log transformation to make the distribution closer to the normal distribution (Avants & Gee, 2004). Jacobian determinants were then smoothed with a 4mm Full-Width, Half Max Gaussian Filter.

The MRI template was study-specific, constructed based on all subjects. Template construction consisted of a multi-resolution strategy (for this study, a four level Gaussian pyramid) as well as the similarity metric for the optimization, along with a maximum number of iterations. We used the region-based cross-correlation similarity metric, which is

optimal in dealing with locally varying inhomogeneity in the appearance of images. The maximum number of iterations in the normalization was set to 200, although convergence may have occurred before the maximum was reached. This approach is particularly applicable to pediatric populations, as it minimized sources of variability (e.g., brain tissue segmentation), used a study-specific anatomical template, and yielded high sensitivity at the voxel level. In addition, recent research validated SyN as one of the best available warping algorithms in a recent comparison of 14 nonlinear registration algorithms (Klein et al., 2009).

Results

Descriptive Statistics for Life-Stress and Relationship with Other Variable

The mean rating of cumulative life stress was 3.14 +/− 2.009 (out of 10). The correlation between cumulative life stress and age was non-significant (r=.157, p=.226), while puberty and cumulative life stress were significantly correlated (r=.263, p=.04). This finding argues against stress-exposure being a simple facet of age and more related to life-experiences, but underscores that life-stress may be affecting pubertal maturation.

Test of Formal Mediation

Hierarchical multiple regression analyses were conducted to specifically examine whether individual differences in the PFC mediated the association between cumulative life stress and executive function. A variable is thought to be mediator when it carries the influence of a given independent variable (IV) to a given dependent variable (DV). A formal test of mediation involves establishing numerous criteria (Baron & Kenny, 1986), each of which is detailed below.

Relationship between cumulative life stress and prefrontal cortex structure and function (Criterion 1)

Criterion 1 requires that the IV (cumulative life stress) is significantly associated with the mediator (the prefrontal regions of interest). We established Criterion 1 based on a logical AND conjunction analysis. Such an analytic approach allowed first for the isolation of regions related to stress and then to examine correlations between volumetric properties of these specific regions and working memory. To do this, we used the voxel-wise correlations of jacobian determinants (a metric of volumetric expansion or contraction) and the child's cumulative life stress score. This correlation was conducted in FMRISTAT (Worsley et al., 2002) and combined with a voxel-wise correlations of jacobian determinants with working memory performance Z-scores, a prefrontally mediated function. In these analyses, whole-brain volume and pubertal status were covaried. A statistical threshold of t(58)=3.966, p=.05 corrected was used for cumulative life stress scores (as shown in Table 2) and a threshold of t(41)= 2.967, p=.005 uncorrected was used for working memory subscores. These correlations were then used in a logical AND conjunction analysis to identify the brain regions that were associated with both cumulative life stress and executive functioning. Assuming independence of this test, these results are significant at 0.000025, (.005*.005), uncorrected. To generate coefficients for use in the mediation analysis for this criterion, we ran multiple regression analyses with cumulative life stress entered as the IV and the prefrontal regions of interest that emerged from our voxel-wise analyses entered as DVs in separate regression models controlling for variations in pubertal status (as shown in Table 3).

As hypothesized, portions of the PFC were smaller with elevated cumulative life stress, and smaller PFC volumes were associated with poorer executive functioning. These associations emerged as two clusters in the PFC: one located in gray matter near the anterior cingulate

and the frontal poles and one located in white matter near the forceps minor (see Figures 1 & 2). This analysis isolates brain regions of interest that are linked with both cumulative life stress and spatial working memory (specifically, the total number of errors on the SWM subtest; see Table 4). In these and all analyses, a z-score of spatial working memory errors was used; a higher z-score indicated fewer errors on this neurocognitive task. The peak coordinates for all analyses were mapped to MNI space by registering the custom template to the MNI152 Average Template (Montreal Neurological Institute, Montreal, Canada) using the SyN algorithm with similar settings to our subject-level normalization (e.g., cross-correlation similarity metric; 200 iterations max).

Association between cumulative life stress and executive functioning (Criterion 2)

Criterion 2 requires that the IV is significantly associated with the DV (working memory performance) in the absence of the mediator. To establish Criteria 2, we conducted multiple regression analyses in which cumulative life stress was entered as the IV and working memory performance scores were entered as DVs in separate regression models. Pubertal status was entered at step 1 to adjust for any possible association between puberty and memory performance.

