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Early childhood cumulative risk is associated with decreased global brain measures, cortical thickness, and cognitive functioning in school-age children

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Abstract

Children exposed to multiple risk factors early in life are increasingly more likely to suffer from a host of cognitive impairments across development. However, little work has identified the neurobiological mechanisms linking early cumulative risk and cognitive functioning. The current study examined the impact of cumulative risk assessed during early childhood on neural and cognitive outcomes measured 3 years later when children were school-aged. Participants included 63 children assessed during preschool (age: *M* = 4.23 years, *SD* = 0.84) and 3 years later (age: *M* = 7.19 years, *SD* = 0.89). Early cumulative risk was defined by the presence of low family income, a single parent household, low parental education, child exposure to parental depression, child exposure to high parental hostility, and high levels of stressful life events. Children's exposure to stressors in the past year, cognitive abilities, and brain structure were assessed at follow-up. Early cumulative risk was prospectively associated with reduced total gray matter volume, cortex volume, right superior parietal and inferior parietal thickness, and poorer attention shifting and memory. Right superior parietal thickness mediated associations between early risk and recall memory. Results highlight neural variations associated with early cumulative risk and suggest potential neural pathways from early risk to later childhood cognitive impairments.

KEYWORDS
brain structure, cortical thickness, early cumulative risk, executive function, memory

1 | INTRODUCTION

Many children experience a single risk factor during early childhood and endure little to no negative consequences (Brooks-Gunn & Duncan, 1997; Evans, Li, & Whipple, 2013). However, children exposed to multiple risk factors early in life are increasingly more likely to suffer from a host of psychological problems and cognitive deficits both in childhood and across development (Evans et al., 2013). Cumulative risk models are based on the theoretical and empirical framework that negative outcomes are enhanced when multiple risk factors are combined and that evaluating a single risk factor may underestimate the impact of risk factors on healthy child development (Anda et al., 2006; Evans et al., 2013; Hughes et al., 2017). Examining the effects of cumulative risk on brain development may shed light on pathways by which early childhood risks "get under the skin" and lead to multiple areas of maladjustment (for reviews see Belsky & de Haan, 2011; Johnson, Riis, & Noble, 2016; Luby, 2015).

Multiple neural measures can be used to examine the impact of cumulative risk on brain development, including global brain measures (e.g., total cortex volume or gray matter volume) as well more specific measures (e.g., thickness of gray matter within particular regions). These measures may reflect the outcome of multiple neural processes underlying brain development including: synaptic proliferation, myelination, and pruning. These processes are particularly influenced by

experiences that occur in the first few years of life (Tierney & Nelson, 2009). Therefore, differences in brain measures may capture widespread impairments across multiple domains of cognitive functioning (Menary et al., 2013). Thus, the goal of this study is to investigate global measures and cortical thickness regions as mediators through which early cumulative risk impacts cognitive functioning in childhood.

1.1 | Cumulative risk and cognition

Executive functioning and episodic memory are core cognitive processes that undergo rapid development during childhood (Ackerman & Friedman-Krauss, 2017; Ghetti & Lee, 2011). Executive functions refer to a group of mental processes, such as attention shifting, working memory, and inhibitory control, which support goal-directed behaviors. Episodic memory refers to the ability to remember previous experiences and contextual information (Ackerman & Friedman-Krauss, 2017; Ghetti & Lee, 2011). The cumulative risk literature, although limited, has shown associations between multiple risk exposures and deficits in children's cognition, specifically, executive functioning, and academic achievement (Lengua, Honorado, & Bush, 2007; Rouse & Fantuzzo, 2009; Stanton-Chapman, Chapman, Kaiser, & Hancock, 2004; Wade, Browne, Plamondon, Daniel, & Jenkins, 2016).

In addition, consistent evidence supports links between a single risk factor and cognitive functioning. First, low socioeconomic status (SES) has been associated with impairments in children's executive functions, including attention, working memory, cognitive flexibility, and inhibitory control (Baker, 2018; Brito, Piccolo, Noble, & Pediatric Imaging, Neurocognition, and Genetics Study, 2017; Duncan et al., 2007; Farah et al., 2006; Hackman, Gallop, Evans, & Farah, 2015; Haft & Hoeft, 2017; Leonard, Mackey, Finn, & Gabrieli, 2015; Noble, McCandliss, & Farah, 2007; Raver, Blair, & Willoughby, 2013; Welsh, Nix, Blair, Bierman, & Nelson, 2010). Although limited, a few studies have also found associations between low SES and deficits in recognition memory and delayed face memory (Farah et al., 2006; Noble et al., 2007). There are also well-established links between severe forms of childhood stress (i.e., abuse/neglect) on children's intelligence, executive functions (for a review see McLaughlin, Sheridan, & Nelson, 2017), visual recognition memory (Bick, Zeanah, Fox, & Nelson, 2018; Wade, Fox, Zeanah, & Nelson, 2019), and autobiographical memory, an aspect of episodic memory (Meesters, Merckelbach, Muris, & Wessel, 2000; Ogle et al., 2013; Valentino, Toth, & Cicchetti, 2009). Overall, there is a consistent link between both minor and major childhood stressors and cognitive dysfunction, yet little work has examined neural mechanisms underlying these associations.

