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Socioeconomic status and hippocampal volume in children and young adults

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Abstract

An individual's socioeconomic status (SES) is often viewed as a proxy for a host of environmental influences. SES disparities have been linked to variance in brain structures particularly the hippocampus, a neural substrate of learning and memory. However, it is unclear whether the association between SES and hippocampal volume is similar in children and adults. We investigated the relationship between hippocampal volume and SES in a group of children (n = 31, age 8–12 years) and a group of young adults (n = 32, age 18–25 years). SES was assessed with four indicators that loaded on a single factor, therefore a composite SES scores was used in the main analyses. Hippocampal volume was measured using manual demarcation on high resolution structural images. SES was associated with hippocampal volume in the children, but not in adults, suggesting that in childhood, but not adulthood, SES-related environmental factors influence hippocampal volume. In addition, hippocampal volume, but not SES, was associated with scores on a memory task, suggesting that net effects of postnatal environmental factors, captured by SES, are more distal determinants of memory performance than hippocampal volume. Longitudinal investigation of the association between SES, hippocampal volume and cognitive functioning may further our understanding of the putative neural mechanisms underlying SES-related environmental effects on cognitive development.

RESEARCH HIGHLIGHTS

- Socioeconomic status (SES), hippocampal volume assessed in children and adults.
- Hippocampal volume measured using manual demarcation with confirmed high reliability.
- Positive relation between SES and hippocampal volume in children but not in adults.
- Consistent with prior work, hippocampal volume was positively related to memory performance.

1 | INTRODUCTION

Childhood is a period of robust gains in knowledge and cognitive abilities (Bjorklund, 2012). This period is also characterized by complex changes in the brain (Gogtay et al., 2004; Giedd et al., 1999) that differ across individuals in pace and magnitude. The sources of individual differences in cognitive development are, at least partially, linked to environmental factors that may shape typical brain growth. For example, growing up in poverty (Evans, 2004; Evans & Schamberg, 2009) and sustaining emotional or physical trauma and deprivation (Perry, 2002; Schore, 2001) can adversely influence brain development. Socioeconomic status (SES) has been extensively studied as a proxy measure of the myriad environmental factors that shape development. SES was found to be associated with children's health outcomes, both physical and mental, as well as with cognitive and brain development (Cohen, Janicki-deverts, Chen, & Matthews, 2010; Conroy, Sandel, & Zuckerman, 2010; Hackman, Farah, & Meaney, 2010; Jednoróg et al., 2012; Mackey et al., 2015).

Disparity in childhood SES is associated with individual differences in cognitive abilities. In children and adolescents, full scale IQ correlates

with family income and parental education (Lange, Froimowitz, Bigler, Lainhart & Brain Developmental Cooperative Group, 2010). Children from lower SES households also obtain lower scores on tests of language, math, executive function, and memory (Farah et al., 2006; Hackman & Farah, 2009; Herrmann & Guadagno, 1997; Jednoróg et al., 2012; Noble, McCandliss, & Farrah, 2007; Noble, Norman, & Farah, 2005). Moreover, individuals raised in lower SES households exhibit lower performance in the classroom than their higher SES counterparts (Brooks-Gunn & Duncan, 1997; Feinstein, 2003), are more likely to fail academically in later childhood (Feinstein, 2003), and obtain lower scores on standardized academic achievement tests during adolescence (Mackey et al., 2015).

The biological mechanisms underlying the relation between early life SES and cognitive abilities in both childhood and adulthood are not yet fully understood. However, early-life SES may account for variability in brain development and, potentially, lasting cognitive effects in adulthood. Indeed, low SES is associated with thinner frontal and cingulate cortices (Lawson, Duda, Avants, Wu, & Martha, 2013; Noble, Korgaonkar, Grieve, & Brickman, 2013; Noble et al., 2015), as well as smaller cerebellar (Cavanagh et al., 2013) and cortical gray matter volume (Jednoróg et al., 2012; Luby et al., 2015; Mackey et al., 2015). Recently, smaller cortical thickness in adolescents from lower income background has been linked to poorer standardized test performance in multiple cognitive domains (Mackey et al., 2015).

The hippocampus is sensitive to both adverse (e.g., stress: Alfarez, Joe, & Krugers, 2003; Carrion, Weems, & Reiss, 2007; Hanson et al., 2015; McEwen, 1999; Mirescu & Gould, 2006) and protective (e.g., enriched environment: Brown et al., 2003; Kempermann, Kuhn, & Gage, 1997; Miller, Colella, Mikulis, Maller, & Green, 2013) effects of childhood, SES-related, factors. Due to its known role in memory functioning (Chaddock et al., 2010; Scoville & Milner, 1957; Tulving & Markowitsch, 1998, see Van Petten, 2004, for findings of a meta-analysis across the lifespan), this structure may partially confer SES-related effects on learning and memory functions during early life. Total hippocampal volume is thought to be stable after the age of 4, yet pronounced individual differences that are independent of age have been documented in both children (Daugherty, Bender, Raz, & Ofen, 2016; Gogtay et al., 2006) and adults (Raz et al., 2005). These findings may suggest that brain anatomy is modified by early factors throughout the lifespan. Indeed, children from households of lower SES have smaller hippocampal volume as compared to counterparts in higher SES households (Hanson, Chandra, Wolfe, & Pollak, 2011; Hanson et al., 2015; Jednoróg et al., 2012; Noble, Houston, Kan, & Sowell, 2012). Among those in the lowest range of estimated SES measured, relatively higher parental education is correlated with larger hippocampal volume (Noble et al., 2015).

