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RESEARCH ARTICLE

Adverse childhood experiences predict neurite density differences in young children with and without attention deficit hyperactivity disorder

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Abstract

Adverse childhood experiences (ACEs) put millions of children at risk for later health problems. As childhood represents a critical developmental period, it is important to understand how ACEs impact brain development in young children. In addition, children with attention-deficit/hyperactivity disorder (ADHD) are more likely than typically developing (TD) peers to experience ACEs. Therefore, the current study examined the impact of ACEs on early brain development, using a cumulative risk approach, in a large sample of children with and without ADHD. We examined 198 young children (M_{age} = 5.45, 82.3% Hispanic/Latino; 52.5% ADHD) across measures of brain volume, cortical thickness, neurite density index (NDI), and orientation dispersion index (ODI). For the NDI measure, there was a significant interaction between group and cumulative risk (β = .18, p = .048), such that for children with ADHD, but not TD children, greater cumulate risk was associated with increased NDI in corpus callosum. No other interactions were detected. Additionally, when examining across groups, greater cumulative risk was associated with reduced ODI and volume in the cerebellum, although these findings did not survive a correction for multiple comparisons. Our results highlight the role early cumulative ACEs play in brain development across TD and children with ADHD.

KEYWORDS
adverse childhood experiences (ACEs), attention-deficit/hyperactivity disorder (ADHD), cumulative risk, neurite density index (NDI), neuroimaging

1 | INTRODUCTION

A developmental psychopathology perspective advocates for (1) studying the full range of variation from normality to psychopathology, (2) understanding origins and mechanisms underlying psychopathology, and (3) use of multiple units and levels of analysis to study salient domains of functioning (Garber & Bradshaw, 2020; Miklosi, Mate, & Balazs, 2020). In the context of this conceptual approach, we examine the effects of cumulative adverse childhood experiences (ACEs) on structural brain development in typically developing (TD) and at-risk youth (i.e., children with attention-deficit/hyperactivity disorder [ADHD]). Each year, ACEs put millions of children at risk for health problems (e.g., heart disease, obesity), psychological illness (e.g., alcoholism, depression, suicide), and even early death (Brown et al., 2009; Dube et al., 2002; McLaughlin et al., 2012). Typically, ACEs are explored in isolation, even though many of these risk factors co-occur and are cumulative (McLaughlin et al., 2010). Such co-occurring exogenous factors—low family income, parental psychopathology, stress—interact with endogenous characteristics of the child, such as their own psychopathology. Examining these factors within a cumulative risk model is thus most appropriate for understanding how ACEs affect brain development during early childhood, in which the brain is especially

vulnerable to early experiences (Fox, Levitt, & Nelson, 2010). Despite this, most of the literature examining ACEs' impact on brain development has been conducted with older, restricted samples that do not consider comorbid risk factors such as developmental disorders. This is especially problematic for common disorders appearing in early childhood, like ADHD, as such children are at increased risk for experiencing ACEs (Walker et al., 2020). Furthermore, the impact of ACEs on brain development may be exacerbated relative to TD children. Thus, the current study looks to fill these gaps by examining the impact of ACEs on early brain development, using a cumulative risk approach, in a large sample of young children with and without ADHD. In line with previous research, the current study will focus on seven ACEs: low family income and parental education (socioeconomic disadvantage), single-parent household status (family structure), and parental factors such as minority status, ADHD, stress, and emotion regulation (parental risk characteristics).

It is important to understand the impact of ACEs across a spectrum of presentations by studying the range of variation from normality to psychopathology. ACEs can lead to pervasive negative health outcomes that continue throughout adulthood (Mäntymaa et al., 2012; McLanahan, Tach, & Schneider, 2013). For example, children in single-parent homes are at an increased risk for decreased cognitive functioning and academic performance (Amato & Anthony, 2014; Brown, 2010), with increased risk for later obesity, mental health problems, antisocial behavior, and substance use (Duriancik & Goff, 2019; McLanahan et al., 2013). These risks are heightened in children with ADHD, as they are more likely to experience multiple ACEs such as socioeconomic disadvantage (Msall et al., 1998), low parental education (Law, Sideridis, Prock, & Sheridan, 2014; Machlin, McLaughlin, & Sheridan, 2020), parental divorce (Schermerhorn et al., 2012; Wymbs et al., 2008), high parental stress (Craig et al., 2016; Ronald, Pennell, & Whitehouse, 2011; Theule, Wiener, Tannock, & Jenkins, 2013), and parent psychopathology (Chronis et al., 2003; Vidair et al., 2011). Understanding the impact of cumulative ACEs across presentations (i.e., TD to ADHD) in early childhood can illuminate pathways of risk and resilience.

In addition to well-studied mental health outcomes, a number of studies have shown that ACEs are associated with neurobiological outcomes, specifically in gray matter brain regions and the white matter connectivity supporting these networks. Most studies have focused on gray matter volume and cortical thickness differences in the limbic system as a result of various ACEs. For example, ACEs have been associated with reductions in volume and thickness in the *hippocampus*, *amygdala*, *anterior cingulate cortex*, and *orbitofrontal cortex* (OFC), in addition to other cortical regions associated with limbic functions (Chad-Friedman et al., 2020; Duan, Hare, Staring, & Deligiannidis, 2019; Hanson, Chandra, Wolfe, & Pollak, 2011; Lawson, Duda, Avants, Wu, & Farah, 2013; Machlin et al., 2020; Marečková et al., 2019; Noble, Houston, Kan, & Sowell, 2012; see Figure 1). Research in TD children has also shown reductions in volume of the cerebellum (Jackowski et al., 2008), and reduced cerebellar volume is a reliable finding in children with ADHD (Rubia, 2018). Indeed, the few studies examining ACEs in children with ADHD have also found that more ACEs were associated with reduced cerebellar volume, in addition to reductions in subcortical limbic regions (i.e., amygdala and hippocampus; Machlin et al., 2020).

