




RESEARCH ARTICLE

Socioeconomic factors, stress, hair cortisol, and white matter microstructure in children

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Abstract

Socioeconomic disadvantage has been linked to increased stress exposure in children and adults. Exposure to stress in childhood has been associated with deleterious effects on cognitive development and well-being throughout the lifespan. Further, exposure to stress has been associated with differences in brain development in children, both in cortical and subcortical gray matter. However, less is known about the associations among socioeconomic disadvantage, stress, and children's white matter development. In this study, we investigated whether socioeconomic disparities would be associated with differences in white matter microstructure in the cingulum bundle, as has been previously reported. We additionally investigated whether any such differences could be explained by differences in stress exposure and/or physiological stress levels. White matter tracts were measured via diffusion tensor imaging in 58 children aged 5–9 years. Results indicated that greater exposure to stressful life events was associated with higher child hair cortisol concentrations. Further, physiological stress, as indexed by hair cortisol concentrations, were associated with higher fractional anisotropy in the cingulum bundle. These results have implications for better understanding how perceived and physiological stress may alter neural development during childhood.

KEYWORDS

child, cortisol, diffusion-weighted imaging, neurodevelopment, socioeconomic status, stress

1 | INTRODUCTION

1.1 | Socioeconomic disadvantage and stress exposure

Socioeconomic status (SES) is a multidimensional construct that includes measures of economic resources as well as social factors such as educational attainment, occupational prestige and social status (Hackman & Farah, 2009). Most commonly characterized by family income and parental education, socioeconomic disparities have been

associated with differences in stress exposure in children and adults (Luby et al., 2013). For example, socioeconomic disadvantage has been associated with an increased risk of experiencing chronic stressors such as neighborhood violence, uncertainty about material resources, family conflict, and household chaos (Brooks-Gunn & Duncan, 1997; Evans, 2004). Further, children from socioeconomically disadvantaged backgrounds may experience multiple stressors at once, potentially exacerbating the effects of stress. Indeed, increased exposure to stress may be an important mediating mechanism linking SES to children's outcomes (Evans & Kim, 2013).

1.2 | Stress exposure and cortisol

Stress exposure reflects the type and degree of stressors that children experience or encounter in everyday life. At the physiological level, chronic stress exposure has been linked to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis stress–response system (Gunnar & Donzella, 2001). This dysregulation is one mechanism through which stress exposure may impact developmental outcomes.

Dysregulation of the HPA axis is typically observed through changes in glucocorticoid hormone levels, namely cortisol. Recent studies have measured hair cortisol concentration (HCC) in humans, which indexes average cortisol levels over the prior several months and is less sensitive to situational factors than other cortisol metrics (Flom et al., 2017). Further, recent work has linked HCC to stress exposure in adults (O'Brien et al., 2013), as well as to stress exposure (Vanaelst et al., 2013) and SES (Ursache et al., 2017; Vliegertart et al., 2016) in children. As such, alterations in stress physiology in response to stress may represent one mechanism by which socioeconomic disadvantage may “get under the skin” and influence outcomes (Kim et al., 2017).

1.3 | Socioeconomic disadvantage, stress exposure, and brain structure

Both stress exposure and SES have been associated with differences in cortical and subcortical gray matter in the hippocampus (Humphreys et al., 2019; Noble et al., 2015), the amygdala (Merz et al., 2018), and the prefrontal cortex (Lawson et al., 2013). While work has suggested that stress exposure may serve as a mediating factor between SES and gray matter (Luby et al., 2013; Merz et al., 2019), few studies have examined whether the same holds true for white matter.

White matter plays a critical role in neural signaling and connections between different brain regions (Fields, 2010). Fractional anisotropy (FA), a measure of white matter microstructure, reflects the degree of directionality of water diffusion in white matter tracts, which indicates the microstructural properties of white matter tracts and in turn the capacity for functional communication between connected brain regions (Beaulieu, 2002; Thomason & Thompson, 2011). Given the ability for white matter development to be environmentally influenced (Fields, 2008), understanding how environmental circumstances impact the development of specific white matter tracts may help us better understand brain development in children.

The cingulum bundle is a frontolimbic white matter tract that might be expected to be particularly susceptible to differences in both socioeconomic circumstance and stress exposure. This tract assists with communication between components of the limbic system and the cingulate gyrus, two regions which have high concentrations of glucocorticoid receptors (Patel et al., 2008) and which have been individually associated with both socioeconomic factors and stress (Hanson et al., 2015; McDermott et al., 2019; Merz et al., 2019). Additionally, the cingulum has been implicated in executive function and emotion regulation (dorsal cingulum), as well as memory processes (parahippocampal cingulum) (Bathelt et al., 2019; Bubb et al., 2018; Catani, 2006), cog-

nitive processes that have consistently been linked to both socioeconomic factors and stress (Evans & Schamberg, 2009; Noble et al., 2005; Raver et al., 2013; Ursache et al., 2015). Finally, the cingulum undergoes a protracted period of development, with typically developing individuals showing increases in FA throughout childhood and young to middle adulthood (Lebel & Beaulieu, 2011; Lebel et al., 2017), suggesting that it may be particularly susceptible to postnatal differences in socioeconomic circumstances, stress exposure, and alterations in stress physiology in childhood (Peters et al., 2014; Tamnes et al., 2010).