SES may impact the developing hippocampus and, in turn, cognitive performance, via a confluence of adverse and favorable environmental influences whose final biological effect may be assumed to fall along a continuum. At one end of this continuum, one may consider the result of deleterious environmental factors such as elevated stress level. Indeed, animal studies have shown that the hippocampus is vulnerable to stress (see McEwen, 1999, for review), and that stress-related elevated cortisol levels can interfere with plasticity and neurogenesis (McEwen, 1999; Mirescu & Gould, 2006), the posited cellular mechanics of learning and memory functions. Research in humans has shown effects of stress on hippocampal structure (Carrion et al., 2007; Duman, 2002; Hackman et al., 2010; Hanson et al., 2015) and function (Sheridan, How, Araujo, Schamberg & Nelson, 2013). Moreover, low SES has been linked to higher levels of salivary cortisol in elementary school children (Lupien, King, Meaney, & McEwen, 2001; Sheridan et al., 2013). Finally, studies of the long-term effects of childhood maltreatment, another deleterious factor that is potentially associated with lower levels of SES (Cancian, Slack, & Yang, 2010), have also documented reduced hippocampal volume in children exposed to maltreatment (McLaughlin et al., 2016). On the opposite end of the continuum, higher SES may furnish positive environmental factors such as increased quality of parental care, enriched home, pre-academic and academic environments, and facilitated access to health services and an overall healthier lifestyle, factors that may contribute to healthy brain and cognitive development. Indeed, in animal studies, researchers have shown that an enriched living environment may promote neural plasticity and higher rates of neurogenesis in the hippocampus (Brown et al., 2003; Kempermann et al., 1997). It was also shown that the maternal care of offspring may buffer adverse effects of stress on the hippocampus (Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997; Weaver et al., 2004). Protective effects of higher level of life enrichment and of maternal care have also been documented in children and adults (Gunnar, 1998; Miller et al., 2013). Thus, the impact of early life SES on hippocampal functional development may have a lasting impact into adulthood. Yet, little is known of this presumed association, in part due to the shortcomings of methods that limit valid comparisons of hippocampal volume across ages.

Although studies have been published on the relationship between childhood SES and hippocampal volume, the findings in the extant literature rely chiefly on hippocampal volume measures obtained from semi-automatic segmentation methods using FreeSurfer (Jednoróg et al., 2012; Noble et al., 2015; Noble, Grieve et al., 2012; Noble, Houston et al., 2012), voxel-based morphometry (Hanson et al., 2011; Jednoróg et al., 2012), and SPM (Rao et al., 2010). When compared to gold-standard manual tracing, however, the convergent validity of these semi-automatic segmentation methods is questionable (Mechelli, Price, Friston, & Ashburner, 2005; Oscar-Berman & Song, 2011; Shen et al., 2010). For example, Morey et al. (2009) found poor to moderate percent volume overlap (0.77–0.82) between FreeSurfer, FSL-FIRST, and manual demarcation in adults. Dewey et al. (2010) showed poor percent volume overlap (0.37–0.75) when comparing FreeSurfer and IBASPM with an auto-assisted manual tracing in HIV-infected adults. Pipitone et al. (2014) found moderate Dice's Similarity Coefficient in older adults and patients with first episode psychosis (0.87–0.89), and low correlation ($r \leq 0.70$) between Multiple Automatically Generated Templates and manual demarcation. Importantly, none of the above studies provided evidence of the validity of FreeSurfer hippocampal segmentation in children. In a sample of 6–11-year-old children, poor agreement between two automated methods (FreeSurfer and FSL-FIRST) and manual demarcation was found by Schoemaker et al.

(2016). Importantly, Wenger et al. (2014) found that an overestimation bias by FreeSurfer systematically varies with age when comparing groups of younger and older adults. Therefore, age-related effects obtained using such methods may be spurious and should be interpreted with caution. We aim to address these limitations by employing a manual demarcation procedure, performed by raters with confirmed high inter-rater reliability for the demarcation of the hippocampus (ICC(2) > 0.9). We note that another study that used reliable manual segmentation showed an association between hippocampal volume and SES in a sample of children (see Hanson et al., 2015). However, a similar comparison was not conducted in adults. Hence, the extent to which SES may account for differences in hippocampal volume and mnemonic correlates across age groups remains unknown.

In the present study, we investigated the relation of SES to hippocampal volume in typically developing children (ages 8–12 years) and in young adults (ages 18–25 years). We then examined age group as a possible moderator of the magnitude of this relationship. We predicted that because children may be more vulnerable to adverse environmental influences, hippocampal volume would be differentially related to SES in children compared to adults, with a stronger association observed in children. In addition, in this sample we also examined the association of hippocampal volume to performance on a memory task.

