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ORIGINAL ARTICLE

Associations Between Preterm Birth, Inhibitory Control-Implicated Brain Regions and Tracts, and Inhibitory Control Task Performance in Children: Consideration of Socioeconomic Context

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Abstract
Preterm birth (PTB) is associated with increased risk for unfavorable outcomes such as deficits in attentional control and related brain structure alterations. Crucially, PTB is more likely to occur within the context of poverty. The current study examined associations between PTB and inhibitory control (IC) implicated brain regions/tracts and task performance, as well as the moderating role of early life poverty on the relation between PTB and IC-implicated regions/tracts/task performance. 2,899 children from the ABCD study were sampled for this study. Mixed effects models examined the relation between PTB and subsequent IC performance as well as prefrontal gray matter volume, white matter fractional anisotropy (FA), and mean diffusivity (MD). Household income was examined as a moderator. PTB was significantly associated with less improvement in IC task performance over time and decreased FA in left uncinate fasciculus (UF) and cingulum bundle (CB). Early life poverty moderated the relation between PTB and both CB FA and UF MD.

Keywords Preterm birth · Inhibitory control · Neuroimaging · Early life poverty

In the United States, approximately one in 10 infants is born preterm (Centers for Disease Control and Prevention [CDC], 2021). The relationship between prematurity and unfavorable outcomes has been well established. Preterm birth (PTB) is associated with a host of short term complications such as underdeveloped immune systems, brain injuries, respiratory issues, and infant mortality [49, 60, 68]. Perhaps more worryingly, PTB has been found to confer increased risk for many long term issues such as developmental delays, asthma, and psychological/behavioral problems, including challenges to brain development and cognitive functions such as attentional control [1, 28, 45, 59, 63]. PTB is more common among low SES mothers, and low SES is also associated with many of the neural and cognitive outcomes associated with PTB [5, 51, 71]. However, relatively little research has examined whether SES influences the relationship of PTB to either brain or cognitive outcomes. Thus, the goal of the current work was to examine the relationship between PTB and the behavioral and neural indicators of attentional control, as well as whether SES influences the strength of the relationship between PTB and brain or cognitive outcomes.

Johnson and Marlow [38] have proposed a "preterm phenotype" that consists of three symptom clusters typically found among individuals who were born preterm. These symptom clusters are: (1) inattention symptoms and reduced performance on attention and inhibitory control (IC) tasks, characteristic of ADHD, (2) internalizing symptoms characteristic of anxiety disorders, and (3) social withdrawal/communication problems characteristic of autism spectrum disorder (ASD). These clusters were found when comparing individuals who were full term and very preterm (VPT; 28–32 weeks gestation). The results of a follow-up study

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suggested that this phenotype emerged for individuals born late preterm (LPT; 34–37 weeks gestation) as well, although the associated symptoms did not meet a clinical threshold in LPT youth in the same way as in VPT youth [37]. It is important to note, however, that even subclinical symptomology characterized by inattention, internalizing, and social withdrawal can confer notable functional deficits [37]. Further, several studies have shown that PTB adolescents performed significantly worse than full term adolescents across a number of cognitive domains, including math, reading, and spelling [38, 47, 64].

One of the ways in which PTB may lead to the preterm behavioral phenotype is through disruption in brain development. As described above, the first cluster of symptoms in Johnson and Marlow's [38] preterm phenotype is characterized by inattention and subsequent poorer performance on attention tasks. For example, de Kieviet et al. [17] found that children born preterm performed significantly worse on visuospatial working memory tasks and were also rated as having more inattention problems by teachers and parents. Inattention problems have been linked to deficits in executive function processes like working memory, cognitive flexibility, and inhibitory control. These executive function processes are thought to be primarily supported by brain regions in the prefrontal cortex [22, 23], 73]. The literature has supported this with findings of alterations in these regions in individuals born preterm. For instance, infants and children born preterm were found to have reduced prefrontal and hippocampal volumes when compared to controls [15]. Additionally, white matter tracts between these regions have been shown to demonstrate increased mean diffusivity and reduced relative anisotropy in children born preterm, potentially indicating either reduced white matter maturity or white matter injury [7, 14, 15]. For example, Constable et al. [14] found that individuals born preterm exhibited reduced fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF). Additional research has demonstrated that these alterations persist into adolescence among PTB youth [6, 14]. Researchers have hypothesized that these structural differences could be reflective of an altered course of neurodevelopment that is potentially caused by birth before the brain has fully developed in utero [50].

The occurrence of preterm birth has been demonstrated to be more likely in lower SES households [19, 46, 66, 72]. DeFranco et al. [19] found that the rate of preterm birth in more impoverished areas was 4.9%, in comparison to a 2.8% rate in less impoverished areas, with an overall odds ratio of 1.18. There are several hypothesized mechanisms to explain poverty's association with preterm birth. Less access to and ability to afford medical services, nutritional supplements, and general prenatal care are some proposed reasons for increased rates of preterm birth among lower SES households [19, 69]. Individuals who live in impoverished areas are also more likely to be exposed to toxins in their environments (lead, poor air quality, ground water contamination, etc.), which has been associated with increased risk for preterm birth [41, 61, 62, 65]. Finally, previous studies suggest that stressful home environments, characterized by overcrowding, excessive noise, and inconsistent sources of social support are associated with preterm birth [9, 56]. More recently, poverty has been theorized to exert chronic stress on pregnant women via the aforementioned mechanisms, and this chronic activation of the stress response has also been associated with preterm birth [9, 43].