Providing support for Criterion 2, heightened cumulative life stress was associated with poor executive functioning, as indexed by memory errors ($r=-.474$, $p=.001$). Multiple regression analysis revealed that this association was significant after controlling for individual differences in pubertal status, $F\Delta(1,41)=11.56$; $R^2\Delta=.219$, $p=.002$ (see Table 5).

Test of formal mediation (Criterion 3)

Criterion 3 requires that the mediator has a significant unique effect on the DV after adjusting for the IV, and the effect of the IV on the DV is reduced upon the addition of the mediator to the model. To establish Criteria 3, we conducted multiple regression analyses in which cumulative life stress was entered at step 1 (while adjusting for pubertal status) and the brain regions resulting from the logical AND conjunction analysis corrected for whole-brain volume were entered at step 2 (see Table 5). In these models, we entered the log-jacobian determinant for each participant from the prefrontal cluster identified by the logical AND conjunction analysis (of the whole-brain correlation with cumulative life stress and the whole-brain correlation with executive functioning; see below). The output of this model contains regression coefficients and measurement of standard error for the effect of both cumulative life stress and prefrontal morphometry on executive functioning.

As shown in Table 5, the necessary conditions for mediation were met as the IV affected the mediator, the mediator had a significant unique effect on the DV and the effect of the IV on the DV lessened upon the addition of the mediator to the model. When the prefrontal regions of interests were added to the model, the association between cumulative life stress and executive functioning was non-significant for total errors. Of important note, variations in the PFC significantly predict executive functioning even after accounting for stress (as indexed by an association between prefrontal clusters and spatial working memory when cumulative life stress is included in our simultaneous regression models).

To further establish mediation (see Preacher & Hayes, 2004), we conducted Sobel tests (Sobel, 1986) using an interactive Sobel-test calculator to examine the significance of the indirect effects of cumulative life stress on executive functioning as mediated by prefrontal volumes. These tests revealed that frontal white matter volume, $Z = -2.11$, $SE = 0.038$, $p = 0.034$, and frontal grey matter volume, $Z = -2.31$, $SE = 0.038$, $p = 0.02$, mediated the association between life stress and SWM total errors Z-Score, a metric of spatial working memory performance.

Similar results were seen when controlling for age. All of the criteria detailed previously were met. In addition, frontal white matter volume, $Z = -1.98$, $SE = 0.035$, $p = 0.047$, and frontal grey matter volume, $Z = -2.190$, $SE = 0.037$, $p = 0.028$, mediated the association between cumulative life stress and SWM total errors Z-Score.

Relationships between Other Brain Structures, Cumulative life stress, and CANTAB Performance

In addition to hypothesized differences in the PFC, examination of the logical AND conjunction analysis revealed parts of the Temporal Lobe and the Precuneus were associated with both cumulative life stress and executive functioning (as shown in Table 6). Greater cumulative life stress was associated with smaller volumes in these regions and smaller volumes in these regions were associated with poorer executive functioning.

Effects of Acute v. Chronic Stress

As noted earlier, we assessed different facets of life stress (i.e., cumulative life stress or acute stress in the last year) through use of the YLSI. To interrogate the unique effects of acute stress, the average of parent's and child's reports of stress in the last year was entered into regression models as an independent variable along with pubertal stage, whole-brain volume, cumulative life stress, and prefrontal regions of interest. Spatial working memory performance (as indexed by total errors) was then entered as the dependent variable. Interestingly, as shown in Table 7, the effects of stress on spatial working memory are more strongly related cumulative life stress rather than stressors in the last year (Lifetime Stress, p=.030; Acute Stress, p=.363). Of important note, our brain regions of interest are still significant when Acute Stress is present in our regression models (Frontal White Matter, p=.038; Frontal Gray Matter: BA 10, p=.028).

Additional examination of brain regions affected by stress

As detailed in Table 2, a number of brain regions were related to cumulative life stress. Our analyses are conducted on a voxelwise basis to more specifically localize the effects of stress. Multiple independent clusters of interest merged in specific regions (e.g., two right occipital clusters). Each of these cluster uniquely contribute to associations between stress exposure and alterations in the brain, so they are detailed here. These relationships were significant using both pearson and spearman correlations, indicating such results were not driven by outliers.