2 | METHOD

2.1 | Participants

Thirty-one healthy, typically developing children (ages 8–12 years, $M = 10.49$, $SD = 1.36$; 42% female; 19% African American, 74% Caucasian, 7% more than one race) and 32 young adults (ages 18–25 years, $M = 21.71$, $SD = 1.94$; 50% female; 19% Asian, 19% African American, 56% Caucasian, 3% more than one race, 3% Other/Unknown) were recruited. The two groups did not differ in IQ (children: $M = 111.71$, $SD = 11.77$; adults: $M = 109.81$, $SD = 11.14$; $t(61) = 0.66$, $p = .51$). Participants were recruited from the Metro Detroit area as part of a larger study of cognitive and brain development. Participants were self-reported right-hand dominant, spoke English as a native language, had no reported developmental or neurological disorders, and no history of head trauma. For MRI compatibility and safety, participants had no metallic implants, braces, or permanent retainers. Participants were consented in accord with procedures approved by the University Institutional Review Board, which included parental consent for minors.

2.2 | Socioeconomic status

Four variables were measured to reflect the participants' SES. Subjective SES rating was assessed through self-report on the MacArthur Scale of Subjective Social Status (MAS; http://www.macses.ucsf.edu/). The MAS measures perception of one's own social status in relation to the population of the United States. This measure consists of a 10-point Likert scale displayed as a vertical ladder. Participants were told that the ladder represented the social standing of people in the United States, with individuals having the most money and education and most respected jobs occupying the top rungs, and those with the least money and education and least respected or no job at the bottom. Participants indicated the rung that best matched their subjective rating of their relative social status. Placement on the rungs was coded as corresponding to a number between 1 and 10, with a score of 1 given to the rung at the very bottom of the ladder. This self-report measure was completed by the parents of minor participants. Adult participants were administered the same questions and instructed to respond regarding their parents' household. MAS data were collected from 56 participants (29 children and 27 adults). We note that MAS data ranged between 3 and 9 out of a possible range of 1 to 10, suggesting that in this sample there was no representation of the lowest end of the subjective SES scale. In addition to the MAS, we obtained information about participants' total yearly family income, as well as the father's and the mother's levels of education. Both income and education data were collected in bins, and education data were recoded into ordinal variables (Table 1). Family income data were collected from 53 participants (29 children and 24 adults), and father's and mother's education from 58 participants (30 children and 28 adults). To account for the number of members per household, income-to-needs ratio for each participant was calculated as the median of the selected income bin, divided by the federal poverty level, based on the family size for the year of data collection (see Table 2 for descriptive statistics of the four SES measures). The complete set of four SES measures were collected from a total of 52 participants (29 children and 23 adults). To reduce the number of SES measures, with the data from these 52 participants we conducted a Principal Component Analysis with orthogonal rotation. The four measures loaded on a single factor (loadings ranged between 0.70 and 0.81). Therefore, we calculated the standardized weighted factor composite score which was used in subsequent analyses. In addition, we verified that the scores on each of the four SES measures were normally distributed (z-value of skewness and kurtosis < |1.81|).

TABLE 1 Recorded income and education levels

Income level	Education level
Less than $5000	None of below (1)
$5000–11,999	Less than high school (2)
$12,000–15,999	High school (3)
$16,000–24,999	Associate degree (4)
$25,000–34,999	Bachelor's degree (5)
$35,000–49,999	Master's degree (6)
$50,000–74,999	PhD/MD (7)
$75,000–99,999	–
$100,000 and greater	–

Participants indicated income and education data in discrete levels listed here. The median value of each income level was used in calculation of income-to-needs ratio. Education was entered as the number in parenthesis next to each level.

TABLE 2 Descriptive statistics of the four measures used to capture socioeconomic status in the total sample, and by age group

	Total sample		Children		Adults		^Group Diff.:
SES measure	Mean (*SD*)	Range	Mean (*SD*)	Range	Mean (*SD*)	Range	*t*, *p*
MacArthur Scale	6.3 (1.3)	[3, 9]	6.2 (1.6)	[3, 9]	6.3 (1.1)	[4, 8]	−0.4, 0.69
Income-to-needs ratio	2.9 (1.4)	[0.3, 5.4]	2.8 (1.2)	[0.3, 5.1]	3.0 (1.5)	[0.3, 5.4]	−0.3, 0.73
Father's education	4.2 (1.3)	[1, 7]	4.2 (1.2)	[1, 6]	4.3 (1.5)	[1, 7]	−0.5, 0.66
Mother's education	4.9 (1.4)	[2, 7]	5.3 (1.3)	[3, 7]	4.4 (1.4)	[2, 7]	2.6, 0.02*
Composite SES score	0.0 (1.0)	[−2.2, 1.6]	0.1 (1.0)	[−2.2, 1.6]	−0.1 (1.0)	[−1.7, 1.4]	n.a.

^Group differences (right column) were evaluated with a 2-tailed *t*-test.