Although a few studies have reported associations between the cingulum bundle microstructure and socioeconomic factors and/or stress in children and young adults (see Noble & Giebler, 2020 for a review), results have been mixed, with some studies reporting that socioeconomic disadvantage (Dufford & Kim, 2017; Ursache & Noble, 2016) and stress (Dufford & Kim, 2017) are associated with *lower* cingulum FA, while others reporting that socioeconomic disadvantage (Noble et al., 2013) and stress (Weis et al., 2018) are associated with *higher* FA in this tract. These discrepancies may be due to differences in how stress exposure and/or SES were measured. Further, only one study (Dufford & Kim, 2017) looked concurrently at SES and stress in relation to the cingulum bundle, leaving it unclear whether increased stress exposure may mediate any relationship between SES and the cingulum.

1.4 | Cortisol and brain structure

Previous studies have reported associations between cortisol and brain structure (Chen et al., 2016; Merz et al., 2019). For example, higher HCC has been associated with smaller hippocampal volume (Chen et al., 2016; Merz et al., 2019) and greater cortical thickness in the anterior cingulate cortex (ACC) in children (Merz et al., 2019).

Although white matter tracts such as the cingulum bundle, which connects regions with an abundance of glucocorticoid receptors, might be expected to be particularly vulnerable to increased cortisol levels, few studies have examined links between cortisol and white matter. One study of girls reported that high salivary cortisol reactivity was associated with lower white matter FA in several tracts, including the cingulum (Sheikh et al., 2014). Another study found that decreased cortisol production in response to a stressor was related to increased FA in the uncinate fasciculus (though the cingulum was not examined) (Kircanski et al., 2019). To our knowledge, no study has investigated associations between HCC and white matter microstructure in children.

1.5 | The current study

As reviewed above, previous studies have investigated links between SES and white matter microstructure in children (Dufford & Kim, 2017; Ursache & Noble, 2016). However, the extent to which these links may be mediated by stress exposure, and/or alterations in stress physiology, has not been examined. Previous work in the present sample investigated whether socioeconomic factors were associated with

TABLE 1 Descriptive statistics for sample characteristics ($N = 94$)

	M	SD
Child age (years)	7.03	1.29
	%	<i>n</i>
Child sex (female)	60.64	57
Child race/ethnicity		
African American, non-Hispanic/Latino	30.85	29
Hispanic/Latino	50.00	47
European American, non-Hispanic/Latino	13.83	13
Other	5.32	5
Family income below U.S. poverty threshold	29.79	28

differences in hair cortisol, and in turn whether HCC was associated with differences in hippocampal and ACC structure (Merz et al., 2019). Building on that work, we hypothesized that socioeconomic factors would also be associated with differences in cingulum microstructure—the white matter tract that communicates between the limbic system and the cingulate gyrus—and that these associations would be mediated by differences in stress exposure and/or stress physiology.

We had four main hypotheses: (1) Socioeconomic disadvantage would be associated with lower FA in the cingulum bundle, (2) greater stress exposure would be associated with lower FA in the cingulum, (3) higher physiological stress, as operationalized by children's HCC, would be associated with lower FA in the cingulum, and (4) physiological stress would mediate the link between stress exposure and cingulum FA. Exploratory post hoc analyses examined these questions in relation to FA of different segments of the cingulum bundle.

2 | METHOD

2.1 | Participants

Participants were recruited in the New York City area by posting flyers and meeting families at local community events. Children aged 5–9 years ($N = 94$; 61% female) and their parents participated in this study. Children were included if they were primarily English speakers in the home, born from a singleton pregnancy, and had no history of premature birth (< 37 weeks), or medical or psychiatric problems. Children with MRI contraindications were also excluded from the study. Families were socioeconomically diverse, with average parental education ranging from 7 to 20 years and family income-to-needs (ITN) ratio ranging from 0.17 to 15.21 (see Table 1 for sample characteristics).

At the first study visit, all parents ($N = 94$) completed questionnaires regarding socioeconomic factors and exposure to stress. Hair samples were collected for a total of 67 children (77% female), with some children unable to provide a sample because their hair was too short ($n = 24$) or because their parents declined to have a sample taken ($n = 3$). Of the 67 hair samples collected, hair cortisol data were available for 65 children. The children who comprised the final sample of

hair cortisol data differed significantly from the full sample in regards to sex ($t(93) = -5.263$, $p < .0001$), as boys were less likely to have hair long enough (at least 3 cm in length) to participate. During the first study visit, participants were also offered the opportunity to participate in the MRI portion of the study.