1.2 | Cumulative risk and brain development

Studies on early risk most commonly examine effects on gray matter volume, which is a multidimensional metric including cortical thickness and surface area (Winkler et al., 2010). However, solely examining gray matter volume obscures individual differences in thickness, due to its distinct morphometry, developmental trajectory, and associations with cognitive processes (Schnack et al., 2015; Wierenga, Langen, Oranje, & Durston, 2014; Winkler et al., 2010). Cortical thickness provides a measure of the thickness of gray matter in the cortex and is measured as the distance between the cortical surface and the gray/white matter border (Fischl & Dale, 2000; Wierenga et al., 2014). Cortical thickness may provide a better/more precise measure of how early exposure to risk alters neurodevelopment.

Cortical thickness is an important measure of developmental change and reflects biological processes underlying the development of cortical structure, including increased myelination, synaptic overproduction, and eventual pruning (Natu et al., 2019; Tierney & Nelson, 2009; Vidal-Pineiro et al., 2019), which are experience-dependent processes that serve as the bases for much of the learning that takes place during early life (McLaughlin et al., 2017; Tierney & Nelson, 2009). Thus, children's cortical thickness can be examined to capture more fine-grained impacts of risk on the brain. The developmental trajectory of cortical thickness has not reached consensus, with some work showing that thickness in the cortex increases into school age, and then steadily decreases into young adulthood (Ducharme et al., 2016) and others showing that the cortex steadily thins from early childhood into young adulthood (Walhovd, Fjell, Giedd, Dale, & Brown, 2017). These findings may be mixed due to differences in the trajectories of cortical thickness across different brain regions.

Prior studies on severe forms of stress (e.g., maltreatment) in children demonstrate reductions in global measures of brain volume, as well as reductions in cortical thickness in parietal, temporal, and frontal regions implicated in memory, executive functioning, and emotional problems (Gold et al., 2016; Kelly et al., 2013; Lim et al., 2017; McLaughlin et al., 2014). Less severe forms of stress or risks for stress (e.g., low SES, aggressive parenting, prenatal maternal depression) have also been related to reductions in global measures of brain volume and increased cortical thinning in children's parietal, temporal, and frontal cortices (Hair, Hanson, Wolfe, & Pollak, 2015; Lawson, Duda, Avants, Wu, & Farah, 2013; Piccolo et al., 2016; Sandman, Buss, Head, & Davis, 2015; Whittle et al., 2016). Together, this prior work supports an association between early risk and cortical thickness in children; however, these previous studies have not linked these variations in cortical thickness to children's cognition.

In addition, few previous studies use prospective longitudinal designs. Prospective, longitudinal studies beginning in childhood are sorely needed to delineate associations between early cumulative risk and children's later cortical thickness and cognitive functioning during a developmental period when cortical thickness and cognitive processes undergo rapid changes and may be most vulnerable to environmental insults (Ducharme et al., 2016; Gagnon & Wagner, 2016; Gee & Casey, 2015; Raver et al., 2013; Shields, Sazma, & Yonelinas, 2016). One notable exception is a prospective study in youth (ages 4 to 18 years at baseline) that found

reductions in frontal and temporal gray matter volume (brain metrics that include both thickness and surface area) mediated the relation between poverty and academic achievement assessed 3 years later (Hair et al., 2015).

1.3 | The current study

The current study addresses important gaps in the literature by prospectively examining associations between early childhood cumulative risk and brain structure (using both global and regional metrics), and cognition (i.e., executive functioning and memory) at school-age. We aimed to address the following questions: whether (a) cumulative risk early in life as measured at Wave 1 (W1: ages 3–5 years) was associated with reduced global brain measures and cortical thickness 3 years later at Wave 2 (W2: ages 5–9 years); (b) early cumulative risk was associated with poorer executive functioning and memory at W2; (c) cumulative risk-associated brain measures were concurrently associated with cognitive functioning at W2; and (d) cumulative risk-associated brain measures mediated associations between early cumulative risk and later executive functioning and memory.

These questions were examined in a longitudinal study that oversampled for children of depressed mothers; this sampling approach allowed us to capture greater variability in the early risk factors. At W1, cumulative risk was assessed using a comprehensive index that included: low family income, exposure to parental depression, high levels of hostile parenting, single parent household, low parental education, and high levels of stressful events. At W2, children completed a structural MRI scan and a battery of executive functioning and memory tasks. To assess brain structure, we examined global brain measures (i.e., total gray matter volume, cortical white matter volume, and cortex volume) that have previously been linked to environmental adversity and are important in multiple domains of cognitive functioning. We also assessed more regionally specific metrics using cortical thickness regions related to executive functioning (fronto-parietal regions) and episodic memory (fronto-parietal regions, parahippocampal cortex, and entorhinal cortex). We hypothesized that cumulative risk would be associated with reduced global brain measures and cortical thickness, as well as poorer executive functioning and memory. We further expected cumulative risk-associated brain measures to mediate the longitudinal effects of early cumulative risk on children's executive functioning and memory.

2 | METHODS

2.1 | 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, D.C. metropolitan area using advertisements and a commercial mailing list. Children were assessed at W1 (child age M = 4.23 years, SD = 0.84) and approximately 3 years later at W2 (child age M = 7.19 years, SD = 0.89). At W1, eligible children were aged 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. 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.