2.3 | MRI acquisition and post-acquisition processing

Hippocampal volume measures were taken from a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence that was collected using a 32-channel head coil in a 3 Tesla Siemens Verio scanner (Siemens Medical AG, Erlangen, Germany). The 3D sequence was acquired in the coronal plane, perpendicular to the anterior-posterior commissural axis with the following parameters: echo time = 4.26 ms; repetition time = 2200 ms; inversion time = 1200 ms; flip angle = 9.0°; pixel bandwidth = 130 Hz/pixel; GRAPPA acceleration factor PE = 2; interpolated voxel size 0.5 mm × 0.5 mm × 1.0 mm.

Prior to hippocampal manual demarcation, the T1 MPRAGE image set was corrected for inhomogeneity, resampled to a 0.5 mm^3 isotropic voxel and manually realigned to be perpendicular to the longitudinal axis of the hippocampus, aligning the interhemispheric fissure. Individual differences in tilt and roll were also corrected manually. All preprocessing and manual demarcation were completed with Analyze v11.0 (Biomedical Imaging Resource, Mayo Clinic College of Medicine, Rochester, MN, USA).

2.4 | Hippocampal volumetry

Manual demarcation procedures were modified from Raz et al. (2004). Images were displayed (magnified × 2) on a 21-inch digitizing tablet (Wacom Cintiq) and manually demarcated with a stylus by three independent raters (QY, MN, and WL). The reliability between independent raters was tested using an intra-class correlation coefficient with the assumption of random raters (ICC(2); Shrout and Fleiss, 1979) of at least 0.90 for all raters. See Figure 1 top for an example of manual demarcation.

The hippocampus was measured in the coronal plane on every third slice extending from the mammilary bodies to the most posterior slice on which the pulvinar nucleus was still visualized, for a total of 15–22 slices (see Figure 1 bottom for an example of the anterior-posterior range). Reducing the number of slices sampled within the range has little impact on the accuracy and reliability as compared to measuring from every 0.5 mm slice (Eritaia et al., 2000). Volume was calculated as the sum area across traced slices, multiplied by the thickness between two consecutive traced slices. Per the specific protocol instructions, we did not trace on each slice, rather on every third slice, and volume is calculated based on the distance between traced slices. Multiplying by the thickness between two consecutive traced slices assures that the computed volume includes the extent of the traced range.

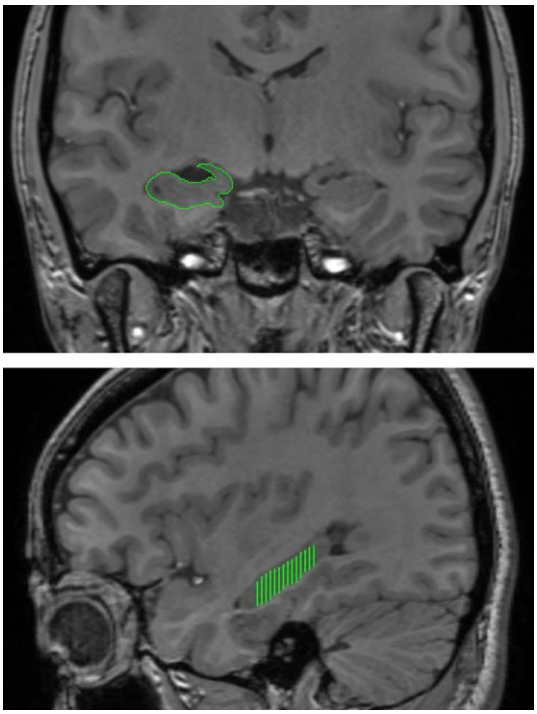

FIGURE 1 Example of manual demarcation of the hippocampus. The hippocampus was traced bilaterally in the coronal plane and an example of the tracing is shown on the right hippocampus (top). The range, anterior-to-posterior used in tracing the hippocampus is shown on a saggital (bottom). Images are presented in standard radiological orientation

2.5 | Intracranial volume measurement and volumetry correction

Intracranial volume (ICV) was measured from the T1 MPRAGE that was aligned to the anterior-posterior commissures with resampled voxel size to 0.5 mm^3 during post-processing. Independent raters manually demarcated ICV following procedures adapted from Raz et al. (2004) with high reliability (ICC(2) > 0.90). ICV was measured on every 20th slice, beginning with the most dorsal slice on which brain tissue was visualized and extending 10 slices ventrally. The hippocampal volume

was corrected for differences in ICV via analysis of covariance (Jack et al., 1989) and the equation: $volume_{adj} = volume_i - b(ICV_i - ICV_{mean})$, where i denotes certain individual, b is the unstandardized coefficient of whole sample volume regressed on ICV, and ICV_{mean} is the sample mean. The slope of regional volumes regressed on ICV was similar between children and adults ($F(1, 56) = 0.19$, $p = .66$); thus, the assumption of homogeneous slopes across age groups was met and the same correction was applied to the whole sample.

2.6 | Memory performance

To assess, within this sample, the possible relationship between hippocampal volume and memory performance, all participants were given the Visual-Auditory Learning task, a subtest of the Woodcock-Johnson III cognitive tasks (Woodcock and McGrew, 2001). This task was selected because it likely tests participants' ability for associative learning and efficient integration of multi-modal associations, aspects of cognitive function supported by the hippocampus (Achim, Bertrand, Montoya, Malla, & Lepage, 2007; Duff & Brown-Schmidt, 2012). Indeed, performance on this task has been shown to be influenced by hippocampal integrity (Lancelot et al., 2005).

