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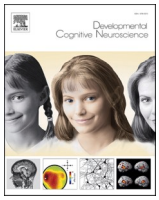

Longitudinal alterations in brain morphometry mediated the effects of bullying victimization on cognitive development in preadolescents.

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ABSTRACT

Bullying victimization is associated with a doubled risk of attempting suicide in adulthood. Two longitudinal brain morphometry studies identified the fusiform gyrus and putamen as vulnerable to bullying. No study identified how neural alterations may mediate the effect of bullying on cognition. We assessed participants with caregiver-reported bullying (N = 323) and matched non-bullied controls (N = 322) from the Adolescent Brain Cognitive Development Study dataset to identify changes in brain morphometry associated with ongoing bullying victimization over two years and determine whether such alterations mediated the effect of bullying on cognition.

Bullied children (38.7% girls, 47.7% racial minorities, 9.88 ± 0.62 years at baseline) had poorer cognitive performance ($P < 0.05$), larger right hippocampus ($P = 0.036$), left entorhinal cortex, left superior parietal cortex, and right fusiform gyrus volumes (all $P < 0.05$), as well as larger surface areas in multiple other frontal, parietal, and occipital cortices. Thinner cortices were also found in the left hemisphere, particularly in the left temporal lobe, and right frontal region (all $P < 0.05$). Importantly, larger surface area in the fusiform cortices partially suppressed (12–16%), and thinner precentral cortices partially mitigated, (7%) the effect of bullying on cognition ($P < 0.05$). These findings highlight the negative impact of prolonged bullying victimization on brain morphometry and cognition.

1. Introduction

Bullying victimization affects 20% of adolescents across the US (K. Wang et al., 2020), and is a risk factor for suicide attempts (Meltzer et al., 2011) in adulthood. Various cognitive outcomes were reported in bullied children at different ages. For instance, children bullied before age 6 years showed reduced executive function two years later (Holmes et al., 2016), 8–9-year-old children who were bullied had 6–9 months delays in reading, writing, and grammar (Mundy et al., 2017), and adolescent victims had more impulsive decision-making behaviors (Poon, 2016). Although there were no sex differences in executive function among bullied children (Holmes et al., 2016), bullied girls performed worse than non-bullied girls on writing and grammar tasks (Mundy et al., 2017).

The mechanism by which bullying impacts brain morphology and cognition is poorly understood. Rodent studies of social victimization (Golden et al., 2011) identified changes in several brain regions, including decreased spine density in the prefrontal cortex (Colyn et al., 2019), enhanced dendritic arborization in the amygdala (Colyn et al., 2019), and altered spine morphology in the hippocampus (Iñiguez et al.,

Abbreviations: ABCD Study, Adolescent Brain Cognitive Development Study; CBCL, Child Behavioral Checklist; MP-RAGE, Magnetization Prepared – Rapid Gradient Echo; LMM, Linear mixed-effects model; FDR, False discovery rate; Y1, Year 1; Y3, Year 3; LH, Left hemisphere; RH, Right hemisphere; STS, Superior Temporal Sulcus.

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2016). A study of 10-year-old children who were bullied at age 8 identified thicker cortex in the fusiform gyrus two years following bullying victimization (Muetzel et al., 2019). Another study found that generalized anxiety in 682 bullied adolescents was mediated through decreases in putamen and caudate volumes between ages 14 and 19 (Quinlan et al., 2020). Assessing preadolescent children will determine the impact of bullying on brain development at a younger, more stress-vulnerable age (Varma et al., 2021). This will validate earlier findings and evaluate how these changes may mediate cognitive outcomes, which in turn may lead to prevention strategies that can mitigate risks associated with childhood bullying.

We used the longitudinal Adolescent Brain Cognitive Development (ABCD) dataset to test the hypotheses that (i) over the two-year follow-up, relative to non-bullied children, young adolescents who were bullied would show persistently poorer cognitive performance and exhibit reductions in subcortical volume, cortical surface area, and cortical thickness in regions involved in cognition (e.g., prefrontal cortex, hippocampus) and emotion processing (e.g., putamen, amygdala); and (ii) these brain morphometric changes would mediate the effect of bullying on cognitive outcomes.

2. Materials and methods

2.1. Data source

The ABCD study is an ongoing, 10-year longitudinal study of children, starting at ages 9–10 years old, and includes data from the parents regarding their children at 21 sites across the United States. Baseline (Year 1) and second annual follow-up (Year 3) ABCD datasets (NDA release v.3.0.1) from 6571 participants were assessed. Site selection, recruitment, inclusion, and exclusion criteria were described elsewhere (Garavan et al., 2018; Thompson et al., 2019). All caregivers gave written informed consent and children provided assent. Local (site-specific) and central (University of California, San Diego) institutional review boards approved the study. The sample size allows for detection of medium to small effects (Garavan et al., 2018).

2.2. Measures

Age, sex at birth, race/ethnicity, caregiver education level, and family income level were self-reported by each caregiver. Height and weight were measured at the baseline visit and were used to calculate BMI in R, (weight (lb)/[height (in)]^2 × 703).

2.3. Bullying victimization

The caregivers were asked whether their children experienced bullying at school or in their neighborhood as part of the Kiddie Schedule for Affective Disorders and Schizophrenia background items (Kaufman et al., 2000). A "yes" response at Years 1 and 3 was classified as *"Bullied"* and a "no" response at both visits was classified as *"Non-bullied."* Participants whose caregiver responded "yes" at one visit but "no" at the other visit were not included in the analyses. Youth reports were not available in the NDA 3.0.1 data release.

2.4. Cognitive measures

One composite and five domain-based uncorrected scores were derived from the NIH Cognition Battery Toolbox® (Luciana et al., 2018), a widely used, validated assessment of cognitive performance in children. The NIH Toolbox assesses reading (Oral Reading Recognition), episodic memory (Picture Sequence Memory), processing speed (Pattern Comparison Processing Speed), inhibitory control and attention (Flanker Inhibitory Control and Attention), and vocabulary comprehension (Picture Vocabulary). The crystallized composite score comprises reading and vocabulary scores.

2.5. Child psychopathology

Caregiver report of youth psychopathology on the baseline Child Behavioral Checklist (CBCL) was also included. Specifically, we used the grouped total problem score, derived from the eight domain scales of anxious/depressed, withdrawn/depressed, somatic, social, thought, attention, rule-breaking, and aggression.

2.6. Imaging acquisition and processing

T1-weighted MP-RAGE (Magnetization Prepared - RApid Gradient Echo) scans (Casey et al., 2018) were acquired at each timepoint on 3 T Siemens, Philips, or General Electric scanners (1-mm isotropic resolution). Cortical surface area, cortical thickness, and subcortical volume measurements were derived from automated reconstruction and segmentation using FreeSurfer v5.3 (Hagler et al., 2019). Both the cortical and subcortical parcellations were automatically segmented using the Desikan-Killiany atlas. The full lists of cortical (34 regions per hemisphere) and subcortical ROIs (13 regions per hemisphere and 15 additional regions) are provided in Tables S1-2.

