ABSTRACT

Title of Thesis:	Early Life Stress Predicts Decreased Total Brain Volume, Cortical Thickness, and Cognitive Functioning in School-Age Children
	Emma Chad-Friedman, Master of Science, 2019
Thesis Directed By:	Dr. Lea R. Dougherty, Associate Professor, Department of Psychology

Severe early life stress (ELS) (e.g., maltreatment/institutionalization) is associated with atypical neurological and cognitive development. Few studies have prospectively examined the neurological mechanisms underlying the cognitive deficits associated with less severe and more common forms of ELS. The current study examined the impact of common forms of ELS assessed during early childhood on children's brain volume, cortical thickness, and memory and executive functioning assessed three years later in school age children, controlling for current stress. Participants included 63 children (50.8% female) assessed during preschool (Wave 1 age: M=4.23 years, SD=.84) and three years later (Wave 2 age: M=7.19 years, SD=.89). ELS included low socioeconomic status, single parent household, low parental education, child exposure to parental depression, and child exposure to high parental hostility. Children's current life stress, cognitive abilities, and brain structure

were assessed at Wave 2. ELS predicted reduced total gray volume, cortex volume, right inferior parietal thickness, and right superior parietal thickness, controlling for covariates and current stress. ELS also predicted poorer memory and attention shifting, controlling for current stress. Right superior parietal thickness mediated the effects of ELS on story recall memory. Results highlight the possible consequences of less severe forms of ELS on brain volume and cognitive functioning, suggesting potential neural mechanisms to further explore. Early childhood may be a particularly important time for intervention efforts to mitigate the neural and cognitive risks associated with early stress exposure.

Early Life Stress Predicts Decreased Total Brain Volume, Cortical Thickness, and Cognitive Functioning in School-Age Children

by

Emma Chad-Friedman

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Advisory Committee:
 Associate Professor Lea R. Dougherty Chair
 Associate Professor Tracy Riggins
 Assistant Professor Jessica Magidson

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Chapter 1: Introduction

Early life stress (ELS) includes the exposure to environmental demands that challenge children's emotional and physical well-being beyond their coping abilities (Pechtel & Pizzagalli, 2011). ELS manifests as severe maltreatment, including physical and emotional abuse or neglect, as well as less severe forms of stress, such as poverty and parental psychopathology. While robust evidence supports the deleterious effects of severe ELS on children's neurological, cognitive, emotional and behavioral development, leading to increased risk for psychopathology and chronic health problems in adulthood (Belsky & de Haan, 2011; Felitti et al., 1998; Hughes et al., 2017; McLaughlin, Sheridan, & Nelson, 2017; Pechtel & Pizzagalli, 2011), little work has examined how less severe and more common forms of early stress "get under the skin" and impact development. Less severe forms of stress are often cumulative, chronic and characterized by rearing environments that lack rich cognitive stimulation, structure, and play (Luby, 2015), and have been proposed to hinder the development of core cognitive processes, such as memory and executive functioning via alternations in brain development. Deficits in memory and executive functioning hold clinical significance as they are transdiagnostic problems that underlie and predict worse outcomes across psychiatric disorders (Raver, Blair, & Willoughby, 2013). Nevertheless, little is known about the effects of common forms of ELS on these abilities in children nor their underlying neurological mechanisms.

ELS and Cognition

Childhood exposure to common, chronic stressors has been linked to deficits in executive functioning, including working memory, cognitive flexibility, and

inhibitory control (for reviews see Mani, Mullainathan, Shafir, & Zhao 2013; Raver et al. 2013; Shields, Sazma, & Yonelinas 2016). Children raised in stressful environments, especially within low SES families, are often exposed to less child-focused speech, complex speech, and fewer educational materials that shape typical neural and cognitive development (Johnson, Riis, & Noble, 2016; Luby, 2015). This early deprivation likely contributes to deficits in children's executive functioning and memory (Johnson et al., 2016). However, little research has examined neural mechanisms linking ELS and cognitive functioning. Cross-sectional studies have reported that prefrontal cortex volume mediates links between cumulative adversity and 11-year-old children's working memory (Hanson et al., 2012) and that total surface area mediates links between family income and inhibitory control and working memory in children ages 3 to18 years of age (Noble et al., 2015). Finally, a prospective study in children ages 4 to 17 years found that decreases in frontal and temporal gray matter mediate the relation between poverty and children's intelligence assessed 3 years later (Hair, Hanson, Wolfe, & Pollak, 2015). No study, however, has prospectively examined brain mechanisms linking ELS to core cognitive processes, namely executive functioning and memory ability, despite evidence that these cognitive processes may be particularly susceptible to the effects of stress (Gagnon & Wagner, 2016; Shields et al., 2016).

ELS and Brain Development

Research has documented that severe maltreatment predicts poor cognitive functioning and reductions in total brain volume structures, as well cortical thinning in the parietal, temporal and frontal lobes, regions implicated in memory and

executive functioning (McLaughlin et al., 2017; Pechtel & Pizzagalli, 2011; Saleh et al., 2017). Research on less severe forms of ELS, however, has predominantly focused on associations between ELS and decreased hippocampal and amygdala volume (Hair et al., 2015; Luby, 2015; Luby et al., 2013). Limited work has examined relations between less severe ELS and cortical thickness and surface area, two distinct morphometric properties of the brain that assess brain volume (Noble et al., 2015; Raznahan et al., 2011). While the cortex, which is comprised of gyri and sulci, likely has a strong genetic foundation (Fernández, Llinares☐Benadero, & Borrell, 2016), cortical thickness is thought to be a meaningful measure of developmental change that reflects the process of synaptic pruning and myelination and has been shown to relate to child behavior (McLaughlin et al., 2017). Research has reported concurrent associations between socioeconomic disadvantage and increased cortical thinning in children's frontal, temporal, and fusiform gyri (Lawson, Duda, Avants, Wu, & Farah, 2013; Piccolo et al., 2016), and decreased surface area in children's parietal, temporal, and frontal lobes (Noble et al., 2015). However, these studies used cross-sectional designs and socioeconomic status (SES) as the sole measure of ELS, which reflects just one possible source, as opposed to a multi-faceted, comprehensive approach to assessing ELS (Johnson et al., 2016). Further, only one study (Noble et al., 2015) examined whether these differences at the neural level were related to behavioral/cognitive outcomes. Given these limitations of previous studies, more research is needed to elucidate relations between ELS and differences in brain structure and whether they are associated with variations in behavior and cognition. Moreover, prospective longitudinal studies beginning in early

childhood are necessary to delineate the effects of early stress exposure on children's later brain structure and cognitive functioning during a developmental period when the brain may be most vulnerable to environmental insults (Gee & Casey, 2015).