2.1.1 | 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 cumulative risk index (M = 1.52, SD = 1.24) compared to children who completed the W2 behavioral assessment only (M = 0.90, SD = 1.16), $t(89.87) = -2.60$, p = .012.

2.2 | Wave 1 assessment

2.2.1 | Cumulative risk

Consistent with the cumulative risk model (Evans et al., 2013; Jensen et al., 2015), cumulative risk included several indices of stress (see Table 1): (a) single parent household (0 = absent, 1 = present); (b) low parental education (0 = at least one parent with a 4-year college degree, 1 = neither parent with a 4-year college degree); (c) low family income (0 = income ≥$40,000, 1 = income< $40,000[1]); (d) high levels of observed parental hostility (0 = hostility score <2 SD below the mean, 1 = hostility score ≥2 SD above the mean); (e) child exposure to parental depression (0 = no exposure, 1 = exposure to parental depression from birth to W1); and (f) child experienced ≥4 non-redundant stressful life events (e.g., moving, separation from parent, parental divorce) in the 12 months prior to W1. The stressors were chosen to reflect multiple distinct, yet related, aspects of the early rearing environment. Each stressor was dummy coded as absent versus present so that each stressor would contribute equal weight to the overall

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 (0.84)	3–5.96	7.19 (0.89)	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)		
Early cumulative risk factors				
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)		
Parental hostility ≥2 SDs above the mean: n (%)	7	(11.1)		
Cognitive ability				
Block design	10.13 (3.16)	4–18		
Cognitive ability				
Source memory % correct			0.57 (0.19)	0–0.95
Story recall			−0.01 (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				
Number of stressors in past 12 months			1.89 (1.43)	0–5

stress index, in line with the cumulative risk model (Evans et al., 2013). To examine the additive effect of cumulative risk, the number of stressors present was summed, with higher scores indicating greater levels of cumulative risk.

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; Egeland et al., 1995). Children's exposure to parental depression was assessed using the Structured Clinical Interview for DSM-IV, Non-Patient version (SCID-IV; 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. All of these stressors were non-overlapping with the other stress indices. We selected a 12-month window, given the focus on capturing stressful events present within the child's lifetime and reducing retrospective recall bias of more distal events. We dichotomized hostility and the number of stressors so that all stressors in the cumulative risk index would be weighted equally. We created cut-offs at points that

indicate levels of hostility (≥2 *SD* above the mean) and stressors (≥4) that were non-normative in the current sample (i.e., present in <10% of the study sample).

2.2.2 | Early 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).

2.3 | Wave 2 assessment

2.3.1 | 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.

2.3.2 | Child executive functioning

Children completed three validated tasks to measure aspects of executive functioning: working memory, attention shifting, and inhibitory control. To assess working memory, children completed a modified version of the digit span task that used colored triangles instead of digits (Wechsler, 2014). Children were shown a series of colored triangles with each trial increasing in the number of triangles presented (Dougherty, Barrios, Carlson, & Klein, 2017). 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 (Arbuthnott & Frank, 2000), 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" (Carlson, 2005; Strommen, 1973), 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.

2.3.3 | Memory ability

Children completed memory tasks to assess different aspects of episodic memory. Episodic memory 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: (a) was living or non-living; (b) could fit or not fit in a box; and (c) 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), which provided a measure of source memory. 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 1 hr, resulting in measures of immediate and delayed recall. Total scores were calculated by summing the total number of story units the child correctly remembered out of the total number of possible story units, with higher scores reflecting greater recall memory. The immediate and delayed recall scores were highly correlated ($r = 0.92$, $p < .001$) and thus standardized and averaged to create a composite recall score.

2.3.4 | 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) with a 12-channel coil. Children participated in a 4 min and 18 s high-resolution T1 magnetization-prepared rapid gradient-echo (MPRAGE) structural scan sequence consisting of 176 contiguous sagittal slices (1.0 mm^3; 1900 ms TR; 2.52 ms TE; 900 ms inversion time; 9° flip angle; pixel matrix = 256 × 256). During the collection of the structural scan, children watched a video of their choice as a way to foster engagement and limit motion during the scan. If motion artifacts were identified during the scan, the structural scan was repeated. Fifteen children had their structural scan repeated: two ($n = 12$), three ($n = 2$), and four scans ($n = 1$). Images were analyzed using the standard automatic segmentation software FreeSurfer Version 5.1.0 (surfer.nmr.mgh.harvard.edu; Fischl, 2012). Experienced coders inspected the pial surface boundary of each slice for errors. If the boundary included portions of the skull or dura mater and this error lasted for more than seven slices, edits were completed to correct the boundary. Edits were made by first changing

the watershed value within FreeSurfer, which adjusts the skull stripping parameters, and then by making manual edits, if necessary (n = 11, see Botdorf & Riggins, 2018 for a similar approach). Total gray matter volume, cortical white matter volume, cortex volume, and intracranial volume (ICV) were extracted for each participant. Cortical thickness was calculated by measuring the distance from the gray/white matter boundary to the pial boundary. The Desikan–Killiany Atlas was used for cortical parcellation (Desikan et al., 2006). Right and left hemispheres were analyzed separately.

2.3.5 | Global brain measures

We selected global brain measures previously associated with early cumulative risk stress and cognitive functioning (Gagnon & Wagner, 2016; McLaughlin et al., 2017; Shields et al., 2016). Specifically, we included total gray matter volume, white matter volume, and cortex volume to assess global aspects of brain development.