2.7. Experimental design and statistical analysis

323 bullied participants (125 girls, 154 racial minorities, 9.88 years at baseline) were matched to 322 non-bullied participants (132 girls, 171 racial minorities, 9.84 years at baseline) derived from the ABCD cohort for sex, age, race/ethnicity, caregiver education level, and family income level using the MatchIt package in R (version 4.1.1). Participants were matched for sex, age, race/ethnicity, parent education, and family income to minimize potential confounding factors. Matched samples were used to prevent the introduction of bias in the estimated effect from increased sample size of the unexposed (non-bullied) group (Austin, 2010). Any participants with missing or incomplete variables, or those not reported as bullied at both or neither visit were excluded from the analyses (Fig. 1). Our power calculations indicated an 80% probability of detecting a small effect size (f) of 0.11 with our sample size of 646 and the alpha set at 0.05.

We used linear mixed-effects models (LMM) (Raudenbush and Anthony, 2002; "Lmer Function - RDocumentation." n.d, 2022) and emmeans (Lenth et al., 2022) in R to determine whether being bullied affected changes in cognitive scores or brain structures over time, using the lme4 and emmeans packages. LMMs include hierarchical distributions, which allow for the inclusion of nesting by site and scanner, as well as repeated measures within a participant. Emmeans were used to derive estimated marginal means, calculate effect sizes with 95% confidence intervals for the main (being bullied) and interaction (bullying*visit and bullying*sex) effects, and to generate plots. The emmeans effect sizes used were Cohen's d, which defines effects as small when d= 0.2 but < 0.5, medium when d= 0.5 but < 0.8, and large when d> 0.8 (Cohen, 1988)." For the main effect of bullying, a positive effect indicated larger morphometry/greater cognition and a negative effect indicated smaller morphometry/lower cognition in bullied children compared to non-bullied children. Statistical significance was set at $P < 0.05$ and covariates included age, sex, visit, race/ethnicity, parent education, family income, CBCL total problem scores, BMI, and intracranial volume (ICV). Although sex, age, race/ethnicity, parental/caregiver education, and family income were matched between groups, we also included them as covariates to eliminate any potential confounds for our findings. As mentioned above, LMMs were also nested by participant by scanner site (1|ID/Scanner ID). All p-values were adjusted for multiple comparisons using the Benjamini & Hochberg (false discovery rate [FDR]) or Tukey (Dunn, 1961) methods (Benjamini and Hochberg, 1995).

We then used mediation analyses (Mascha et al., 2013) to determine whether changes in brain morphometry mediated the effect of being bullied on cognitive scores, focusing on "bullying-impacted" brain

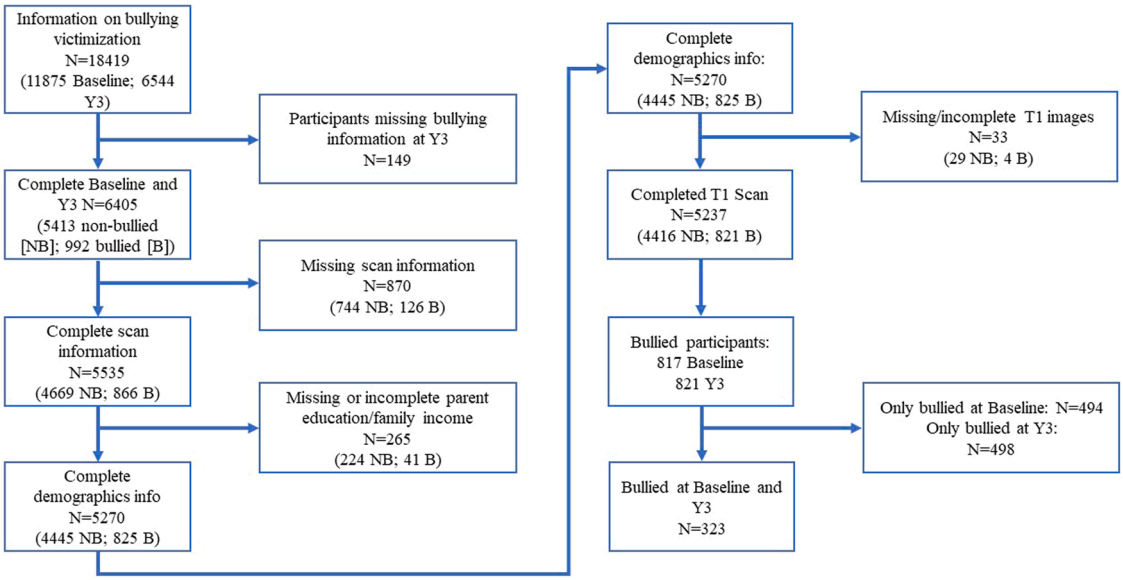

Fig. 1. Flow chart indicating participant inclusion/exclusion from study population. Fig. 1 Legend. This flow chart describes the participant information available for each measure used, and how many participants were included and excluded for the analysis, to derive our final matched sample.

regions. The "bullying-impacted" regions used for these analyses were those found to be significantly associated with bullying status using the LMM and emmeans method described above. Specifically, individual LMMs were used to calculate the effects of (a) bullying [X] on brain morphometry ($X \xrightarrow{a} M$) and (b) brain morphometry on cognitive scores [Y] ($M \xrightarrow{b} Y$). We then used a mediation model to calculate the total effect (c) of being bullied on cognitive scores, as well as the mediation effect [M: ($X \xrightarrow{c} Y$)] of subcortical volume, cortical volume, cortical surface area, and cortical thickness of affected regions. This mediation model also generated estimates and p-values for the direct effect (c′) and indirect effect (a*b) of bullying on cognition scores ($X \xrightarrow{c'} Y$), as well as the proportion of the effect attributed to the mediator. The temporal precedence of the variables used was as follows. We calculated the effect of being bullied on cognition, because while several studies have implicated an association between victimization and lower cognitive scores (Menken et al., 2022; Poon, 2016; Samper-García et al., 2021), cognition did not influence the likelihood of being bullied (Miguel and Urzúa, 2015). Additionally, a study of social defeat stress in mice showed rodents that were victimized had dendritic atrophy (Fox et al., 2020), which can impact regional brain volume. Lastly, studies in aging and diseases showed that changes in brain morphometry can impact cognition (Cao et al., 2021; Leong et al., 2017). The covariates used in the LMMs above were also used for each portion of the mediation analyses. The mediation model did not allow for nesting; hence the scanner type was included as a covariate instead of nesting by scanID. Effect sizes for the total effect were calculated by multiplying the estimates of 'a′ and 'b′ (David, 2021). Cohen's *d* standards (Cohen, 1988) were squared (David, 2021); a small effect size was 0.04 but < 0.25, medium was 0.25 but < 0.64, and large was > 0.64. Our mediation reporting and results followed the AGReMA (A Guideline for Reporting Mediation Analyses) statement (Lee et al., 2021).

3. Results

3.1. Description of participant characteristics

Data from 645 children were included for the MRI analyses (Table 1, Fig. 1). At Year 1, the youth were 9.9 ± 0.6 years of age, 60% were boys and 50% were racial/ethnic minorities (Hispanic, black, mixed/other). The participant demographic characteristics were not different between groups (P = 0.09–0.049, Table 1).

3.2. Cognitive outcomes of bullying

Overall, after inclusion of all covariates, bullied children had lower scores than non-bullied children on reading (emmeans Cohen's d effect size (d) = −0.33, [95% Confidence Interval (CI), —0.66 to —0.01; P = 0.046), processing speed (d= −0.31, [95% CI, —0.53 to —0.08]; P = 0.008), and inhibitory control and attention (d= −0.20, [95% CI, —0.38 to —0.02]; P = 0.030) (Fig. 2A, Table S3). No group differences were found between bullied and non-bullied children in scores on crystallized cognition composite (P = 0.14), episodic memory (P = 0.67), and vocabulary comprehension (P = 0.51; Table S3). Episodic memory (picture sequence memory) scores increased over two years only in the bullied group (bullied: P = 0.010; non-bullied P = 0.11), but interaction effects were not significant (interaction-P = 0.21; Fig. 2B, Table S4).