We probed whether these same regions were related to behavior through the use of logical AND conjunction analyses where we looked for spatial overlap between voxel-wise correlations with cumulative life stress and voxel-wise correlations with spatial working memory. The majority of the regions related to cumulative life stress were not related to behavior, as only 2 clusters in the PFC along with clusters in the precenus and middle temporal gyrus emerged from voxel-wise correlations analyses. Such analyses may be under-powered so we also examined basic bivariate correlations for brain regions that emerged from voxel-wise correlations with cumulative life stress. These analyses yielded similar results, as only portions of prefrontal gray matter (near the left anterior cingulate), prefrontal white matter, right middle temporal gyrus, and right parietal white matter were related to spatial working memory at $p<.05$. These regions were then entered into a multiple regression models with the brain regions entered as independent variables and spatial working memory was entered as the dependent variable. Only portions of the prefrontal cortex (both gray and white matter clusters) were associated with spatial working memory at $p<.05$ as shown in Table 8.

Multiple Regression Analyses with PFC and other regions from conjunction analyses

To probe the specificity of our results, we conducted multiple regression analyses with all of the regions that emerged from the logical AND conjunction analyses. These regions were associated with both cumulative life stress and behavior (spatial working memory errors). Total spatial working memory errors was entered as the dependent variable, while cumulative life stress, pubertal stage, acute stressors that occurred in the last year, and the four brain clusters of interest (clusters in prefrontal white matter, in prefrontal gray matter, in the precuneus and in a portion of the medial temporal lobe) were entered as independent variables. The clusters in the PFC were the only variables that are significant at $p<.05$ in simultaneous regression models (as shown in Table 9). There was a near-significant association with the precuneus ($p=.053$) and spatial working memory errors.

Asymmetrical effects of cumulative life stress on the brain

We conducted exploratory analyses to assess asymmetry in the relationships between cumulative life stress and brain morphometry, as many effects were lateralized. We employed one-way ANOVAs to compare clusters identified previously (as shown in Table 2) against inverted version of these same clusters (flipped left to right hemisphere, or right to left). We found significant asymmetrical effects for the left frontal pole ($p<.001$), along with portions of the right ($p<.001$), and left occipital lobe ($p=.009$). A trend towards asymmetrical effects was also noted for the putamen. Means, standard deviation, along with p-values for this preliminary test of asymmetry are shown in Table 10.

Discussion

Our findings indicate that cumulative life stress is associated with structural variations in the prefrontal cortex, such that heightened cumulative life stress is associated with smaller volumes in both white and gray matter. Both cumulative life stress and smaller PFC volumes are associated with individual differences in an important domain of executive functioning-spatial working memory. Higher levels of cumulative life stress were associated with poorer spatial working memory performance, while smaller PFC volumes (in both gray and white matter) were associated with poorer spatial working memory.

These data are consistent with research showing that stress can impair cognitive functioning, as well as with research in human and non-human animals showing stress-specific alterations in the PFC (for review, see Arnsten, 2009). Previous pediatric and adult imaging research has found an association between greater white matter volumes and superior performance in various cognitive tasks (Brickman et al., 2006; Sowell et al., 2001). For gray matter, our research finding fits with adult imaging studies showing less gray matter being related to lower performance on cognitive tasks (Gunning-Dixon & Raz, 2003 Tisserand et al., 2004). However, contextualizing these results in an adolescent sample where the brain is still developing rapidly is more complex. Adolescent subjects who have experienced a great deal of stress may be “losing” gray matter at a greater rate (in addition, to the normative reductions in gray matter seen in development, reported by others, e.g., Lenroot & Giedd, 2006) than subjects who have experienced less stress. It is possible that stress-induced impairments in cognitive functioning may have similar neurobiological correlates across the lifespan: lower gray and white matter being related to poor cognitive functioning. Future longitudinal research is needed to confirm this idea.