2.3.6 | Regionally-specific measures of cortical thickness

We selected specific regions of interest to assess cortical thickness of areas associated with the cognitive domains of interest. Episodic memory is known to engage the posterior parietal, parahippocampal, and prefrontal cortices (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Hutchinson, Uncapher, & Wagner, 2009; Sestieri, Shulman, & Corbetta, 2017; Tulving & Markowitsch, 1998; Uncapher & Wagner, 2009; Vilberg & Rugg, 2008). Executive functioning is known to rely on fronto-parietal regions (Lee, Wallace, Raznahan, Clasen, & Giedd, 2014; Van Petten et al., 2004; Yuan & Raz, 2014). Thus, our regions of interest consisted of the right and left superior parietal cortex, inferior parietal cortex, entorhinal cortex, parahippocampal cortex, and middle frontal cortex. Middle frontal cortex was created by averaging thickness in the caudal and rostral portions of middle frontal cortex. These middle frontal regions, as delineated by the Desikan–Killiany Atlas (Desikan et al., 2006), most closely map onto the lateral prefrontal cortex. For descriptive statistics of all brain regions, see Supplementary Material Table 1.1.

2.4 | Data analysis plan

All analyses were conducted in SPSS Version 24. First, multiple linear regressions were used to examine whether W1 cumulative risk was associated with global 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. In models examining W2 global brain metrics, dependent variables included total gray matter volume, cortex volume, and cortical white matter volume. Independent variables included ICV, child's W2 age, and W1 cumulative risk. In models examining 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 and W1 cumulative risk. In models examining W2 cognitive functioning, dependent variables included source memory, story recall, attention shifting, working memory, and inhibitory control. In each of the models examining W2 cognitive functioning, independent variables included child age, cognitive ability, and cumulative risk at W1.

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

3 | RESULTS

3.1 | Covariates

Prior to conducting analyses, possible covariates were explored. W2 child age was positively associated with source memory (r = 0.33, p = .009), story recall (r = 0.27, p = .035), attention shifting (r = 0.41, p = .001), and working memory (r = 0.29, p = .022). Child age was not associated with any brain measures. Child sex (1 = male, 2-female) was associated with cortical white matter, (r = −0.37, p = .003), with males having greater white matter volume than females. Child sex was also associated with right superior parietal thickness (r = 0.31, p = .014), left superior parietal thickness (r = 0.29, p = .022), right entorhinal thickness (r = 0.30, p = .016), and right middle frontal thickness (r = 0.28, p = .029), with females having greater thickness than males.

3.2 | Early cumulative risk and global brain measures

After controlling for ICV and age, cumulative risk at W1 was associated with lower total gray matter volume (b = −8134.25, SE = 3,297.72, pr = −0.31, p = .017, Figure 1a) and cortex volume (b = −8182.04, SE = 2,890.75, pr = −0.35, p = .006, Figure 1b), but not cortical white matter volume (b = 5.22, SE = 2,244.20, pr < 0.001, p = .998) at W2.