Maturation of white matter in the brain is also susceptible to influence from early exposure to ACEs. This is not surprising, given the protracted developmental timeline of myelination of axons in early childhood through adolescence (Giedd et al., 1999). Several studies have shown reductions in volume or diffusion properties of the *corpus callosum* (Jackowski et al., 2008; McCarthy-Jones et al., 2018; Rinne-Albers et al., 2016). These changes persist into adulthood, suggesting prolonged negative impacts of early ACEs on brain development.

Information about gross gray matter and white matter changes are informative, but they do not provide information about subtle changes in local neural connections and structure. More recent methods, such as neurite orientation dispersion and density imaging (NODDI), have been developed to take advantage of the complex signal available in diffusion-weighted images (Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012). The neurite density index (NDI) recovered from NODDI reconstruction can provide detailed information about how the cytoarchitecture of neurons changes in response to exposure to ACEs, specifically measuring the potential loss or maintenance of neurons. The advantage of this metric is that it can be used to investigate changes in both gray matter (primarily neurons) and white matter (primarily axons). Similarly, the orientation dispersion index (ODI) is sensitive to reduction or maintenance of the complexity of dendritic arborization. These indices can potentially provide information about changes in local neural organization in response to specific experiences, leading to a more comprehensive picture of the neural response to ACEs.

1.1 | The current study

Although individual ACEs have been shown to impact later brain development (Chad-Friedman et al., 2020; Hair, Hanson, Wolfe, & Pollak, 2015), there is extremely limited research examining how cumulative risk factors impact brain development as early as preschool (Hawkey, Tillman, Luby, & Barch, 2018). While some studies have included only younger children (e.g., Luby et al., 2013), most include a large age range of children at different stages of brain development (e.g., children aged 3–21). Further, as children with ADHD are at an increased risk for experiencing these aforementioned ACEs, it is extremely important to understand if ACEs differentially impact brain development in children with ADHD. The current study looked to fill these gaps by examining how ACEs, utilizing a cumulative risk approach, are associated with brain development in young children with and without ADHD. Moreover, the current study tested if the impact of cumulative risk is exacerbated in children with ADHD compared to TD. The current study aimed to establish this comprehensive picture by examining volumetric, cortical thickness, NDI, and ODI differences in response to ACEs.

We hypothesized that cumulative risk would be negatively associated with children's volume within the cerebellum, corpus collosum,