Developmental Timing of Stress

Early childhood marks a period of rapid neural development, which leaves children particularly vulnerable to environmental influences. The absence of species-expectant experiences as a result of early chronic stress likely interferes with synaptogenesis, accelerating and increasing synapse elimination during this sensitive period in development (Gee & Casey, 2015; McLaughlin et al., 2017). Studies in animals demonstrate critical periods for life stress, with earlier stress predicting worse outcomes (Gee & Casey, 2015; Roque, Mesquita, Palha, Sousa, & Correia-Neves, 2014; Sabatini et al., 2007). Much of the human literature on timing of ELS has focused on adoption studies, which consistently find that earlier adoption is related to better outcomes (Gee & Casey, 2015; Pechtel & Pizzagalli, 2011; Tottenham et al., 2010). Moreover, relative to later stress, ELS predicted smaller prefrontal cortex volume and poorer working memory (Hanson et al., 2012) and altered prefrontal resting state functional connectivity in children (Demir et al., 2016). However, both studies examined current and early stress during the same assessment (Demir et al., 2016; Hanson et al., 2012), relying on retrospective recall of stress. While these studies highlight the significance of early, compared to later, stress exposure on children's development, more human research is needed to understand how the timing of stress differentially impacts brain structure and cognitive functioning across development.

The Current Study

The current study addresses these gaps by prospectively examining the effects of early childhood ELS on brain volume, cortical thickness, as well as memory and executive functioning in school age children, over and above current stress. We selected cortical thickness regions of interest important for episodic memory (fronto-parietal regions, medial temporal cortices: parahippocampal, entorhinal) and executive functioning (fronto-parietal regions), as well as total brain volume metrics, previously demonstrated to be impacted by severe ELS and important in multiple domains of cognitive functioning (total gray matter volume, cortical white matter volume, and cortex volume). The study aimed to examine whether 1) ELS at Wave 1 (W1: ages 3-5 years) predicts reduced total brain volume and cortical thickness three years later at Wave 2 (W2: ages 5-9 years), controlling for current stress, 2) ELS predicts poorer memory and executive functioning at W2, controlling for current stress, 3) ELS-predicted brain regions are concurrently associated with cognitive functioning, and 4) ELS-predicted brain regions mediate the effects of ELS on later memory and executive functioning.

These aims were tested in a longitudinal study that oversampled for children of depressed mothers; this sampling approach allowed us to capture greater variability in key components of ELS (parenting, family composition, stressful life events, SES). At W1, ELS was assessed using a comprehensive measure that included: low SES, exposure to parental depression, high levels of hostile parenting, single parent household, low parental education, and high levels of stressful events. We quantified greater ELS as the higher *number* of stressors present given that research indicates

that the total number of risk factors is more detrimental than the severity of any one

stressor (Sameroff, Seifer, Baldwin, & Baldwin, 1993). At W2, children completed a

structural MRI scan and a battery of memory and executive functioning tasks. We

hypothesized that ELS would predict reduced total brain volume and cortical

thickness, as well as poorer memory and executive functioning. We further expected

cortical thickness of ELS-predicted brain regions to mediate the longitudinal effects

of ELS on children's memory and executive functioning.

Chapter 2: Method
Participants

Participants were a subset of 63 children from a longitudinal study (*N*=175)

that oversampled offspring of parents with a history of depression (Dougherty, Tolep,

Smith, & Rose, 2013). Participants were recruited from the Washington, DC

metropolitan area using advertisements and a commercial mailing list. Children were

assessed at W1 (child age *M*=4.23 years, *SD*=.84) and approximately 3 years later at

W2 (child age *M*=7.19 years, *SD*=.89). At W1, eligible children were ages 3-5 years

old, had an English speaking biological parent with at least 50% legal custody, had no

biological parent with a history of bipolar or psychotic disorder, and had no parent-

reported history of developmental disabilities or serious medical conditions. At W2,

104 families returned to complete the behavioral sessions, and of these families, 64

agreed to participate in the neuroimaging assessment. Of the 64 children, one did not

complete a scan due to claustrophobia; thus, 63 children contributed data for analyses.

Sample characteristics are provided in Table 1.

Attrition analyses. We compared the subset of children who completed the W2 neuroimaging assessment (n=63) to children who completed the W1 baseline assessment but not the W2 neuroimaging assessment (n=112) and to children who completed the W2 behavioral assessment only (n=41). There were no significant differences on demographic and study variables with one exception: the neuroimaging subsample had higher scores on the ELS index (M=1.52, SD=1.24) compared to children who completed the W2 behavioral assessment only (M=.90, SD=1.16), t(89.87)=-2.60, p=.012.

Procedure

At W1, children and a biological parent attended a laboratory visit during which observations of parenting behavior were collected and parents completed clinical interviews about their child and their own mental health. Approximately 3 years later, children and parents attended a behavioral assessment, during which life stress, child memory and executive functioning were assessed, followed by a neuroimaging assessment. This study was approved by the University's Institutional Review Board and informed consent was obtained from parents and assent was obtained from children at least 7 years-old.