In short, during a learning phase, participants were presented with several visual stimuli (pictures) and simultaneously provided the associated individual auditory stimulus (words) that are paired with each picture. Participants were then asked to recall the words that were associated with each picture. The picture-word pairs were arranged in short, meaningful sentences, and participants were instructed to 'read' the pictures during each recall phase. Recall phase was completed immediately following the learning phase, and again after a delay ($M = 57.22$ minutes, $SD = 16.81$). The number of errors was recorded for each recall phase and converted, using the norms provided for the subtest, to a Standard Score used in all analyses.

2.7 | Statistical analyses

Prior to evaluating associations between hippocampal volume and other variables, we evaluated possible differences in hippocampal volume between the hemispheres with a general linear model (GLM). Hemispheric hippocampal volumes were included as a two-level repeated dependent variable (left, right), with age group, sex, and the age group by sex interaction included as independent variables. When neither hemispheric effect nor hemisphere by age group effect was significant, the total hippocampal volume was used in subsequent analyses.

To examine the association between SES, age and hippocampal volume, GLMs were conducted with hippocampal volume as the dependent variable, and age group, SES composite score, and their interaction (SES × age group) as independent variables. Sex was entered in the models as a control variable, because we were not expecting sex differences in memory performance or hippocampal volume. In addition, we were not specifically interested in the interaction between sex and SES in predicting hippocampal volume. Evidence of a significant SES × age group interaction was further investigated with a post-hoc Fischer's Z test to evaluate the difference in the correlations of SES with hippocampal volume between children and young adults.

Finally, to evaluate the functional relevance of SES-related differences in hippocampal volume we conducted a secondary GLM analysis. In this analysis, we examined the association between hippocampal volume and cognitive ability, assessed by the Woodcock Johnson III Visual-Auditory Learning task. Age group, hippocampal volume and SES composite score were included as predictors in the model, and sex was included as a covariate.

All GLMs were bootstrapped with bias correction (5000 draws of the original sample) to produce 95% confidence intervals (CI) so as to avoid spurious effects related to smaller sample size. Examination of the 95% CI that do not include zero can be interpreted as evidence in support of a significant effect at $p < .05$.

3 | RESULTS

3.1 | Preliminary analyses

3.1.1 | No hemispheric difference in hippocampal volume estimation

Using GLM with right and left hippocampal volumes as dependent variables, there was no significant difference between hemispheres ($F(1, 60) = 0.16$, $p = .69$), nor did the difference between hemispheres vary by age group ($F(1, 60) = 0.11$, $p = .74$). Therefore, we used total hippocampal volume as the dependent variable in all subsequent analyses. Importantly, total hippocampal volume was not different between age groups ($F(1, 59) = 1.03$, $p = .32$) or between sexes ($F(1, 59) = 0.001$, $p = .97$).

3.1.2 | No age group difference in composite socioeconomic status score

Before examining whether the association between SES and hippocampal volume was dependent on age group, we evaluated the relation between age and SES. In a GLM controlling for sex, the SES composite score did not differ between age groups ($F(1, 49) = 0.06$, $p = .80$). Within the individual age group, the SES composite score did not correlate with age, controlling for sex (children: $r(26) = -0.17$, $p = .39$; adults: $r(20) = -0.26$, $p = .24$).

3.2 | Major findings

3.2.1 | SES interacted with age to predict hippocampal volume

When controlling for sex and the unique effects of SES and age group, age group interacted with the composite SES score ($F(1, 47) = 9.11$, $p = .004$; 95% CI −484.74/−130.15) to explain a significant portion of the variance in hippocampal volume (see Figure 2). Post-hoc analyses within age groups (controlled for sex) yielded a significant association between the SES score and hippocampal volume in

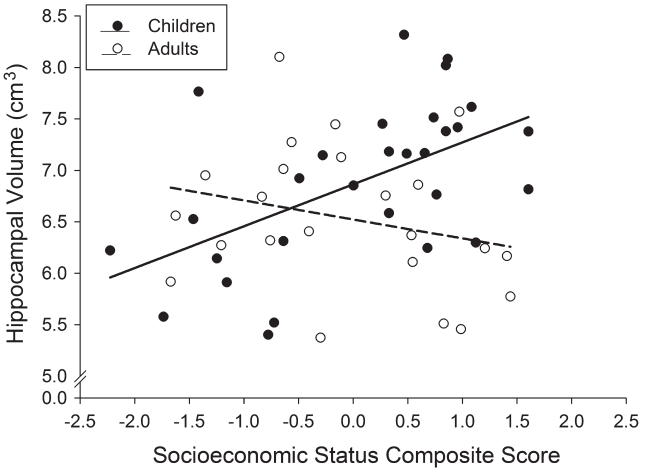

FIGURE 2 The relation between socioeconomic status (SES) and hippocampal volume differed in children and adults. Composite SES score was positively correlated with hippocampal volume in children (filled circles, solid line) but not in adults (open circles, dashed line). Hippocampal volume represents participant's total hippocampal volume corrected for ICV via the analysis of covariance (see Methods for the full description)