Of note, there are aspects of the study design that potentially limit the interpretation of results. Our data are based upon a single scan obtained at one point in development. It is possible that brain development is just delayed in children who were subjected to high levels of cumulative life stress. The major focus of investigation, the PFC, is still developing

during the developmental stage when the MRI scans were obtained. The brains of children who have experienced greater amounts of life stress could 'equalize' over time. The trajectory of brain development has proven to be a robust predictor of cognitive functions during childhood and adolescence (Shaw et al., 2006). In addition, later environmental experience could aid in reducing any differences. Environment enrichment and exercise, for example, have both been linked increases in neurogenesis in the brain (Kempermann, Kuhn, & Gage, 1997; van Praag, Shubert, Zhao, & Gage, 2005; van Praag, Kempermann, & Gage, 1999) and even recovery after a lesion (Will et al., 1977). Future work will attempt to investigate these ideas, by examining longitudinal changes in brain structure and function.

We initially hypothesized that prefrontal circuitry would be uniquely affect by cumulative life stress. However we discovered brain regions in addition to the PFC that were related to cumulative life stress (as shown in Table 2). Many of these areas were related to sensory processing (e.g., occipital regions) and multi-sensory integration (i.e., parietal white matter; precuneus) brain regions. An emerging body of research in adults exposed to traumatic experiences during childhood is in line with these findings. Lower gray matter volumes and white matter fiber integrity in the visual cortex have been noted in adults who witnessed domestic violence or who were sexually abused in childhood (Choi et al., 2011; Tomoda et al., 2009). Such results also fit with non-human models of prenatal stress (Schneider et al., 2008) that have found alterations in sensory processing in rhesus macaques stressed early in development compared to those with no stress exposure. Future research is needed to clarify brain-behavior associations related to stress exposure and sensory processing and integration. Stress may affect these regions through excitotoxic events similar to the hippocampus, especially during development when these regions are still developing greatly. Changes in these brain areas could have large effects on a wide-range of behaviors including the control of attention, the regulation of emotions, and memory formation.

In the regions not initially hypothesized, only two specific areas were related to cumulative life stress and also related to behavior (as shown Table 6): the precuneus and the middle temporal gyrus. These results fit very well with studies examining the effects of acute stress on brain and behavior in humans. Previous research has found acute stress in humans disrupted functional brain activity and connectivity in frontoparietal networks (Dedovic, D'Aguiar, & Pruessner, 2009; Liston et al., 2009). Novel perfusion functional MRI research examining cerebral blood flow during acute psychological stress found associations between blood flow and cortisol in the anterior cingulate, precuneus, and portions of temporal cortex (Wang et al. 2005). When we employed multiple regression models to predict spatial working memory performance, the prefrontal cortex clusters were the only brain regions contributing significant variance, along with cumulative life stress, pubertal stage, and acute stressors. The precuneus was nearly significant, underscoring the need for strong focus on this region in future research examining stress-induced decrements in cognitive functioning.

Previous research suggests stress-induced neurobiological changes may exhibit asymmetries in effects. Work by Sullivan and Gratton (1998), for example, found asymmetric mesocortical dopamine activation dependent on the type of stress and that regulation of dopamine responses to multiple types of stress was tightly coupled in the right hemisphere. Such findings suggest a specialized role for right cortical mechanisms in the integration of emotional and physiological responses to stressful situations. In our sample, we found significant asymmetrical effects for the left frontal pole ($p<.001$), along with portions of the right ($p<.001$), and left occipital lobe ($p=.009$). These regions were however not strongly related to behavior measured in this study (i.e., spatial working memory). Of important note, anatomical variability means that the left and right-sided clusters are not necessarily in homologous locations despite the mirroring of clusters. However despite this limitation, such an analysis does provide some useful information that would not be available without

it. In particular the analysis can reveal that a cluster on one side is significantly different from a homologous cluster. This is important added value. Non-human animal models or research in adult humans employing positron emission tomography could clarify this possible stress-related asymmetry.

This study is one of the first to link cumulative life stress in childhood and adolescence to differences in PFC, and also to find that these structural alterations are associated with executive functioning. We found alterations in prefrontal gray matter (near the frontal poles) and white matter (near the forceps minor). Previous research suggests gray matter in this region is involved with strategic processes in memory retrieval, such as maintaining a pending state for subsequent retrieval and execution upon completion of the ongoing one (Koechlin & Hyafil, 2007). For the white matter results, these brain associations were found in a portion of tissue that connects the lateral and medial surfaces of the frontal lobes. Previous research with diffusion tensor imaging has found associations when looking at fractional anisotropy and cognitive functioning in certain clinical populations, with lower fractional anisotropy being related to poorer cognitive functioning (Van Hecke et al., 2010). Both of these ideas are consistent with our results.