Wave 1 assessment

Early life stress. ELS included several indices of stress (see Table 1): 1) single parent household (0=absent, 1=present); 2) low parental education (0=at least one parent with a four-year college degree, 1=neither parent with a four-year college degree); 3) low family income (0=income ≥$40,000, 1=income< $40,000[1]); 4) high

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[1] A family of 4 making less than $42,850 qualifies as very low income for State of Maryland, based on 2010 income limit data from the US Department of Housing and Urban Development.

levels of observed parental hostility (0=hostility score<2 SD below the mean, 1=hostility score$\geq$2 SD above the mean); 5) child exposure to parental depression (0=no exposure, 1=exposure to parental depression from birth to W1); and 6) child experienced $\geq$4 stressful life events (moving, parental separation) in the 12 months prior to W1. The number of stressors present was summed, with higher scores indicating greater levels of ELS.

Parental hostility was assessed using an observational parent-child interaction task. Parental hostility was rated on a 5-point scale using five tasks, and scores were averaged across tasks (Cronbach alpha=0.76; intraclass correlation coefficient [ICC]=0.89, *n*=38). Children's exposure to parental depression was assessed using the Structured Clinical Interview for DSM-IV, Non-Patient version (First, Spitzer, Gibbon, & Williams, 2002), which incorporated a life-calendar approach to assess the timing of parental depression. Lastly, stressful life events involving the child and family in the 12 months prior to the interview were assessed with the Preschool Age Psychiatric Assessment (PAPA; Egger & Angold, 2004) interview conducted with primary caregivers.

Cognitive ability. General cognitive ability was assessed using the block design subtest of the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (Wechsler, 2002).

Wave 2 Assessment

Current life stressors. Proximal stressful life events involving the child and family in the 12 months prior to W2 were assessed from primary caregivers using the PAPA.

Memory ability. Children completed memory tasks to assess different aspects of episodic memory. Episodic memory, which captures the ability to remember past experiences and their contextual details, was assessed with a source memory task adapted from Ghetti, Mirandola, Angelini, Cornoldi, and Ciaramelli (2011), as well as a story recall task from the Children's Memory Scales, a well-validated assessment battery of children's memory (Cohen, 1997). The source memory task consisted of an encoding stage, in which children were shown three separate series of pictures and instructed to respond to each set of pictures with whether the object in the picture: (1) was living or nonliving; (2) could fit or not fit in a box; and (3) was soft or hard. In the retrieval stage (approximately 30-60 min later), children were shown the same pictures, as well as new pictures, and were instructed to identify whether the picture was old (they had seen it during encoding) or new. If they identified the picture as old, they were asked to recall what judgement they had made about the picture during encoding (living/non-living, fit/not fit, soft/hard). Total source memory scores were created by calculating the number of times the child accurately identified the context (living, fit, hard) out of the total number of times they correctly identified an old picture as old.

To assess children's story recall ability, children were read two stories and asked to recall them immediately and following a delay period of one hour, resulting in measures of immediate and delayed recall. Total scores were calculated by summing the total number of story units the child correctly remembered, with higher scores reflecting greater recall memory. The immediate and delayed recall scores

were highly correlated ($r=.92$, $p<.001$) and thus standardized and averaged to create a composite recall score.

Child executive functioning. Children completed three tasks to measure aspects of executive functioning: working memory, attention shifting, and inhibitory control. To assess working memory, children completed a task in which they were shown a series of colored triangles with each trial increasing in the number of triangles presented. Participants were asked in Part A to name the color of each triangle in the order of presentation and in Part B to name the color of each triangle in the reverse order. Children had to recall all items in at least one out of every two trials to move to the next item. A working memory score was calculated by averaging the total number of correct trials for parts A and B, with higher scores indicating greater working memory capacity. To assess attention shifting, children completed the Trail Making Test, during which they were asked to connect numbers followed by letters in the correct order as quickly as possible. The number of errors was summed to create a total score, which was then standardized and reverse-scored, so that higher scores indicated better attention shifting abilities. Lastly, to assess behavioral inhibitory control, children engaged in 10 trials of "Simon Says", during which they were instructed to follow the experimenter's movements when the researcher preceded the instruction with "Simon Says" and not to follow the experimenter's instruction when the instruction was not preceded by "Simon Says". On each trial, scores ranged from 0 to 3 (Simon trials: 0= child failed to move, 3=child fully made the correct movement; No Simon trials: 0= child incorrectly fully made the movement, 3=child

correctly did not move). A total score was calculated by summing the scores across the 10 trials, with higher scores indicating greater inhibitory control.

MRI assessment. Children completed a mock scan to become acclimated to the scanner and receive motion feedback. Children were scanned in a Siemens 3.0-T scanner (MAGNETOM Trio Tim System, Siemens Medical Solutions, Erlangen, Germany) with a 12-channel coil. Children participated in a 4 minute and 18 second high-resolution T1 magnetization-prepared rapid gradient-echo (MPRAGE) structural scan sequence consisting of 176 contiguous sagittal slices ($1.0mm^3$; 1900ms TR; 2.52ms TE; 900ms inversion time; 9° flip angle; pixel matrix=256x256). Images were analyzed in the standard automatic segmentation software Freesurfer Version 5.1.0 (surfer.nmr.mgh.harvard.edu; (Fischl, 2012). Total gray matter volume, cortical white matter volume, cortex volume, and intracranial volume (ICV) values were extracted for each participant. Cortical thickness was calculated by measuring the distance from the gray/white matter boundary to the pial boundary. Boundaries separating gray/white and pial surfaces were visually examined to ensure accuracy and manual edits were made on about 35% of the sample and involved fewer than 20 slices per participant. The Desikan-Killiany Atlas was used for cortical parcellation (Desikan et al., 2006). Right and left hemispheres were analyzed separately.

Regions of interest. We selected regions and whole brain measures hypothesized to be associated with early stress, executive functioning, and episodic memory (Gagnon & Wagner, 2016; McLaughlin et al., 2017; Shields et al., 2016). Specifically, we included total gray matter volume, white matter volume, and cortex volume as whole brain measurements. We selected specific thickness regions based

on prior research indicating associations between episodic memory and the posterior parietal cortex, hippocampus, and prefrontal cortex (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Hutchinson, Uncapher, & Wagner, 2009; Sestieri, Shulman, & Corbetta, 2017; Tulving & Markowitsch, 1998; Uncapher & Wagner, 2009; Vilberg & Rugg, 2008), and associations between executive functioning and fronto-parietal networks (Lee, Wallace, Raznahan, Clasen, & Giedd, 2014; Van Petten et al., 2004; Yuan & Raz, 2014). Regions of interest consisted of the right and left superior parietal cortex, inferior parietal cortex, entorhinal cortex, parahippocampal cortex, and middle frontal cortex. For descriptive statistics on all brain regions, see Supplementary Material Table 1.