In addition to greater risk of preterm birth, increased poverty is associated with lower academic achievement and performance across cognitive domains and disruptions in brain regions thought to be important for IC, such as the dorsal lateral prefrontal cortex (dlPFC), ventral lateral prefrontal cortex (vlPFC), motor cortex, and dorsal anterior cingulate cortex (dACC) [11, 67]. Working together, these regions allow for the successful inhibition of predominant, or prepotent, behaviors. Research has also suggested that the right hemisphere of the brain is more heavily implicated in inhibitory control (IC) [13, 24]. Notably, these brain regions, as well as their connective tracts, are strongly overlapped with regions that have demonstrated alterations in preterm birth. Altered white matter connectivity between prefrontal and subcortical regions has been shown to be implicated in executive function processes such as IC [29, 40, 58]. For example, Noble et al. [58] found that white matter FA in the cingulum bundle (CB) and SLF mediated the relationship between years of education and performance on an IC task. It is important to note that while these brain regions and their connective tracts have been implicated in IC, they are crucial for a plethora of other executive control and broader cognitive processes, and therefore their functions are not specific to IC.

As aforementioned, the prefrontal cortex undergoes a protracted course of development in comparison to other brain regions, with full maturation not occurring until after adolescence [26]. Many researchers have theorized that this delayed maturation causes the prefrontal cortex to be particularly vulnerable to environmental influence [12]. The negative association between early life poverty and prefrontal brain regions is well documented in the literature, with reduced gray matter volume and reduced cortical surface area being a common neuroanatomical finding [21, 32, 53, 57].

Together the literature reviewed above suggests that individuals living in more impoverished environments are not only more likely to be born preterm, but they are also more likely to experience conditions postnatally associated with poorer cognitive performance and altered brain development. Further, research has suggested that children born

preterm may be particularly vulnerable to the environment compared to children born full term [52]. In a review of the literature, Wong and Edwards [71] demonstrated that SES was a consistent confounding variable in studies relating preterm birth to cognition. Further, SES may also be a moderator of the relationship between preterm birth and subsequent outcomes. Beauregard et al. [5] found that kindergarten children who were born preterm in more impoverished environments performed significantly worse on cognitive tasks compared to children who were born preterm in less impoverished environments. These studies highlight the importance of considering how poverty is differentially impacting the development of preterm individuals in lower versus higher SES settings.

The current study aims to focus on the first cluster of PTB symptoms, which centers on inattention and IC, and to specifically test hypotheses about the mechanisms underlying this altered trajectory by investigating differences in IC-implicated brain regions and tracts among children reported to have been born preterm by parents. Further, the study will examine whether SES moderates the relationship between preterm birth and IC-implicated brain regions and performance. The Adolescent Brain Cognitive Development study (ABCD) is a large, multisite, longitudinal study which aims to better conceptualize the period of development from adolescence into adulthood with multiple time points assessing cognitive function and brain structure and connectivity. The dataset includes data from a questionnaire that asks parents about preterm birth. We predicted that (1) PTB would be associated with lower volume, reduced FA, and increased MD in IC-implicated regions of interest (ROIs) (dlPFC, vlPFC, and dACC) and WM tracts (UF, CB, and SLF) at baseline as well as poorer IC task performance at a follow-up one year later. We further predicted that the strength of the relation between PTB, ROI volume, WM tract FA and MD, and task performance would be stronger in children with low vs. high household income. Finally, we predicted that ROI volume and WM tract FA and MD would explain the hypothesized relationship between PTB and IC task performance (consistent with mediation).

Methods

Participants

The sample for this study consisted of Time 1 (ABCD Baseline) and Time 2 (ABCD Year 1) data from 2,899 children (48% female; see below for explanation of sample selection) recruited as part of the ABCD Study. Data from ABCD Release 3.0 were used for the current study. Race and ethnicity were highly confounded with household income in the participant sample, as they are in the US population, reflecting ongoing structural and explicit racism effects. For this reason, we opted to not include race and ethnicity as covariates in the main analyses, though we included results which included race/ethnicity as covariates in supplemental materials. See Table 1 for reporting of sex and race/ethnicity percentages in the current sample. Informed written consent for child and parent was obtained from parent participants by a trained research assistant. Child participants separately completed a written assent with the aid of a trained research assistant. This work was reviewed and approved by the Washington University Human Subjects Committee.

Table 1 Demographic information

Race	# in sample	Approx. % in sample
White/Caucasian American	1686	58
Black/African American	420	14
Asian	38	1
Other	294	10
Ethnicity		
Hispanic/Latinx	458	16
Sex		
Female	1404	48
Male	1495	52

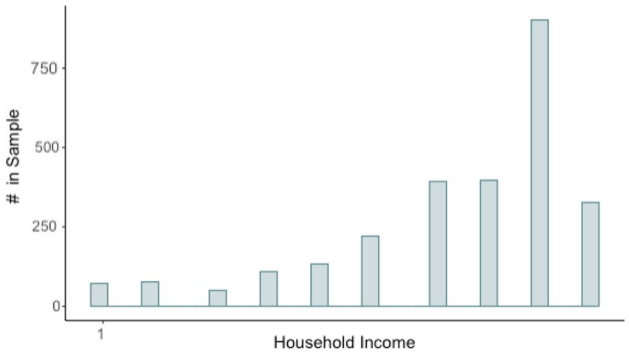

Fig. 1 Distribution of Household Income in the Current Sample

Measures

Household Income

Household income (*Mdn* = 8/$75–90,000) was the parent-reported combined income of the primary caretaker and any additional household members. This measure was assessed in categories that ranged from 1 (less than $5,000) to 10 ($200,000 and greater). See Fig. 1 for distribution of household income.

