Archival Report

Socioeconomic Disparities in Chronic Physiologic Stress Are Associated With Brain Structure in Children

Emily C. Merz, Pooja M. Desai, Elaine A. Maskus, Samantha A. Melvin, Rehan Rehman, Sarah D. Torres, Jerrold Meyer, Xiaofu He, and Kimberly G. Noble

ABSTRACT

BACKGROUND: Socioeconomic factors have been consistently linked with the structure of children's hippocampus and anterior cingulate cortex (ACC). Chronic stress—as indexed by hair cortisol concentration—may represent an important mechanism underlying these associations. Here, we examined associations between hair cortisol and children's hippocampal and ACC structure, including across hippocampal subfields, and whether hair cortisol mediated associations between socioeconomic background (family income-to-needs ratio, parental education) and the structure of these brain regions.

METHODS: Participants were 5- to 9-year-old children (*N* = 94; 61% female) from socioeconomically diverse families. Parents and children provided hair samples that were assayed for cortisol. High-resolution, T1-weighted magnetic resonance imaging scans were acquired, and FreeSurfer 6.0 was used to compute hippocampal volume and rostral and caudal ACC thickness and surface area (*n* = 37 with both child hair cortisol and magnetic resonance imaging data; *n* = 41 with both parent hair cortisol and magnetic resonance imaging data).

RESULTS: Higher hair cortisol concentration was significantly associated with smaller CA3 and dentate gyrus hippocampal subfield volumes but not with CA1 or subiculum volume. Higher hair cortisol was also associated with greater caudal ACC thickness. Hair cortisol significantly mediated associations between parental education level and CA3 and dentate gyrus volumes; lower parental education level was associated with higher hair cortisol, which in turn was associated with smaller volume in these subfields.

CONCLUSIONS: These findings point to chronic physiologic stress as a potential mechanism through which lower parental education level leads to reduced hippocampal volume. Hair cortisol concentration may be an informative biomarker leading to more effective prevention and intervention strategies aimed at childhood socioeconomic disadvantage.

Keywords: Anterior cingulate cortex, Cortisol, Developing brain, Hippocampus, Socioeconomic status, Stress

https://doi.org/10.1016/j.biopsych.2019.05.024

Although socioeconomic background has been consistently linked with children's brain structure (1), the proximal mechanisms underlying these associations are not well understood. Socioeconomic disadvantage is associated with a range of chronic stressors, including family conflict and turmoil; household chaos, noise, and crowding; and neighborhood violence (2). Socioeconomic context has also been linked with the physiologic stress response, including hypothalamic-pituitary-adrenal (HPA) axis function, which is most commonly indexed by salivary cortisol concentration (3). Although salivary cortisol is a robust measure of acute stress, its diurnal variation often requires the collection of multiple samples that are less reflective of chronic stress because of the susceptibility of this measure to situational factors. Recently, socioeconomic factors (family income, parental education level) have been linked with hair cortisol concentration

(4–6), a relatively novel, reliable, and valid measure of chronic stress obtained through a single sample (7,8).

Socioeconomic factors have been associated with the structure of brain regions that are particularly sensitive to chronic stress and strongly implicated in risk for multiple psychiatric disorders. Socioeconomic disadvantage has been repeatedly associated with reduced gray matter in the hippocampus (9–18) and anterior cingulate cortex (ACC) (15,19–22), which are involved in cognitive skills, including episodic memory and executive function (EF), respectively (23–26). Structural differences in the hippocampus and ACC have been observed in a number of psychiatric disorders, including major depressive disorder and attention-deficit/hyperactivity disorder (24–27).

Animal work has established that chronic stress exerts pronounced effects on the morphology of the hippocampus

and ACC, which have a high density of glucocorticoid receptors (28–30). These effects represent adaptations to the context in which the brain develops (30). Chronic stress has been associated with dendritic remodeling and reduced dendritic spine density in hippocampal neurons (28) and dendritic shrinkage in ACC regions (28,29,31). The hippocampus consists of a number of subfields including the cornu ammonis 1 to 4 (CA1–CA4), dentate gyrus (DG), and subiculum (32). The CA3 and DG subfields are particularly susceptible to chronic stress, with stress inducing dendritic remodeling in the CA3 and suppressing neurogenesis in the DG (33,34). These effects are mediated not only by glucocorticoids but also by excitatory amino acids (e.g., glutamate) and other cellular mechanisms (35). Thus, socioeconomic disadvantage may increase chronic stress and alter HPA axis function, which in turn influences the structure of hippocampal regions (particularly CA3 and DG) and the ACC.

In humans, childhood exposure to stressful life events has been associated with hippocampal and ACC structure (12,14,36,37). However, few studies have examined children's HPA axis function in relation to their brain structure, and results have been inconsistent (37–39). In the only such study to focus on hair cortisol, higher hair cortisol concentration was associated with smaller hippocampal volume in a subsample with Child Behavior Checklist total problems scores above the 91st percentile (39). It is unknown whether hair cortisol may be associated with the same hippocampal subfields in humans as those shown to be altered by chronic stress in animal models. In addition, although stressful life events mediate associations of socioeconomic factors with children's hippocampal structure (14) and adults' prefrontal function (36), no work has examined chronic physiologic stress as a mediator of associations between socioeconomic factors and children's brain structure.

The goals of this study were to examine associations between stress exposure and hippocampal and ACC structure in children and whether stress exposure mediated associations between socioeconomic factors and children's hippocampal and ACC structure (see Figure 1 for the full model). Family income-to-needs ratio and parental education were examined separately as they represent distinct aspects of children's environments that relate differentially to their development (40). Indeed, family income-to-needs ratio and parental education level have been linked with material resources and the quality of parent–child interactions, respectively (40), both of which have been linked with variability in children's stress exposure (2). Stress exposure was measured at multiple levels (41), with parent-reported perceived stress representing the family's exposure to stressors (e.g., stressful life events, material hardship) and parent and child hair cortisol concentrations

representing chronic physiologic stress in the parent and child, respectively.