3.3. Bullying victimization on subcortical brain volumes

Bullied children had larger right hippocampal volumes than non-bullied children (d=0.52, [95% CI, 0.03–1.01]; P = 0.036) (Fig. 3A, Table S7), but not in any other subcortical brain volumes (P = 0.09–0.96; Table S7). Emmeans contrast for bullying-by-visit interactions showed that the whole brain (P < 0.05) and supratentorial volumes (P < 0.05) increased in the bullied and non-bullied groups between visits, while left cerebral white matter volumes increased only in the non-bullied group (Fig. 3B, Table S8; non-bullied: P = 0.042; bullied: P = 0.06). However, no significant interactions between bullying and visit were found in any of the subcortical volumes (Table S8). Multiple covariates, including visit (P < 0.05), sex (P < 0.05), age (P < 0.05), race/ethnicity (P < 0.05), family income (P < 0.05), CBCL total problem score (P < 0.05), BMI (P < 0.05), and ICV (P < 0.05) impacted the LMM in at least five subcortical brain regions (Table S9). However, parent education level did not impact the model (P range: 0.15–0.94). Despite relatively larger right hippocampal volumes in the bullied children, it had no impact on any of the three cognition scores (Oral Reading Recognition: P = 0.43; Pattern Comparison Processing Speed: P = 0.71; Flanker Inhibitory Control and Attention: P = 0.09) (Table S12).

Table 1
Participant Characteristics. Bullied children with MRI data from Year 1 (Baseline, Y1) and Year 3 (2nd follow-up, Y3) visits were matched with non-bullied children for sex, age, race, caregiver education and income. None of the demographic variables were significantly different.

	Bullied (n = 323, 50.0)	Non-bullied (n = 322, 50.0)	Chi-square p-value
Sex at Birth: No. (%)			0.43
Boys	198 (61.3)	190 (59.0)	
Girls	125 (38.7)	132 (41.0)	
Age: mean (SD), months			0.34
Baseline (Y1)	118.6 ± 7.4	118.1 ± 7.5	
2nd Follow-up (Y3)	142.4 ± 7.6	142.4 ± 7.6	
Race/Ethnicity: No. (%)			0.09
White	169 (52.3)	151 (46.9)	
Black	45 (13.9)	60 (18.6)	
Hispanic	54 (16.7)	56 (17.4)	
Mixed-Other	55 (17.0)	55 (17.1)	
Caregiver Education:			0.38
High School Graduate	52 (16.1)	43 (13.4)	
College	222 (68.7)	228 (70.8)	
Graduate Degree	49 (15.2)	51 (15.8)	
Family Income:			0.49
< $50k	144 (44.6)	151 (46.9)	
$50-$100k	100 (31.0)	90 (28.0)	
> $100k	79 (24.5)	81 (25.2)	
Site:			
1	7 (2.2)	6 (1.9)	
2	14 (4.3)	22 (6.8)	
3	24 (7.5)	15 (4.6)	
4	33 (10.2)	38 (11.8)	
5	8 (2.5)	6 (1.9)	
6	13 (4)	17 (5.3)	
7	2 (0.6)	7 (2.2)	
8	9 (2.8)	5 (1.5)	
9	10 (3.1)	5 (1.5)	
10	17 (5.3)	20 (6.2)	
11	4 (1.2)	10 (3.1)	
12	15 (4.7)	10 (3.1)	
13	24 (7.5)	30 (9.3)	
14	20 (6.2)	7 (2.2)	
15	16 (5)	26 (8)	
16	25 (7.8)	35 (10.8)	
17	11 (3.4)	10 (3.1)	
18	9 (2.8)	6 (1.9)	
19	22 (6.8)	13 (4)	
20	24 (7.5)	20 (6.2)	
21	14 (4.3)	15 (4.6)	
22	1 (0.3)	0 (0)	

3.4. Bullying victimization on cortical volume

Overall, bullied children had larger cortical volumes in the left entorhinal (d=0.39, P = 0.013), left superior parietal (d=0.51, P = 0.023), and right fusiform regions (d=0.60, P = 0.014) than children in the non-bullied group (Fig. 4A-B, Table S13). Bullying-by-visit showed an interaction in the right pars opercularis (interaction-P = 0.048). Additionally, although no interaction for bullying-by-visit was found in the left entorhinal cortical volume (interaction-P = 1.00), at Year 3 (Y3), the bullied group had larger volumes compared to the non-bullied group (P = 0.049), but not at Year 1 (Y1) (P = 0.17) (Figs. 4**A,** 4**C,** Table S14). Across all participants, regions that displayed increased volume between visits included total (P < 0.05), left (LH) (P = 0.05), and right hemisphere (RH) cortical volumes (P < 0.05), left inferior temporal (P < 0.01), bilateral insula (P < 0.05), and right isthmus cingulate (P < 0.05). Covariates that impacted the main LMM included ICV for every region (P < 0.001); sex (P < 0.05), age (P < 0.05), and race/ethnicity (P < 0.05) in most regions; and visit (P < 0.05), family income (P < 0.05), CBCL total problem score (P < 0.05), and BMI (P < 0.05) in a couple of regions (Table S15). Additionally, none of the three regions (left entorhinal, left superior parietal, right fusiform) that were larger in bullied children compared to non-bullied children affected cognition scores (P-value range: 0.09–0.81) (Table S18-19).

3.5. Bullying victimization on cortical surface area

Overall, after inclusion of covariates, compared to the non-bullied children, bullied children had larger surface areas in multiple cortices, including left entorhinal (d=0.34, P = 0.042), left paracentral (d=0.46, P = 0.036), left pars orbitalis (d=0.46, P = 0.045), left superior parietal (d=0.82, P = 0.004), right fusiform (d=0.88, P = 0.002), right pars orbitalis (d=0.64, P = 0.017), right rostral middle frontal (d=0.72, P = 0.029), and right superior parietal (d=0.67, P = 0.018) (Fig. 5A-B, Table S20). Bullying-by-visit interaction was found in the pars orbitalis (interaction-P = 0.017), where the cortical surface area was only larger in the bullied group at Y3 (d=0.81, P = 0.016), but not at Y1 (d=0.47, P = 0.32). Interactions were also found in the left rostral anterior cingulate (interaction-P = 0.048) and in the right temporal pole (interaction-P = 0.048), where there were greater increases in surface area between visits in the bullied group compared to the non-bullied group. In addition, at both Y1 and Y3, surface areas were larger in the bullied group than in the non-bullied group, in the left superior parietal (Y1: d=0.79, P = 0.031; Y3: d=0.85, P = 0.017) and right fusiform (Y1: d=0.90, P = 0.013; Y3: d=0.87, P = 0.018) (Fig. 5 A, 5 C, Table S21). Across all participants, there were many regions that displayed increases in surface area between visits, including total, LH, and RH surface areas. Importantly, the effect of bullying on Crystallized Composite and Picture Vocabulary test scores were suppressed by the larger right fusiform surface areas (Crystallized indirect effect: 0.12, percent suppressed: −11.8, P = 0.044; Picture Vocabulary indirect effect: 0.07, percent suppressed: −15.6, P = 0.028) (Fig. 5D, Table S25-26). Assessment for the impact of covariates on the bullying LMM showed that visit (P < 0.05), sex (P < 0.05), age (P < 0.05), race/ethnicity (P < 0.05), ICV (P < 0.001) significantly impacted cortical surface area in most regions and income (P = 0.029), CBCL total problem score (P < 0.05), and BMI (P < 0.05) affected the model for several brain regions (Table S22).