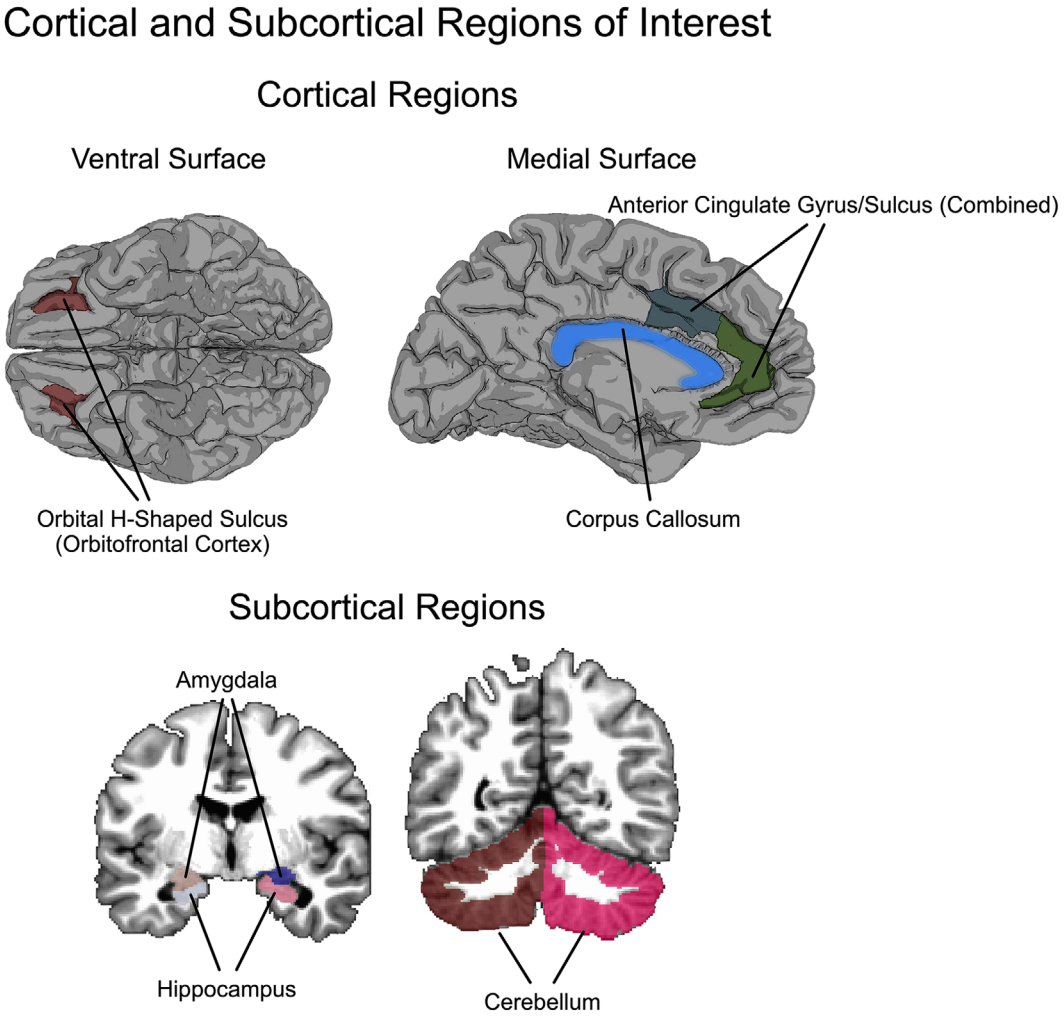

FIGURE 1 Cortical and subcortical regions of interest. This figure shows all regions of interest examined, including the orbital frontal cortex (OFC), anterior cingulate, corpus collosum (cortical regions), amygdala, hippocampus, and the cerebellum (subcortical regions)

the OFC, amygdala, hippocampus, and the anterior cingulate. We also hypothesized that cumulative risk would be negatively associated with cortical thickness in the OFC and cingulate. Given the limited studies on NDI and ODI within young children, we hypothesized that if cumulative risk interferes with synaptic formation, then a negative association with measures of NDI and a positive association with measures of ODI would be found. We expected to find these associations across TD children and those diagnosed with ADHD, although we expected that children with ADHD would have higher risk scores.

2 | METHODS AND MATERIALS

2.1 | Participants and recruitment

Children and their caregivers were recruited from local schools and mental health agencies via brochures, radio and newspaper ads, and open houses/parent workshops. All children were required to be enrolled in school during the previous year, have an estimated IQ of 70 or higher, and have no confirmed history of an autism spectrum disorder.

For the ADHD sample, ADHD diagnosis and comorbid disruptive behavior disorders were assessed through a combination of parent structured interview (Computerized-Diagnostic Interview Schedule for Children [C-DISC]; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), and parent and teacher ratings of symptoms and impairment (Disruptive Behavior Disorders Rating Scale, Impairment Rating Scale; Fabiano et al., 2006; Pelham, Gnagy, Greenslade, & Milich, 1992), as is recommended by standard practice (Pelham, Fabiano, & Massetti, 2005). Dual Ph.D. level clinician review was used to determine diagnosis and eligibility. For the TD sample, parents must have endorsed less than four ADHD symptoms (across either inattention or hyperactivity/impulsivity according to the DSM-5), less than four oppositional defiant disorder (ODD) symptoms, and indicated no clinically significant impairment (score below 3 on the impairment rating scale). The final sample included 198 young children (70.7% male; M_{age} = 5.45, SD = 0.89, 82.3% Hispanic/Latino) with an equivalent distribution of

children diagnosed with ADHD (52.5%) and those characterized as TD (47.5%).

This study was approved by the university's Institutional Review Board. All families participated in a one-time assessment, which included completion of the ADHD, ODD, and conduct disorder modules on the C-DISC and various questionnaires regarding their children's behavioral, academic, and emotional functioning. Similar questionnaires were also obtained from children's teachers. Children also completed a 25-min MRI scan.

2.2 | Risk measures

2.2.1 | Parental stress

The Parenting Stress Index-Short Form (PSI-SF; Abidin, 1995) is a 36-item self-report scale that measures stress in the parent–child relationship due to parent distress, difficult child behavior, and dysfunctional parent–child interaction. For the purposes of this study, the parental distress scale was used as a measure of parental stress (Cronbach's $a = .79$).

2.2.2 | Parental ADHD

The ADHD Self-Report Scale (ASRS; Kessler et al., 2005) is an 18-item self-report measure to assess manifestation of ADHD symptoms in people aged 18 years or older. The ASRS has previously demonstrated good internal consistency and concurrent validity (Adler et al., 2006). The total score was used in this study (Cronbach's $a = .89$).

2.2.3 | Parental emotion regulation

The Difficulties in Emotion Regulation Scale-Short Form (DERS-SF; Kaufman et al., 2016; Victor & Klonsky, 2016) is an 18-item self-report measure that assesses the presence and frequency of symptoms of emotion dysregulation in adults. Responders are asked to rate the frequency at which they experience particular symptoms. The total score was used in this study with higher scores indicating more emotion dysregulation problems (Cronbach's $a = .80$).

2.2.4 | Cumulative risk index

Consistent with prior work (Appleyard, Egeland, van Dulmen, & Alan Sroufe, 2005; Bagner & Graziano, 2013), we transformed seven variables into dichotomous variables, with a score of 1 = *the presence of risk* and 0 = *no risk*. The risk variables included (1) low family income, (2) parental education, (3) single-parent household status, (4) parental minority status, (5) parental ADHD, (6) parental stress, and (7) parental emotion regulation. Cumulative risk was calculated for each participant by summing the seven dichotomized variables (possible range in scores from 0 to 7), with higher scores indicating greater risk. See Table 1 for details on how risk scores were determined for each variable.

2.3 | Image acquisition and processing

2.3.1 | MRI acquisition and processing

All imaging was performed using a research-dedicated 3-T Siemens MAGNETOM Prisma MRI scanner (V11C) with a 32-channel coil located on the University campus. Children first completed a mock scan. In the magnet, children watched a child-friendly movie of their choice. Ear protection was used, and sound was presented through MRI compatible headphones.