We hypothesized a priori that lower family income-to-needs ratio and parental education would be associated with greater stress exposure, which in turn would be associated with reduced gray matter in the hippocampus and ACC (16). Further, we hypothesized that stress exposure would be most strongly associated with volume reductions in the DG and CA3 hippocampal subfields (17,30,42). In particular, we predicted that stress exposure would be more strongly associated with the CA3 and DG compared with two other components of the hippocampal formation—the CA1 and subiculum (32). We tentatively predicted that children's hair cortisol concentration would be the most likely of the three stress measures to relate to their hippocampal and ACC structure since it is the most direct measure of children's stress. To assess the ramifications of these associations for observable cognitive performance, we also examined the associations of hippocampal and ACC structure with episodic memory and EF, respectively.

METHODS AND MATERIALS

Participants

We recruited participants in New York, New York, by posting flyers and meeting families at local community children's events. The recruited families represented a wide range of parental educational attainment. Interested families were contacted by phone and screened for eligibility. Inclusionary criteria for children were the following: 5 to 9 years of age; ≥37 weeks of gestation at birth; born from a singleton pregnancy; no history of medical or psychiatric problems; spoke primarily English in the home; no contraindications for magnetic resonance imaging (MRI) scanning.

Sample Characteristics. Children ranged from 5.06 to 9.87 years of age (N = 94; 61% female) and were from socioeconomically diverse families (parental education range: 6.50–20.00 years; family income-to-needs ratio range: 0.17–15.21). Fifty percent were Hispanic and/or Latino; 31% were African American; and 14% were European American (Table 1).

Hair Samples and MRI Data. In all, 94 families completed questionnaires and the child testing battery. Hair cortisol data were available for 78 of 82 parents (95% female) who provided hair samples (see Supplemental Figure S1 for a flow chart). Hair cortisol data were available for 65 of 67 children (77% female) who provided hair samples (Supplemental Figure S1). MRI data were acquired for 66 of 85 children who enrolled in
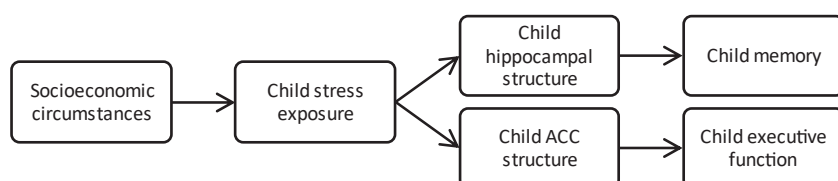
Figure 1. Hypothesized mechanistic model of how socioeconomic factors may influence episodic memory and executive function via brain structure. ACC, anterior cingulate cortex.

Table 1. Descriptive Statistics for Sample Characteristics (N = 94)

	Mean	SD
Child Age, Years	7.03	1.29
Parental Education Level, Years[a]	14.14	2.64
Family Income-to-Needs Ratio	2.68	2.79
	%	n
Child Sex, Female	60.64	57
Child Race and/or Ethnicity		
African American, Non-Hispanic, and Non-Latino	30.85	29
Hispanic and/or Latino	50.00	47
European American, Non-Hispanic, and Non-Latino	13.83	13
Other	5.32	5
Family Income Below U.S. Poverty Threshold[b]	29.79	28

U.S., United States.

[a]Parental education level reflects educational attainment averaged across parents in the household.

[b]Income-to-needs ratio < 1.00.

the MRI portion of the study and participated in a mock scan (Supplemental Figure S1). There were 37 children with both MRI and child hair cortisol data and 41 children with both MRI and parent hair cortisol data.

Procedure

Families participated in 2 campus visits within a month. During the first visit, parents completed questionnaires, hair samples were collected from parents and children, and children completed neurocognitive tasks. Children also participated in a practice MRI session in a mock scanner to familiarize them with scanning. During the second visit, children completed an MRI scanning session. Informed consent/assent was obtained from all families, and all procedures were approved by the Institutional Review Boards at the New York State Psychiatric Institute and Teachers College, Columbia University.

Image Acquisition and Processing

MRI data were acquired on a 3T GE Discovery MR750 scanner with a 32-channel head coil (GE Healthcare, Chicago, IL). A high-resolution, T1-weighted fast spoiled gradient-echo sequence was acquired in the sagittal plane (repetition time = 7.1 ms; echo time = minimum full; inversion time = 500 ms; flip angle = 11°; 176 slices; 1.0-mm slice thickness; field of view = 25 cm; inplane resolution = 1.0 × 1.0 mm). All images were visually inspected for motion artifacts and ghosting, resulting in the exclusion of 15 participants' MRI data from analyses. There was no manual editing of imaging data that passed quality control procedures.

Hippocampal Volume. Hippocampal subfield segmentation was conducted using the automated algorithm available in FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu/) (43). A comprehensive description of the pipeline has been published (see the Supplement) (43,44). For each hemisphere, subfields that are segmented include the CA2/3 (combined in the atlas because of indistinguishable MRI contrast), CA4, granule cell layer of the DG, CA1, and subiculum (Figure 2). The CA4 and granule cell layer of the DG subfields were combined because

both are components of the DG and because the ability to distinguish the molecular layer in T1-weighted images is limited (17). Measures of whole hippocampal volume were obtained by summing the volumes of the subfields (not including the hippocampal fissure). All hippocampal segmentations passed visual inspection for major errors. Hippocampal subfield segmentation could not be completed for 1 participant.

ACC Thickness and Surface Area. Images were processed using standard automated procedures in FreeSurfer 6.0. Following cortical surface reconstruction (45,46), the cortex was parcellated into regions based on gyral and sulcal structure (47,48). Cortical thickness is computed as the closest distance from the gray matter–white matter boundary to the gray matter–cerebrospinal fluid boundary at each vertex on the tessellated surface. Surface area is computed as the sum of the areas of each tessellation falling within a given region. FreeSurfer cortical thickness and surface area measurements have been shown to be reliable and have been well validated (49,50). The boundaries of the rostral and caudal ACC were determined via the Desikan-Killiany atlas (47). Rostral and caudal ACC thickness and surface area data were extracted.

Measures

Socioeconomic Factors. Parents reported their annual household income, the number of adults and children in the household, and their educational attainment in years. The income-to-needs ratio was calculated by dividing household income by the poverty threshold for the size of the family. Family income-to-needs ratio was logarithmically transformed to correct for positive skew. Educational attainment was averaged across all parents in the household.