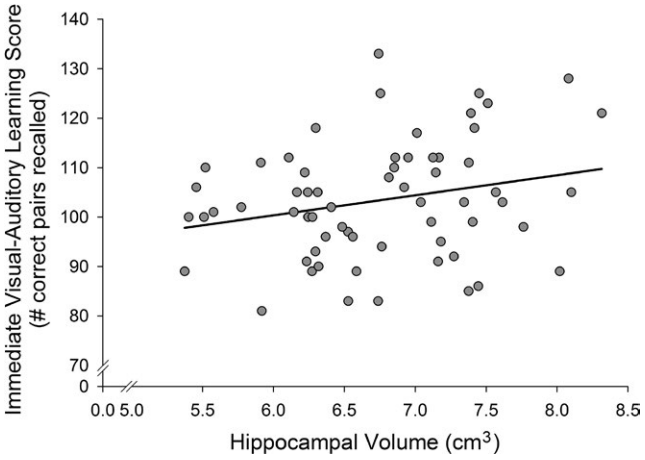

FIGURE 3 Hippocampal volume was related to memory performance. Hippocampal volume represents participant's total hippocampal volume corrected for ICV via the analysis of covariance (see Methods for the full description). Immediate visual-auditory learning scores were calculated as the number of correct visual-auditory pairs recalled. When controlled for sex and age, hippocampal volume significantly predicted immediate visual-auditory learning performance

children ($r(26) = 0.54$, $p = .003$), but not in adults ($r(20) = -0.25$, $p = .26$) (Figure 2). The association in children was significantly greater than that in adults (Fischer's $Z = 2.71$, one-tailed $p = .007$). Thus, a higher SES composite score was associated with increased hippocampal volume in children, yet this pattern was absent in adults.

The interaction between age group and SES in predicting hippocampal volume was also tested using the four individual SES measures. Similar interaction patterns were found for the individual measures, although the interaction between age group and mother's education did not reach statistical significance (see Supporting Information A).

3.2.2 | Hippocampal volume, but not SES, was linked to memory performance

We examined the relevance of SES score and hippocampal volume to immediate and delayed visual-auditory learning performance. In GLM analysis, age group, SES score, hippocampal volume, all three two-way interactions, and the three-way interaction between these variables were entered as predictors for immediate visual-auditory learning, controlled for sex. To simplify the model, interaction terms with a p-value greater than .10 were excluded from the model. Thus, the final model included age group, SES score, hippocampal volume, and a two-way interaction between age group and SES score ($p = .08$). Hippocampal volume was significantly related to task performance ($F(1, 46) = 4.60$, $p = .04$; 95% CI 0.0005/0.011) (Figure 3). In contrast, SES score was not related to task performance ($F(1, 46) = 1.78$, $p = .19$; 95% CI −12.87/2.61).

To assess the relevance of SES score and hippocampal volume to delayed visual-auditory learning performance, another GLM analysis was conducted with delayed visual-auditory learning performance as a dependent variable. Similarly, all possible interaction terms were included, but interaction terms with a p-value greater than .10 were excluded from the model. We found that neither hippocampal volume ($F(1, 45) = 0.15$, $p = .70$; 95% CI −0.005/0.008), nor SES score ($F(1, 45) = 0.54$, $p = .47$; 95% CI −3.127/6.733) were related to delayed learning performance.

In sum, the interaction between age group and SES explained a unique portion of the variance in hippocampal volume. The latter variable, in turn, accounted for a unique portion of the variance in immediate visual-auditory learning performance, while SES did not.

4 | DISCUSSION

Our chief objective was to evaluate whether the relationship between socioeconomic status and hippocampal volume is age-dependent. For this purpose, we measured hippocampal volumes in typical children and young adults. We found that a significant portion of the individual variance in hippocampal volume was explained by an interaction between age group and the composite SES score – indexed based on measures of subjective SES rating, income-to-needs ratio and parents' education. An association between SES and hippocampal volume was observed in the children's group only. Specifically, higher SES composite score in children, but not adults, was associated with greater hippocampal volume. This finding may indicate that the effects of SES disparity on hippocampal volume that exist in childhood are mitigated in adulthood. Moreover, larger hippocampal volume, but not higher SES, was significantly associated with improved performance on a visual-auditory learning task. The latter findings are consistent with the notion that a variable indexing brain anatomy is a more proximal predictor of memory performance than a sociodemographic factor.