3.6. Bullying victimization on cortical thickness

Compared to non-bullied children, bullied children had thinner cortices in the left hemisphere (d= −0.39, P = 0.041), left banks of superior temporal sulcus (STS) (d= −0.43, P = 0.038), left middle temporal gyrus (d= −0.48, P = 0.009), left precentral gyrus (d= −0.48, P = 0.006), and right rostral middle frontal regions (d= −0.36, P = 0.034) (Fig. 6A-B, Table S27). Bullying-by-visit interactions showed that in the right lateral occipital cortex, the non-bullied group displayed a greater decrease in size between visits (P = 0.04) than in the bullied group (P = 0.050) (interaction-P = 0.048; Fig. 6 C, Table S28). In addition, in the left middle temporal gyrus, the bullied children had thinner cortices than non-bullied children at Y3 (P = 0.037), but not at Y1 (P = 0.09) (Fig. 6A, 6C). In both the bullied and non-bullied groups, there were several regions that showed decreased cortical thickness between visits, including the left lateral occipital (P < 0.01) and left precentral gyri (P = 0.05). Thinner cortices in the left precentral gyrus cortices mediated 7.0% of the effect of bullying status on inhibitory control and attention scores (indirect effect: −0.23; P = 0.020) (Fig. 6D, Table S32-33). The LMM for bullying on cortical thickness was influenced by almost all the covariates evaluated: sex (P < 0.05), BMI (P < 0.05), ICV (P < 0.05), visit (P < 0.05), age (P < 0.05), race/ethnicity (P < 0.05), and CBCL total problem scores (P < 0.05) (Table S29).

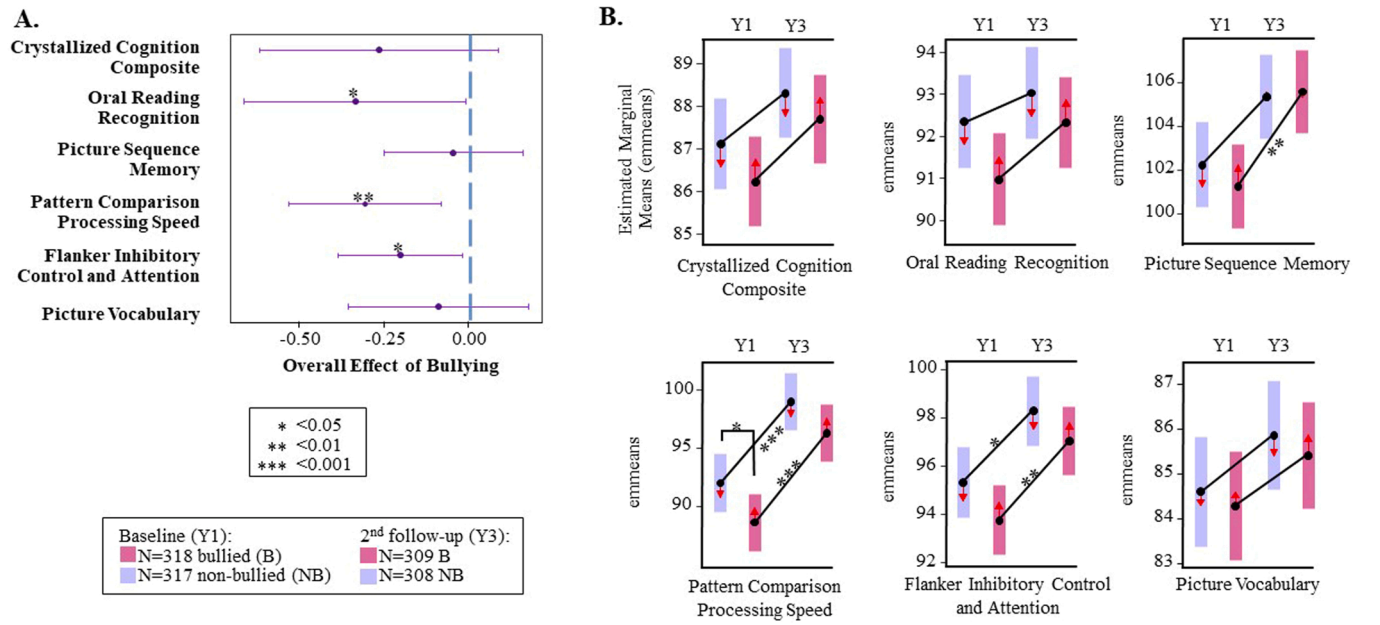

Fig. 2. Bullying status on cognitive scores over time. Fig. 2 Legend. A-B display the main effects of bullying with 95% confidence intervals (A) and interactive effects of bullying and visit (B) on cognition, calculated using emmeans and linear mixed-effects models (*P < 0.05; **P < 0.01; ***P < 0.001; adjusted for multiple comparisons). Pattern Comparison Processing Speed (P = 0.014) and Picture Sequence Memory (P = 0.017; Table S5) had significant sex differences.