Flanker Inhibitory Control Task

The Flanker Inhibitory Control task comes from the NIH Toolbox Cognitive Battery (NIHTB-CB). This task measures interference control, or the ability to not engage in a dominant response when presented with distracting stimuli. The NIHTB-CB is composed of tasks assessing different cognitive domains, and the Flanker Inhibitory Control task is an index of attention and executive function. Scores at Time 2 were included as model outcomes and scores at Time 1 were included as model predictors to allow for estimation of change over time. Scores used in the current study were age-corrected and then z-scored.

Additional Covariates

Child sex and age were collected using parent-report questionnaires. Maternal illness, maternal medication use, maternal illicit drug use during pregnancy, birth-related complications, days spent in incubator, and twin status were collected from the parent-report Developmental History Questionnaire. More detailed information about specific question format and frequency of endorsement across groups can be found in Supplemental Materials ("*Description of Maternal and Birth-Related Covariates*" and eTable 3).

Preterm Birth

The parent-reported Developmental History Questionnaire was used to determine categories for preterm birth in the current sample. Parents were asked if the child participant was born prematurely, and, if endorsed, the parent indicated how many weeks preterm the child was at birth. The number of weeks preterm was used to sort participants into preterm gestational age categories based on guidelines from Barfield [3]: late preterm (LPT) = 33–36 weeks gestational age (n = 1262), very preterm (VPT) = 28–32 weeks gestational age (n = 297), and extremely preterm (EPT) = < 28 weeks gestational age. Children born EPT were excluded from the current analysis as the group was determined to be too small to use for comparisons. A full term (FT) group (children whose parents did not endorse premature birth, n = 1340) was created by matching to LPT by age, sex, site, and propensity score. The propensity score variable allows for equitable matching across groups on the basis of household income, family size and type, and census region where possible [33]. We opted to match by LPT rather than by VPT, due to VPT's smaller group size. See Fig. 2 for distribution of gestational age within the preterm groups.

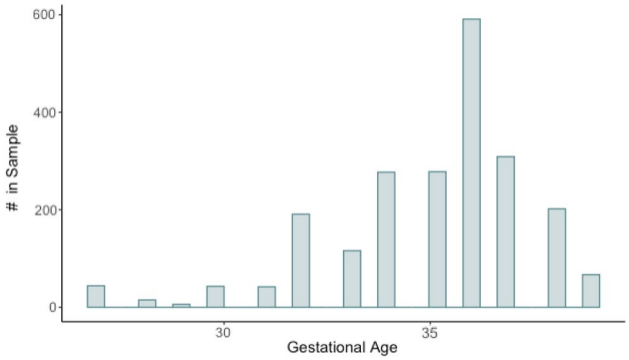

Fig. 2 Distribution of Gestational Age (Weeks) in the Current Sample (Preterm Only)

Imaging Procedure and Segmentation

Participants were scanned using similar sequences on either a 3 T Siemens, Phillips, or General Electric scanner with a 32-channel head coil. A 3D T1-weighted image (1 mm voxel resolution) was acquired as participants viewed a child-appropriate movie of their choice. Real-time motion detection and correction software was utilized at Siemens and GE sites. Diffusion weighted images (1.7 mm isotropic) were acquired using multiband EPI in 96 directions. See Hagler et al. [31] for more details about acquisition and processing of ABCD imaging data.

The a priori cortical regions of interest for volumetric analysis were the dlPFC and vlPFC (atlas labels: G_front_inf-Opercular, G_front_inf-Orbital, G_front_inf-triangul). FreeSurfer v5.3.0 was used for cortical surface reconstruction using the Destrieux [20] atlas. Participant T1s that were rated as having a score of 1 (unusable) were not included in the analysis dataset.

White matter tracts were labelled using *AtlasTrack* [30], which is a probabilistic automatic segmentation software. *AtlasTrack* identifies fiber tracts using a manual map created using DTI Studio. This atlas was created using healthy controls and epilepsy patients and estimates individual fiber tracts using prior probabilities and orientations. There are 23 total fiber tracts included in the atlas. For additional details about Atlas Track and how it was applied to the ABCD study data, see Hagler et al. [31] The a priori white matter tracts selected for the current study were the UF, CB, and SLF. These tracts were selected because they are major tracts which connect executive prefrontal regions to subcortical areas and both FA and MD were examined. White matter segmentation was visually assessed by trained technicians and then assigned a value of either 1(recommended for use) or 0 (recommended for exclusion). Participants with a score of 1 were used for this analysis. Exploratory analyses included all of the additional white matter tracts provided by the *AtlasTrack* segmentation.