Data Analysis Plan

First, multiple regressions were used to examine whether W1 ELS predicted whole brain volume metrics and cortical thickness, as well as executive functioning and memory at W2. The Benjamini-Hochberg false discovery rate (FDR; (Benjamini & Hochberg, 1995) correction for multiple comparisons was employed for each domain of analyses; results that survived FDR corrections at $p<.05$ are reported. Dependent variables in whole brain analyses included total gray matter volume, cortex volume, and cortical white matter volume. Independent variables included child's W2 age, W2 current stressors, and W1 ELS. In models predicting W2 cortical thickness, dependent variables included right and left superior parietal, inferior parietal, entorhinal, parahippocampal, and middle frontal cortices. In each of these models, independent variables included child's W2 age, ICV, W2 current stressors, and W1 ELS. In models predicting W2 cognitive functioning, dependent variables

included source memory, story recall, attention shifting, working memory, and inhibitory control. In each of the models predicting W2 cognitive functioning, independent variables included child age and current stressors at W2 and cognitive ability and ELS at W1.

Next, multiple regressions assessed relations between ELS-predicted total brain volume and cortical thickness in each region and cognitive variables at W2. Lastly, we assessed whether ELS-predicted volume and thickness mediated associations between W1 ELS and W2 cognitive variables. The indirect path from ELS to a specific memory or executive functioning variable was tested for all paths in which the memory or executive functioning variable was associated with ELS-predicted volume and thickness. Mediation analyses were conducted using Andrew Hayes' PROCESS Macro in SPSS (Hayes, 2009; Hayes & Scharkow, 2013). Each mediation model included W1 ELS as the predictor, ELS-predicted volume and thickness as the mediator, and W2 memory (recall or source) or executive functioning (working memory, inhibitory control, or attention shifting) as the dependent variable. Covariates included W1 cognitive ability and W2 child age. Child sex was also examined as a potential covariate across all models described above and included when it was significantly correlated with the dependent variable.

Chapter 3: Results

Covariates

W2 child age was not associated with any brain region of interest. Age was positively associated with source memory (r=.33, p=.009), story recall (r=.27, p=.035), attention shifting (r=.41, p=.001), and working memory (r=.29, p=.022).

Child sex was associated with cortical white matter, (r=-.37, p=.003), with males

having greater white matter volume than females. Child sex was also associated with

right superior parietal thickness (r= .31, p=.014), left superior parietal thickness

(r=.29, p=.022), right entorhinal thickness (r=.30, p=.016), and right middle frontal

thickness (r=.28, p=.029), with females having greater thickness than males.

ELS and Total Brain Volume and Cortical Thickness

After controlling for age and current stress, ELS predicted lower total gray

matter volume, (b=-15953.02, SE=6194.70, pr=-.32, p=.013) and cortex volume (b=-

14471.30, SE=5240.46, pr=-.34, p= .008), but not cortical white matter volume (b=-

4988.04, SE=4009.76, pr=-.16, p=.218) (see Figure 1).

We next examined whether ELS predicted reduced regional thickness.

Bivariate correlations between W1 ELS and thickness in each region are reported in

Supplementary Material Table 2. After adjusting for covariates, which included ICV

and current stressors, ELS predicted reduced right inferior parietal thickness (b=-.03,

SE=.02, pr=-.26, p=.045), and marginally significantly predicted reduced right

superior parietal thickness (b=-.03, SE= .02, pr=-.25, p=.052) (see Figure 1).

ELS and W2 Cognitive Functioning

Bivariate correlations between ELS and cognitive variables are reported in

Table 2. After adjusting for W1 cognitive ability, W2 age and W2 current stressors,

ELS predicted poorer performance on source memory (b=-.04, SE=.02, pr=-.28,

p=.034), story recall (b=-.24, SE=.10, pr=-.31, p=.017), and attention shifting (b= -23,

SE= .10, pr = -.30, p=.023). ELS did not predict inhibitory control or working

memory at W2.

Associations between Brain Volume and Thickness and Cognitive Function

We focused on concurrent associations between cognitive functioning and brain regions that were significantly predicted by ELS. Therefore, we tested whether total gray matter volume, cortex volume and the right inferior and superior parietal thickness regions were associated with W2 memory and executive functioning. Bivariate correlations are reported in Table 2. After controlling for age, total gray volume was positively associated with story recall (b=4.48e-6, SE < .01, pr=.276, p=.030; Figure 2) and attention shifting (b=4.42e-6, SE< .001, pr=.29, p=.022; Figure 2). Similarly, cortex volume was positively associated with story recall (b=5.49e-6, SE<.001, pr=.289, p=.023; Figure 2) and attention shifting (b=4.87e-6, SE<.01, pr= .275, p=.032; Figure 2). Right superior parietal thickness was positively associated with story recall (b=2.232, SE=.652, pr=.404, p=.001; Figure 2). No other associations were found between ELS-predicted brain regions and cognitive functioning.

Do Brain Regions of interest Mediate the Effects of ELS on Cognitive Functioning?

We tested whether ELS-predicted brain metrics (i.e., total gray matter, cortex volume, right superior parietal thickness, right inferior parietal thickness) mediated the effects of ELS on W2 story recall, source memory, and attention shifting ability, controlling for ICV, W2 age, and W1 cognitive ability. We only tested mediation for pathways in which ELS-predicted regions were associated with specific memory or executive functioning variables. This resulted in five tests of mediation (total gray to recall and attention shifting; cortex volume to recall and attention shifting; right

superior parietal to recall). We found a significant indirect effect of ELS on story recall through right superior parietal thickness (b [10,000 bootstrapped samples]=-.09, SE=.06, bias corrected 95% CI [-.24, -.005]). Specifically, greater ELS predicted decreased right superior parietal thickness, which predicted poorer recall ability. No other indirect effects were significant.