Eighty-five children were enrolled in the MRI portion of the study. Out of these 85, 66 children participated in an actual MRI scanning session. Scans were completed for a total of 61 children, with 58 children having usable diffusion-weighted imaging (DTI) scans. The remaining children were either unwilling or unable to participate in the MRI portion of the study after mock scanning ($n = 12$) or began to attempt scanning but were afraid, fidgety, or uninterested in completing the session before the session started ($n = 7$). Furthermore, some children opted to stop the session early before DTI data could be collected ($n = 5$). Finally, some participants' data were dropped due to excessive head motion upon visual inspection ($n = 3$), leading us to our final sample of 58 children with usable DTI data.

The children who completed the MRI portion of the study did not differ from the larger sample in terms of age, sex, race/ethnicity, family income, or parental education. However, the subsample with usable DTI data was generally older ($t(92) = -4.545$, $p < .01$), as older children were more likely to complete the mock scan and entire MRI scan. In total, 38 children had full hair cortisol, DTI, and questionnaire data.

2.2 | Procedure

Parents and children visited the lab on two separate occasions within 1 month. During the first visit, hair samples were collected and parents completed questionnaires. Children then completed a mock MRI session in order to gain familiarity with the conditions of MRI scanning. During the second visit, children participated in an MRI scan which included a diffusion-weighted sequence. Informed consent/assent was provided by all families, and all study procedures were approved by the New York State Psychiatric Institute and Teachers College, Columbia University Institutional Review Boards.

2.3 | DTI acquisition and processing

MRI data were acquired on a 3-Tesla General Electric (GE) MR750 scanner with a 32-channel head coil. Whole brain DTI data were acquired with the following parameters: 60 axial slices were collected (posterior to anterior) each at 2.5 mm thickness, TR = 15,700 ms, TE = 86.4 ms, FOV (x) = 24 mm, FOV (y) = 24 mm, matrix size = 132 × 128 (machine-interpolated to 256 × 256 for postprocessing), and voxel size = 0.94 mm × 0.94 mm × 2.5 mm. The diffusion-weighted images were acquired along 15 noncollinear directions, with a b value of 1000 s/mm², and three baseline images with $b = 0$ s/mm². Total scan duration for DTI was 9 min, 57 s (number of excitations = 2). All images were visually inspected by two trained research assistants, independently. Research assistants visually checked the raw diffusion-weighted images, eddy current corrected diffusion-weighted

images, the color-encoded FA images, and each participant's FA image after alignment to potentially exclude participants who had motion-corrupted DTI data ($n = 3$).

Images were processed using the Oxford Center for Functional MRI of the Brain's (FMRIB) Software (FSL version 5.0.11) (Smith et al., 2004). DWI acquisitions were corrected for subject motion and Eddy current-induced distortion using FSL Eddy (Andersson et al., 2017). The FSL DTIFIT was used to fit diffusion tensors at each voxel, and FA image was derived from the fitted diffusion tensors. The Johns Hopkins University White Matter Tractography Atlas (Mori et al., 2008; Wakana et al., 2007) was used to extract mean FA values for white matter tracts of interest after running tract-based spatial statistics (TBSS) (Smith et al., 2006). Due to the age of the sample, the most representative subject was automatically identified as the target image from all subjects using TBSS script (tbss_2_reg) and the target was then affine-aligned into MNI152 standard space. Each participant's FA image was then transformed into standard space by applying the nonlinear transform to the target FA image, followed by the affine transform from that target to the standard space. A skeleton of white matter tracts that were common to all participants was then created by thinning the mean FA image using a threshold of 0.2. This value was chosen to exclude FA values from gray matter or cerebrospinal fluid. Aligned FA image of each subject was then projected onto the skeleton and mean FA values were extracted from region of interest tracts used for statistical analyses. After projecting the aligned FA image onto the skeleton, the skeletonized FA image for each subject was visually inspected for quality control. For the current study, mean FA values of the cingulum bundle were extracted.

2.4 | Measures

2.4.1 | Socioeconomic factors

Parents reported their total annual household income and the number of adults and children in the household. A family ITN ratio was calculated for each participant by dividing the total household income by the nationally set poverty threshold for a family of that size. Family ITN was log-transformed in all analyses to correct for positive skew. Parents also reported their years of educational attainment, which were then averaged across all parents.

2.4.2 | Stress exposure

Life experiences survey

The Life Experiences Survey (LES; Sarason et al., 1978) is a measure of the quantity and impact of life events. Parents indicated whether a series of 44 events occurred within the last year. Parents rated the impact of events that occurred on a 7-point scale from -3 (extremely negative) to $+3$ (extremely positive). If the event did not occur or occurred but was rated as neutral, the item was scored as 0. A negative life experiences score was computed as the absolute value of the sum

of the impact of events rated as negative. The LES is a reliable measure of recent life changes and their impact, with well-established internal consistency ($\alpha = .77$), test-retest reliability, and validity (Sarason et al., 1978).