Statistical Analysis

Preterm Birth Predicting Inhibitory Control Performance

Mixed effects models were computed using the lmer() function within the lme4 package [4] in R with models nesting participants within families. We first examined whether the PTB factor was associated with Flanker scores at Time 1, and then determined whether PTB predicted change in Flanker scores at Time 2, using Time 1 Flanker scores as a covariate to assess change. We conducted each of these analyses with a series of three models that added increasing covariates to examine the role of potential confounds. Model 1 included PTB as the main predictor, base covariates (household income, sex, and age) and maternal-related covariates (maternal illness, illicit drug use, and prescription drug use). Model 2 added birth-related covariates: complications, number of days spent in an incubator, and twin status. Finally, Model 3 added household income as a moderator of the preterm birth factor. See supplemental materials for more information about covariates included in the models.

Preterm Birth to Brain Volume Predicting White Matter Tract Fractional Anisotropy

A priori brain regions (right and left dlPFC and right and left vlPFC) and white matter tracts (UF, CB, SLF) at Time 1 were included in models as individual outcomes. Model 1 included PTB as the main predictor, base covariates (household income, sex, age, and intracranial volume for brain volume outcomes), and maternal related covariates (maternal illness, illicit drug use, and prescription drug use). Models were nested by family. Model 2 added birth-related covariates: birth complications, number of days spent in an incubator, and twin status. Finally, Model 3 added household income as a moderator of PTB.

Brain Volume and White Matter Tract Integrity Predicting Inhibitory Control

To determine the relationship between brain region volume/white matter tract integrity and IC performance, an additional model (Model 4) included significant brain region and white matter tracts with the most conservative set of covariates used in Model 3, with Flanker scores at Time 2 as the outcome and Flanker scores at Time 1 as a covariate to assess change.

Brain Volume Mediating Preterm Birth Relationships to Inhibitory Control

In order to provide evidence as to the plausibility of mediation, a final model (Model 5) would include both PTB and individual statistically significant brain volume/white matter tracts, along with all covariates (including Time 1 Flanker scores) with Flanker scores at Time 2 as the outcome.

All variables (predictors, covariates, and outcomes) were standardized for ease of comparison. Estimates were chosen to optimize the restricted maximum likelihood criterion. T-tests were performed to look at each variable using the Sattherwaithe's degrees of freedom method via the lmerTest package [42]. Multiple comparisons were corrected using false discovery rate.

Results

Preterm Birth to Inhibitory Control

In Model 1 (including maternal covariates) LPT significantly predicted lower Flanker task performance at Time 1 while VPT did not. In Model 2 (including birth covariates), LPT continued to significantly predict lower Flanker task performance at Time 1. In Model 3 (including household income as a moderator of PTB), LPT continued to significantly predict lower Flanker task performance at Time 1, but there were no significant interactions of household income with PTB. See Table 2 for specific estimate, t-values, and confidence intervals.

For PTB predicting change in IC performance over time (Flanker Task Time 1 included as a covariate with Flanker Task Time 2 as the outcome), results indicated that in Model 1 (including maternal covariates), LPT significantly predicted less improvement in Flanker task performance at Time 2, while VPT did not. In Model 2 (including birth

Table 2 Preterm birth to changes in inhibitory control performance at time 1

	Std. b	b	CIs	*t*	*p*
Model 1 (Household Income [HI], sex, and age as well as maternal−related covariates)					
LPT	−0.099	−1.347	−2.522 to −0.171	−2.26	0.024
VPT	−0.138	−1.882	−3.935 to 0.143	−1.82	0.07
HI	0.126	0.764	0.575 to 1.068	5.94	<0.001
Model 2 (addition of birth−related covariates)					
LPT	−0.104	−1.413	−2.747 to −0.085	−2.08	0.038
VPT	−0.147	−2.011	−4.603 to 0.569	−1.52	0.129
HI	0.112	0.686	0.42 to 0.956	5.02	<0.001
Model 3 (addition of HI as a moderator)					
LPT	−0.102	−2.021	−6.284 to 2.237	−0.93	0.354
VPT	−0.134	−4.942	−11.607 to 1.731	−1.45	0.148
HI	0.099	0.612	0.246 to 0.982	3.26	0.001
HI * LPT	0.014	0.083	−0.454 to 0.62	0.3	0.762
HI * VPT	0.068	0.416	−0.458 to 1.286	0.93	0.352

Table 3 Preterm birth to changes in inhibitory control performance at time 2

	Std. b	b	CIs	*t*	*p*
Model 1 (Household Income [HI], sex, and age as well as maternal−related covariates)					
LPT	−0.149	−2.129	−3.63 to −0.636	−2.78	0.009
VPT	−0.129	−1.845	−4.387 to 0.684	−1.42	0.155
HI	0.079	0.506	0.169 to 0.856	2.94	0.009
Model 2 (addition of birth−related covariates)					
LPT	−0.154	−2.195	−3.815 to −0.587	−2.66	0.012
VPT	−0.101	−1.44	−4.656 to 1.77	−0.87	0.382
HI	0.075	0.483	0.133 to 0.848	2.69	0.012
Model 3 (addition of HI as a moderator)					
LPT	−0.178	−2.547	−4.236 to −0.864	−2.94	0.015
VPT	−0.118	−1.678	−4.934 to 1.571	−1.01	0.498
HI	0.046	0.292	−0.183 to 0.783	1.19	0.498
HI * LPT	0.048	0.309	−0.402 to 1.02	0.85	0.498
HI * VPT	0.056	0.361	−0.83 to 1.551	0.59	0.555

covariates), LPT continued to predict significantly less improvement in Flanker Task performance at Time 2. In Model 3 (including household income as a moderator of PTB), LPT continued to predict less improvement on Flanker Task performance at Time 2. There were no significant interactions of household income with PTB. See Table 3 for specific estimates, t-values, and confidence intervals.