Chapter 4: Discussion

The study's findings indicate that children who experience greater levels of ELS show reduced brain volume and cortical thickness and poorer cognitive functions three years following stress exposure. To our knowledge, this is the first longitudinal study that examined whether less severe and more common ELS predicted reduced brain metrics and cognitive functioning, controlling for the effects of current life stress. Results revealed prospective associations between ELS and total brain volume structures (total gray matter and cortex volume), as well as cortical thickness regions (right superior parietal and right inferior parietal cortex), after controlling for covariates and current life stress. Greater ELS predicted smaller total brain volume and thinner parietal cortices, as well as poorer story recall, source memory, and attention shifting ability 3 years later. Importantly, right superior parietal thickness mediated the relation between ELS and story recall memory, controlling for covariates, total brain volume, and current life stress. Thus, this study both demonstrated regional specificity in the effects of ELS on the thickness of parietal regions and also extended findings on the widespread effects of poverty and severe ELS on total brain volume to less severe, more common ELS (Hair et al., 2015).

These findings begin to fill gaps in the literature on associations between common, chronic ELS and brain structure and behavior. Whereas previous studies have demonstrated links between low socioeconomic and reduced total brain, amygdala, and hippocampal volume (Johnson et al., 2016; Luby, 2015), only two cross-sectional studies assessed cortical thickness, and only one of these examined regional specificity in parietal cortices and did not find any effects (Noble et al., 2015; Piccolo et al., 2016). However, these previous studies did not capture other chronic stressors that often co-occur with low socioeconomic status (Bradley & Corwyn, 2002) and characterize many children's early rearing environments (Barch, Belden, Tillman, Whalen, & Luby, 2017). This comprehensive approach to defining ELS contributes to our understanding on how common forms of early adversity contribute to later childhood cognitive deficits. The present results show a compounding effect of less severe forms of early adversity on not only smaller total gray volume, but also cortex volume and reduced cortical thickness in parietal regions associated with memory. Interestingly, these findings are similar to many of the results reported in the severe ELS literature (McLaughlin et al., 2017, 2014), suggesting that different forms of stress may have similar effects on brain structures implicated in cognitive processes.

Although untested in the current study, one possible mechanism underlying the effects of ELS on memory and executive functioning is the limited cognitive stimulation present in a child's early life (McLaughlin et al., 2017); fewer games, books, child-directed talk and consistent caregiver-child interaction in the homes of children exposed to ELS may lead to fewer synaptic connections, increased synaptic

pruning of these unused connections, and thus, exaggerated cortical thinning in these regions implicated in deficits in executive functions and memory processes (McLaughlin et al., 2017). Results from this study also confirm previous findings on the link between ELS and deficits in executive functions (McLaughlin et al., 2017; Raver et al., 2013; Shields et al., 2016). Additionally, this study demonstrated associations between ELS and source and recall memory, highlighting the widespread implications of prevalent forms of early adversity on a variety of critical cognitive functions that set the stage for academic, professional, and psychosocial success throughout the life span.

Across the early stress literature, no previous study has longitudinally assessed the influence of early, relative to later childhood stress exposure on brain and cognitive outcomes, which is critical for delineating periods in childhood when intervention efforts might be most beneficial. Consistent with cross-sectional work and animal studies (Gee & Casey, 2015; Hanson et al., 2012; Sabatini et al., 2007), this study found that early, after accounting for later childhood stress, predicted atypical neurological and worse cognitive outcomes. These findings highlight the unique consequences of stress endured during early childhood on the developing brain and memory and executive functioning processes.

Among the strengths of this study are the comprehensive assessment of ELS, the longitudinal design that allowed us to delineate early and later stress exposure, and our use of developmentally appropriate cognitive tasks that targeted various aspects of executive functioning and memory to parse apart distinct aspects of these heterogeneous processes. This study was also able to demonstrate that ELS predicted

later cognitive abilities after accounting for children's early cognitive ability. Nevertheless, one of the limitations of the current study is that we did not assess brain structure at W1 and therefore could not examine changes in brain metrics over time. Second, our sample size was relatively small and may have been underpowered to observe additional mediation pathways. Third, children were oversampled for mothers with a history of depression, which makes the sample less representative than the general population.

Future studies should attempt to replicate these results in larger samples with repeated neuroimaging assessments over time. An important direction is to examine the temporal unfolding of structural brain development and cognitive functions and possible mediators over time. Additionally, future studies should examine the construct of ELS as both a count and severity measure to clarify whether greater stress should be captured as a greater *number* of stressors experienced or the experience of one or more *severe* stressors (McLaughlin, 2016). Finally, future studies should test different mediation pathways (including directly testing cognitive stimulation in the environment) linking ELS to cortical thinning and cognitive functions.

In conclusion, this study contributes to a growing literature demonstrating the detrimental consequences of early adverse experiences on the developing brain and cognition that may cause poorer functioning throughout the lifespan. Our findings may also provide insight into the mechanisms underlying educational and mental health disparities among low income, minority children who can be disproportionately exposed to early stress. Insights from this study can inform the

development of early prevention and intervention efforts that target children at

increased risk for falling behind cognitively, emotionally, and academically.

Critically, this study may aid in the development of policies to support children born

in families lacking sufficient resources to optimize long-term achievement.