Perceived stress scale

The Perceived Stress Scale (PSS) (Cohen et al., 1983) is a 14-item scale that asked parents about their feelings and thoughts about their stress and ability to control their stress during the last month). For each item, they were asked to mark how often they felt or thought a certain way on a 5-point scale ranging from 0 (never) to 4 (very often). Items were reverse coded when appropriate and then summed to create a total score ($\alpha = .84$).

Material deprivation scale

In the Material Deprivation Scale (Pilkauskas et al., 2012) parents were asked a series of 14 questions about possible hardships in bills, utilities, food, medical care, and housing insecurity. Parents were asked if they experienced hardships in these areas within the past year and provided a dichotomous answer (yes or no). All affirmative answers were recorded and summed to create a total score ($\alpha = .77$).

2.4.3 | Hair cortisol concentration

A trained research staff member cut a small section of hair proximal to the posterior vertex of the participant's scalp. Each hair sample weighed at least 15 mg and was approximately 3 cm long in order to account for cortisol deposited during roughly the 3 months prior to collection. Samples were stored at -20°C until being sent to the University of Massachusetts for analysis. Samples were processed and analyzed using previously validated methods, described in detail elsewhere (Meyer et al., 2014).

Briefly, each sample was weighed, washed twice in isopropanol to remove external contaminants, ground to a fine powder, and extracted with methanol. The methanol extract was evaporated, redissolved in assay buffer, and analyzed in duplicate along with standards and quality controls by a sensitive and specific enzyme-linked immunosorbent assay (Arbor Assays, Ann Arbor, MI). Assay readout was converted to pg cortisol per mg dry hair weight. Intra- and inter-assay coefficients of variation for this assay are $<10\%$. Hair cortisol values outside of 3 standard deviations from the mean were examined and ultimately excluded from the final analyses, due to their values being biologically implausible ($n = 5$), and hair cortisol data were log-transformed to correct for skew, similar to previous methods (Chen et al., 2016). There were no significant associations between hair cortisol and potential confounds, including hair washing frequency, steroid medication use, and hair dye use.

2.5 | Statistical plan

Descriptive statistics and preliminary analyses were conducted in SPSS (version 25). Subsequent analyses were conducted in R (version 3.5.1).

TABLE 2 Descriptive Statistics for socioeconomic factors, stress exposure, HCC, and white matter microstructure

	N	M	SD	Range
Parental education (years)	94	14.14	2.64	7–20
Income-to-needs Ratio	94	2.68	2.79	0–15
Perceived stress exposure Score	94	−0.01	0.99	−2.08 to 2.98
Hair cortisol concentration (pg/mg)	60	25.20	25.34	1–104
Parahippocampal cingulum FA	58	0.53	0.04	0.43–0.61
Dorsal cingulum FA	58	0.59	0.03	0.50–0.66

Abbreviation: FA, fractional anisotropy; M, mean; SD, standard deviation.

Note. Parental education reflects educational attainment averaged across parents in the household.

Principal component analysis was used to assess the extent to which the LES, the PSS, and Material Deprivation Scale loaded onto a single “parental perceived stress” factor. Multiple linear regression analyses were used to examine associations between socioeconomic factors, parental perceived stress, HCC, and white matter microstructure (FA) in the cingulum bundle. Covariates included child age, sex, and race/ethnicity. Race/ethnicity was not significant in any of the regression models and did not improve model fit and was therefore dropped from final analyses. Measures with outliers more than 3 SD from the mean were Winsorized; in addition, models were run both with and without any outliers to investigate any substantive differences. Thirty-eight participants had completed DTI data, hair cortisol data, and survey data (i.e., stress and SES measures). For models examining DTI data and survey data, 58 participants had complete data. For models examining hair cortisol and survey data, 60 participants had complete data. All tests were two-tailed, $\alpha = 0.05$. To account for multiple comparisons, false discovery rate corrections were applied (via p_{adjust} in R) to analyses. Uncorrected p -values are reported in regard to exploratory post hoc analyses.

To test the significance of indirect effects when a and b paths were supported in mediation analyses (see Figure 2), bias-corrected bootstrapping via the lavaan library in R was conducted using a 95% confidence interval (Rosseel, 2012). In mediation analyses, Full Information Maximum Likelihood Estimation was employed to account for missing data and produce unbiased parameter estimates and standard errors (Enders & Bandalos, 2001).

3 | RESULTS

Descriptive statistics are provided in Table 2. Two LES scores were outliers (3.20 and 4.07 standard deviations from the mean), as was as one participant’s FA value (3.07 standard deviations from the mean). These scores were Winsorized in models below. Results were also examined when outliers were excluded, as discussed below.

3.1 | Parent perceived stress

As described previously (Merz et al., 2019), principal component analysis was used to assess the extent to which the LES, the PSS, and Material

Deprivation Scale loaded onto the same construct. A single factor with an eigenvalue greater than 1.0 (1.69) was extracted, explaining 56.4% of the total variance. Factor loadings ranged from 0.63 to 0.85. This factor score was termed “parent perceived stress.”