Preterm Birth to Brain Volume, White Matter Tract Fractional Anisotropy, and White Matter Tract Mean Diffusivity

As shown in Table 4, in Model 1 for volume (including maternal covariates), VPT was significantly associated with lower volume in right dlPFC, as well as right and left vlPFC after FDR correction. LPT was not significantly associated with lower volume in either dlPFC or vlPFC. When birth covariates were added in Model 2, neither VPT nor LPT continued to be significantly related to any of the brain volumes. In Model 3 (including household income as a moderator of PTB), there was no evidence of household income as a significant moderator of PTB.

As shown in Table 5, in Model 1 for FA (including maternal covariates), VPT was significantly related to reduced FA in the left CB after FDR correction. LPT was significantly related to reduced FA in the left UF. In Model 2 (including birth covariates), VPT continued to be a significantly associated with lower FA in the left CB and LPT also continued to be a significantly associated with lower FA in the left UF. In Model 3 (including household income as a moderator of PTB), there was an interaction wherein the relationship between VPT and lower bilateral CB FA differed depending on household income. More specifically, the relationship between VPT and lower bilateral CB FA is particularly evident at lower levels of household income, indicating that increased poverty conferred reduced CB FA within the context of VPT (See Fig. 3).

In Model 1 for MD (including maternal covariates), neither index of PTB was significantly related to MD in any of the white matter tracts. Similarly, in Model 2 (including birth covariates), PTB was not significantly related to MD in the white matter tracts. In Model 3 (including household income as a moderator of PTB), there was a significant interaction that passed FDR correction (Table 6) wherein the relationship between VPT and higher bilateral UF differed depending on household income. So as with FA, the relationship between VPT and higher bilateral UF MD was more evident at lower levels of household income, indicating that increased poverty related to increased UF MD in the context of VPT (See Fig. 4). Of note, a similar interaction was seen for CB MD (which was significant for FA), with a similar pattern to UF, but these interactions did not pass FDR correction.

Brain Volume and White Matter Tract Integrity to Inhibitory Control

FA in the bilateral CB and left UF were the only two brain metrics that continued to be related to PTB in the most conservative models that included both maternal and birth-related covariates. However, neither CB nor left UF were related to IC at either Time 1 or Time 2. Thus, we chose not to conduct mediation analyses.

Discussion

The goal of the current study was to further investigate mechanisms underlying the often-observed delayed trajectory of attentional/inhibitory development in preterm children and to examine whether SES may moderate the relationship between PTB and cognitive performance. The results of this study demonstrated that PTB was significantly associated with lower performance on an IC task, and was further associated with less improvement on the task over time than children born full term, consistent with our hypotheses. The current study also found that PTB was associated with lower FA in the left UF and left CB, connective tracts that are both heavily implicated in IC processes. Further, a moderation was observed, wherein lower FA in bilateral CB was especially prominent among preterm individuals from lower income households. A similar moderation was found when examining the relationship between bilateral UF and MD, wherein increased MD was especially evident in preterm individuals from lower income households. However,