We collected structural anatomical scans using a whole-head 3D T1-weighted acquisition inversion prepared RF-spoiled gradient echo protocol with prospective motion correction (Siemens vNAV; Tisdall et al., 2012). We collected 93 axial slices at 1-mm isotropic resolution. Each scan was reviewed by a licensed radiologist, and incidental findings were reported to the parent/guardian. We also collected multishell high-angular resolution diffusion-weighted imaging (HARDI) data according to the Adolescent Brain and Cognitive Development (ABCD) protocol (Hagler et al., 2019). These scans were collected with a 1.7-mm isotropic voxel size, using multiband imaging echo planar imaging (acceleration factor = 3). The acquisition consisted of 96 diffusion directions, 6 $b = 0$ frames, and 4 b-values (102 diffusion directions; 6 $b = 500$ s/mm^2, 15 $b = 1000$ s/mm^2, 15 $b = 2000$ s/mm^2, and 60 $b = 3000$ s/mm^2).

2.3.2 | Diffusion-weighted imaging post-processing

Initial postprocessing was accomplished with DTIPrep v1.2.8 (Oguz et al., 2014), TORTOISE DIFFPREP v3.1.0 (Irfanoglu, Nayak, Jenkins, & Pierpaoli, 2017; Pierpaoli et al., 2010), AFNI (v 20.6.02), and FSL v6.0.1 topup (Andersson, Skare, & Ashburner, 2003; Smith et al., 2004). We also implemented a pre- and postanalysis quality check assessing signal-to-noise of each diffusion b-value (Roalf et al., 2016). Initial quality control was accomplished in DTIPrep to complete the following steps: (1) image/diffusion information check; (2) padding/cropping of data; (3) Rician noise removal; (4) slice-wise, interlace-wise, and gradient-wise intensity and motion checking. The number of acquisitions removed was used as a proxy for movement/bad data quality and was included as a covariate in subsequent regression analyses.

TORTOISE DIFFPREP was used to accomplish motion and eddy current correction, and registration to the T1-weighted structural scan, which was maintained in original subject space. An additional registration step established that the region of interest (ROI) mask (defined below) was appropriately registered to the diffusion image. This was accomplished in AFNI using a 12 degree of freedom affine registration of the T1 to the first b0 image of the DWI scan (AFNI fat_proc_map_to_dti using *3dAllineate*). Registration was visually

TABLE 1 Descriptive and cumulative risk factors

	Total sample ($N = 198$)	ADHD only ($n = 104$)	TD only ($n = 94$)	p
Child age	5.45 (0.89)	5.47 (0.91)	5.43 (0.87)	.742
Child sex (% male)	70.7%	74%	67%	.279
Child IQ	99.74 (12.63)	96.17 (12.92)	103.68 (11.08)	<.001
Child ethnicity (% Latinx)	82.3%	81.7%	83%	.712
P/T DBD inattention	1.27 (1.06)	2.25 (.60)	0.39 (.41)	<.001
P/T DBD hyperactivity	1.53 (1.03)	2.37 (.56)	0.59 (.47)	<.001
P/T DBD ODD	0.97 (.88)	1.58 (.76)	0.30 (.37)	<.001
Risk categories*				
Low income[a]	36.9%	38.5%	35.1%	.625
Parental education[b]	31.3%	31.7%	30.9%	.894
Minority status[c]	87.4%	88.5%	86.2%	.628
Single parent[d]	26.8%	25.0%	17.0%	.003
Parent stress[e]	16.2%	25.2%	6.4%	<.001
Parent ADHD[f]	23.7%	33.7%	12.8%	.001
Parent ER[g]	19.7%	26.9%	11.7%	.007
Cumulative risk scores*				
0	4.0%	1.9%	6.4%	
1	28.3	22.1%	35.1%	
2	24.2%	20.2%	28.7%	
3	21.2%	26.0%	16.0%	
4	14.1%	16.3%	11.7%	
5	4.5%	8.7%	0.0%	
6	2.5%	2.9%	2.1%	
7	1.0%	1.9%	0.0%	
Total risk score	2.41 (1.46)	2.80 (1.52)	2.00 (1.26)	<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DBD, disruptive behaviors disorders rating scale; ER, emotion regulation; ODD, oppositional defiant disorder; P/T, highest teacher or parent report; TD, typically developing.

*Percentage in risk group.

[a]Low income was dummy coded as above/below 150% of the poverty line.

[b]Parental education was dummy coded as either parent having/not having a 4-year college degree.

[c]Although race/ethnicity itself is not a risk factor, there is persistent evidence of racial/ethnic disparities in domains, such as health care, that may mitigate negative outcomes. Parental minority status is included as a proxy for such disparities, with a dummy code indicating Caucasian/non-Hispanic or not.

[d]Single parent was dummy coded as either single parent/not single parent household.

[e]Parent report of clinically elevated distress on the Parenting Stress Index-Short Form was dummy coded as above/below 85th percentile.

[f]Parent report of clinically elevated levels of ADHD on the ADHD Self-Report Scale was dummy coded as clinically elevated/not elevated.

[g]Parent report of clinically elevated levels of emotion dysregulation on the Difficulties in Emotion Regulation Scale-Short Form was dummy coded as clinically elevated/not elevated.

inspected at this phase and to assure alignment of the diffusion image to the T1-weighted image derived from the Freesurfer atlas.