3.2 | Socioeconomic circumstance and white matter microstructure

Neither family ITN nor parental education was significantly associated with FA in the cingulum when controlling for child age and sex (all corrected p s > .05).

3.3 | Stress exposure and white matter microstructure

Parent perceived stress was not associated with FA in the cingulum bundle when controlling for child age and sex ($p > .05$). We reasoned that perhaps *parental perception* of stress was too indirect a measure of the child’s exposure to stress. We further reasoned that perhaps exposure to explicit stressful life experiences, as measured by the Life Experiences Scale, would more proximally reflect the child’s own experiences over the last year (acknowledging that, while the LES may be more likely to capture children’s own exposure to stress than measures specifically focused on parental perception, it is still a parent-report measure). We therefore explored, post hoc, whether greater exposure to stressful life experiences, as measured by a higher LES negative life experience score, was associated with white matter microstructure. Indeed, greater exposure to stressful life events was associated with lower FA in the cingulum ($\beta = -.25, p = .03$).

When results were rerun without the LES and FA outliers, results remained similar ($\beta = -.24, p = .04$).

3.4 | Hair cortisol and white matter microstructure

Higher child HCC was significantly associated with higher FA in the cingulum ($\beta = .35, p = .007$) when controlling for child age and sex. This result remained consistent when removing the outlying FA value ($\beta = .29, p = .04$).

3.5 | Stress exposure, hair cortisol, and white matter microstructure

The composite of parent perceived stress was not associated with children's HCC. We then examined, post hoc, whether greater exposure to stressful events, as measured by LES, was significantly associated with higher child HCC. Indeed, we found that greater exposure to stressful life events was associated with higher HCC in children, controlling for child age and sex ($\beta = .25, p = .03$) (see Figure 1). This result remained similar when removing the two outlying LES scores, although results were no longer statistically significant ($\beta = .23, p = .13$).

HCC did not significantly mediate the association between stressful life experiences and FA of the cingulum.

3.6 | Post hoc analyses: cingulum segments

To further understand whether the current findings were specific to different segments of the cingulum bundle, we conducted exploratory analyses using extracted mean FA values of the parahippocampal and cingulate gyrus (henceforth referred to as the dorsal cingulum) segments of the cingulum. Greater socioeconomic disadvantage was significantly associated with higher FA in the dorsal cingulum (family ITN: $\beta = -.27, p = .03$; parental education: $\beta = -.28, p = .02$), but not with the parahippocampal cingulum. In contrast, higher parental perceived stress was neither associated with FA in the parahippocampal cingulum ($\beta = -.22, p = .06$) nor with the dorsal cingulum ($\beta = .07, p = .48$). Higher levels of parent-reported stressful life events over the past year, as measured by the LES, were significantly associated with lower FA in the parahippocampal cingulum ($\beta = -.30, p = .005$), but not the dorsal cingulum. These results remained similar when removing the outlying LES value (parahippocampal cingulum: $\beta = -.28, p = 0.03$). Finally, higher HCC was significantly associated with higher FA in both the dorsal and parahippocampal cingulum (dorsal cingulum: $\beta = .39, p = .04$; parahippocampal cingulum $\beta = .31, p = .02$).

Based on these results, exposure to stressful life experiences was not further considered as a mediator linking socioeconomic disadvantage to FA in either segment of the cingulum. On the other hand, both socioeconomic disadvantage and HCC were associated with increased FA in the dorsal cingulum. HCC was thus probed as a potential mediator of the link between socioeconomic disparities and dorsal cingulum FA. Hair cortisol did not mediate the relationship between parental education and dorsal cingulum FA, however, as the association between cortisol and the dorsal cingulum (*b* path) was no longer statistically significant after parent education was added to the model. Since ITN was not significantly associated with hair cortisol in this sample (Merz et al., 2019), we did not explore ITN in association with dorsal cingulum FA and hair cortisol.

We then tested whether HCC mediated the association between exposure to stressful life experiences and parahippocampal cingulum FA and found a significant indirect effect (indirect effect = 0.09, 95% CI [0.003, 0.180]). Greater exposure to stressful life experiences was

related to higher HCC, which in turn was associated with higher FA in the parahippocampal cingulum (see Figure 2).

4 | DISCUSSION

The goal of this study was to build upon previous work by examining associations among socioeconomic factors, stress exposure, HCC, and white matter microstructure in children. Our first hypothesis was that socioeconomic disadvantage would be associated with lower FA in the cingulum bundle. Contrary to predictions, parental education and family ITN were not associated with cingulum bundle FA. Our second hypothesis was that greater parent perceived stress would be associated with lower FA in the cingulum bundle. While a composite of parental perceived stress was not linked with cingulum FA, greater exposure to stressful life experiences—arguably a more proximal measure of the child's own experiences of stress, and therefore perhaps more relevant for brain development—was significantly associated with lower FA in the cingulum bundle. Third, we hypothesized that higher physiological stress, as operationalized by children's HCC, would also be associated with lower FA in the cingulum bundle. Counter to expectations, higher HCC was associated with *higher* FA in the cingulum bundle. Finally, we hypothesized that HCC would mediate the link between exposure to stressful life experiences and cingulum FA. This hypothesis was not supported, as the indirect effect was not significant.