Parental Perceived Stress. Parents completed the Perceived Stress Scale (51), Life Experiences Survey (52), and Material Deprivation Scale (53) (see the Supplement). Principal component analysis was used to extract one factor with an eigenvalue >1.0 (1.69), which explained 56.37% of the total variance. Factor loadings ranged from 0.63 to 0.85. This factor score (termed "perceived stress") was used in analyses.

Hair Cortisol Concentration. A small section of hair (≥15 mg) proximal to the posterior vertex of the participant's scalp was cut. Each hair sample was approximately 3 cm long, thereby containing cortisol deposited during roughly the past 3 months. Samples were stored at −20°C until being sent for analysis. Samples were processed and analyzed using methods previously validated and described in detail (see the Supplement) (54,55). Hair cortisol values outside of 3 SDs from the mean were excluded (n = 3 parents; n = 5 children), and hair cortisol data were logarithmically transformed to correct for skew (39). Previous studies have been inconsistent in terms of whether certain potential confounding variables are associated with hair cortisol concentration (6). In this study, there were no significant associations between hair cortisol and hair washing frequency, use of steroid medications, use of oral contraceptives, or use of hair dye.
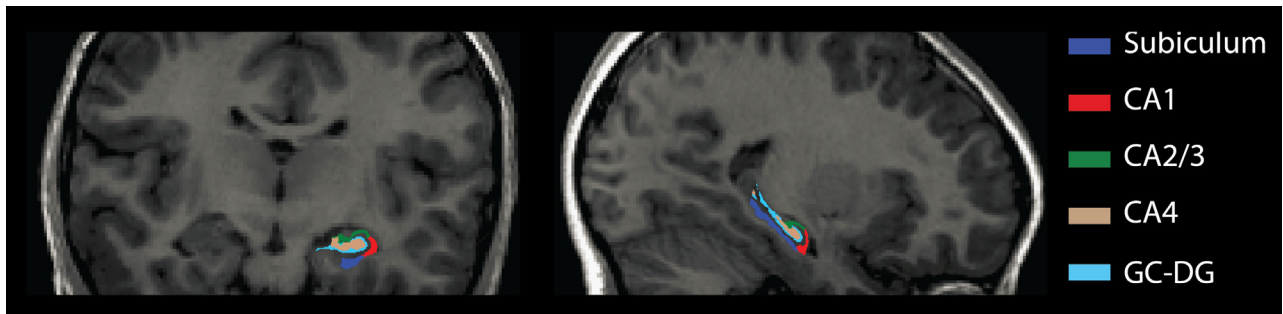
Figure 2. Color-coded depiction of the focal hippocampal subfields in coronal (left) and sagittal (right) views from a representative participant. The subfield volumes are overlaid on the whole-brain T1-weighted processed image. CA, cornu ammonis; GC-DG, granule cell layer of the dentate gyrus.

Episodic Memory and EF. Children completed the Picture Sequence Memory, Flanker Inhibitory Control and Attention, List Sorting Working Memory, and Dimensional Change Card Sort Tests from the National Institutes of Health Toolbox Cognition Battery (56–59). Raw scores were used in analyses. Scores on the latter 3 tasks, putative measures of core EF components, were significantly correlated (r = .28–.43, p < .001) and were thus standardized and averaged to create an EF composite.

Statistical Analyses

Using SAS software version 9.4 (SAS Institute, Cary, NC), multiple linear regression analyses were conducted to examine associations between socioeconomic factors and children's hippocampal and ACC structure (c paths); socioeconomic factors and children's stress exposure (a paths); and children's stress exposure and their hippocampal and ACC structure (b paths). Covariates included child (or parent) age, sex, and race and/or ethnicity. Race and/or ethnicity was not significant in any of the regression models and did not improve model fit, and was thus dropped from the final models for parsimony. In models predicting hippocampal volume, whole-brain volume was included as a covariate. Cortisol concentration has been shown to correlate with cognitive functioning in an inverted U-shaped pattern (60). Thus, a quadratic term (hair cortisol concentration squared) was initially included in regression analyses, but it was not significant across models and was dropped from the final analyses. Effect sizes (η_p^2) are presented, with values of .01, .06, and .14 indicating small, medium, and large effects, respectively. To control for multiple comparisons, false discovery rate correction (61) was applied (via PROC MULTTEST in SAS) to the hippocampal subfield and ACC analyses, separately (α = .05). False discovery rate–corrected p values are reported in the text in addition to the tables (see the Supplement). For instances in which the a and b paths were both supported in regression analyses, the significance of the indirect or mediated effect (ab path) was assessed using bias-corrected bootstrapping via the PROCESS macro (62,63). Indirect effects were significant if the 95% confidence intervals (CIs) did not include zero (62,64).

RESULTS

Descriptive statistics and zero-order correlations are presented in Table 2 and Supplemental Table S1, respectively.

Socioeconomic Factors and Children's Hippocampal and ACC Structure

Higher parental education level was significantly associated with larger total hippocampal volume (β = .18, p = .04, η_p^2 = .08), DG volume (β = .22, p = .04, η_p^2 = .10), and CA1 volume (β = .26, p = .04, η_p^2 = .12) (Supplemental Table S2). Effect sizes were medium to large in the DG, CA1, and CA3 subfields and small-to-medium in the subiculum (Supplemental Figure S2). Family income-to-needs ratio was not significantly associated with hippocampal volume.

Higher parental education level was significantly associated with reduced rostral (β = −.39, p = .01, η_p^2 = .18) and caudal (β = −.30, p = .03, η_p^2 = .10) ACC thickness and greater rostral (β = .30, p = .02, η_p^2 = .13) and caudal (β = .24, p = .046, η_p^2 = .08) ACC surface area (Supplemental Table S2). Family income-to-needs ratio was not significantly associated with rostral or caudal ACC thickness or surface area.

Socioeconomic Factors and Children's Stress Exposure

Higher parental education level was significantly associated with lower parental perceived stress (β = −.29, p = .01, η_p^2 = .08) and lower child hair cortisol concentration (β = −.40, p = .01, η_p^2 = .16) (Supplemental Figure S3 and Supplemental Table S3). The latter association remained significant after additionally controlling for parental hair cortisol (β = −.25, p = .03, η_p^2 = .10). Parental education level was not significantly associated with parent hair cortisol. Family income-to-needs ratio was not significantly associated with the stress-exposure measures.