Table 4 Preterm birth to brain volume

	Std. b	b	CIs	*t*	*p*	Std. b	b	CIs	*t*	*p*
L dlPFC						R dlPFC				
Model 1										
LPT	−0.048	−120.3	−283.4 to 42.9	−1.44	0.149	−0.046	−114.4	−283.6 to 54.8	−1.32	0.186
VPT	−0.096	−239.6	−523.9 to 43.6	−1.65	0.149	−0.153	−376.9	−672.7 to −82.2	−2.5	0.019
HI	0.051	57.1	20.7 to 93.5	3.07	0.006	0.078	85.5	47.9 to 123.3	4.44	< 0.001
Model 2										
LPT	−0.062	−155.1	−333.4 to 23.5	−1.7	0.089	−0.053	−129.3	−313.7 to 55.5	−1.37	0.171
VPT	−0.144	−358.8	−717 to −0.2	−1.96	0.075	−0.138	−340.4	−712.2 to 31.3	−1.79	0.111
HI	0.057	63.4	25.1 to 101.8	3.23	0.003	0.082	90.1	50.5 to 129.8	4.44	< 0.001
Model 3										
LPT	−0.07	−171.7	−359.14 to 16.69	−1.79	0.074	−0.03	−71.08	−264.49 to 123.18	−0.72	0.474
VPT	−0.17	−414.1	−781.12 to −45.88	−2.20	0.028	−0.13	−312.3	−693.75 to 69.68	−1.6	0.11
HI	0.05	59.06	7.56 to 110.56	2.24	0.025	0.08	88.87	36.11 to 141.64	3.29	0.001
HI * LPT	0.03	28.17	−46.72 to 103.32	0.73	0.463	0.03	28.8	−48.38 to 106.52	0.73	0.467
HI * VPT	−0.07	−77.38	−198.85 to 44.15	−1.24	0.214	−0.05	−56.05	−181.81 to 69.74	−0.87	0.384
L vlPFC						R vlPFC				
Model 1										
LPT	−0.021	−37.7	−132.5 to 57.3	−0.78	0.437	−0.06	−97.2	−189.5 to −4.8	−2.06	0.059
VPT	−0.125	−222.2	−386.7 to −57.9	−2.64	0.018	−0.16	−266.8	−426.7 to −107.6	−3.27	0.003
HI	0.034	27.1	6.2 to 48.2	2.53	0.018	−0.01	−7.6	−28.1 to 13.1	−0.73	0.467
Model 2										
LPT	−0.08	−43.88	−147.08 to 59.95	−0.829	0.407	−0.046	−78.5	−178.9 to 22.2	−1.53	0.191
VPT	−0.07	−183.3	−390.5 to 24.33	−1.73	0.126	−0.1	−169.6	−370.9 to 31.3	−1.65	0.191
HI	0.06	19.88	−2.11 to 42.04	1.76	0.126	−0.017	−12.7	−34.2 to 8.9	−1.15	0.249
Model 3										
LPT	−0.01	−20.95	−128.89 to 88.37	−0.38	0.806	−0.04	−74.42	−331.76 to 0.43	−1.37	0.211
VPT	−0.09	−16.75	−379.5 to 45.74	−1.54	0.35	−0.1	−171.1	−429.03 to 220.15	−1.62	0.175
HI	0.03	22.16	−7.56 to 52.16	1.45	0.35	−0.04	−26.91	−48.25 to 42.94	−1.80	0.175
HI * LPT	0.01	5.46	−37.96 to 49.09	0.25	0.806	0.05	38.54	−24.98 to 107.89	1.78	0.175
HI * VPT	−0.03	−25.26	−95.74 to 45.09	−0.7	0.806	−0.04	−2.97	−103.27 to 112.89	−0.09	0.932

neither FA in the CB, left UF, nor MD in the UF related to performance on the Flanker task, contrary to our hypotheses that these brain differences would mediate the relationship of PTB to attentional/IC impairments.

The study results indicated that PTB was significantly associated with lower performance and less improvement over time on an IC task even after controlling for several relevant covariates. This finding speaks to the robustness of the relationship, and is consistent with previous literature that has demonstrated a relationship between PTB and increased deficits in attention and general executive function processes in children. Marlow et al. [48] found that children born preterm exhibited significant executive function deficits during preschool age in comparison to full term peers. A review by Burnett et al. [10] suggested that children born preterm continue to exhibit these executive function deficits into adolescent years, indicating the potential for enduring effects on developmental trajectory. The finding that there is less improvement in IC performance in children born preterm is particularly interesting as it suggests that subsequent IC performance may be hindered by relatively immature preceding IC. One possibility is that immature IC processes earlier on may reduce adaptability to formalized schooling environments, thus further dampening gains in IC. For example, Utendale & Hastings [70] found that reduced IC was associated with increased externalizing behavior in school-aged children.

It is interesting that LPT, but not VPT was related to poorer IC task performance, since we would expect that increased prematurity (i.e., VPT) would be related to more pronounced executive function deficits. Although the direction of the effect for VPT was as hypothesized, the relationship did not meet the threshold for statistical significance. It is possible that we saw effects for the LPT but not VPT group