Exploratory analyses separately examined the individual segments of the cingulum bundle. Results revealed that socioeconomic disadvantage was associated with higher FA in the dorsal segment of the cingulum. In contrast, greater exposure to stressful life events was associated with lower FA in the parahippocampal cingulum. Moreover, hair cortisol was significantly associated with higher FA in both segments of the cingulum. Lastly, these analyses revealed a significant indirect effect linking exposure to stressful life events to greater parahippocampal cingulum FA via HCC. While exploratory and requiring replication, these results provide some evidence of physiological stress as a mediating factor between stress exposure and white matter microstructure in children.

4.1 | Socioeconomic disadvantage and cingulum bundle FA

Higher family ITN and higher parental education were not associated with FA in the total cingulum. However, exploratory analyses revealed that higher ITN and parental education were both associated with lower FA in the dorsal cingulum. While one study has reported a similar relationship in young adults (Noble et al., 2013), other findings have been mixed. In contrast with these results, some studies among children have reported associations between higher family income and higher FA in the cingulum (Dufford & Kim, 2017; Ursache & Noble, 2016), whereas others have found no associations between SES and white matter microstructure in children (Jednorog et al., 2012).

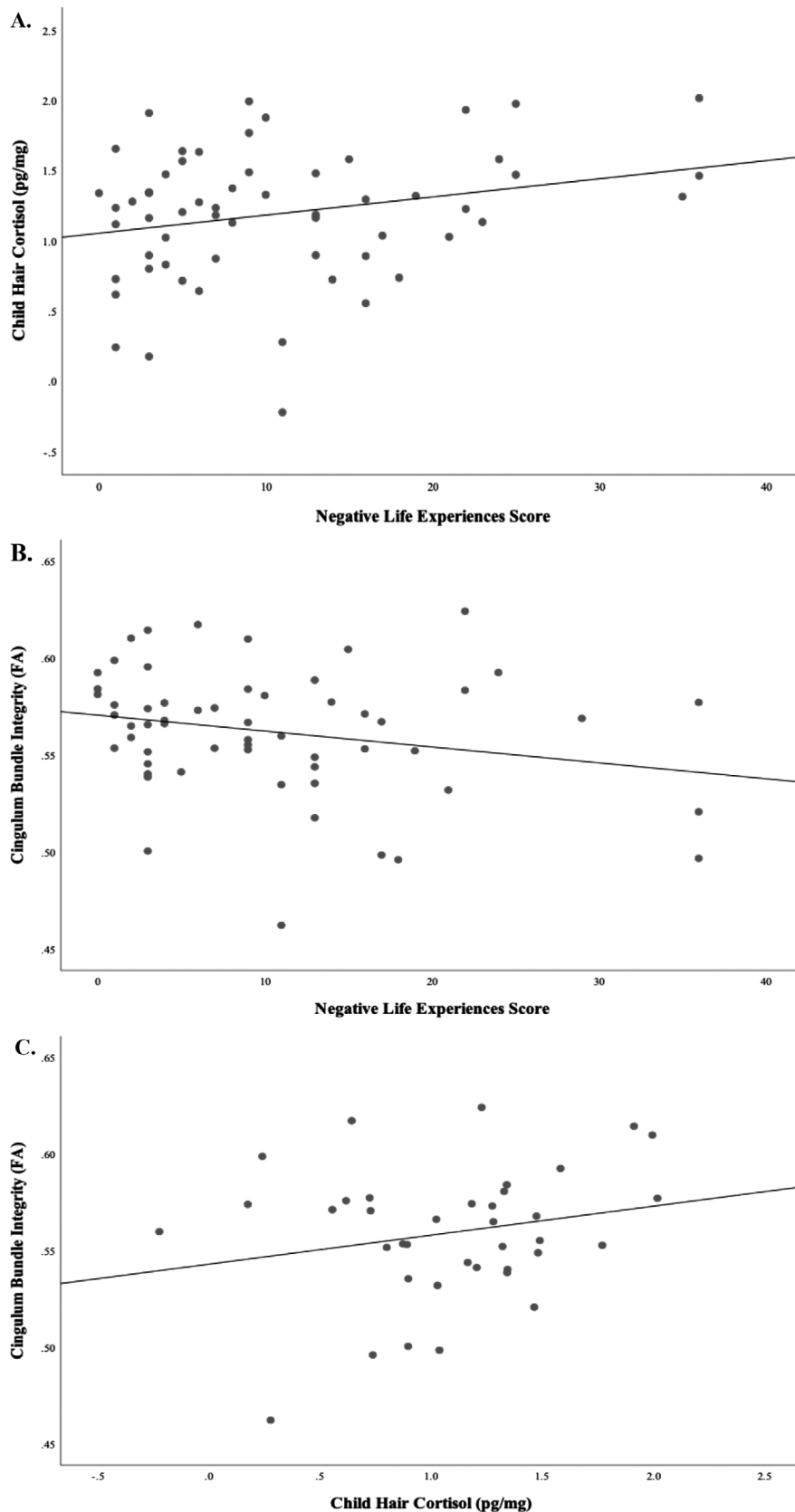


FIGURE 1 (a) Higher parent-reported negative life experiences scores were significantly associated with higher levels of (logarithmically transformed) hair cortisol in children. (b) Negative life experiences scores were significantly associated with lower FA in the cingulum bundle. (c) HCCs (logarithmically transformed) were significantly associated with higher FA in the cingulum bundle. Child age and sex were included as covariates in these models

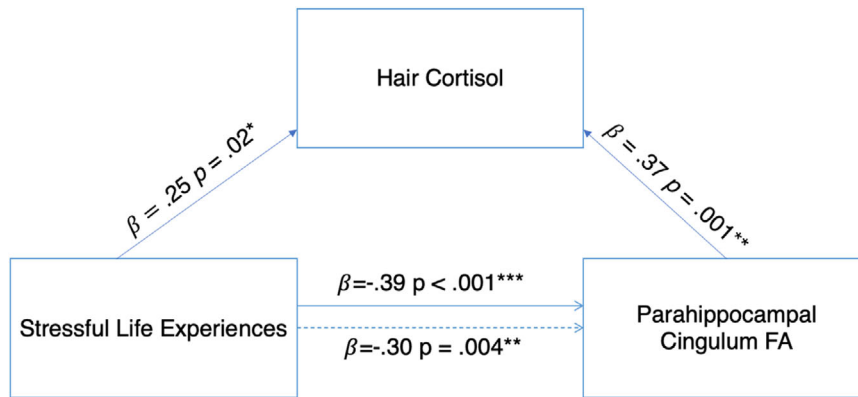


FIGURE 2 Hair cortisol significantly mediated the association between exposure to stressful life experiences and FA in the parahippocampal cingulum. Higher negative life experience scores were associated with higher HCC, which in turn was associated with higher FA in the parahippocampal cingulum. The dotted line between exposure to stressful life experiences and parahippocampal cingulum FA represents the total effect (c), while the solid line represented the direct effect after accounting for the mediated or indirect effect (c'). FA, fractional anisotropy * $p < .05$ ** $p < .01$ *** $p < .001$

Additional work is needed to better understand possible moderating factors that may account for these differences.

4.2 | HCC is associated with higher cingulum FA