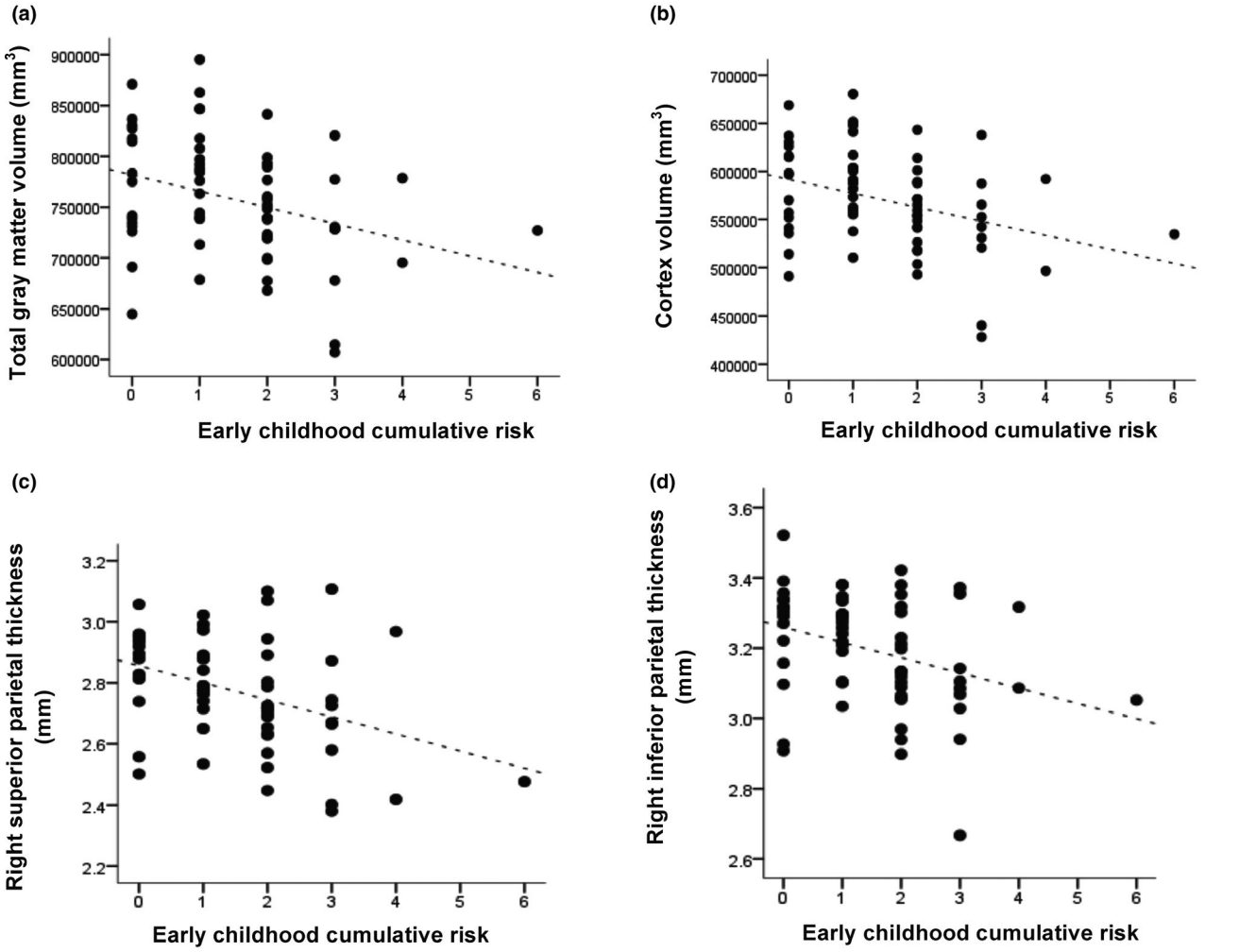

FIGURE 1 Early childhood cumulative risk was associated with reduced (a) total gray matter volume, (b) cortex volume, (c) right superior parietal thickness, and (d) right inferior parietal thickness

3.3 | Early cumulative risk and cortical thickness

We next examined whether early cumulative risk was associated with reduced regional thickness. Bivariate correlations between W1 cumulative risk and thickness in each region are reported in Supplementary Material Table 1.2. After adjusting for covariates, cumulative risk at W1 was associated with reduced right superior parietal thickness (b = −0.05, SE = 0.02, pr = −0.37, p = .003; see Figure 1c) and reduced right inferior parietal thickness (b = −0.04, SE = 0.02, pr = −0.33, p = .010, Figure 1d) at W2. No other associations persisted after controlling for covariates.

3.4 | Early cumulative risk and cognitive functioning

Bivariate correlations between cumulative risk and cognitive variables are reported in Table 2. After adjusting for W1 cognitive ability and W2 age, early cumulative risk was associated with poorer performance on source memory (b = −0.04, SE = 0.02, pr = −0.30, p = .022), story recall (b = −0.27, SE = 0.10, pr = −0.34, p = .007), and attention shifting (b = −0.24, SE = 0.10, pr = −0.31, p = .015) at W2. Early cumulative risk was not associated with inhibitory control or working memory at W2.

3.5 | Associations between brain measures and cognitive function

We examined concurrent associations between cognitive functioning and brain measures that were significantly associated with cumulative risk (i.e., total gray matter volume, cortex volume, right inferior, and superior parietal thickness; see Table 2) at W2. After controlling for age, total gray volume was positively associated with attention shifting (b = 4.42e-6, SE < 0.001, pr = 0.29, p = .022; Figure 2a) and story recall (b = 4.48e-6, SE < 0.01, pr = 0.28, p = .030; Figure 2b). Similarly, cortex volume was positively associated with attention shifting (b = 4.87e-6, SE < 0.01, pr = 0.28, p = .032; Figure 2c) and story recall (b = 5.49e-6, SE < 0.001, pr = 0.29, p = .023; Figure 2d). Right superior parietal thickness was positively associated with story recall (b = 2.23, SE = 0.65, pr = 0.40, p = .001; Figure 2e).

TABLE 2 Bivariate Correlations among cumulative risk, cognitive functioning, cumulative risk-associated brain measures, and current stress

		1	2	3	4	5	6	7	8	9	10	11
1.	Wave 1 early cumulative risk	—										
2.	Wave 2 current stress	0.24	—									
	Wave 2 cognitive functioning											
3.	Source memory	−0.34**	−0.12	—								
4.	Story recall	−0.31**	−0.26*	0.35**	—							
5.	Attention shifting	−0.41**	−0.16	0.32*	0.48**	—						
6.	Working memory	−0.15	−0.19	0.24*	0.24*	0.31*	—					
7.	Inhibitory control	−0.04	0.10	0.27**	0.12	0.18	0.09	—				
	Wave 2 cumulative risk-associated brain measures											
8.	Total gray matter volume	−0.33**	−0.12	0.16	0.27*	0.28*	0.03	0.15	—			
9.	Cortex volume	−0.35**	−0.14	0.20	0.29*	0.26*	0.03	0.14	0.98**	—		
10.	Right inferior parietal thickness	−0.34**	−0.23	0.17	0.24	0.14	−0.04	−0.09	0.39**	0.42**	—	
11.	Right superior parietal thickness	−0.39**	−0.21	0.15	0.41**	0.17	−0.10	−0.05	0.45**	0.49**	0.72**	—

*$p < .05$,
**$p < .01$.

3.6 | Do brain regions of interest mediate associations between early cumulative risk and cognitive functioning 3 years later?