Tables

Table 1

Descriptive statistics of sample and study variables (*n*=63)

	Wave 1		Wave 2	
Demographic Characteristics				
Child mean age: years SD; range	4.23 (.84)	3-5.96	7.19 (.89)	5.57-10
Mother's mean age: years SD; range	35.65 (6.57)	21-50	39.14 (6.41)	24.98-53.38
Father's mean age: years SD; range	37.72 (6.97)	23-54	42.30 (6.08)	31.08-54.87
Child sex: female *n* (%)	32	(50.8)		
Child race: *n* (%)				
White	30	(47.6)		
Black/African-American	22	(35.9)		
Multi-racial/Other	9	(14.2)		
Child Hispanic ethnicity: *n* (%)	9	(14.3)		
Biological parents' marital status: *n* (%)				
Married	38	(60.3)		
Divorced, separated, or widowed	6	(9.5)		
Never married	19	(30.2)		

	Wave 1			
Early Life Stressors				
Mean early life stress Index: SD; range	1.52 (1.24)	0-6		
Single parent household: *n* (%)	16	(25.4)		
Neither parent attended college: *n* (%)	17	(27)		
Household income < $40,000: *n* (%)	7	(11.1)		
>4 stressors in past 12 months: *n* (%)	18	(28.6)		
Child exposure to parental depression: *n* (%)	31	(49.2)		
Mother	25	(39.7)		
Father	6	(9.5)		

			Wave 2	
Parental hostility ≥ 2 SDs above the mean: *n* (%)	7	(11.1)		
Block design	10.13 (3.16)	4-18		
Cognitive Ability				
Source memory			.60 (.19)	0-.95
Story recall			-.01 (1.01)	-2.19-1.97
Working memory			8.89 (2.40)	2-14
Attention shifting			0 (1)	-3.10-1.33
Inhibitory control			23.1 (3.8)	15-30
Current life stress			1.89 (1.43)	0-5

Table 2.

Bivariate Correlations among ELS, cognitive functioning, and ELS-predicted brain metrics

	1	2	3	4	5	6	7	8	9	10
1. Wave 1 ELS	-									
Wave 2 Cognitive Functioning										
2. Source Memory	-.34**	-								
3. Story Recall	-.31**	.35**	-							
4. Attention Shifting	-.41**	.32*	.48**	-						
5. Working Memory	-.15	.24*	.24*	.31*	-					
6. Inhibitory Control	-.04	.27**	.12	.18	.09	-				
Wave 2 ELS-predicted Brain Metrics of Interest										
7. Total Gray Volume	-.33**	.16	.27*	.28*	.03	.15	-			
8. Cortex Volume	-.35**	.20	.29*	.26*	.03	.14	.98**	-		
9. Right Inferior Parietal Thickness	-.34**	.17	.24	.14	-.04	-.09	.39**	.42**	-	
10. Right Superior Parietal Thickness	-.39**	.15	.41**	.17	-.10	-.05	.45**	.49**	.72**	-

Notes: ELS=early life stress; *p<.05, **p<.01.