The relation between SES and hippocampal volume during childhood likely reflects the cumulative effects of both adverse and protective environmental factors associated with family SES. Adverse factors, such as acute and chronic stress, can impair hippocampus-related learning and memory processes, as shown in rodents (Alfarez et al., 2003). Human neuroimaging studies also show that increased stress experienced during pregnancy and early postnatal life is related to smaller hippocampal volume (Carrion et al., 2007; Hanson et al., 2015). In contrast, protective environmental factors may buffer the ill-effects of stress on the developing hippocampus in animal models (Francis et al., 1999; Liu et al., 1997; Weaver et al., 2004), and a similar effect has been shown in humans (Gunnar, 1998; Luby, Belden, Harms, Tillman, & Barch, 2016). Higher SES has been linked to an increased level of parental support that, in turn, accounts for larger hippocampal volumes (Luby et al., 2015). In addition, an enriched environment can benefit the development of the rodent hippocampus (Brown et al., 2003; Kempermann et al., 1997), and in humans, can mitigate hippocampal atrophy following traumatic brain injury (Miller et al., 2013). In sum, these findings both underscore the sensitivity of the hippocampus to environmental influences and suggest that SES, as a proxy measure of the environment, warrants further investigation in relation to hippocampal structure and function.

The relation between SES and hippocampal volume was absent in young adults in the present study. Coupled with the pronounced effect we identified in children, this finding may indicate that the effects of SES-related environmental factors on developmental trajectories in typical individuals are most relevant in early life, and that the effects are minimized, perhaps negated, in young adulthood. However, based on studies of clinical populations, SES may partially determine sensitivity to pathology and traumatic injury during adulthood (Miller et al., 2013). In this regard, the role of environmental factors, for which SES serves as a proxy, may have differential relevance across the lifespan. In children, environmental influences may have a more direct impact on neural and cognitive development, whereas in adulthood such influences serve as modifiers of factors relevant to meeting challenges associated with quality of life, such as access to quality medical care (Conroy et al., 2010). Our findings are consistent with other reports of adverse exposure during an early developmental period that may delay, but not stunt, typical development (Francis et al., 1999; Liu et al., 1997; Weaver et al., 2004). The differential association between SES and hippocampal volume by age also echoes a proposal that the negative effects of low SES may be reversible (Hackman et al., 2010), which has largely been supported by animal models (Lemaire, Lamarque, Le Moal, Piazza, & Abrous, 2006). The differential association between SES and hippocampal volume at different ages demonstrated here calls for future studies investigating this issue over the lifespan. More critically, longitudinal studies are needed to establish these developmental effects with more sensitive instruments to measure SES constituents or correlates.

Economic circumstances, parental education and social tier perceptions are all crude proxies for the environmental influences on cognitive and brain development. SES is commonly measured by a composite of multiple indicators including parental education, household income-to-need ratio, and the individual's subjective perception of belonging to a certain social tier (Oakes & Rossi, 2003). Although these indicators are highly correlated, they may differentially relate to the multitude of factors that shape development (Brito & Noble, 2014; Duncan & Magnuson, 2012). Indeed, income may relate more directly to the material resources available to the family, whereas parental education may more directly relate to the nature of parent–child interaction (Duncan & Magnuson, 2012; Noble et al., 2015). In this study, we used a composite SES score that was determined by factor analysis showing that all four SES measures loaded highly on a single factor. When examining the individual measures, we found a similar pattern of relationship with hippocampal volume as the relationship observed for the composite score. However, the nature of the self-report in this study should be considered. For the children's group, parents completed the survey and ranked their social tier, whereas in the young adult group the participants themselves completed the selection. The social tier ranking is highly subjective and the reporting from parents versus young adults indicating familial SES may be differentially accurate. Nonetheless, we believe this had little, or negligible, impact on the effects observed between age groups. First, the rating of a social tier was one of four measures that strongly loaded onto a single SES factor used in all our analyses. Second, in supplemental analyses we assessed the interaction between age and SES for each of the four SES indicators separately (see Supporting Information A). The pattern of age group by SES interaction in predicting hippocampal volume, by which a link between SES and hippocampal volume was found only in children, was similar across individual SES measures, except for the effect of mother's education which failed to reach significance. Taken together, the findings presented here and in our supplemental analyses suggest that the SES indices used in our study measure a unitary construct, that may be robust to identifying a link between SES and hippocampal volume across age.

We found that hippocampal volume was related to immediate visual-auditory learning performance but not delayed performance, which may reflect the relevance of the hippocampus in the process of forming new associations. Ostby, Tamnes, Fjell, and Walhovd (2012), on the contrary, found that hippocampal volume was related to delayed, but not immediate, memory recall. There are several possible reasons for the contradictory findings. First, the discrepancy may be the result of the different stimuli used in the current study. While we required participants to memorize verbal-visual associations, the task used by Ostby et al. (2012) required recall of pictures with geometrical figures. Second, the definitions of 'immediate' were different. The immediate recall in the current study was administered right after encoding, in contrast to about 30-minutes delay in the study by Ostby et al. (2012). Participants completed our delayed task about an hour after the immediate recall, roughly matching the timing of the 'immediate' task in the study by Ostby et al. (2012). Thus our findings are consistent with Ostby et al. (2012) in that participants' performance in our delayed task was not related to hippocampal volume. As for the one-week delayed retain in the study by Ostby et al. (2012), we do not have a similar measure for comparison. Finally, Ostby et al. (2012) used FreeSurfer to estimate hippocampal volume, which may

be another factor that contributed to divergent results, considering the uncertain validity of anatomical indices obtained with this technique in different populations (Wenger et al., 2014).