We tested whether early cumulative risk-associated brain measures (i.e., total gray matter, cortex volume, right superior parietal thickness, and right inferior parietal thickness) mediated the relations between early cumulative risk and cognition at W2 (i.e., story recall, source memory, and attention shifting ability), controlling for W2 age and W1 cognitive ability. We also included child sex as an additional covariate when it was associated with the mediator or the dependent variable and ICV as an additional covariate for all models in which a global brain measure (total gray matter volume or cortex volume) was the mediator. Additionally, to limit the number of tests conducted, we only tested mediation for pathways in which cumulative risk-associated brain measures were associated with executive functioning or memory variables. This resulted in five tests of mediation (total gray matter volume to story recall and attention shifting; cortex volume to story recall and attention shifting; right superior parietal thickness to story recall). We found a significant indirect effect of cumulative risk on story recall through right superior parietal thickness (b [10,000 bootstrapped samples] = −0.08, SE = 0.06, bias corrected 95% CI [−0.23, −0.002] R^2 = 0.23). Specifically, greater early cumulative risk was associated with decreased right superior parietal thickness, which was associated with poorer story recall ability 3 years later. No other indirect effects were significant.

3.7 | Testing the robustness of effects

We conducted additional analyses to test the robustness of our findings. First, we repeated all analyses and controlled for the number of current stressors and found that all analyses remained significant (ps < 0.035). As documented in Table 2, the number of current stressors in the past year was not associated with any cumulative risk-associated brain metrics. Current stress was associated with story recall ability; however, this effect was no longer significant after adjusting for W1 cumulative risk, W1 cognitive ability, and W2 age (b = −0.11, SE = 0.08, pr = −0.18, p = .18).

Second, given that we dichotomized continuous variables of hostility and total stressors, we also tested whether our findings would replicate using a cumulative risk index with continuous variables of hostility and number of stressors. All results remained similar with this alternative cumulative risk index, highlighting that findings are robust and are not driven by artificial cut-off points of the continuous variables (See Supplementary Material 1 and Table 1.3).

Third, given that our sample was enriched with offspring of mothers with a history depression, we examined associations between maternal lifetime depression history and cumulative risk-associated brain metrics to ensure that effects were not driven by maternal depression. A lifetime history of maternal depression was associated with reduced right inferior parietal thickness only (r = −0.28, p = .028); no significant associations between maternal depression history and right superior parietal thickness (r = −0.15, p = .233), total gray matter volume (r < 0.01, p = .980), or cortex volume (r = −0.022, p = .866) were observed. When controlling for maternal lifetime depression, cumulative risk continued to be associated with reduced right inferior parietal thickness (b = −0.04, SE = 0.02, pr = −0.27, p = .037). In addition, mothers' current depressive symptoms assessed with the Diagnostic Inventory for Depression (Zimmerman, Sheeran, & Young, 2004) were not significantly associated with any cumulative risk-associated brain metrics (ps > .152). These findings provide further support that associations between cumulative risk and brain structure are not driven by maternal depression history.