Stress Exposure and Hippocampal Volume in Children

Higher child hair cortisol concentration was significantly associated with smaller volume in the CA3, (β = −.26, p = .04, η_p^2 = .12) and DG (β = −.23, p = .04, η_p^2 = .13) (Figure 3), but not in the CA1 or subiculum, after accounting for child age, sex, and whole-brain volume. Effect sizes for the CA3 and DG were medium to large, whereas those for the CA1 and subiculum were negligible to small (Supplemental Figure S4). When child hair cortisol (p = .07–.08) and parental education level (p = .19–.20) were entered simultaneously into models predicting CA3 and DG volume, neither remained significant, but child hair cortisol retained its medium to large effect size

Table 2. Descriptive Statistics for Stress Exposure and Hippocampal and ACC Structure

	n	Mean	SD
Perceived Stress Scale Score	94	29.38	7.54
Life Experiences Survey Score	94	10.77	10.25
Material Deprivation Scale Score	94	2.56	2.12
Parent Hair Cortisol Value, pg/mg[a]	75	32.00	91.96
Child Hair Cortisol Value, pg/mg[a]	60	25.20	25.34
Total Hippocampal Volume, mm^3	50	3145.65	311.86
CA1 Volume, mm^3	50	585.15	66.70
CA3 Volume, mm^3	50	183.55	25.71
Dentate Gyrus Volume, mm^3	50	474.03	53.27
Subiculum Volume, mm^3	50	392.30	37.89
Rostral ACC Thickness, mm	51	3.35	0.24
Caudal ACC Thickness, mm	51	3.05	0.24
Rostral ACC Surface Area, mm^2	51	1257.78	254.50
Caudal ACC Surface Area, mm^2	51	1301.59	228.86

ACC, anterior cingulate cortex; CA, cornu ammonis.

[a]Logarithmically transformed hair cortisol values were used in analyses, but raw scores are shown here for ease of interpretation.

(η_p^2 = .08–.09) while parental education did not (η_p^2 = .04–.05). Parental perceived stress and hair cortisol concentration were not significantly associated with hippocampal volume (Supplemental Table S4).

### Stress Exposure and ACC Structure in Children

Higher child hair cortisol concentration was significantly associated with greater caudal ACC thickness after accounting for child age and sex (β = .40, p = .04, η_p^2 = .17) (Figure 4 and Supplemental Table S4). Parent perceived stress and hair cortisol were not associated with ACC thickness. When child hair cortisol (p = .05) and parental education level (p = .10) were entered simultaneously, neither remained significant, but child hair cortisol retained its medium to large effect size (η_p^2 = .10). Parental perceived stress and parent and child hair cortisol were not associated with ACC surface area.

Parental Education, Child Hair Cortisol Concentration, and Hippocampal and ACC Structure

Child hair cortisol concentration significantly mediated the associations between parental education level and CA3 volume (ab path = 0.11, SE = 0.07, 95% CI 0.01–0.29), and between parental education level and DG volume (ab path = 0.10, SE = 0.06, 95% CI 0.01–0.25). Lower parental education level was associated with higher child hair cortisol concentration, which in turn was associated with smaller CA3 and DG volumes (Figure 5). Child hair cortisol concentration did not significantly mediate the association between parental education and caudal ACC thickness.

Socioeconomic Factors, Hippocampal and ACC Structure, and Cognitive Functioning

Higher family income-to-needs ratio (β = .21, p = .04, η_p^2 = .04) and parental education level (β = .25, p = .03, η_p^2 = .06) were significantly associated with higher episodic memory. Higher
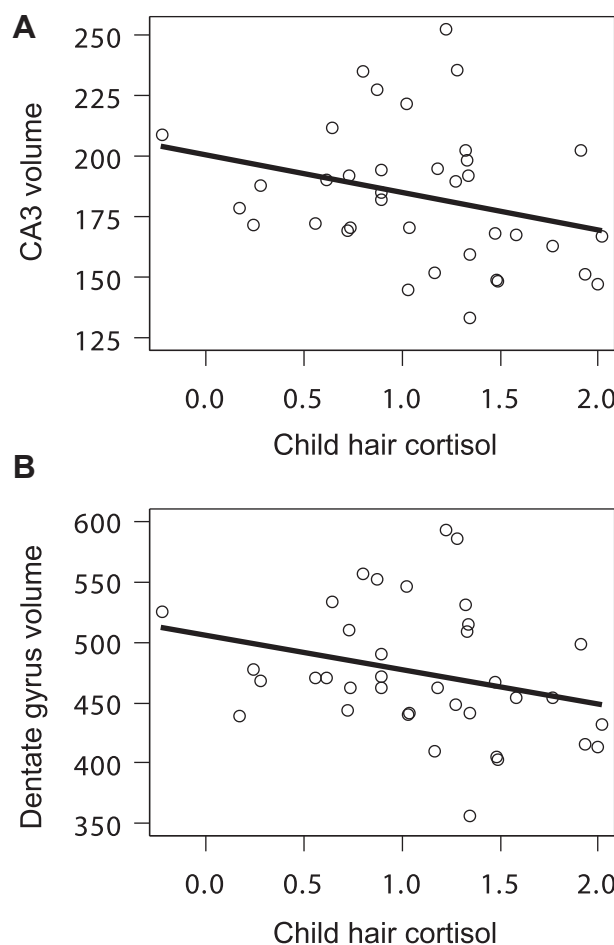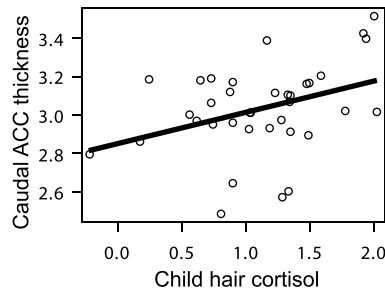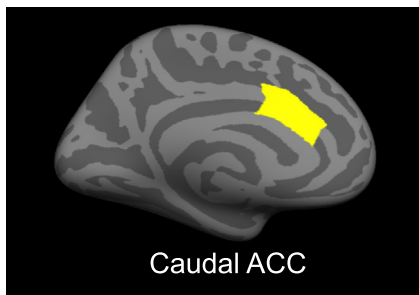
Figure 3. Higher hair cortisol concentration (logarithmically transformed) was significantly associated with **(A)** smaller CA3 volume (mm^3) and **(B)** smaller dentate gyrus volume (mm^3) in children (n = 37).

family income-to-needs ratio was significantly associated with higher EF (β = .26, p = .02, η_p^2 = .07), but parental education level was not (Supplemental Table S5). However, hippocampal structure was not significantly associated with episodic memory, and ACC structure was not significantly associated with EF task performance.