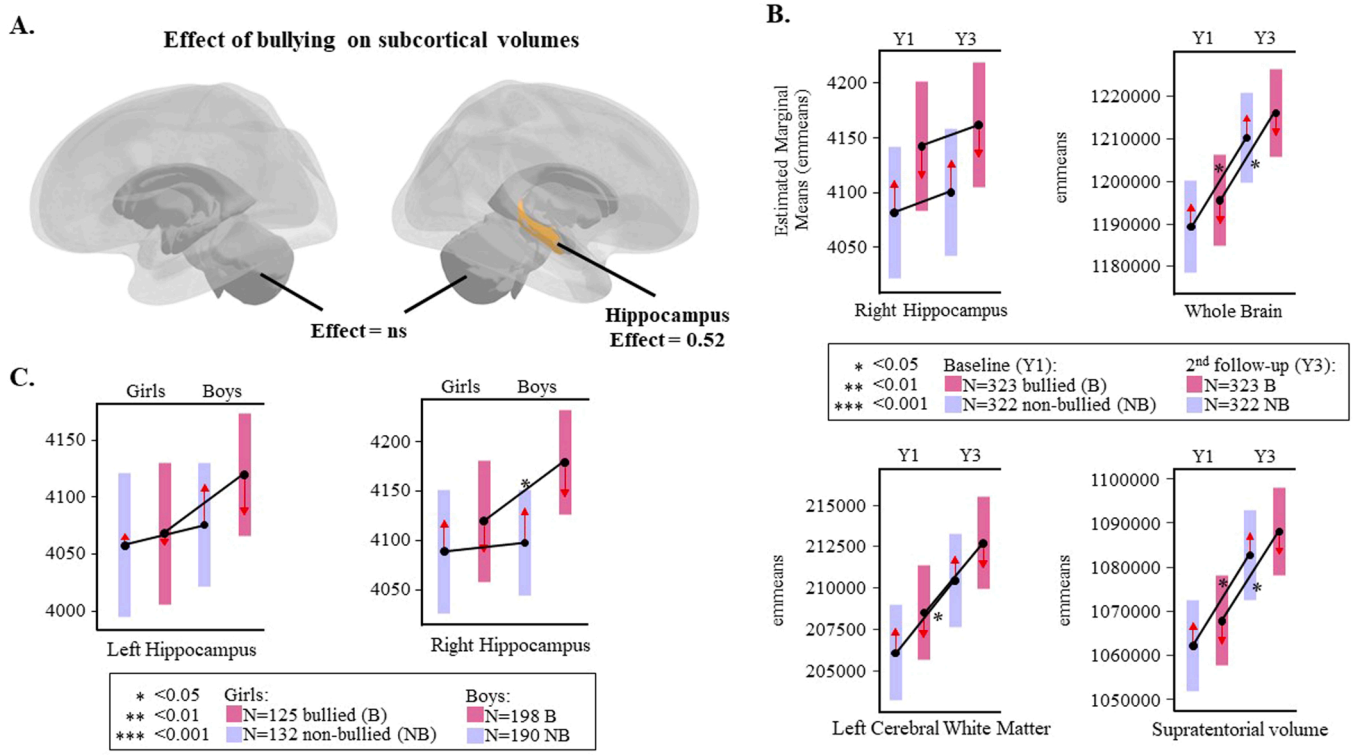

Fig. 3. Bullying victimization status and subcortical volume over time. Fig. 3 Legend. A-B display the main effects of bullying (A) and interactive effects of bullying and visit (B) on subcortical volumes, calculated using emmeans and linear mixed-effects models. C plots the interactive effects of bullying and sex on hippocampal volumes, using emmeans and linear mixed-effects models. (*P < 0.05; **P < 0.01; ***P < 0.001; adjusted for multiple comparisons).

3.7. Sex differences in cognitive and brain measures

Regardless of bullying status, boys had lower cognitive scores on episodic memory (d=0.23, [95% CI, 0.04–0.42]; P = 0.017) and processing speed tasks (d=0.26, [95% CI, 0.05–0.47]; P = 0.014) than girls (Table S5). In the non-bullied group, girls scored higher than boys on the episodic memory task (P = 0.013), but the bullied groups showed no sex differences on this task (P = 0.97) (Table S6). This led to a trend for an interaction between bullying and sex on episodic memory (interaction-P = 0.06). The same occurred on the processing speed task, where in the non-bullied group alone, girls scored higher than boys (non-bullied: P = 0.04; bullied: P = 0.78). In addition, bullied girls performed worse

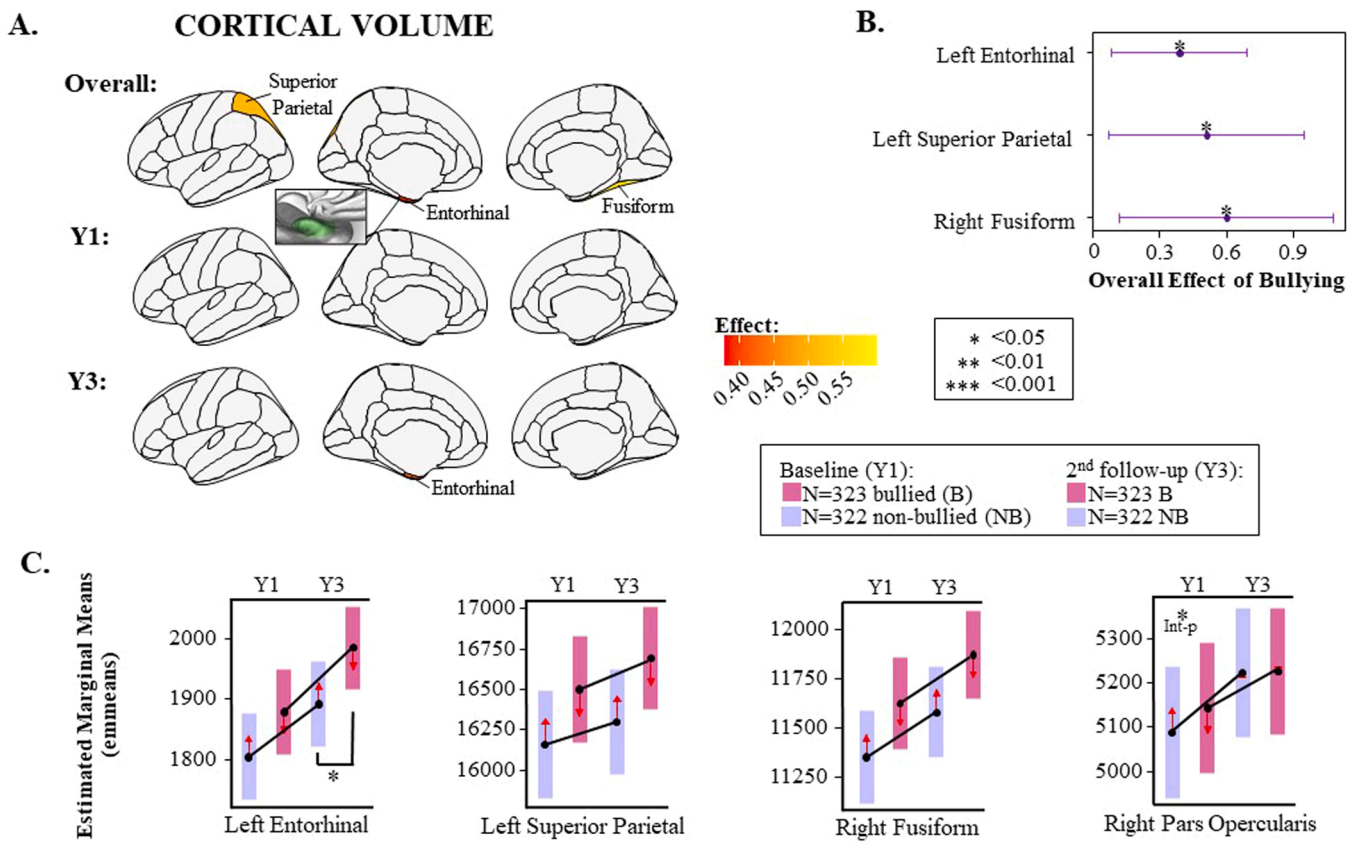

Fig. 4. Bullying victimization status and cortical volume over time. Fig. 4 Legend. A-C display the effects of bullying (A-B) and interactive effects of bullying and visit with 95% confidence intervals (C) on cortical volume, calculated using emmeans and linear mixed-effects models. (*P < 0.05; **P < 0.01; ***P < 0.001; adjusted for multiple comparisons). Entorhinal image (zoomed in) adapted from Gaillard et al., 2023.

than non-bullied girls on the processing speed task (P = 0.030), but the boys performed similarly regardless of bullying status (P = 0.47). However, no interaction was found between bullying and sex on processing speed (interaction-P = 0.21; Table S6).