Although in the current study we showed that larger hippocampal volume predicted better memory performance, and that higher SES explained larger hippocampal volumes in children, SES did not explain unique variability in memory function. Taken together, the net effects of postnatal environmental factors that are captured by SES may be more distal determinants of memory performance when compared to hippocampal volume. This is in contrast with other reports (Noble et al., 2007) and may reflect reduced sensitivity of the subtest used here to gauge SES-related differences in cognitive abilities. The null finding may be the result of our sample size and the limited representation of participants from the lowest SES ranks, where effects of SES on cognition are strongest (Noble et al., 2015). Future studies need to employ reliable and valid measures of hippocampal volume in larger samples. Additional behavioral outcome measures are also needed to investigate a mediating effect of hippocampal volume on the relation between SES and cognitive development. Future studies may also evaluate the mediating effects of other brain regions on the relation between SES and cognitive development (Jednoróg et al., 2012; Lawson et al., 2013; Noble et al., 2013; Noble et al., 2015) with the goal of gaining further insight into the putative mechanisms underlying SES effects.

The reported association between SES and hippocampal volume in children is largely consistent with prior findings (Hanson et al., 2011; Jednoróg et al., 2012; Noble, Grieve et al., 2012; Noble et al., 2015) and those suggesting that the effects are age-dependent (Noble, Grieve et al., 2012; Staff et al., 2012). However, a few limitations should be noted. First, our findings are based on cross-sectional data, and thus the age group differences in the association between SES and hippocampal volume cannot be interpreted as evidence of a developmental change. Cross-sectional studies are incapable of providing reliable estimates of change (Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011) or its mediators (Maxwell & Cole, 2007). Additional longitudinal studies are necessary to determine whether the age-moderated effect reported here is a true developmental effect. The intriguing possibility that adverse effects of low SES during early development may be mitigated as one enters adulthood can only be assessed with longitudinal data. Moreover, only longitudinal data can provide additional support for the specific neural substrates underlying the age-dependent associations between SES and hippocampal volume, and offer insights regarding sensitive periods when low SES may exert particular deleterious effects on development. Longitudinal studies with specific interventions targeted at relevant SES-related factors such as parental care or income (Hackman et al., 2010) may be best situated to elucidate the neural mechanisms mediating environmental effects on development. In addition, given the unavailability of childhood SES data for the current adult sample, it is also possible that the differential SES-hippocampal volume associations in the adults', versus children's, sample was a result of discrepant childhood SES experienced by the adults' sample from their own experience as children. Investigating the effect of childhood SES on the SES–hippocampal volume association in early adulthood would be an interesting direction for future research. Finally, one must acknowledge the inherent difficulty in interpreting the null effect in adults. The tests within the relatively small sample size may be underpowered to detect an association between SES and hippocampal volume in this group. Though care was taken to recruit a representative and matched sample (confirmed by similar overall SES and IQ in the two groups), the relatively small sample size across groups calls for caution in interpreting the interaction between age and SES in predicting hippocampal volume. It is possible that with larger samples, and a broader representation of lower SES scores, we could have found an association between SES and hippocampal volume in adults.

We report the association between SES and the total volume of the hippocampus estimated by manual demarcation, a gold-standard approach to derive hippocampal volume measures (see Supporting Information B for a complementary analysis using FreeSurfer to generate estimates of hippocampal volumes). It is possible, however, that the effect of SES on the hippocampus may differ across the hippocampal subfields (Daugherty et al., 2016) or its anterior-posterior subregions (Daugherty, Yu, Flinn, & Ofen, 2015). For example, dentate gyrus is characterized by persistent postnatal neurogenesis (Eriksson et al., 1998) and appears to demonstrate protracted development (Daugherty et al., 2016). The dentate may be more vulnerable to the adverse effects of low SES compared to other subfields, an effect otherwise obscured when testing association with the total volume of the hippocampus. Furthermore, volumes of hippocampal subfields (Bender, Daugherty, & Raz, 2013) and subregions (Riggins, Blankenship, Mulligan, Rice, & Redcay, 2015) show differential relation to memory across age. These recent findings suggest that the relation between SES and human hippocampal volume may be specific to sub structures of the hippocampus (e.g., subfields or subregions), although at this point defining a specific a priori hypothesis about such associations is difficult. Nonetheless, it raises an important direction for future investigations. Such investigations may take advantage of improvements in high-resolution imaging and the development of reliable methods of measuring variability in hippocampal regional measures (Wisse et al., 2017).

In conclusion, we found evidence for an association between SES and hippocampal volume in childhood, but not in young adulthood. This finding seems to be consistent with the notion that low SES effects on the brain may be transient. We also found that hippocampal volume accounted for individual difference in memory performance, although SES was unrelated to performance on a memory task. The latter findings are consistent with the notion that the net effects of SES are more distal determinants of memory performance in comparison to the effects of hippocampal volume. Future investigation using longitudinal designs, additional brain measures and diverse cognitive tasks may provide further insight into the age-dependent effects of low SES on brain development and the intriguing possibility that adverse effects of low SES early in life may be subsequently mitigated.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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