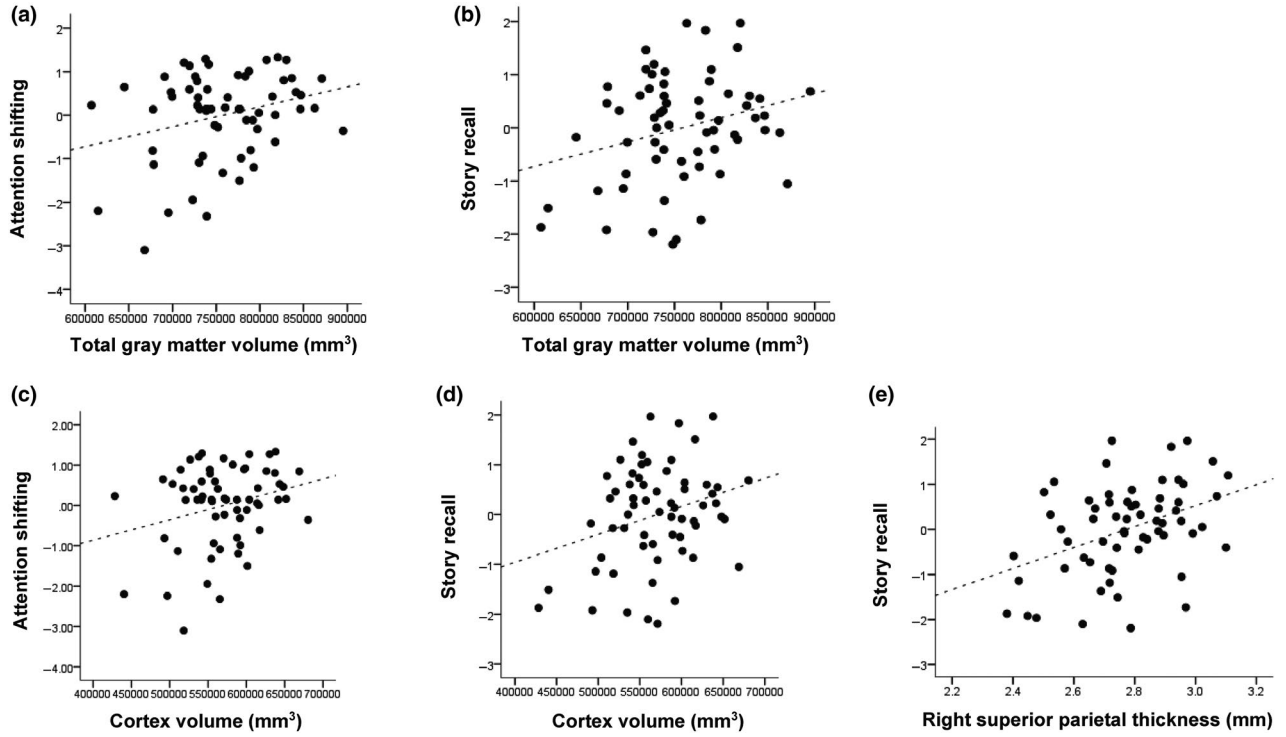

FIGURE 2 Brain regions associated with memory and executive functioning: (a) association between total gray volume and attention shifting ability; (b) association between total gray volume and story recall; (c) association between cortex volume and attention shifting ability; (d) association between cortex volume and story recall; (e) association between right superior parietal thickness and story recall

Fourth, in addition to cortical thickness, surface area is a fine-grained surface-based metric that makes up cortical volume, and is genetically and phenotypically distinct from cortical thickness (Raznahan et al., 2011). To examine the specificity of our findings, we also examined associations between cumulative risk, surface area, and cognitive functioning. See Supplementary Material Table 2.1 for descriptive information on regions of interest for surface area analyses. Overall, findings show a prospective association between greater early childhood cumulative risk and reduced left entorhinal surface area ($b = -28.95$, $SE = 7.38$, $pr = -0.46$, $p < .001$) and a concurrent association between reduced left entorhinal surface area and poorer story recall ability ($b = 0.005$, $SE = 0.001$, $pr = 0.40$, $p = .002$), controlling for covariates. Left entorhinal surface area also mediated associations between cumulative risk and story recall ability, controlling for covariates (b [10,000 bootstrapped samples] = −0.11, $SE = 0.05$, bias corrected 95% CI [−0.22, −0.02] $R^2 = 0.31$; See Supplementary Material 2). Thus, early cumulative risk was associated with different cortical thickness and surface area regions, supporting prior work evidencing phenotypic differences between cortical thickness and surface area (Winkler et al., 2018).

4 | DISCUSSION

Findings from our study showed that children exposed to greater early childhood cumulative risk demonstrated reductions in global brain measures and thickness in parietal cortices, as well as poorer story recall, source memory, and attention shifting ability 3 years later. Furthermore, reduced right superior parietal thickness mediated the longitudinal association between early cumulative risk and poorer story recall memory. These findings persisted even after accounting for current life stress, suggesting that stress exposure during early childhood has lasting effects on neural and cognitive development. The findings suggest potential neural pathways through which early risk may influence children's cognitive development.

Our findings linking cumulative risk and both global brain measures as well as cortical thickness of parietal regions are consistent with studies that have linked SES and other single risk factors with total gray matter volume and specific reductions in parietal areas (Hair et al., 2015; Hanson et al., 2012; Noble et al., 2015; Whittle et al., 2016). We expanded this literature by demonstrating associations between a less researched metric of stress, *cumulative risk*, and reduced total gray matter volume, cortex volume, and right superior and inferior parietal thickness. These cumulative risk-associated brain measures mapped onto cognitive functions of attention shifting and story recall ability. Moreover, right superior parietal thickness, but not global brain measures, mediated associations between cumulative risk and later memory. Thus, although we observed widespread effects of cumulative risk on global brain measures, our findings suggest that regional specificity in parietal cortical thickness may uniquely account for the effects of cumulative risk on memory.

We did not find associations between cumulative risk and cortical thickness in middle frontal regions, despite evidence that prefrontal regions are sensitive to environmental factors and implicated

in executive functioning (Lawson et al., 2013). Some prior studies, although not well replicated, have found links between early risks and volume and cortical thickness in certain regions of the prefrontal cortex (PFC; e.g., anterior cingulate cortex, superior frontal cortex, inferior frontal cortex, ventromedial PFC, ventrolateral PFC, dorsolateral PFC; Colich et al., 2017; Hanson et al., 2012; Kelly et al., 2013; Lawson et al., 2013; McDermott et al., 2019; Noble, Houston, Kan, & Sowell, 2012; Yang et al., 2016). However, these studies largely examined older youth and adolescents. Given the protracted development of the PFC, it is possible that associations between early risk and PFC do not emerge until later in development (Fuster, 2002).

Both early cumulative risk and global brain measures (total gray matter volume and cortex volume) were associated with attention shifting ability in school-age children. Previous work has found associations between single risks or cumulative risk and aggregate measures of executive functioning that include attention (Baker, 2018; Raver et al., 2013; Wade et al., 2016). We extend these findings by pointing to one aspect of executive functioning, attention, that was related to cumulative risk as well as its global neural correlates. These findings highlight the impact of early childhood cumulative risk on attention in children. Attention-dependent processes, such as alerting, orienting, and shifting attention are fundamental to cognitive ability and regulating social behavior (Mezzacappa, 2004). Thus, targeting attention processes in children exposed to early stress may be an important point of intervention to promote academic and social functioning in at-risk youth.