DISCUSSION

The goals of this study were to examine associations between children's stress exposure and their hippocampal and ACC structure and to investigate stress exposure as a mediator of socioeconomic differences in hippocampal and ACC structure. Stress exposure was measured in terms of parent-reported family stressors and parent and child hair cortisol concentration (41), with parental stress reflecting children's exposure to stress in the home environment. Animal models have consistently demonstrated that chronic stress impacts hippocampal and ACC structure (29,30). However, no previous human study has focused on hair cortisol in both parents and children as indices of chronic physiologic stress in relation to children's brain structure.

Figure 4. Higher hair cortisol concentration (logarithmically transformed) was significantly associated with greater thickness (mm) in the caudal anterior cingulate cortex (ACC) in children (*n* = 37).

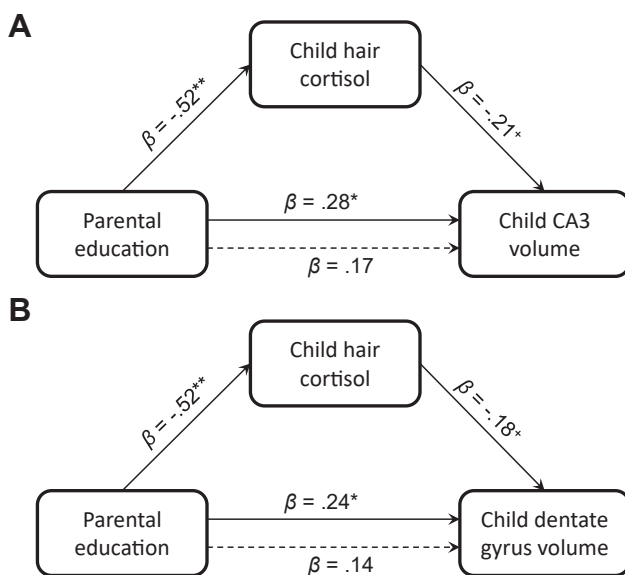## Hair Cortisol Concentration Is Associated With Hippocampal Subfield Volume in Children

This study is the first to report that higher child hair cortisol concentration is significantly associated with reduced volume in the CA3 and DG hippocampal subfields, consistent with animal work showing these subfields to be particularly susceptible to chronic stress (33,34). While medium to large effect sizes were found for the CA3 and DG subfields, negligible to small effect sizes were found for the CA1 and subiculum (Supplemental Figure S4). These results are consistent with the notion that prolonged exposure to circulating cortisol may alter hippocampal structure (65). At the cellular level, animal research has shown stress-induced reductions in dendritic length and branching in CA3 neurons and impaired neurogenesis in the DG (30). The single previous study of hair cortisol and hippocampal structure in children yielded mixed results (39) that were possibly due in part to variability in associations across hippocampal subfields, which were not assessed in that study (39). In addition to glucocorticoids,

excitatory amino acids and other mechanisms are also involved in stress-induced remodeling of hippocampal neurons (30,35), and future work could help disentangle these processes.

Hair Cortisol Concentration Mediates Socioeconomic Differences in Children's Hippocampal Volume

Parental education level was significantly positively associated with DG and CA1 volume, with medium to large effect sizes for those subfields plus the CA3 subfield (Supplemental Figure S2). Child hair cortisol concentration significantly mediated associations between parental education level and CA3 and DG subfield volume. Lower parental education level was associated with higher hair cortisol concentration [consistent with previous work on a portion of this sample (4)], which in turn was linked with smaller CA3 and DG volumes. Whereas stressful life events have been found to mediate the association between socioeconomic background and children's hippocampal volume (14), this is the first study to show that chronic physiologic stress may partially explain these associations. Socioeconomic disadvantage may increase long-term cortisol exposure and in turn alter the structural development of stress-sensitive hippocampal subfields.

Results were specific to parental education level rather than family income-to-needs ratio, although the two were strongly correlated (*r* = .68). Parental education level may more directly reflect the quality of parent–child interactions, whereas family income-to-needs ratio may more directly reflect material resources (40). Thus, one possibility is that variation in parent–child interaction quality may be partially responsible for associations between parental education level and children's hair cortisol concentration. In addition, results were specific to child hair cortisol rather than parental hair cortisol or perceived stress. Thus, direct measures of children's physiologic stress responses may be valuable in understanding stress-related variability in brain structure. More work with larger samples is needed to unpack the ways in which poverty-related stressful environments alter HPA axis function (e.g., circadian disruption due to sleep deprivation) and in turn brain structure.

A

B

Figure 5. Hair cortisol concentration significantly mediated the associations between **(A)** parental education level and CA3 volume and **(B)** parental education level and dentate gyrus volume in children (*n* = 37). The solid and dotted lines from parental education to child CA3 or dentate gyrus volume represent the total (*c* path) and direct associations (*c*′ path), respectively. **p* < .05, ***p* < .01, ⁺*p* < .10.

Hair Cortisol Concentration Is Associated With ACC Thickness in Children

Higher child hair cortisol concentration was also associated with greater thickness in the caudal (dorsal) ACC, consistent

with research identifying the ACC as particularly susceptible to chronic stress (29,66). This association could be related to the ACC's role in regulating the HPA axis (41,67,68), resolving conflict associated with threat detection, or filtering out threat-related stimuli during cognitive processing (e.g., trying to complete a task in the midst of stressors) (66,69–71). This result contrasts in direction with animal models of stress showing dendritic shrinkage in the ACC (28,29,31) and null findings from one previous study of children (39). These discrepancies could be due to differences in the nature of these associations by age or other sample characteristics.