Table 5 Preterm birth to white matter tract fractional anisotropy

	Std. b	b	Cis	*t*	*p*	Std. b	b	Cis	*t*	*P*
L Cingulum						R Cingulum				
Model 1										
LPT	−0.016	−0.001	−0.005 to 0.003	−0.39	0.696	0.033	0.002	−0.003 to 0.006	0.76	0.45
VPT	−0.204	−0.011	−0.018 to −0.003	−2.84	0.017	−0.11	−0.006	−0.013 to 0.002	−1.46	0.327
HI	−0.055	−0.001	−0.002 to −0.001	−2.72	0.017	−0.037	−0.001	−0.002 to 0.001	−1.73	0.327
Model 2										
LPT	−0.02	−0.001	−0.006 to 0.004	−0.42	0.671	0.03	−0.001	−0.003 to 0.006	0.54	0.587
VPT	−0.2	−0.011	−0.02 to −0.001	−2.21	0.04	−0.1	−0.005	−0.015 to 0.004	−1.1	0.411
HI	−0.06	−0.002	−0.003 to −0.001	−3.03	0.006	−0.04	−0.001	−0.002 to 0.001	−1.93	0.162
Model 3										
LPT	−0.01	−0.001	−0.005 to 0.004	−0.21	0.954	0.02	0.001	−0.004 to 0.006	0.48	0.632
VPT	−0.16	−0.008	−0.018 to 0.001	−1.73	0.142	−0.08	−0.004	−0.013 to 0.006	−0.79	0.62
HI	−0.087	−0.002	−0.003 to −0.001	−3.1	0.005	−0.07	−0.002	−0.003 to −0.001	−2.45	0.035
HI * LPT	0.002	0.001	−0.002 to 0.002	0.06	0.954	0.03	0.001	−0.001 to 0.003	0.68	0.62
HI * VPT	0.025	0.006	0.002 to 0.009	3.5	0.005	0.2	0.004	0.001 to 0.008	2.63	0.035
L Uncinate						R Uncinate				
Model 1										
LPT	−0.098	−0.005	−0.008 to −0.002	−3.19	0.009	−0.022	−0.001	−0.004 to 0.002	−0.76	0.601
VPT	−0.11	−0.005	−0.01 to −0.001	−1.99	0.107	−0.07	−0.003	−0.008 to 0.002	−1.34	0.601
HI	0.004	0	−0.001 to 0.001	0.23	0.818	−0.008	0.001	−0.001 to 0.002	−0.52	0.601
Model 2										
LPT	−0.09	−0.004	−0.008 to −0.001	−2.74	0.018	−0.04	−0.001	−0.005 to −0.001	−1.27	0.31
VPT	−0.04	−0.001	−0.008 to 0.004	−0.59	0.833	−0.08	−0.004	−0.01 to 0.002	−1.21	0.31
HI	0.001	0.001	−0.001 to 0.001	0.01	0.994	−0.02	−0.001	−0.001 to 0.001	−1.02	0.31
Model 3										
LPT	−0.084	−0.004	−0.007 to −0.001	−2.37	0.09	−0.038	−0.002	−0.005 to 0.001	−1.11	0.443
VPT	−0.017	−0.001	−0.007 to 0.006	−0.25	0.864	−0.061	−0.003	−0.009 to 0.003	−0.91	0.456
HI	0.004	0.001	−0.001 to 0.001	0.17	0.864	−0.01	−0.001	−0.001 to 0.001	−0.47	0.641
HI * LPT	−0.029	−0.001	−0.002 to 0.001	−0.91	0.607	−0.042	−0.001	−0.002 to 0.004	−1.35	0.44
HI * VPT	0.089	0.002	−0.001 to 0.004	1.66	0.245	0.102	0.002	0.001 to 0.004	1.97	0.245
L Superior Longitudinal Fasciculus						R Superior Longitudinal Fasciculus				
Model 1										
LPT	−0.008	−0.001	−0.002 to 0.002	−0.22	0.903	−0.003	0	−0.003 to 0.002	−0.08	0.94
VPT	−0.008	−0.001	−0.005 to 0.004	−0.12	0.903	−0.035	−0.001	−0.007 to 0.003	−0.51	0.94
HI	0.078	0.001	0.001 to 0.002	4.19	< 0.001	0.035	0.001	−0.001 to 0.001	1.82	0.621
Model 2										
LPT	−0.04	−0.001	−0.004 to 0.001	−1.02	0.31	−0.05	−0.002	−0.004 to 0.001	−1.09	0.275
VPT	−0.1	−0.003	−0.009 to 0.002	−1.19	0.31	−0.13	−0.004	−0.01 to 0.001	1.46	0.213
HI	0.07	0.001	0.001 to 0.002	3.96	0.003	0.03	0.005	−0.001 to 0.001	1.54	0.213
Model 3										
LPT	−0.026	−0.001	−0.004 to 0.002	−0.59	0.553	−0.028	−0.001	−0.004 to 0.002	−0.61	0.543
VPT	−0.079	−0.002	−0.008 to 0.003	−0.91	0.553	−0.09	−0.003	−0.009 to 0.003	−1	0.394
HI	0.099	0.001	0.001 to 0.002	3.82	0.005	0.045	−0.001	−0.001 to 0.001	1.68	0.243
HI * LPT	−0.061	−0.001	−0.002 to 0.002	−1.54	0.31	−0.057	−0.001	−0.002 to 0.003	−1.4	0.272
HI * VPT	0.04	0.001	−0.001 to 0.003	0.61	0.552	0.114	0.002	−0.001 to 0.004	1.66	0.243

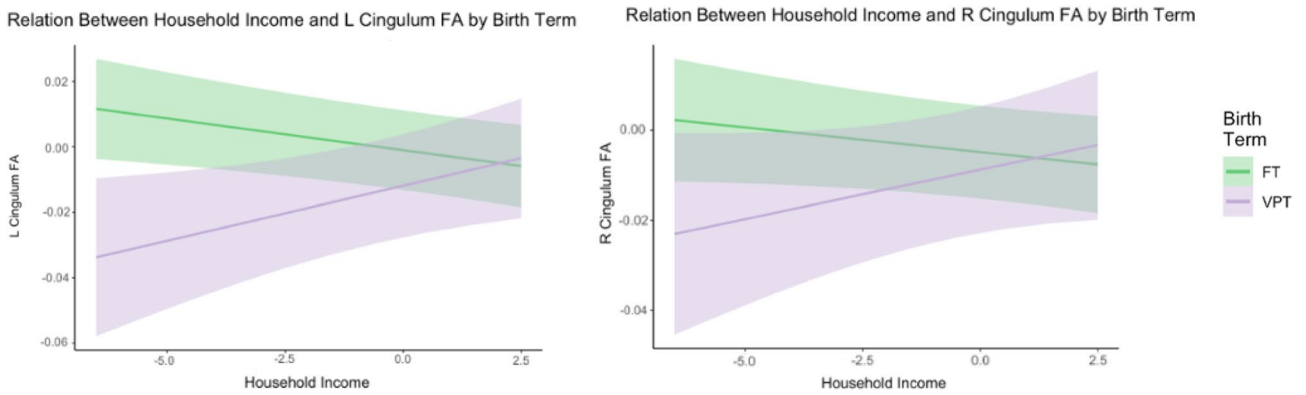

Fig. 3 Interaction of household income and cingulum FA by birth term. *FT* full term, *VPT* very preterm 95% confidence intervals