Assessment for sex differences in subcortical volumes showed that bullied boys had larger right hippocampal volumes than non-bullied boys (P = 0.022), but the girls were similar regardless of bullying status (P = 0.46) (Table S11). However, no sex-specific effects for bullying were observed (interaction-P = 0.85). Additionally, for sex differences in cortical volumes, girls had smaller total, LH, and RH brain volumes than boys (d= —1.17 to —1.09; P < 0.001) (Table S16). Girls also had smaller regional volumes in the three areas affected by bullying victimization (left entorhinal: P < 0.001; left superior parietal: P = 0.006; right fusiform: P < 0.001). Regarding the sex-by-bullying effects, both the left entorhinal and right fusiform were larger in bullied boys compared to non-bullied boys (left entorhinal: P = 0.024; right fusiform: P = 0.032), but these cortical volumes were similar in girls, regardless of bullying status (left entorhinal: P = 0.15; right fusiform: P = 0.12) (Table S17). The opposite occurred in the left superior parietal, where it was larger among bullied girls compared to non-bullied girls (P = 0.026), but the cortical volumes were comparable among bullied and non-bullied boys (P = 0.18). Regardless, none of the sex-by-bullying interactions were significant (P = 1.00).

Evaluation for sex differences in cortical surface area showed that girls had smaller surface area than boys in nearly every region (P < 0.001; Table S23). Although none of the sex-specific interactions were significant (interaction-P = 1.00), bullied boys had larger surface area than non-bullied boys in the left entorhinal (P = 0.046; girls P = 0.32), right fusiform (P = 0.008; girls P = 0.06), and right superior parietal regions (P = 0.037; girls P = 0.14), whereas girls only trended towards significance in the right fusiform (Table S24). Bullied girls had larger surface area than non-bullied girls in the left (P = 0.005; boys P = 0.60) and right pars orbitalis (P = 0.003; boys P = 0.38) and right rostral middle frontal regions (P = 0.012; boys P = 0.32), while boys displayed no group differences.

Across all participants, girls had thicker cortices than boys (including total LH and total RH) (P < 0.001) and in all four bullying-impacted regions (P < 0.05) (Table S30). However, in the left STS, bullied girls had thinner cortices than non-bullied girls (P = 0.049), while the boys had similar thickness between the bullied and non-bullied group (P = 0.20; interaction-P = 1.00) (Table S31). In addition, in the left middle temporal gyrus, bullied boys had thinner cortices than non-bullied boys (P = 0.038), while the girls only tended to show a group difference (P = 0.06; interaction-P = 1.00).

4. Discussion

In this study of bullied children and their brain morphometric and cognitive development, we identified novel brain areas involved in cognitive processes that are vulnerable to consistent bullying victimization over two years. We found thinner left hemisphere, banks of STS, middle temporal, precentral, and rostral middle frontal cortices, and enlarged right hippocampus, superior parietal, entorhinal, paracentral, pars orbitalis and fusiform regions. This is the first study to identify altered morphometry in many of these regions. We further demonstrated that several of these abnormal brain measures (larger surface areas in the fusiform cortices, but thinner precentral cortices) partially suppressed or mediated ongoing bullying victimization status on cognition, including episodic memory, crystallized composite scores, inhibitory control, and attention. These findings provide novel insights into the neural correlates of bullying on cognition.

Similar to an earlier study (Muetzel et al., 2019), we found

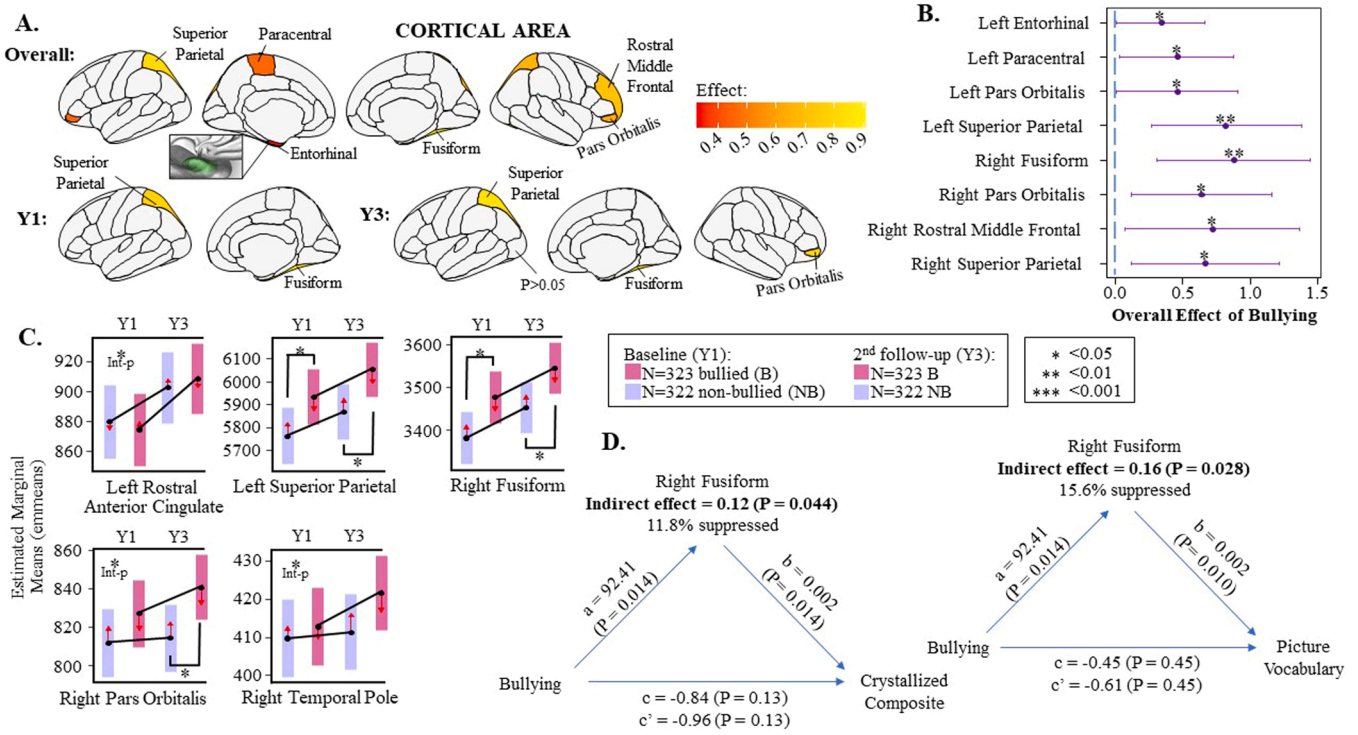

Fig. 5. Bullying victimization status and cortical surface area over time. Fig. 5 Legend. A-C display the effects of bullying (A-B) and interactive effects of bullying and visit with 95% confidence intervals (C) on cortical areas, calculated using emmeans and linear mixed-effects models. (*P < 0.05; **P < 0.01; ***P < 0.001; adjusted for multiple comparisons). D displays mediation estimates and p-values generated using linear mixed-effects models to show the relationship between bullying and cognition, and how cortical surface area acts as a partial mediator. Entorhinal image (zoomed in) adapted from Gaillard et al., 2023.