Developmentally, cortical thickness decreases rapidly in childhood and early adolescence, after which it more gradually thins, and ultimately it plateaus in early to mid adulthood (72). One possibility is that lower levels of chronic physiologic stress may foster greater age-related cortical thinning in the caudal ACC. Some evidence has linked positive parenting (often a buffer of children's stress) with an increased rate of prefrontal cortex thinning (73) and, conversely, maternal aggressive behavior with thickening of superior frontal cortex in adolescents (74). Another possibility is that higher chronic stress may lead to blunting of the HPA axis stress-response system (41), leading to paradoxically lower levels of hair cortisol, which in turn are associated with reduced ACC thickness. Longitudinal studies that assess chronic stress in relation to rates of cortical thinning over time are needed to address these possibilities.

Children from more advantaged families demonstrated higher episodic memory and EF skills, consistent with the results of a large body of work (1,3). However, children's hippocampal and ACC structure were not associated with these cognitive outcomes. In previous research, hippocampal volume has been associated with episodic memory (18,23), and ACC thickness has been inversely associated with EF (24–26,75,76). However, other work has suggested that links between gray matter morphology and cognition vary by age and socioeconomic background (9,77–79). Thus, it is possible that in this socioeconomically diverse sample of 5- to 9-year-old children, associations between brain structure and cognitive task performance were obscured because of variability in these characteristics across the sample. Furthermore, more work is needed to elucidate the implications of these results for socioeconomic differences in risk for psychiatric disorders (80).

There are several limitations of this study that should be taken into account when interpreting these results. First, causal inferences cannot be made because this was a cross-sectional, correlational study, and all possible confounds (e.g., parent IQ) could not be ruled out. Second, it was more difficult to collect hair samples from boys because their hair was often too short, similar to sampling constraints noted in previous studies (81). And, previous work has identified sex-specific effects of early-life stressors on hippocampal volume (82). Third, head motion has a negative effect on estimates of cortical thickness, and younger participants generally move more during image acquisition (83). Accordingly, motion-corrupted images were excluded from analyses and all statistical models were controlled for age. Fourth, subcortical volume estimates derived from automated segmentation algorithms may differ from those resulting from manual tracing (12,84,85). In this study, we used the FreeSurfer 6.0

hippocampal subfield segmentation procedures, which are accurate and reliable (43,44,85).

This study showed that higher hair cortisol concentration is significantly associated with smaller CA3 and DG hippocampal subfield volume in children, a finding consistent with results of animal research underscoring the adaptive plasticity of the hippocampus (30,35). Hair cortisol concentration significantly mediated associations between socioeconomic background and CA3 and DG volume. Socioeconomic disadvantage may lead to increased long-term cortisol exposure that in turn alters the structural development of the hippocampus. Prevention and intervention strategies that reduce children's exposure to poverty-related chronic stress may be instrumental in ensuring their healthy neurodevelopment across the life span.

REFERENCES

1. Farah MJ (2017): The neuroscience of socioeconomic status: Correlates, causes, and consequences. Neuron 96:56–71.
2. Evans GW, Kim P (2013): Childhood poverty, chronic stress, self-regulation, and coping. Child Dev Perspect 7:43–48.
3. Blair C, Granger DA, Willoughby M, Mills-Koonce R, Cox M, Greenberg MT, et al. (2011): Salivary cortisol mediates effects of poverty and parenting on executive functions in early childhood. Child Dev 82:1970–1984.
4. Ursache A, Merz EC, Melvin S, Meyer J, Noble KG (2017): Socioeconomic status, hair cortisol and internalizing symptoms in parents and children. Psychoneuroendocrinology 78:142–150.
5. Vaghri Z, Guhn M, Weinberg J, Grunau RE, Yu W, Hertzman C (2013): Hair cortisol reflects socio-economic factors and hair zinc in preschoolers. Psychoneuroendocrinology 38:331–340.
6. Gray NA, Dhana A, Van Der Vyver L, Van Wyk J, Khumalo NP, Stein DJ (2018): Determinants of hair cortisol concentration in children: A systematic review. Psychoneuroendocrinology 87:204–214.
7. Flom M, St John AM, Meyer JS, Tarullo AR (2017): Infant hair cortisol: Associations with salivary cortisol and environmental context. Dev Psychobiol 59:26–38.

8. Short SJ, Stalder T, Marceau K, Entringer S, Moog NK, Shirtcliff EA, et al. (2016): Correspondence between hair cortisol concentrations and 30-day integrated daily salivary and weekly urinary cortisol measures. Psychoneuroendocrinology 71:12–18.

9. Ellwood-Lowe ME, Humphreys KL, Ordaz SJ, Camacho MC, Sacchet MD, Gotlib IH (2017): Time-varying effects of income on hippocampal volume trajectories in adolescent girls. Dev Cogn Neurosci 30:41–50.

10. Hair NL, Hanson JL, Wolfe BL, Pollak SD (2015): Association of child poverty, brain development, and academic achievement. JAMA Pediatr 169:822–829.

11. Hanson JL, Chandra A, Wolfe BL, Pollak SD (2011): Association between income and the hippocampus. PLoS One 6:e18712.

12. Hanson JL, Nacewicz BM, Sutterer MJ, Cayo AA, Schaefer SM, Rudolph KD, et al. (2015): Behavior problems after early life stress: Contributions of the hippocampus and amygdala. Biol Psychiatry 77:314–323.

13. Jednoróg K, Altarelli I, Monzalvo K, Fluss J, Dubois J, Billard C, et al. (2012): The influence of socioeconomic status on children's brain structure. PLoS One 7:e0042486.

14. Luby JL, Belden A, Botteron K, Marrus N, Harms MP, Babb C, et al. (2013): The effects of poverty on childhood brain development: The mediating effect of caregiving and stressful life events. JAMA Pediatr 167:1135–1142.

15. Noble KG, Houston SM, Brito NH, Bartsch H, Kan E, Kuperman JM, et al. (2015): Family income, parental education and brain structure in children and adolescents. Nat Neurosci 18:773–778.