By specifically linking cumulative life stress to focal neuroanatomical alterations, and linking those alterations to behavioral performance, our results suggest that structural differences in the PFC may serve as one mechanism through which greater cumulative life stress engenders poorer executive functioning. The PFC is central to attention, working memory, cognitive control, and emotion regulation processes, with damage to this region leading to impairments in planning, goal attainment, problem-solving ability, and the regulation of emotion (Braver, Cole, & Yarkoni, 2010; Stuss & Levine, 2002). Structural stress-induced changes in this region may lead to impairments in these processes, thereby undermining cognitive performance during development.

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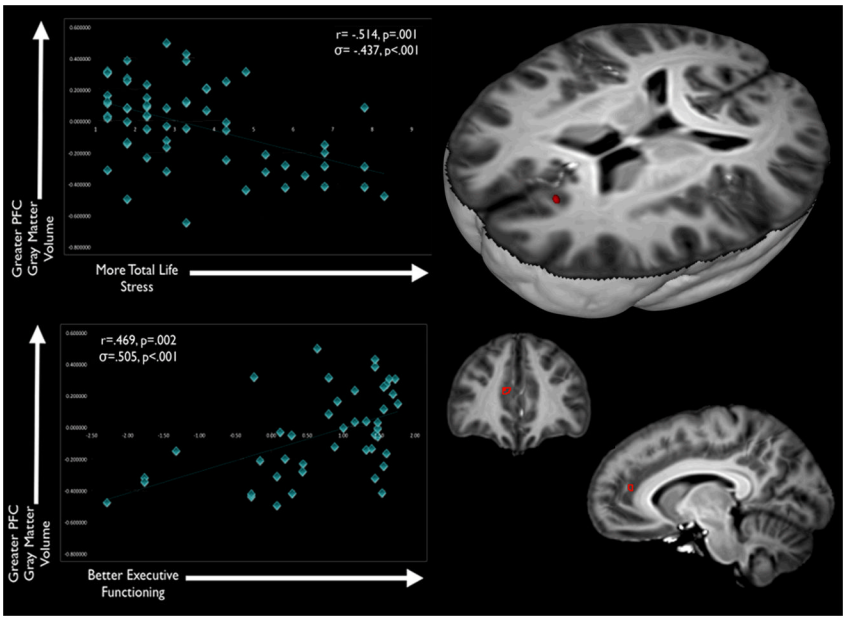

Figure 1.

Variations in prefrontal cortex gray matter are associated with individual differences in both cumulative life stress and spatial working memory performance. Brain images show the results of Logical AND conjunction analyses, in which prefrontal cortex gray matter is negatively associated with cumulative life stress ($p<.005$, uncorrected) and positively associated with SWM performance (as indexed by fewer errors and higher z-scores) ($p<.005$, uncorrected). The scatterplot for cumulative life stress and PFC gray matter volume is shown in the top left corner, while the scatterplot for spatial working memory performance and PFC gray matter volume is shown in the bottom left corner.

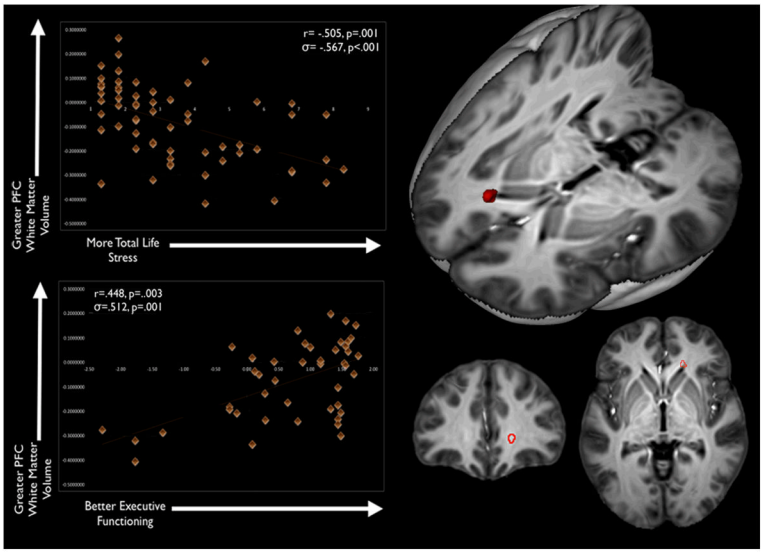

Figure 2.