2.3.3 | NODDI metrics

NODDI is an alternative diffusion model that can distinguish among three tissue-property contributions to the diffusion signal: intracellular, extracellular, and cerebrospinal fluid. The model is possible to implement with the multishell HARDI protocol (Zhang et al., 2012). With respect to the present study, the NODDI model allows estimation of the contributions of neurite morphology from the diffusion signal, and such estimates such as neurite density from the NODDI model have been verified with histology in animals (Sato et al., 2017) and pathological findings in humans (Sone et al., 2020). In the present study, we focus on the NDI and ODI metrics, derived from the NODDI model, with higher values NDI correlated with higher density of neuronal tissue, and higher values of ODI indicating increased dendritic arborization and complexity (Shao et al., 2021). We computed the NDI and ODI metrics using the Microstructure Diffusion Toolbox (Harms, Fritz, Tobisch, Goebel, & Roebroeck, 2017; Harms & Roebroeck, 2018). The two diffusivities representing the diffusion coefficient of the isotropic

compartment (d_{iso}) and the intrinsic diffusivity of the intra-neurite compartments (d||) were fixed to $d_{iso} = 3.00 \times 10^{-3}$ mm^2/s (for free water in the brain at 37°C) and $d|| = 1.70 \times 10^{-3}$ mm^2/s, which are the standard values recommended in Zhang et al. (2012).

In addition to NDI and ODI, the NODDI model provides a compartment estimating the free-water isotropic diffusion component (ISO). This component can be used as a mask to mitigate partial volume effects, especially where brain tissue directly interfaces with cerebrospinal fluid (i.e., near the ventricles and in the extracortical space under the skull). We implemented a mask here such that voxels with an ISO volume fraction >0.80 were removed from analysis, which masked the ventricles and extracortical space.

2.4 | Construction of cortical surfaces and semiautomated segmentation and parcellation

For each participant, in order to provide a semiautomated segmentation of subcortical structures, a cortical parcellation, and an estimate of intracranial volume (Buckner et al., 2004), we constructed individual cortical surfaces for each subject from the T1-weighted volume using Freesurfer v6.0 (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). We then defined regions anatomically on individual cortical surfaces using the semiautomated Freesurfer parcellation procedure (Desikan et al., 2006; Fischl et al., 2004), which is itself based on the anatomical conventions of Duvernoy et al. (1999).

We computed cortical thickness and subcortical volume as part of the standard FreeSurfer reconstruction pipeline (Fischl & Dale, 2000), as these have been shown to have high correspondence to histological measurements (Cardinale et al., 2014). The use of a program originally developed for studies on adults is a legitimate concern. However, Freesurfer has been used to successfully create brain surface representations for children (Tamnes et al., 2010), and even neonates (Pienaar, Fischl, Caviness, Makris, & Grant, 2008), and has been used in previous research on preschool children with ADHD (Jacobson et al., 2018). We employed a similar procedure as these prior studies.

2.5 | Definition of brain regions

We focused on the regions reviewed in the Introduction, which comprise a distributed network of regions previously associated with ACEs in development, and identified several regions of interest (ROIs) that were based on the Destrieux parcellation from Freesurfer (Desikan et al., 2006; Fischl et al., 2004). These ROIs, detailed in Figure 1, were: (1) left and right amygdala; (2) left and right hippocampus; (3) left and right OFC; defined anatomically as the orbital H-shaped sulcus; (4) left and right anterior cingulate cortex, defined as the average of the anterior part of the cingulate gyrus and sulcus, and the middle-anterior part of the cingulate gyrus and sulcus; (5) cerebellum; and (6) corpus callosum. Data for volume were retrieved for all regions and data for cortical thickness were retrieved for cortical regions using Freesurfer v.6.0. The Freesurfer parcellation/segmentation was exported to the T1-weighted volume space in AFNI (*@SUMA_Make_Spec_FS*). Then NDI and ODI were retrieved for all regions defined in the T1-derived ROI mask (AFNI *3dROIstats*), following visual verification of the registration of the Freesurfer parcellation/segmentation to the DWI scan in the volume space.

2.6 | Quality control of magnetic resonance imaging scans

Movement artifacts in T1-weighted MRI scans are common, especially in pediatric populations in this age range, and especially in children with ADHD. Fortunately, Freesurfer is robust to movement-related artifacts, as, except in extreme cases, the program is able to accurately identify intensity differences between white matter and gray matter inherent in the T1-weighted image. In some cases, however, manual intervention is necessary. In this manual intervention, each individual MRI scan is inspected, and in cases where the program does not adequately identify the appropriate regional boundaries, manual edits are employed. We also visually rated each T1-weighted image on a 7-point scale ranging from "1 = *Poor*" to "4 = *Excellent*," with allowances for half-points (e.g., 3.5). Scans for both groups were generally rated "*Very Good*" to "*Excellent*," with an average of 3.56 (SD = 0.59) for the ADHD group, and 3.44 (SD = 0.68) for the TD group. There were no significant group differences for the quality of the scans, $t(195) = -1.39$, $p = .17$.

2.7 | Data analyses

All analyses were conducted using SPSS Version 26. Data were first inspected for missingness, with no missing data present for any variables of interest. We then examined whether there were differences in cumulative risk categories between ADHD and TD groups.

Next, multiple regression analyses were conducted to examine how cumulative risk (the predictor) was associated with brain measures (the outcome). Thus, we examined volume, NDI, and ODI of the cerebellum, corpus collosum, OFC, amygdala, hippocampus, and the anterior cingulate. For cortical regions (i.e., OFC and anterior cingulate), we also examined cortical thickness. These regions were chosen based on previous literature linking early risk factors to brain development, as we reviewed in the introduction. For all regressions, the following covariates of noninterest were included: child age, child sex, child IQ, average cortical thickness (for cortical ROIs), intracranial volume (for brain volume measures), average brain NDI (for NDI measures), and average brain ODI (for ODI measures). Intracranial volume was defined using the procedure from Buckner et al. (2004).