16. Noble KG, Houston SM, Kan E, Sowell ER (2012): Neural correlates of socioeconomic status in the developing human brain. Dev Sci 15:516–527.

17. Brody GH, Gray JC, Yu T, Barton AW, Beach SRH, Galván A, et al. (2017): Protective prevention effects on the association of poverty with brain development. JAMA Pediatr 171:46–52.

18. Yu Q, Daugherty AM, Anderson DM, Nishimura M, Brush D, Hardwick A, et al. (2018): Socioeconomic status and hippocampal volume in children and young adults. Dev Sci 21:e12561.

19. Gianaros PJ, Horenstein JA, Cohen S, Matthews KA, Brown SM, Flory JD, et al. (2007): Perigenual anterior cingulate morphology covaries with perceived social standing. Soc Cogn Affect Neurosci 2:161–173.

20. Lawson GM, Duda JT, Avants BB, Wu J, Farah MJ (2013): Associations between children's socioeconomic status and prefrontal cortical thickness. Dev Sci 16:641–652.

21. Yang J, Liu H, Wei D, Liu W, Meng J, Wang K, et al. (2016): Regional gray matter volume mediates the relationship between family socioeconomic status and depression-related trait in a young healthy sample. Cogn Affect Behav Neurosci 16:51–62.

22. McDermott CL, Seidlitz J, Nadig A, Liu S, Clasen LS, Blumenthal JD, et al. (2019): Longitudinally mapping childhood socioeconomic status associations with cortical and subcortical morphology. J Neurosci 39:1365–1373.

23. Ghetti S, Bunge SA (2012): Neural changes underlying the development of episodic memory during middle childhood. Dev Cogn Neurosci 2:381–395.

24. Tamnes CK, Østby Y, Walhovd KB, Westlye LT, Due-Tønnessen P, Fjell AM (2010): Neuroanatomical correlates of executive functions in children and adolescents: A magnetic resonance imaging (MRI) study of cortical thickness. Neuropsychologia 48:2496–2508.

25. Kharitonova M, Martin RE, Gabrieli JDE, Sheridan MA (2013): Cortical gray-matter thinning is associated with age-related improvements on executive function tasks. Dev Cogn Neurosci 6:61–71.

26. Squeglia LM, Jacobus J, Sorg SF, Jernigan TL, Tapert SF (2013): Early adolescent cortical thinning is related to better neuropsychological performance. J Int Neuropsychol Soc 19:962–970.

27. Burgess N, Maguire EA, O'Keefe J (2002): The human hippocampus and spatial and episodic memory. Neuron 35:625–641.

28. Chattarji S, Tomar A, Suvrathan A, Ghosh S, Rahman MM (2015): Neighborhood matters: Divergent patterns of stress-induced plasticity across the brain. Nat Neurosci 18:1364–1375.

29. McEwen BS, Morrison JH (2013): The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79:16–29.

30. McEwen BS, Nasca C, Gray JD (2016): Stress effects on neuronal structure: Hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology 41:3–23.

31. Kolb B, Harker A, Mychasiuk R, de Melo SR, Gibb R (2017): Stress and prefrontal cortical plasticity in the developing brain. Cogn Dev 42:15–26.

32. Roddy DW, Farrell C, Doolin K, Roman E, Tozzi L, Frodl T, et al. (2019): The hippocampus in depression: More than the sum of its parts? Advanced hippocampal substructure segmentation in depression. Biol Psychiatry 85:487–497.

33. Conrad CD, LeDoux JE, Magariños AM, McEwen BS (1999): Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav Neurosci 113:902–913.

34. Pham K, Nacher J, Hof PR, McEwen BS (2003): Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. Eur J Neurosci 17:879–886.

35. McEwen BS (2016): Stress-induced remodeling of hippocampal CA3 pyramidal neurons. Brain Res 1645:50–54.

36. Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE, et al. (2013): Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. Proc Natl Acad Sci U S A 110:18442–18447.

37. Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC, et al. (2014): Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. Neuropsychopharmacology 39:1245–1253.

38. Wiedenmayer CP, Bansal R, Anderson GM, Zhu H, Amat J, Whiteman R, Peterson BS (2006): Cortisol levels and hippocampus volumes in healthy preadolescent children. Biol Psychiatry 60:856–861.

39. Chen R, Muetzel RL, El Marroun H, Noppe G, van Rossum EFC, Jaddoe VW, et al. (2016): No association between hair cortisol or cortisone and brain morphology in children. Psychoneuroendocrinology 74:101–110.

40. Duncan GJ, Magnuson K (2012): Socioeconomic status and cognitive functioning: Moving from correlation to causation. Wiley Interdiscip Rev Cogn Sci 3:377–386.

41. Hostinar CE, Sullivan RM, Gunnar MR (2014): Psychobiological mechanisms underlying the social buffering of the hypothalamic-pituitary-adrenocortical axis: A review of animal models and human studies across development. Psychol Bull 140:256–282.

42. Teicher MH, Anderson CM, Polcari A (2012): Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. Proc Natl Acad Sci U S A 109:E563–E572.

43. Iglesias JE, Augustinack JC, Nguyen K, Player CM, Player A, Wright M, et al. (2015): A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. Neuroimage 115:117–137.

44. Whelan CD, Hibar DP, van Velzen LS, Zannas AS, Carrillo-Roa T, McMahon K, et al. (2016): Heritability and reliability of automatically segmented human hippocampal formation subregions. Neuroimage 128:125–137.

45. Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194.

46. Fischl B, Dale AM (2000): Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 97:11050–11055.

47. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980.

48. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, et al. (2004): Automatically parcellating the human cerebral cortex. Cereb Cortex 14:11–22.

49. Ghosh SS, Kakunoori S, Augustinack J, Nieto-Castanon A, Kovelman I, Gaab N, et al. (2010): Evaluating the validity of volume-

based and surface-based brain image registration for developmental cognitive neuroscience studies in children 4-to-11 years of age. Neuroimage 53:85–93.

50. Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, *et al.* (2006): Reliability of MRI-derived measurements of human cerebral cortical thickness: The effects of field strength, scanner upgrade and manufacturer. Neuroimage 32:180–194.