Variations in prefrontal cortex white matter are associated with individual differences in both cumulative life stress and spatial working memory performance. Brain images show the results of Logical AND conjunction analyses, in which prefrontal cortex white matter is negatively associated with cumulative life stress ($p<.005$, uncorrected) and positively associated with SWM performance (as indexed by fewer errors and higher z-scores) ($p<.005$, uncorrected). The scatterplot for cumulative life stress and PFC white matter volume is shown in the top left corner, while the scatterplot for spatial working memory performance and PFC white matter volume is shown in the bottom left corner.

Table 1

	All Subjects	Subjects with MRI scans, YLSI, and CANTAB data	Subjects with ONLY MRI scans and YLSI data	P-value (comparing subjects with and without CANTAB data)
Age (Mean Months +/− SD)	142.357 (+/−21.1226) months	140.714 (+/−19.758) months	146.610 (+/−24.44) months	F=.954, p=.333
Puberty (Tanner Staging)	1.725 (+/−1.283)	1.7045 (+/− 1.280)	1.7794 (+/− 1.328)	F=.041, p=.840
Whole-Brain Volume (mm^3)	1431.792 (+/−130.30) mm^3	1431.202 (+/−117.34) mm^3	1433.3212 (+/−163.30) mm^3	F=.003, p=.955
Gender (Male, Female)	32 males, 29 females	22 males, 22 females	10 males, 7 females	χ^2=.383, p=.536
SES (as indexed by maternal education)	6.0851 (+/−.974)	6.20 (+/− .868)	5.75 (+/− 1.215)	F=1.946, p=.170

* NB: Maternal Education varied on a numeric scale from 1 to 8, denoting level of education obtained with possible choices of Grade School, High School or GED, 2 Year college, trade or technical school, 4 year college, or Graduate School

Table 2

Negative Associations between Cumulative Life Stress and Brain Structure (greater cumulative life stress was related to smaller volumes). All regions noted significant at p<.05 corrected for multiple comparisons, initial statistical threshold p=.0001 uncorrected.

Region	Cluster Size; corrected p-value	Pearson r-value	Cluster Coordinates (MNI space)
Right Putamen	249 voxels; p<.001	r = −0.525	+28, +7, +0
Left Putamen	62 voxels; p=.016	r = −0.377	−21, +11, +1
Right Occipital Lobe	233 voxels; p<.001	r = −0.419	+30, −88, −13
Right Occipital Lobe	72 voxels; p=.007	r = −0.439	+9, −88, −4
Left Occipital Lobe	65 voxels; p=.013	r = −0.456	−8, −96, −18
Right Middle Temporal Gyrus	175 voxels; p<.001	r = −0.418	+52, −11, −12
Left Middle Temporal Gyrus	151 voxels; p<.001	r = −0.469	−62, −17, −7
Right Parietal White Matter	109 voxels; p<.001	r = −0.429	+32, −27, +33
Right Middle Parietal Gyrus	67 voxels; p=.011	r = −0.411	+59, −42, +9
Right Precuneus	137 voxels; p=.001	r = −0.438	+8, −58, +14
Right Cerebellum	137 voxels; p<.001	r = −0.415	+41, −67, −22
Ventral Medial PFC	189 voxels; p<.001	r = −0.418	+0, +23, −24
Right Prefrontal White Matter	121 voxels; p<.001	r = −0.417	+18, +38, +1
Right Frontal White Matter	87 voxels; p=.002	r = −0.461	+18, −12, +42
Left Frontal Pole	98 voxels; p<.001	r = −0.422	−20, +62, −9
Left Anterior Cingulate	50 voxels; p=.043	r = −0.424	−11, +45, +17

NB: No Positive Associations with Cumulative Life Stress and Brain Structure survived correction for multiple comparisons

Table 3

Criterion 1 for Prefrontal Regions of Interest: Independent variable (cumulative life stress) is significantly associated with the mediator (the prefrontal regions of interest).