The first set of regressions also included diagnostic status as a moderating variable on cumulative risk (i.e., group [ADHD vs. TD] by cumulative risk interaction). This assesses whether the impact of ACEs on brain development is exacerbated in children with ADHD relative to TD children. In a second set of regressions, we removed the categorical ADHD diagnosis and examined, as covariates, more continuous measures of inattention, hyperactivity, and oppositional defiant behaviors

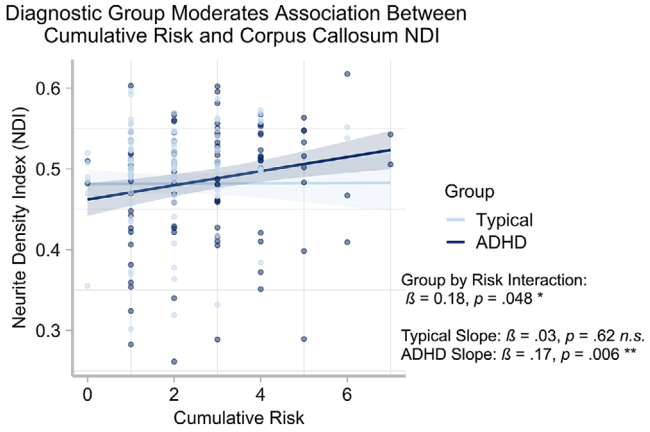

FIGURE 2 Diagnostic group moderates association between corpus callosum NDI and cumulative risk. This figure shows the significant interaction of group (i.e., ADHD and typically developing children; TD) and cumulative risk. Analyses controlled for child age, child sex, child IQ, and mean white matter neurite density index (NDI)

from the Disruptive Behaviors Disorders (DBD) rating scale. For the DBD, the highest score from either the parent or the teacher was used.

2.8 | Correction for multiple comparisons

We focused on a small number of brain regions based on our review of the literature, but the number of comparisons necessitates statistical correction to control for Type I error. We employed the false discovery rate (FDR) correction (Benjamini & Hochberg, 1995) at two different nominal levels (q = .05 and .10), which defines the proportion of errors committed by falsely rejecting null hypotheses. Family was defined within each brain measure. Thus, there were 10 comparisons each for volume, NDI and ODI, and four comparisons for cortical thickness. We interpret results in the context of these FDR proportions, and in the context of effect sizes considered against the associated 95% CIs.

3 | RESULTS

Descriptive and demographic variables are presented in Table 1. As expected, there were significant group differences in inattention, hyperactivity, and oppositional defiant behaviors. In addition, there were significant differences in several risk categories, including single parent status, parental stress, parental ADHD, parental emotion dysregulation, and total cumulative risk scores.

Confirming group differences, we examined whether group status moderated the association between cumulative risk and brain outcomes. There was a significant interaction between group and cumulative risk when predicting the corpus callosum NDI ($ß = .18$, $B = 0.009$, $t(189) = 1.99$, $p = .048$, B 95% CI [0.0001, 0.016]; see Figure 2). Probing of the interaction revealed there was no association for TD children ($ß = .03$, $B = 0.001$, $t(88) = 0.49$, $p = .62$, B 95% CI [−0.005, 0.007]). However, for children with ADHD, greater cumulative risk scores were associated with increased NDI ($ß = .17$, $B = 0.008$, $t(97) = 2.81$, $p = .006$, B 95% CI [0.002, 0.013]; see Figure 2). There were no significant interactions across other areas of interest (p's > .05).

Next, we examined the main effect of cumulative risk across the diagnostic groups, adding the continuous measures of inattention, hyperactivity, and ODD as covariates. Table 2 shows these results. Within NDI, higher cumulative risk scores were significantly associated with increased NDI in the corpus callosum. However, this main effect is best interpreted in the context of the significant group by risk interaction (noted above) showing that the effect holds for children with ADHD, but not TD children.

Examining the ODI measure, cumulative risk was significantly associated with reduced ODI of the cerebellum. However, this result did not survive FDR correction at q = .05 or .10. No other statistically significant effects for ODI were identified. Examining volume, we found that cumulative risk was negatively associated with cerebellar volume, although again this did not survive the multiple comparison correction. For the thickness measure, no statistically significant effects were identified in any regions that were examined.

4 | DISCUSSION

In this study, we demonstrated that greater cumulative ACEs were associated with increased NDI in the corpus collosum across all children. However, an interaction emerged indicating that for the TD children, there was no significant association between cumulative risk and neurite density. In contrast, for children diagnosed with ADHD, increased risk was associated with increased NDI. The differential association between cumulative ACEs and microstructural indices of neurite density in corpus callosum underscores the potential negative consequences to brain development in this region, especially in children who are at increased risk for cumulative ACEs (Jackowski et al., 2008; McCarthy-Jones et al., 2018; Rinne-Albers et al., 2016). Furthermore, this interaction reinforces the notion that endogenous characteristics of the child (i.e., existing psychopathology) interact with environmental factors to affect brain development in early childhood. Taken together, our results highlight the role early cumulative ACEs play in brain developmental across TD and children with ADHD.