Contrary to our hypothesis that higher HCC would be associated with reduced FA in the cingulum bundle, we found that higher HCC was associated with *higher* FA. Further, exploratory analyses found that this association held in both segments of the cingulum. One possible explanation for these findings may stem from the “stress-acceleration hypothesis” (Callaghan & Tottenham, 2016), which posits that chronic stress may induce earlier and more rapid maturation of stress-sensitive brain regions as an adaptive mechanism (Belsky, 2019; Callaghan & Tottenham, 2016). Indeed, animal work suggests that increased exposure to stress may lead to increased FA in several white matter tracts. For example, one study in rodents found that precocious weaning led to earlier and more rapid myelination in the brain (Ono et al., 2008). Another study found that increases in stress and glucocorticoid levels led to increases in oligodendrogenesis in rats, a key process that precedes changes in myelination and white matter structure (Chetty et al., 2014). One possibility is therefore that chronically elevated cortisol in childhood may lead to accelerated myelination in certain white matter tracts. Indeed, some work has linked higher cortisol to increased FA in other white matter tracts such as the uncinat fasciculus (Kircanski et al., 2019; Dennison et al., 2019; though see Lichtin et al., 2021, which linked material deprivation to lower FA in this tract). In the future, longitudinal research is needed to elucidate developmental mechanisms and discern how stress physiology relates to changes in white matter organization over time.

While it is typically hypothesized that physiological measures such as cortisol affect brain structure, the cross-sectional nature of these data precludes us from making causal inferences as to the directionality of this relationship. Another possible explanation for these results is therefore that higher FA in the cingulum, a white matter tract associated with stress and limbic system communications, may contribute to differences in physiological stress levels in children, such as higher levels of cortisol being released over time in response to stress exposure.

4.3 | Socioeconomic disadvantage, stress exposure, hair cortisol, and cingulum FA

We examined, post hoc, whether hair cortisol mediated the relationship between socioeconomic disadvantage and dorsal cingulum FA. Despite the associations between parental education and hair cortisol, and between hair cortisol and dorsal cingulum FA, hair cortisol did not statistically mediate the association between parent education and dorsal cingulum FA. It is possible that an indirect effect may exist, but that we did not have the statistical power to detect such an effect, as our sample size with all three measures in this model was small ($n = 38$). As such, more research with larger sample sizes is needed in order to better understand whether hair cortisol may serve as a mediator between socioeconomic factors and white matter microstructure.