DV	IV	Unstandardized regression coefficients, Standard Error, p-value	F-change(df)	R-square change
Frontal Gray Matter (Left Anterior Cingulate Cluster)	Youth Life- Stress Interview	B=−0.059, SE= 0.016, p=.001	FΔ (1,57)=13.2	$R^2\Delta$=.173
Frontal White Matter (Right Prefrontal White Matter Cluster)	Youth Life- Stress Interview	B=−0.031, SE= 0.008, p=.001	FΔ (1,57)=13.6	$R^2\Delta$=.138

Table 4

Cluster Size (size in 1mm^3)	Pearson Correlation with YLSI, p-value	Spearman's Correlation with YLSI, p-value	CANTAB Z- score, Pearson Correlation with, p-value	CANTAB Z- score, Spearman's Correlation with, p-value	Approximate MNI Coordinates
49 voxels	r= −.505, p=.001	r_s= −.567; p<.001	Total Errors: r=.448, p=.003	Total Errors: r_s= .512; p<.001	(+18, +36, 0)
13 voxels	r= −.514, p=.001	r_s= −.437; p<.001	Total Errors: r=.469, p=.002	Total Errors: r_s= .505; p<.001	(−11, +45, +15)

*All results are partial correlations, controlling for individual difference in whole-brain volume and pubertal status

Table 5

Criteria 2 and 3 for Spatial Working Memory Total Errors Z-Scores, Cumulative Life Stress, and Prefrontal Regions Of Interest; Dependent Variable: Spatial Working Memory Total Errors Z-Scores (Higher z-score = fewer errors)

Model	Variables	Unstandardized regression coefficients, Standard Error, p-value	F-change(df)	R-square change, p values
1	Pubertal Status	B=.009, SE=.112, p=.937	FΔ(2,41)=5.933	$R^2\Delta$=.224, p=.005
	Cumulative Life Stress	B= −.245, SE=.072, p=.002		
2	Pubertal Status	B=.072, SE=.101, p=.481	FΔ (2,39)=8.037	$R^2\Delta$=.226, p=.001
	Cumulative Life Stress	B= −0.038, SE=.082, p=.647		
	Frontal Gray Matter (Left Anterior Cingulate Cluster)	B= 1.37, SE=.532, p=.014		
	Frontal White Matter (Right Prefrontal White Matter Cluster)	B=2.834, SE=.925, p=.004		

Criterion 2 requires that the independent variable (cumulative life stress) is significantly associated with the dependent variable (working memory performance) in the absence of the mediator. Criterion 3 requires that the mediator (prefrontal regions of interest) has a significant unique effect on the dependent variable after adjusting for the independent variable, and the effect of the independent variable on the dependent variable is reduced upon the addition of the mediator to the model.

Table 6

Brain regions not hypothesized, which were also related to both cumulative life stress and executive functioning

Region	Cluster Size (size in 1mm^3)	Correlation with YLSI, p-value	CANTAB Z-score, Correlation with, p- value	Approximate MNI Coordinates
Temporal Lobe (near Middle Temporal Gyrus)	41 voxels	r= −.346, p=.025	Total Errors: r=.560, p<.001	(+57, −6, −19)
Precuneus	21 voxels	r= −.381, p=.013	Total Errors: r=.457, p=.002	(+52, +8, −34)

*All results are partial correlations, controlling for individual difference in whole-brain volume and pubertal status

Table 7

Regression Dependent Variable: Spatial Working Memory Performance (as index by Total Error Z-Score; Higher z-score = fewer errors)

Model	Variables	Unstandardized regression coefficients, Standard Error, p-value	F-change(df)	R-square change, p values
1	Pubertal Stage	B=.113, SE=.109, p=.308	FΔ(1,41)=7.477	R^2Δ=.359, p<.001
	Cumulative Life Stress	B= −.205, SE=.068, p=.001		
2	Pubertal Stage	B=.134, SE=.112, p=.238	FΔ(1,39)=.847	R^2Δ=.014, p=.363
	Cumulative Life Stress	B= −.172, SE=.077, p=.030		
	Acute Stress	B=−0.35, SE=.038, p=.363		
3	Pubertal Stage	B=.092, SE=.104, p=.380	FΔ(2,37)=4.67	R^2Δ=.126, p=.016
	Cumulative Life Stress	B= −.010, SE=.088, p=.908		
	Acute Stress	B=−.033, SE=.035, p=.352		
	Frontal White Matter (Right Prefrontal White Matter Cluster)	B=2.142, SE=.995, p=.038		
	Frontal Gray Matter (Left Anterior Cingulate Cluster)	B=1.213, SE=.530, p=.028		