4.1 | ACEs affect axonal density in corpus callosum

The strongest effect of ACEs on brain development in our preschool sample was detected using the more sensitive measure of brain morphology, namely, in the novel measure of neurite density derived from the NODDI diffusion model. Thus, we did not detect strong effects for more common metrics of volume and cortical thickness, even though these effects have been reported in the previous literature (Chad-Friedman et al., 2020; Duan et al., 2019; Lawson et al., 2013; Machlin et al., 2020; Marečková et al., 2019; Noble et al., 2012). Further, while one effect for ODI (in cerebellum) was nominally significant, it did not survive FDR correction even at the more liberal q = .10 level.

TABLE 2 Associations between cumulative risks and brain morphometric measures

	B (SE)	*β*	*t*-Value	*p*	95% CI for *B*
Neurite density index (NDI)					
Corpus collosum	0.006 (0.002)	.08	2.67	**.009**++	0.002, 0.010
Cerebellum	−0.008 (0.005)	−.08	−1.64	.10	−0.020, 0.002
Left hemisphere					
OFC	0.0008 (0.002)	−.02	0.36	.72	−0.004, 0.005
Amygdala	0.002 (0.002)	.03	0.77	.44	−0.002, 0.006
Hippocampus	0.0001 (0.002)	.003	0.06	.95	−0.004, 0.004
Cingulate	−0.0003 (0.002)	−.01	−0.14	.89	−0.004, 0.004
Right hemisphere					
OFC	−0.002 (0.002)	−.05	−1.11	.27	−0.007, 0.002
Amygdala	0.004 (0.002)	.07	1.85	.07	−0.0002, 0.008
Hippocampus	−0.002 (0.002)	−.03	−0.77	.44	−0.005, 0.002
Cingulate	0.0003 (0.002)	.01	0.15	.88	−0.004, 0.004
Orientation dispersion index (ODI)					
Corpus collosum	−0.0002 (0.004)	−.003	−0.06	.95	−0.008, 0.008
Cerebellum	−0.01 (0.005)	−.10	−2.02	**.045**	−0.021, -0.0003
Left hemisphere					
OFC	0.001 (0.003)	.02	0.37	.71	−0.005, 0.008
Amygdala	−0.0007 (0.002)	−.02	−0.32	.75	−0.005, 0.004
Hippocampus	−0.0005 (0.002)	−.01	−0.21	.83	−0.005, 0.004
Cingulate	−0.001 (0.003)	−.03	−0.47	.64	−0.007, 0.004
Right hemisphere					
OFC	−0.001 (0.003)	−.03	−1.55	.12	−0.001, 0.010
Amygdala	0.0005 (0.002)	.01	0.22	.83	−0.004, 0.005
Hippocampus	−0.001 (0.003)	.02	0.47	.64	−0.004, 0.006
Cingulate	−0.002 (0.003)	−.04	−0.86	.39	−0.007, 0.003
Volume					
Corpus collosum	5.09 (3.81)	.09	1.33	.18	−2.43, 12.61
Cerebellum	−410.57 (185.06)	−.11	−2.22	**.028**	−775.63, -45.52
Left hemisphere					
OFC	0.000 (0.000)	.02	0.21	.83	−0.001, 0.001
Amygdala	2.34 (6.92)	.02	0.34	.74	−11.31, 15.98
Hippocampus	−6.64 (14.52)	−.03	−0.46	.65	−35.33, 22.03
Cingulate	0.000 (0.000)	.03	0.42	.67	−0.001, 0.001
Right hemisphere					
OFC	0.000 (0.000)	.02	0.31	.75	−0.001, 0.001
Amygdala	4.04 (8.02)	.03	0.50	.62	−11.78, 19.87
Hippocampus	−25.19 (14.88)	−.10	−1.69	.09	−54.54, 4.16
Cingulate	0.000 (0.000)	−.02	−0.26	.79	−0.001, 0.001
Cortical thickness					
Left hemisphere					
OFC	0.008 (0.008)	.08	1.00	.32	−0.008, 0.024
Cingulate	0.008 (0.005)	.10	1.50	.14	−0.003, 0.019

(Continues)

TABLE 2 (Continued)

	B (SE)	*β*	*t*-Value	*p*	95% CI for *B*
Right hemisphere					
OFC	0.007 (0.008)	.07	0.91	.36	−0.008, 0.022
Cingulate	0.004 (0.006)	.05	0.77	.45	−0.006, 0.013

Note: Bold indicates that the *p*-value is less than the nominal alpha of .05. All regressions controlled for child symptoms of inattention, hyperactivity, oppositional defiant disorder, child age, child sex, and child IQ. Volume regressions controlled for total cranial volume, thickness regressions controlled for total average thickness, and NDI and ODI regressions controlled for mean white matter NDI or ODI, respectively.
Abbreviation: OFC, orbitofrontal cortex.
p-Values marked with "++" indicate that these effects survived a False Discovery Rate (FDR) correction for multiple comparisons at $q = .10$.

The finding for cerebellar volume also does not survive this FDR correction. Thus, we focus our initial discussion on the NDI metric as it pertains to corpus callosum microstructure.

Interpretation of the NDI metric as it pertains to white or gray matter microstructure must proceed with caution. The diffusion signal in gray matter is derived from a combination of several tissue components, including axons, dendrites, and cell bodies of both neurons and glia. The NODDI model helps to segregate these contributions to some degree, and indeed in gray matter, the NDI metric from the NODDI model has been verified in several histologic studies to be sensitive to the density of neurons, such that reduced NDI is associated with the loss or reduction of neurons in cases of lesion or tumor (Shao et al., 2021) or degenerative disease (Kamagata et al., 2016). There is also some modest sensitivity to density differences in cytoarchitectonically diverse tissue samples (Crombe et al., 2018).