4.4 | Exposure to stressful life experiences is associated with hair cortisol and cingulum FA

We found no link between a composite of parental perceived stress and children's hair cortisol. However, post hoc analyses revealed that child exposure to stressful life experiences (measured using the LES) was linked with higher hair cortisol levels. Though this finding requires replication, it suggests that greater exposure to explicit stressful events—as opposed to parental perceptions of stress—may be more closely tied to children's stress physiology and brain development. Further, while our parent perceived stress composite was not significantly associated with white matter microstructure, our exploratory analyses revealed that the experience of more stressful life events was significantly associated with lower FA in the parahippocampal cingulum. This finding is consistent with some previous studies examining stress exposure and white matter microstructure, (Dufford & Kim, 2017; Hanson et al., 2013).

Importantly, although greater exposure to stressful life events was associated with *reduced* parahippocampal cingulum FA, we found a significant positive indirect effect when testing whether HCC mediated the relationship between stressful life events and white matter microstructure. That is, more stressful life events were associated with

higher HCC, which in turn was associated with *higher* parahippocampal cingulum FA. This difference in directionality between the indirect and total effect is referred to as “competitive mediation” (Zhao et al., 2010). This pattern may be likened to the classically cited example of stress, coping, and mood: Stress worsens mood, but stress is also associated with coping strategies, which in turn increase mood (MacKinnon et al., 2000). In the context of the current study, it is possible that while exposure to stressful life events may generally lead to lower FA in the parahippocampal cingulum, stress-related increases in cortisol may suppress the relationship between exposure to stress and decreased parahippocampal FA. These results may indicate that the cortisol response may be involved in adaptive white matter development in response to exposure to stress. Indeed, other studies have suggested cortisol may play the role of a suppressor variable in the context of stress exposure and neural outcomes (Oei et al., 2014).

5 | CONCLUSION

Our results may help disentangle inconsistencies in previously reported findings between stress exposure and white matter microstructure in children. When not accounting for cortisol, our results show that exposure to stress is predictive of *lower* FA in the cingulum, in concordance with previous studies. At the same time, HCC was associated with *higher* FA in the parahippocampal cingulum bundle, which is a relatively novel finding that may be supported by research-linking exposure to physiological stress to accelerated neurodevelopment.

While studies generally suggest that higher FA is associated with higher performance on a number of outcomes, some studies have reported that higher FA is associated with worse performance, or in some cases, associated with developmental disorders (Bashat, et al., 2007; Hoefl, et al., 2007). To better understand the long-term development of white matter in response to physiological stress and stress exposure, future work should examine brain development longitudinally in order to examine the extent to which stress may alter white matter microstructural development. Such research will be needed in order to better understand the relationship between stress, both perceived and physiological, and brain development in children.

Several limitations should be taken into account when interpreting these findings. First, the cross-sectional and correlational design of this study precludes the ability to make causal inferences. Second, this study had a small sample, precluding the statistical power to detect small effects, indicating the need for future examinations of these questions with larger sample sizes. Additionally, our exploratory results require replication and should be interpreted with caution, as they were not subject to any type of correction for multiple comparisons. Further, while the number of stressful life events may be more proximal to the child's experiences than a survey asking about parental perception of stress, it still relies on parent report. In addition, while this measure is reliable and has been used as a measure of stress exposure in children in previous work (e.g., Cohen et al., 1987), it may not account for all the stressful events that a child may experience in their

day-to-day lives. With regard to our measure of white matter organization, future studies should use additional measures in addition to FA, such as medial diffusivity. Further, while we examined here one form of physiologic stress, it is worth noting that other indices of physiologic stress need to be examined in order to elucidate the potential effects of increased physiologic stress on neural development. Lastly, we had significantly fewer hair samples from boys than from girls, as boys' hair was often too short to provide an adequate sample.

Despite these limitations, this is among the first studies to examine associations among socioeconomic circumstance, exposure to stress, hair cortisol, and white matter microstructure in children. Taken together, these results contribute to our understanding of how socioeconomic disadvantage and exposure to stress may “get under the skin” and contribute to developmental outcomes. Replicating these effects in a larger sample is a necessary next step to strengthen confidence in many of the exploratory findings discussed here. Building on this work has the potential to lead to more effective prevention and intervention strategies, increasing the odds that children's developmental trajectories lead to positive academic and mental health outcomes.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

K.R.S and K.G.N conceptualized the study and design. E.C.M and P.M.D collected data, and X.H and J.S.M prepared data for analysis. K.R.S ran and interpreted analyses with assistance from K.G.N and E.C.M. All authors approved the final published version of the manuscript. K.R.S drafted the manuscript, and K.G.N and E.C.M reviewed the first draft. All other authors critically reviewed the manuscript and provided feedback.

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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