Figure 1. Early life stress predicted reduced a) total gray volume, b) cortex volume, c) right superior parietal thickness, and d) right inferior parietal thickness.
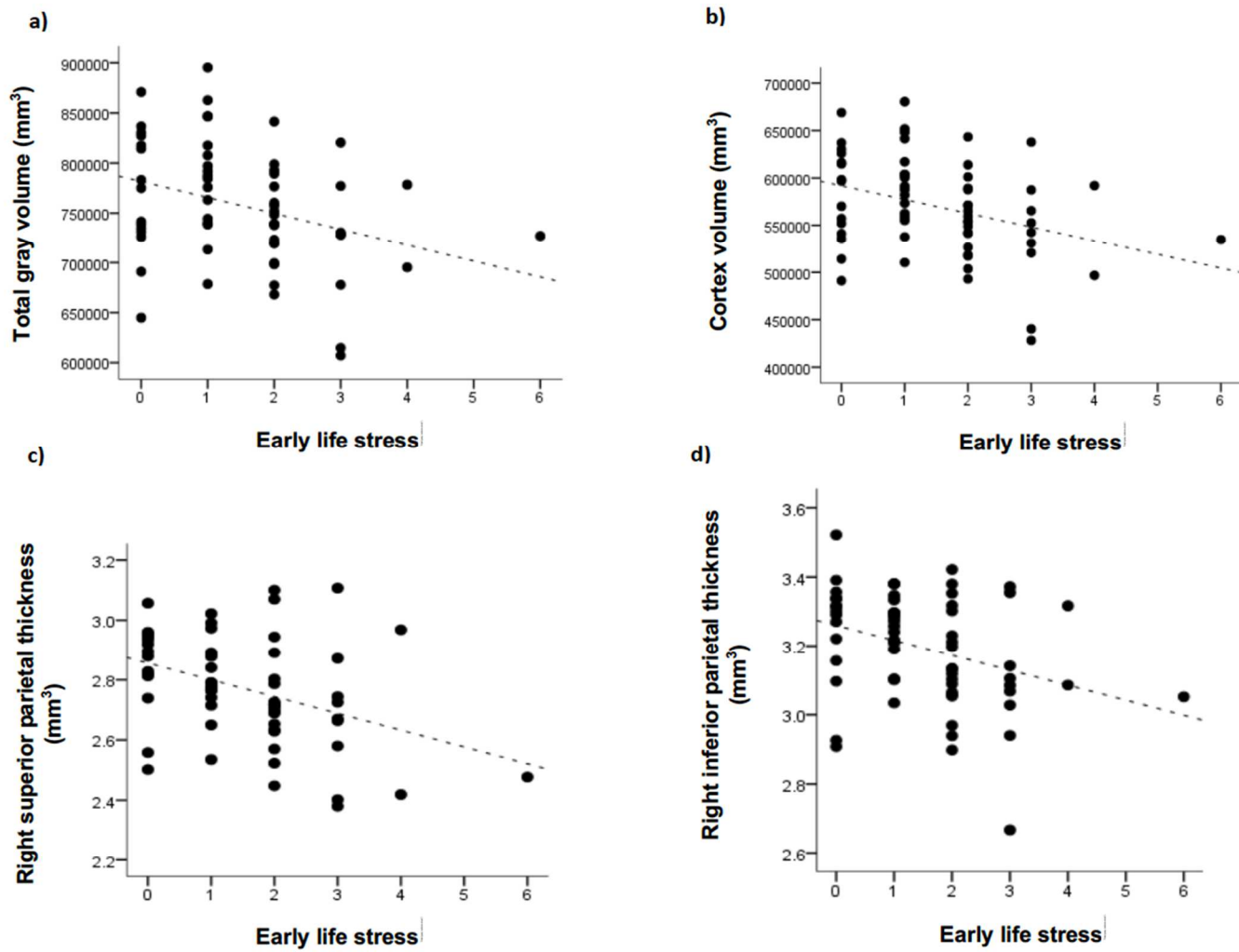
Figure 2. Brain regions associated with memory and executive functioning: a) association between total gray volume and attention shifting ability; b) association between total gray volume and story recall; c) association between cortex volume and attention shifting ability; d) association between cortex volume and story recall; e) association between right superior parietal thickness and story recall.
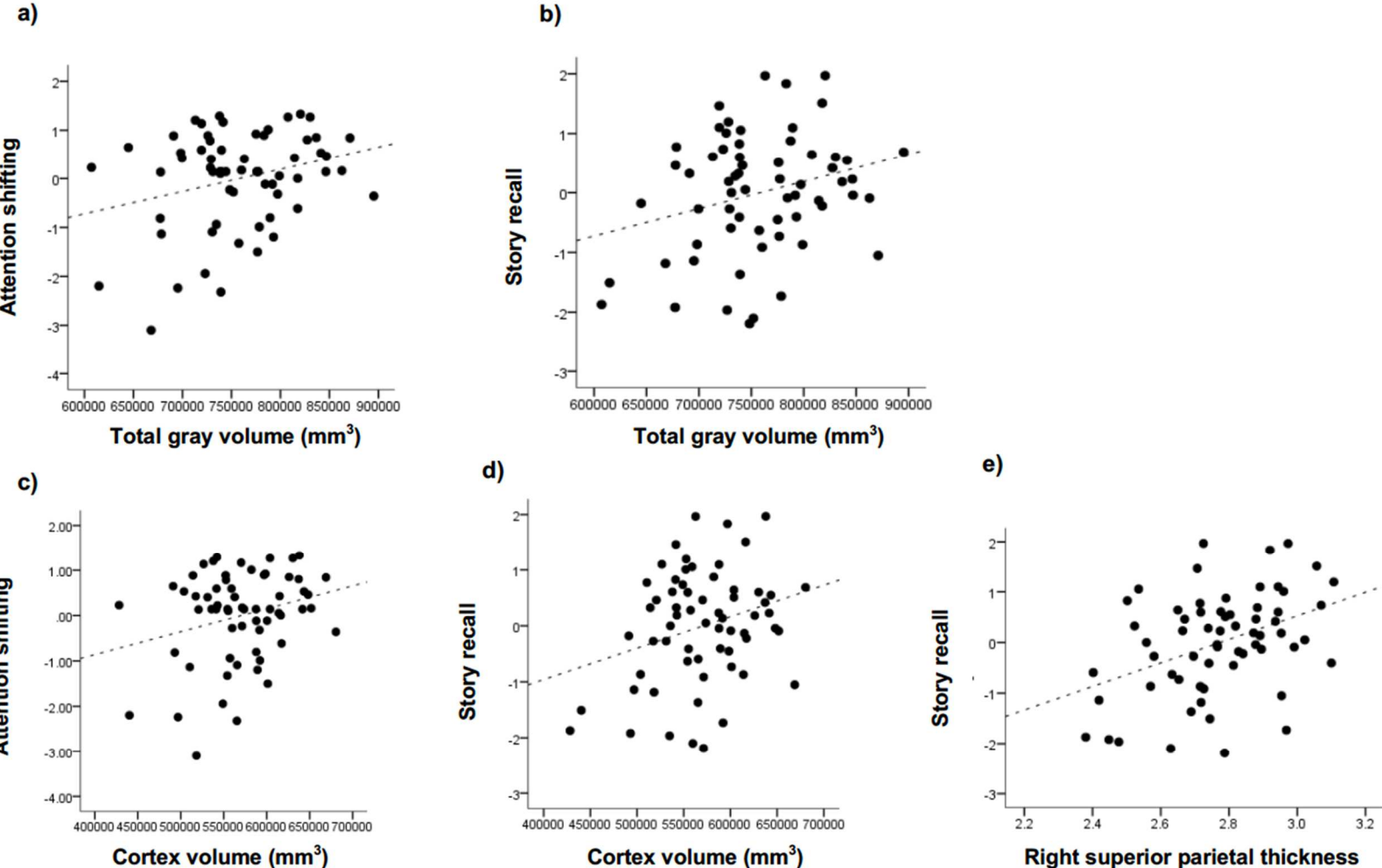
Appendices

Supplementary materials

Supplementary Table 1. *Wave 2 brain volume and thickness.*

	Mean (*SD*)	Range
Total gray volume	757236.38 (59983.28)	607181.8-895304.80
Cortex volume	569670.68 (51311.99)	428229.85-680432.80
Cortical white volume	407279.37 (37917.98)	335233.42-491961.17
Right superior parietal thickness	2.77 (.18)	2.38-3.11
Right inferior parietal thickness	3.19 (.16)	2.67-3.52
Right parahippocampal thickness	3.07 (.30)	2.48-3.80
Right entorhinal thickness	3.73 (.36)	2.83-4.69
Right middle frontal thickness	2.92 (.22)	2.20-3.42
Left superior parietal thickness	2.76 (.17)	2.34-3.06
Left inferior parietal thickness	3.14 (.18)	2.66-3.45
Left parahippocampal thickness	3.07 (.32)	2.36-3.74
Left entorhinal thickness	3.56 (.37)	2.42-4.27
Left middle frontal thickness	2.99 (.17)	2.57-3.33

Notes: Total volume measured in mm^3; cortical thickness measured in mm.