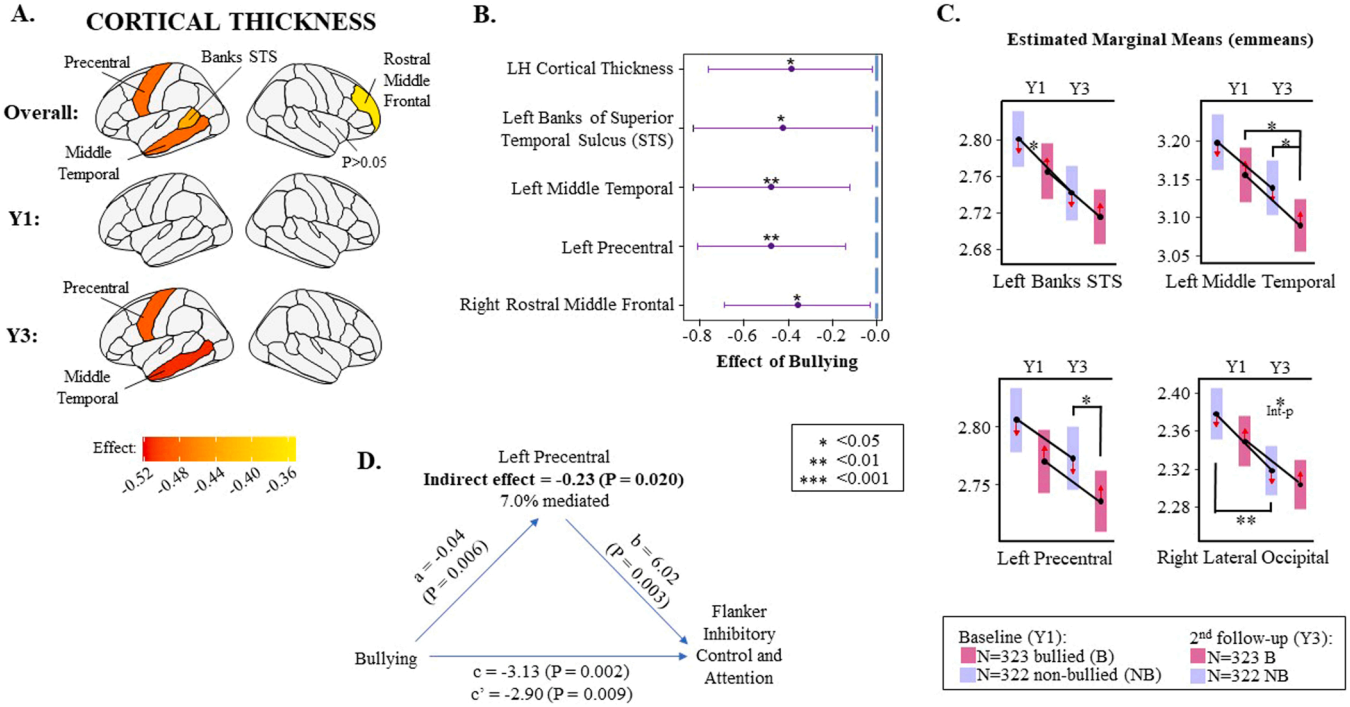

Fig. 6. Bullying victimization status and cortical thickness over time. Fig. 6 Legend. A-C display the effects of bullying (A-B) and interactive effects of bullying and visit with 95% confidence intervals (C) on cortical thickness, calculated using emmeans and linear mixed-effects models. (*P < 0.05; **P < 0.01; ***P < 0.001; adjusted for multiple comparisons). D displays mediation estimates and p-values generated using linear mixed-effects models to show the relationship between bullying and cognition, and how cortical thickness acts as a partial mediator.

alterations in the fusiform gyrus among bullied children. However, while the prior study reported thicker than normal left fusiform gyrus in 47 children bullied by age 8 and scanned at age 10 (Muetzel et al., 2019), the bullied children in our study, at similar ages, had relatively larger cortical surface area and volume, but normal cortical thickness, in the right fusiform cortex.

4.1. Cognitive outcomes of bullying

Consistent with previous studies, we found that bullied children had poorer reading (Mundy et al., 2017; Menken et al., 2022) and inhibitory control (Samper-García et al., 2021; Poon, 2016; Menken et al., 2022) than non-bullied children. Lacking emotional regulation may worsen the effects of bullying because of its role in adapting to stressful or traumatic events (Frederick and Le Menestrel, 2016). Additionally, low impulse control may cause bullying victims to put themselves in risky situations (Poon, 2016). Like our earlier study of cognition in the ABCD baseline cohort (Menken et al., 2022), we identified novel findings that bullied children had lower processing speed scores than their non-bullied peers. Delayed processing speed may impact their communication skills, as seen in adults with autism spectrum disorder (Haigh et al., 2018) or schizophrenia (McClure et al., 2007), and would exacerbate any social issue in school and disturb their ability to ask for help.

4.2. Larger right hippocampal volumes associated with ongoing bullying

The hippocampus plays a significant role in learning and memory and is distinctively vulnerable to stress (Anand and Dhikav, 2012). Although no previous studies identified hippocampal structural changes following bullying, one study linked smaller hippocampal white matter to childhood emotional neglect in adult depressed patients (Frodl et al., 2010), while another found smaller hippocampal volume was linked to higher levels of perceived stress in adults (Lindgren, Bergdahl, and Nyberg, 2016). Importantly, bullying victimization was linked to stress disorders, including post-traumatic stress disorder (Idsoe et al., 2012).

The larger right hippocampus in the bullied children is novel. Another study of older adults found that those with larger hippocampi had greater white matter fiber coherence with higher fractional anisotropy and better learning (Bender et al., 2020). However, the abnormally large right hippocampus in our bullied children did not act as a mediator or contribute to better cognition in bullied children. Future studies should evaluate whether the hippocampal volumes might mediate the effects of bullying on psychiatric symptoms.

4.3. Larger cortical volume in children with ongoing bullying victimization

Our finding of abnormalities in the right fusiform gyrus is comparable to a study that identified thicker cortex in the fusiform among children of a similar age range to our cohort (Muetzel et al., 2019). However, in this brain region, while the prior study found thicker cortex, we found normal cortical thickness, but relatively larger right cortical volume and surface area, in the bullied children. It was hypothesized that due to the role of the fusiform in facial and emotion processing, the bullied victims may be more perceptive to the faces of their bullies and would react more to fearful or threatening faces (Muetzel et al., 2019). Although the fusiform gyrus did not mediate the effect of bullying on reading scores in our study, it is possible that the role of the fusiform gyrus in verbal fluency (Abrahams et al., 2003) may be indirectly influencing this relationship.

Smaller volume of the entorhinal cortex was associated with episodic memory impairments in geriatric depression (Bell-McGinty et al., 2002), as well as altered functional activity of the medial frontal cortex during the recognition portion of an episodic memory task in mild cognitive impairment patients, which was thought to contribute to their lower scores (Y. Wang et al., 2019). Therefore, the larger entorhinal volume in our bullied children should have led to relatively higher episodic memory scores, but we saw no group differences. One explanation for this finding is that the larger entorhinal volume is a compensatory response to normalize the episodic memory following bullying, allowing the bullied children to perform at the same level as non-bullied children.

Our finding of enlarged left superior parietal volumes in bullied children is similar to an earlier study that showed enlarged right superior parietal volumes in adolescents with major depressive disorder and a history of trauma (Pan and Thomas, 2016). Another study found altered superior parietal activation during a social inclusion task relative to the social exclusion task in bullied adolescents (Kiefer et al., 2021). Since the superior parietal lobule plays an important role in attention and visuospatial function (Maurizio et al., 1995), together with prior studies, our findings suggest that the superior parietal lobule may be affected by the stress or trauma of bullying victimization, which might lead to slower information processing. However, cortical volume of the superior parietal lobule did not mediate the effect of bullying on processing speed.