Inconsistent with previous work (Farah et al., 2006; Lengua et al., 2007; Noble et al., 2007), we did not find associations between cumulative risk and working memory or inhibitory control. Nevertheless, some data suggest that environmental risks may differentially impact specific neurocognitive processes and certain impairments in cognition may not emerge until later in development (Farah et al., 2006; Wade et al., 2019). For example, a recent study observed that children who were institutionalized experienced attention deficits at age 8, which persisted into adolescence, whereas their working memory was only slightly impaired at age 8, but increasingly declined into adolescence (Wade et al., 2019). Thus, as children in our sample were ages 5 through 9 years at the time of the MRI and cognitive assessments, it is possible that cumulative risk-dependent impairments in certain domains of executive functioning, such as working memory and inhibitory control, may not become evident until later in development. Alternatively, our study may have lacked sufficient power to detect these smaller effects or these effects may not have been present at all.

We also found that early childhood cumulative risk was associated with poorer source memory and story recall 3 years later. These findings are consistent with the limited previous literature showing associations between SES and memory in children (Farah et al., 2006; Noble et al., 2007) and adults (Kaplan et al., 2001), as well as more established findings on trauma and autobiographical memory, a form of episodic memory (Edwards, Fivush, Anda, Felitti, & Nordenberg, 2001; Meesters et al., 2000; Ogle et al., 2013; Valentino et al., 2009). We extend the previous findings by demonstrating that cumulative risk impacts multiple aspects of episodic memory (source memory and story recall) in childhood. Along with executive functions, these features of memory help set the stage for success academically, socially, and emotionally throughout the lifespan.

Importantly, our prospective study is the first to identify a neural correlate linking early risk to children's later memory ability. The identification of superior parietal cortex as the mediator through which cumulative risk relates to memory is in line with work demonstrating links between episodic memory and the posterior parietal cortex. Our findings support work showing parietal cortex activation during episodic retrieval and the influence of this region on episodic memory via attention processing (Cabeza et al., 2008). Furthermore, our lack of findings in the prefrontal cortex are also consistent with work showing that although the posterior parietal cortex and prefrontal cortex are important for memory, different regions may support memory processes at different stages in development. As the parietal cortex develops earlier in childhood than the prefrontal cortex, parietal regions may contribute to memory earlier in development, while late developing prefrontal regions may contribute to memory later in development (Shing & Lindenberger, 2011; Shing, Werkle-Bergner, Li, & Lindenberger, 2008). However, other interpretations of these data are possible and future research should test these age-dependent associations.

There are many possible developmental processes that may explain links between cumulative risk, brain development, and cognitive ability. One possibility is that the lack of cognitive stimulation (e.g., fewer games, books, child-directed talk, and consistent caregiver–child interaction) in the homes of children exposed to cumulative risk factors may lead to fewer synaptic connections, increased synaptic pruning of unused connections, and exaggerated cortical thinning in these regions (McLaughlin et al., 2017). Likewise, heightened stress arising from atypically increased demands placed on children exposed to cumulative risk may lead to allostatic load (i.e., “wear and tear of the body”), which in turn may impact stress hormone release and brain structure and function (McEwen & Gianaros, 2010). It is likely that multiple forms of risk exposure contribute to both of these cascades of events, possibly explaining why we see widespread neurological aberrations following stress exposure. Future research should test these pathways directly.

Among the strengths of this study are the comprehensive assessment of cumulative risk and the prospective, longitudinal design that allowed us to examine impacts of risk over development. The study also employed a cognitive assessment battery that targeted various aspects of executive functioning and memory to parse apart distinct aspects of these heterogeneous processes. Another strength of the study was our examination of different components of memory, a domain less researched in the risk literature.

Our study also has limitations. First, we did not assess brain structure at baseline and therefore could not examine changes in brain measures over time. Second, our sample size was relatively small and may have been underpowered to observe additional mediation pathways. Third, given we had specific a priori

hypotheses about certain brain regions of interest, we did not conduct exploratory whole brain analyses and instead used an atlas commonly employed in adult and child populations (Kharitonova, Martin, Gabrieli, & Sheridan, 2013; Walhovd, Tamnes, Østby, Due-Tønnessen, & Fjell, 2012). Nevertheless, our use of this atlas to select regions of interest may have led to some loss of specificity by assigning an average cortical thickness value to regions of the cortex. Future studies with larger samples should explore a whole brain analysis approach to further investigate whether cortical thickness in additional regions relate to cumulative risk and cognitive functioning, potentially enhancing specificity of localized regions. Fourth, while we captured a wide range of early risks, there are likely additional factors that could have also been included (e.g., exposure to other parental illnesses and neighborhood violence). Finally, although cumulative risk indices are in line with theoretical and empirical models demonstrating that multiple risks are more detrimental than any single risk, cumulative risk models are also limited by giving equal weight to all risks and not testing the unique effects of specific risks (Evans et al., 2013).

In conclusion, this study contributes to a growing literature demonstrating the detrimental consequences of early childhood cumulative risk on the developing brain and cognition that may contribute to maladjustment throughout the lifespan. Although our sample is not characterized by low income, our findings may provide insight into the mechanisms underlying educational and mental health disparities among low income, minority children who are disproportionately exposed to early risk factors. 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 to optimize their long-term achievement.

CONFLICT OF INTEREST

The authors report no biomedical financial interests or potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ENDNOTE

[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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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