Supplementary Table 2. *Bivariate Correlations among early life stress (ELS), total brain volume and cortical thickness regions.*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Wave 1 ELS	-													
Wave 2 Total Brain Volume and Cortical Thickness														
2. Total Gray Volume	-.33**	-												
3. Cortex Volume	-.35**	.98**	-											
4. Cortical White Volume	-.20	.70**	.67**	-										
5. Right Inferior Parietal Thickness	-.34**	.39**	.42**	.11	-									
6. Right Superior Parietal Thickness	-.39**	.45**	.49**	.06	.73**	-								
7. Right Entorhinal Thickness	-.12	.21	.22	-.03	.24	-.17	-							
8. Right Parahippocampal Thickness	-.19	.24	.24	.16	.32*	-.17	.13	-						
9. Right Middle Frontal Thickness	-.12	.39**	.42**	-.01	.55**	-.17	.13	-.35**	-					
10. Left Inferior Parietal Thickness	-.28*	.50**	.54**	.19	.74**	-.17	.13	-.35**	-.03	-				
11. Left Superior Parietal Thickness	-.26*	.36**	.41**	.05	.65**	-.17	.13	-.35**	-.03	-.01	-			
12. Left Entorhinal Thickness	-.12	.33**	.37**	.15	-.17	-.17	.13	-.35**	-.03	-.01	.28*	-		
13. Left Parahippocampal Thickness	-.07	.21	.20	.09	-.17	-.17	.13	-.35**	-.03	-.01	.28*	.12	-	
14. Left Middle Frontal Thickness	-.27*	.47**	.52**	.08	-.17	-.17	.13	-.35**	-.03	-.01	.28*	.12	.12	-

Notes: *p<.05, **p<.01.

Supplementary Table 3. *Bivariate correlations among separate early life stress indices, current stress, and Wave 2 outcome measures.*

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1.	Single parent household	-																	
2.	Low parental education	.30*	-																
3.	Income< $40,000	.39**	.37**	-															
4.	>4 stressors in past 12 months	.07	.13	-.01	-														
5.	Stressors in past 12 months (continuous)	.06	.22	.13	.83**	-													
6.	Parental depression exposure	.01	-.10	-.15	.12	.09	-												
7.	Parental hostility≥2 SDs above mean	.14	.24	.05	.20	.12	.06	-											
8.	Parental hostility (continuous)	.24	.38**	.12	.23	.17	.02	.86**	-										
9.	W1 ELS (as used in manuscript)[a]	.70**	.61**	.58**	.52**	.46**	.53**	.42**	.47**	-									
10.	W1 ELS (alternative)[b]	.57**	.73**	.61**	.27**	.36**	.11	.35**	.46**	.75**	-								
11.	Total gray matter volume	-.33**	-.35**	-.17	-.09	-.09	.05	-.18	-.36**	-.33**	-.46**	-							
12.	Cortex volume	-.34**	-.34**	-.14	-.10	-.09	-.01	-.18	-.34**	-.35**	-.45**	.98**	-						
13.	Right superior parietal thickness	-.25	-.24	-.30*	-.05	-.01	-.28*	-.04	-.12	-.39**	-.27**	.45**	.49**	-					
14.	Right inferior parietal thickness	-.19	-.16	-.05	-.14	-.03	-.32*	-.08	-.17	-.34**	-.16	.39**	.42**	.72**	-				
15.	Source memory	-.26*	-.17	-.01	-.24	-.18	-.14	-.24	-.28*	-.34**	-.29**	.16	.20	.15	.17	-			
16.	Story recall	-.32*	-.41**	-.32*	-.10	-.08	-.02	-.13	-.22	-.31**	-.37**	.27*	.29*	.41**	.24*	.35**	-		
17.	Attention shifting	-.28*	-.38**	-.05	-.14	-.22	-.15	-.12	-.29*	-.40**	-.45**	.28*	.26*	.17	.14	.32**	.48**	-	
18.	Wave 2 current life stress	-.08	.07	.01	.26*	.28*	.23	.28*	.25*	.15	.20*	-.12	-.14	-.21	-.23	-.12	-.26*	-.16	-

Notes: *p*<.05, **p*<.005; [a]W1 ELS index was calculated using empirically derived cut-offs for continuous variables; [b]W1 ELS alternative index used continuous indicators of parental hostility and count of stressors.

Methods

To test the robustness of our ELS index, we computed an alternative ELS index that kept observed parental hostility and life stressors continuous, rather than dichotomizing them to indicate severe levels (≥90%). Thus, this ELS index included 1) single parent household (0=absent, 1=present); 2) low parental education (0=at least one parent with a four-year college degree, 1=neither parent with a four-year college degree); 3) low family income (0=income ≥$40,000, 1=income< $40,000[2]); 4) observed parental hostility (continuous); 5) child exposure to parental depression (0=no exposure, 1=exposure to parental depression from birth to W1); and 6) continuous count of the number of stressful life events the child experienced in the past 12 months (moving, separation from parent, parental divorce). All of these stressors were standardized and summed to create an ELS index, similar to that used in Barch et al., 2017.

Results

As seen in Supplementary Table 3, the alternative ELS index was correlated with all of the same brain and cognitive variables as was the original ELS index reported in the manuscript. When controlling for appropriate covariates (as described in the manuscript), the alternative ELS index significantly predicted reduced total gray matter volume (b=-3924.99, SE=1288.98, pr=-.37, p=.003), cortex volume (b=-3480.59, SE=1143.90, pr=-.37, p=.004), right superior parietal thickness (b=-.02, SE=.007, pr=-.31, p=.015), and right inferior parietal thickness (b=-.01, SE=.01, pr=-.23, p=.08). The alternative ELS index also significantly predicted poorer attention shifting (b=-.10, SE=.04, pr=-.34, p=.008), source memory (b=-.02, SE=007, pr=-.26, p=.049), and story recall (b=-.10, SE=.04, pr=-.31, p=.015). Additionally, the indirect effect of this

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[1]A family of 4 making less than $42,850 qualifies as very low income for State of Maryland, based on 2010 income limit data from the US Department of Housing and Urban Development.

alternative ELS index on story recall via story recall was significant (b [10,000 bootstrapped samples]=-.04, SE=.03, bias corrected 95% CI [-.10, -.003]). Results using this alternative ELS index are similar to those using dichotomous indicators of each of the stressors presented in the manuscript, highlighting that findings are robust and are not driven by artificial cut offs of continuous variables.

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