Table 8

Regression Dependent Variable: Spatial Working Memory Performance (as index by Total Error Z-Score; Higher z-score = fewer errors)

Model	Variables	Unstandardized regression coefficients, Standard Error, p-value
1	Pubertal Stage	B= .1, SE=.097, p=.308
	Right middle temporal gyrus	B= .720, SE=.732, p=.332
	Right parietal white matter	B=.440, SE=1.03, p=.671
	Prefrontal gray matter (near the left anterior cingulate)	B=1.410, SE=.490, p=.007
	Right prefrontal white matter	B=2.556, SE=1.110, p=.026

Table 9

Regression Dependent Variable: Spatial Working Memory Performance (as index by Total Error Z-Score; Higher z-score = fewer errors)

Model	Variables	Unstandardized regression coefficients, Standard Error, p-value
1	Cumulative Life Stress	B= −.244, SE=.07, p=.001
2	Cumulative Life Stress	B= .038, SE=.085, p=.661
	Acute Stress	B= −.039, SE=.035, p=.269
	Temporal Lobe (near Middle Temporal Gyrus)	B=.841, SE=.813, p=.308
	Precuneus Cluster	B=1.335, SE=.666, p=.053
	Frontal White Matter (Right Prefrontal White Matter Cluster)	B=2.020, SE=.988, p=.049
	Frontal Gray Matter (Left Anterior Cingulate Cluster)	B=1.065, SE=.5, p=.04

NB: Whole-brain volume has been controlled for with all brain regions of interest.

Table 10

Asymmetrical effects of cumulative life stress on the brain

Original Region (MNI Coordinates)	Mean of original cluster (+/− standard deviation)	Mean of Inverted Cluster (+/− standard deviation)	Test of the difference between regions
Right Putamen (+28, +7, +0)	−0.136 (+/−0.132)	−0.092 (+/0.122)	F=3.675 p=.056
Left Putamen (−21, +11, +10)	−0.161 (+/−0.123)	−0.149 (+/−0.127)	F=.259 p=.612
Right Occipital Lobe (+30, −88, −13)	0.076 (+/0.253)	0.057 (+/0.224	F=.191 p=.662
Right Occipital Lobe (+9, −88, −4)	0.017 (+/−0.236)	−0.158 (+/−0.264)	F=14.875 p<.001
Left Occipital Lobe (−8, −96, −18)	0.217 (+/−0.177)	0.136 (+/−0.158)	F=7.087 p=.009
Right Middle Temporal Gyrus (+52, −11, −12)	−0.102 (+/−0.218)	−0.127 (+/0.213)	F=.392 p=.553
Left Middle Temporal Gyrus (−62, −17, −7)	−0.0071 (+/− 0.199)	−0.024 (+/−0.218)	F=.187 p=.667
Right Parietal White Matter (+32, −27, +33)	−0.147 (+/−0.147)	−0.141 (+/−0.129)	F=.073 p=.788
Right Middle Parietal Gyrus (+59, −42, +9)	−0.117 (+/−0.25)	−0.141 (+/−0.25)	F=.274 p=.602
Right precuneus (+8, −58, +14)	0.019 (+/− 0.21)	−0.039 (+/−0.189)	F=2.504 p=.116
Right Cerebellum (+41, −67, −22)	−0.056 (+/−0.243)	−0.121 (+/−0.24)	F=2.154 p=.145
Right Prefrontal White Matter (+18, +38, +1)	−0.08 (+/0.15)	−0.047 (+/0.156)	F=1.483 p=.226
Right Frontal White Matter (+18, −12, +42)	−0.019 (+/−0.146)	−0.028 (+/−0.164)	F=.077 p=.782
Left Frontal Pole (−20, +62, −9)	−0.193 (+/−0.266)	−0.0396 (+/−0.158)	F=14.854 P<.001
Left Anterior Cingulate (−11, +45, +17)	−0.046 (+/−0.255)	−0.086 (+/−0.228)	F=.848 p=.359

The cluster in the ventral medial PFC (MNI coordinates: +0, +23, −24) was omitted from these analyses because it was located on the midline.