51. Cohen S, Kamarck T, Mermelstein R (1983): A global measure of perceived stress. J Health Soc Behav 24:385–396.

52. Sarason IG, Johnson JH, Siegel JM (1978): Assessing the impact of life changes: Development of the Life Experiences Survey. J Consult Clin Psychol 46:932–946.

53. Pilkauskas NV, Currie J, Garfinkel I (2012): The Great Recession, public transfers, and material hardship. Soc Serv Rev 86:401–427.

54. Davenport MD, Tiefenbacher S, Lutz CK, Novak MA, Meyer JS (2006): Analysis of endogenous cortisol concentrations in the hair of rhesus macaques. Gen Comp Endocrinol 147:255–261.

55. Meyer J, Novak M, Hamel A, Rosenberg K (2014): Extraction and analysis of cortisol from human and monkey hair. J Vis Exp e50882.

56. Bauer PJ, Dikmen SS, Heaton RK, Mungas D, Slotkin J, Beaumont JL (2013): III. NIH Toolbox Cognition Battery (CB): Measuring episodic memory. Monogr Soc Res Child Dev 78:34–48.

57. Tulsky DS, Carlozzi N, Chevalier N, Espy K, Beaumont J, Mungas D (2013): NIH Toolbox Cognitive Function Battery (NIHTB-CFB): Measuring working memory. Monogr Soc Res Child Dev 78:70–87.

58. Zelazo PD, Anderson JE, Richler J, Wallner-Allen K, Beaumont JL, Weintraub S (2013): II. NIH Toolbox Cognition Battery (CB): Measuring executive function and attention. Monogr Soc Res Child Dev 78:16–33.

59. Akshoomoff N, Newman E, Thompson WK, McCabe C, Bloss CS, Chang L, *et al.* (2014): The NIH Toolbox Cognition Battery: Results from a large normative developmental sample (PING). Neuropsychology 28:1–10.

60. Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE (2007): The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. Brain Cogn 65:209–237.

61. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 57:289–300.

62. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V (2002): A comparison of methods to test mediation and other intervening variable effects. Psychol Methods 7:83–104.

63. Hayes AF (2013): Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach, 1st ed. New York, NY: Guilford Press.

64. Preacher KJ, Hayes AF (2008): Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 40:879–891.

65. Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009): Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 10:434–445.

66. McEwen BS, Gianaros PJ (2010): Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. Ann N Y Acad Sci 1186:190–222.

67. Diorio D, Viau V, Meaney MJ (1993): The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. J Neurosci 13:3839–3847.

68. Eisenberger NI, Taylor SE, Gable SL, Hilmert CJ, Lieberman MD (2007): Neural pathways link social support to attenuated neuroendocrine stress responses. Neuroimage 35:1601–1612.

69. Bishop S, Duncan J, Brett M, Lawrence AD (2004): Prefrontal cortical function and anxiety: Controlling attention to threat-related stimuli. Nat Neurosci 7:184–188.

70. Milad MR, Quirk GJ, Pitman RK, Orr SP, Fischl B, Rauch SL (2007): A role for the human dorsal anterior cingulate cortex in fear expression. Biol Psychiatry 62:1191–1194.

71. Milad MR, Rauch SL (2012): Obsessive compulsive disorder: Beyond segregated cortico-striatal pathways. Trends Cogn Sci 16:43–51.

72. Mills KL, Tamnes CK (2014): Methods and considerations for longitudinal structural brain imaging analysis across development. Dev Cogn Neurosci 9:172–190.

73. Whittle S, Simmons JG, Dennison M, Vijayakumar N, Schwartz O, Yap MBH, *et al.* (2014): Positive parenting predicts the development of adolescent brain structure: a longitudinal study. Dev Cogn Neurosci 8:7–17.

74. Whittle S, Vijayakumar N, Dennison M, Schwartz O, Simmons JG, Sheeber L, Allen NB (2016): Observed measures of negative parenting predict brain development during adolescence. PLoS One 11: e0147774.

75. Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, *et al.* (2006): Intellectual ability and cortical development in children and adolescents. Nature 440:676–679.

76. Vijayakumar N, Whittle S, Yücel M, Dennison M, Simmons J, Allen NB (2014): Thinning of the lateral prefrontal cortex during adolescence predicts emotion regulation in females. Soc Cogn Affect Neurosci 9:1845–1854.

77. Brito NH, Piccolo LR, Noble KG (2017): Associations between cortical thickness and neurocognitive skills during childhood vary by family socioeconomic factors. Brain Cogn 116:54–62.

78. Duval ER, Garfinkel SN, Swain JE, Evans GW, Blackburn EK, Angstadt M, *et al.* (2017): Childhood poverty is associated with altered hippocampal function and visuospatial memory in adulthood. Dev Cogn Neurosci 23:39–44.

79. Ofen N, Tang L, Yu Q, Johnson EL (2018): Memory and the developing brain: From description to explanation with innovation in methods. Dev Cogn Neurosci 36:100613.

80. Sheline YI, Liston C, McEwen BS (2019): Parsing the hippocampus in depression: Chronic stress, hippocampal volume, and major depressive disorder. Biol Psychiatry 85:436–438.

81. Grotzinger AD, Mann FD, Patterson MW, Tackett JL, Tucker-Drob EM, Harden KP (2018): Hair and salivary testosterone, hair cortisol, and externalizing behaviors in adolescents. Psychol Sci 29:688–699.

82. Teicher MH, Anderson CM, Ohashi K, Khan A, McGreenery CE, Bolger EA, *et al.* (2018): Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. Neuroimage 169:443–452.

83. Alexander-Bloch A, Clasen L, Stockman M, Ronan L, Lalonde F, Giedd J, Raznahan A (2016): Subtle in-scanner motion biases automated measurement of brain anatomy from in vivo MRI. Hum Brain Mapp 37:2385–2397.

84. Morey RA, Petty CM, Xu Y, Hayes JP, Wagner HR, Lewis DV, *et al.* (2009): A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. Neuroimage 45:855–866.

85. Schmidt MF, Storrs JM, Freeman KB, Jack CR, Turner ST, Griswold ME, Mosley TH (2018): A comparison of manual tracing and FreeSurfer for estimating hippocampal volume over the adult lifespan. Hum Brain Mapp 39:2500–2513.