4.4. Larger cortical surface area in children with ongoing bullying victimization

We identified larger surface areas in the bilateral superior parietal lobule and pars orbitalis; left entorhinal and paracentral; and right fusiform and rostral middle frontal in bullied children compared to non-bullied children. Because surface area is more closely related to cortical volume than cortical thickness (Winkler et al., 2010), larger surface areas in the left superior parietal, left entorhinal, and right fusiform regions among bullied children, at least in part, are likely contributing to their greater cortical volumes.

Our mediation findings in the fusiform gyrus may follow a suppression effect (MacKinnon, Krull, and Lockwood, 2000), since the total effect calculated was larger than the direct effect of bullying on cognition. A suppression effect in this context indicates that the changes in the fusiform gyrus likely help explain the relationship between bullying and lower cognitive score as being attributed to the non-neural impact of bullying. This also indicates a weakening of the relationship between bullying and the fusiform gyrus. The larger fusiform surface area, which is linked to visual processing (Dickerson and Eichenbaum, 2010), may mitigate a negative relationship between bullying, crystallized composite, and episodic memory cognitive scores, which may explain why bullying was not associated with lower cognitive scores in these domains. Since the rostral middle frontal region is involved in working memory (Michalski, 2016), which is essential for reading comprehension (Nouwens et al., 2017), we had expected that the larger surface area in this region might mediate the association between bullying and reading. However, this region did not show a mediation or suppression effect. Furthermore, since the pars orbitalis is involved in language processing (Belyk et al., 2017), the abnormal enlargement of this brain region may explain why bullied children performed worse on the reading task. Also, our finding that bullied children had larger surface areas in the pars orbitalis at Y3, but not at Y1, may suggest differential growth trajectories between the bullied and non-bullied groups, which can only be evaluated through further follow-up scans. The paracentral region showed relatively greater connectivity in the sensorimotor network under prolonged stress conditions (Soares et al., 2013), hence, it's increased surface area in bullied children may reflect the prolonged stress of ongoing bullying.

4.5. Thinner cortices in children with ongoing bullying

Cortical thickness is positively associated with intelligence across the lifespan (Menary et al., 2013). Therefore, our findings of relatively thinner cortices in the left hemisphere, left precentral gyrus, left banks of STS, left middle temporal, and right rostral middle frontal regions of bullied children implicate a potential association between bullying victimization and lower intelligence. However, another study found that

greater intelligence was associated with a thinner cortex at ten years, followed by a greater rate of thinning (Schnack et al., 2015). Whether these bullied children with relatively thinner cortices will develop lower or greater intelligence remains to be determined with future longer follow-up studies within the ABCD Study.

Thinner cortices in the precentral gyrus, a region involved in voluntary motor movement (Banker and Tadi, 2021), mediated the relationship between bullying and inhibitory control and attention scores, likely because this task's scores are dependent on motor response times. Additionally, since the middle temporal gyrus is involved in semantic memory processing (Xu et al., 2015) and object recognition (Chao et al., 1999), while the banks of STS is implicated in overall cognition (Deen et al., 2015), and the rostral middle frontal gyrus is involved in executive function and working memory (Michalski, 2016), we expected that the thinner cortices in these regions of the bullied children might also mediate the poorer performance on these cognitive tasks. However, we did not find such mediation effects. Our finding of a greater decrease of the right lateral occipital cortical thickness in non-bullied group may be negatively related to cognition, similar to how lateral occipital cortical thickness negatively impacted cognition in a study of adults with Huntington's disease (Johnson et al., 2015).

4.6. Sex differences in cognitive and brain measures

Similar to previous findings, girls performed better on processing speed (Daseking and Franz Petermann, 2017) and episodic memory tasks (Herlitz, Nilsson, and Bäckman, 1997) than boys, although these effect sizes were small. Assessment for bullying-by-sex interaction showed that girls tended to outperform boys on episodic memory only in the non-bullied group. This lack of sex effect in the bullied group may be due to higher perceived stress from being bullied among females (Graves et al., 2021), which can impair learning and memory (Vogel and Schwabe, 2016).

All our findings related to sex differences in the bullying-affected brain regions are consistent with earlier studies. Specifically, the lack of sex differences in hippocampal volume is similar to earlier reports that included correction for intracranial volumes (Yagi and Liisa, 2019). Additionally, our findings of larger left cortical volumes, smaller surface areas, and thicker cortices in girls compared to boys over two years is consistent with prior studies of healthy children or adults (Ritchie et al., 2018; Lotze et al., 2019; Y. Wang et al., 2019; Frederikse et al., 1999; Sowell et al., 2007).

4.7. Magnitude of bullying effects

For analyses with a main effect of bullying status, effect sizes were small to medium for cognition, cortical volume, and cortical thickness, medium for right hippocampal volume, and small to large for cortical surface area. For mediation analyses on surface area and cortical thickness, the total effects calculated were small. However, all results were meaningful (Sullivan and Feinn, 2012) and allude to the importance of bullying prevention among preadolescent youth.

4.8. Limitations

One limitation of the current study is that caregivers only answered one question whether the child was bullied at baseline. However, several studies within (Menken et al., 2022) and outside of (Pervanidou et al., 2019) the ABCD Study also used one bullying variable with a "yes/no" answer for their analyses. Additionally, the data archive did not release the youth's self-report of being bullied at the baseline visit. Because of the limited information regarding bullying at this study timepoint, we are likely missing several factors that might affect our findings. Specifically, we could not evaluate the relationships between the frequency/intensity of bullying and cognitive or neural factors. Future studies will expand this longitudinal analysis to include additional years of follow-up with data on the frequency/intensity of victimization, reported by the caregiver and youth. While the matching procedure that we used has the benefit of reducing unrelated variability or confounding factors, it is important to note that this procedure might limit the generalizability of our findings to a larger population. Maternal psychopathology may also be a confounding factor for cognitive (Paquin et al., 2020; Schechter et al., 2017) and neurological findings (Adamson, Letourneau, and Lebel, 2018; Niehaus et al., 2019). Because over 15% of the caregivers in the ABCD study were not the biological mother, this potential confounding variable was not evaluated.

5. Conclusions

Our novel findings support our hypotheses of delayed brain morphometric and cognitive developmental trajectories in bullied children, and that changes in "bullying-impacted" brain regions may mediate the relationships between bullying and cognition. Further research is needed to determine whether these alterations remain over a longer period during adolescence, and how the frequency and intensity of bullying might impact the neurodevelopmental trajectories. Due to the critical roles of these brain regions in emotional processing and regulation, early intervention may be critical to prevent negative psychiatric outcomes.

Additional contributions

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These funding sources were involved in the overall study design of the ABCD Study.

CRediT authorship contribution statement

Ms. Menken takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the dataset used in the current study.

Miriam Menken: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Pedro Rodriguez Rivera:** Formal analysis, Investigation, Writing – review & editing. **Amal Isaiah:** Conceptualization, Methodology, Writing – review & editing,

Supervision. **Thomas Ernst:** Conceptualization, Writing – review & editing, Supervision, Funding Acquisition. **Christine Cloak:** Conceptualization, Investigation, Writing – review & editing. **Linda Chang:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data from the ABCD Study Data Release 3.0 is available for access through the NIMH Data Archive (https://dx.doi.org/10.15154/1520591). Only researchers with an approved NDA Data Use Certification (DUC) can obtain ABCD Study data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101247.

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