In white matter, signal contributions are derived mainly from axons and glia. Developmental studies of neurite density, measured by the NODDI model, show increases in NDI in the white matter from ages 7 to 63 years (Chang et al., 2015) and in gray matter from ages 0 to 14 years (Zhao et al., 2021). However, our main finding is with respect to NDI in the "corpus callosum," which is a dense collection of interhemispheric fibers, and thus the NODDI measure in this region is most sensitive to axonal density, not neural or glial cell body density or dendritic density. Fortunately, two studies have linked NDI in the corpus callosum to histological differences in axonal density in developmental and adult samples. Indeed, NODDI of the corpus callosum closely aligns with the known longitudinal distribution of fiber density in the corpus callosum, such that the NDI metric decreases with a high degree of correlation as fiber density increases (Garic, Yeh, Graziano, & Dick, 2021; Genc, Malpas, Ball, Silk, & Seal, 2018). These studies found that this association applies to children in the age range we study here. We can thus speculate that the maintenance of callosal fibers following exposure to ACEs, indicated by the positive association with NDI and cumulative risk, may reflect a disruption of callosal axonal pruning, a process that takes place in typical development in response to experience (LaMantia & Rakic, 1990). Atypical axonal pruning in the corpus callosum is linked with a number of psychopathologies (Raine et al., 2003) and seems to mainly affect excitatory rather than inhibitory interhemispheric connections (Saugstad, 1994). Functionally, this may translate to altered network connectivity across the two hemispheres, such that typical processes of establishment of functional laterality over development are disrupted (Everts et al., 2009). Such disruption may impact the neural processes implementing several cognitive and affective functions, including the onset of mental health disorders associated with early risk exposure (McLaughlin et al., 2012). Notably, this disruption seems to be specific to children with ADHD who are repeatedly exposed to stressful situations, as the association with ACEs and corpus callosum NDI only applied to the ADHD group (Figure 2). One can speculate that children with ADHD already differ to some degree in terms of their trajectories of brain development relative to TD children (Rubia, 2007), and that the additional burden of repeated ACEs exacerbates these differences. However, the directionality of this proposed causal pathway is speculative given the quasi-experimental nature of the study design. That said, it is an intriguing possibility that could be explored in future work.

4.2 | ACEs may influence cerebellar development

Two findings related to ODI and volume of the cerebellum were nominally significant, but did not survive FDR correction. Thus, our brief discussion below should be considered in that context. Here, we found that greater cumulative risk scores were associated with reduced ODI and volume of the cerebellum. This is an interesting result when considered in the context of cerebellar development and function. First, with respect to cerebellar development, the cerebellum is unique with respect to the rest of the brain because, unlike regions of the cortex and other subcortical areas, neural proliferation in the cerebellum proceeds beyond birth, and refinement of cerebellar neuronal maps is heavily experience-dependent (Sotelo, 2004). Thus, the cerebellum may be especially sensitive to cumulative ACEs, as developmental processes related to neural proliferation may be affected both pre- and postnatally. Second, with respect to cerebellar function, the cerebellum has been implicated in a number of cognitive, affective, and sensorimotor processes, and it is densely connected to cortical regions supporting function in these domains. For example, lesions of the posterior lobe of the cerebellum result in a well-described cerebellar cognitive affective syndrome, which manifests as deficits in executive function, visual spatial processing, linguistic processing, and emotion regulation (Schmahmann, 2019). The cerebellum is part of a comprehensive cortico-subcortical network supporting these functions and given its potential susceptibility to experiential influences during

development, it may contribute significantly to negative outcomes following exposure to ACEs in both children with and without ADHD.

4.3 | Limitations

Although the current study represents the first step in understanding how cumulative risk impacts brain development in young children with and without ADHD, it is not without limitations. First, the current study is cross-sectional, which substantially limits our ability to make causal claims. Longitudinal investigation of the cumulative impact over development is necessary to better understand the neurobiological sequelae of ACEs throughout development. However, this snapshot of the preschool period does provide an opportunity to understand resilience to ACEs as children develop and may especially be relevant for understanding what factors predict later resilience. The current study also focuses on children diagnosed with ADHD as the clinical group of interest, which may limit generalizability to other clinical disorders that emerge in childhood. However, as children with ADHD are notably at higher risk for experiencing ACEs, a finding that was replicated in the present study, the current study extends our understanding of this common childhood disorder. Finally, an additional methodological limitation was the use of the standard recommended values for the diffusion coefficients of d_{iso} and the intrinsic diffusivity of the intra-neurite compartments d||, which were fixed to $d_{iso} = 3.00 \times 10^{-3}$ mm^2/s (for free water in the brain at 37°C) and d|| $= 1.70 \times 10^{-3}$ mm^2/s. Studies have shown that these simplifying model assumptions for parallel diffusivity are reasonable for white matter in adults, but may be suboptimal for gray matter, or for infants earlier in development (Fukutomi et al., 2018; Guerrero et al., 2019). Such optimal parallel diffusivity values may vary across the brain, which may lead to better fitting NODDI models in some regions as opposed to others. This is a limitation when both gray matter and white matter regions are considered in the same analysis.

5 | CONCLUSION

Taken together, the impact of cumulative ACEs on microstructural indices of cellularity across TD and children with ADHD underscores the potential negative consequences of early ACEs on brain. Future work should investigate if early intervention of malleable risk factors (e.g., parent stress, parent ADHD) will prevent and/or reverse the negative impact of ACEs on brain development and alter subsequent psychosocial functioning.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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