because the larger sample size of the LPT group afforded greater statistical power. Further, we did not see that SES moderated this relationship, meaning that the relationship between PTB and IC task performance was similar across the spectrum of SES. This was contrary to our hypotheses which predicted that the strength of relationship between PTB and IC task performance would depend on level of SES. However, the lack of moderation for IC does not rule out the possibility that we would see such moderation for the other components of the pre-term phenotype, such as internalizing symptoms or social withdrawal/communication challenges. In addition, while poorer IC task performance can be an indicator of inattention/attention deficits, IC does not fully capture this construct. It is possible that SES would moderate the relationship between PTB and other tasks of inattention.

PTB was associated with lower FA in the left UF and bilateral CB after controlling for relevant covariates. Interestingly, the relationship was stronger for LPT than VPT for left UF, but significant for VPT and not LPT for bilateral CB. Moderating effects of household income on PTB's relation to CB FA and UF MD were similarly demonstrated in the VPT group but not the LPT group. This could suggest that children in the ABCD sample who are born more preterm are especially vulnerable with regard to white matter structures, and particularly so when the individuals are coming from lower financially resourced environments. It is also worth noting that estimates trended in expected directions even when significance threshold was not met. The regions examined are consistently implicated in IC processes as they provide connective pathways between prefrontal and subcortical regions [7, 14, 15]. Reduced connectivity in the UF and CB has been frequently found in individuals who were born preterm [27, 44, 54]. Interestingly, none of the gray matter brain volumes were significantly related to PTB after controlling for relevant covariates. It was notable that intracranial volume (one of the covariates) accounted for a significant amount of model variance (see supplemental materials). This could mean that PTB's relationship with gray matter volume could be more global than hypothesized. However, in follow-up exploratory analyses using the current study sample, it was found that PTB was not significantly associated with intracranial volume (see supplemental materials for tables). Future work may want to investigate the relationship between PTB and more global indices of brain volume further. Additionally, there was no evidence for a mediation effect of the brain region on PTB and IC performance. This is an unexpected finding, and an explanation for it is not entirely clear. It is possible that either other brain regions that might also be involved in executive function may contribute to the relationship between PTB and poorer performance on this IC task, or that other metrics of brain function or structure (e.g., functional connectivity) might show more evidence for mediation.

This study's findings provide some preliminary evidence to support the proposed mechanism whereby immature brain structures may be contributing to increased inattention and decreased inhibition in preterm children. While there was no evidence of a mediating effect in the current study, the independent relations of PTB to IC performance and brain structure suggest that PTB may impact IC development in terms of both behavioral performance and IC-implicated brain structures. As aforementioned, the lack of association between brain and behavioral indices of IC was not as hypothesized, but it is worth nothing that this lack of coherence between modalities is often observed within the cognitive development research literature [18, 35].

The current study has several strengths. The hierarchical model approach used allowed for systematic and stringent control of relevant covariates which increases confidence in the robustness of the study findings. The study used two timepoints of data which allowed researchers to provide preliminary evidence for a causal pathway. The current study findings are consistent with findings of prior longitudinal

Table 6 Preterm birth to white matter tract mean diffusivity

	Std. b	b	CIs	*t*	*p*	Std. b	b	CIs	*t*	*p*
L Cingulum						R Cingulum				
Model 1										
LPT	0.036	~0	−0.002 to 0.002	0.25	0.799	−0.001	~0	−0.002 to 0.002	−0.29	0.969
VPT	0.084	0.002	−0.002 to 0.005	1.25	0.318	0.028	~0	−0.003 to 0.004	0.11	0.969
HI	0.029	~0	−0.001 to 0.001	1.6	0.318	0.005	~0	−0.001 to 0.001	0.12	0.969
Model 2										
LPT	0.012	~0	−0.002 to 0.002	0.29	0.777	−0.009	~0	−0.002 to 0.002	−0.22	0.851
VPT	0.102	0.003	−0.002 to 0.007	1.21	0.339	−0.016	~0	−0.004 to 0.004	−0.19	0.851
HI	0.039	~0	−0.001 to 0.001	1.94	0.159	0.013	~0	−0.001 to 0.001	0.62	0.851
Model 3										
LPT	−0.004	~0	−0.002 to 0.002	−0.1	0.92	−0.004	~0	−0.002 to 0.002	−0.1	0.922
VPT	0.058	0.001	−0.003 to 0.006	0.67	0.631	−0.047	−0.001	−0.006 to 0.003	−0.54	0.74
HI	0.06	0.001	0 to 0.001	2.3	0.078	0.041	~0	−0.001 to 0.001	1.54	0.308
HI * LPT	−0.03	~0	−0.001 to 0.001	−0.76	0.631	−0.038	~0	−0.001 to 0	−0.95	0.57
HI * VPT	−0.141	−0.002	−0.003 to −0.001	−2.16	0.078	−0.161	−0.002	−0.003 to −0.001	−2.42	0.08
L Uncinate						R Uncinate				
Model 1										
LPT	0.006	~0	−0.002 to 0.002	0.17	0.865	0.029	~0	−0.002 to 0.002	0.7	0.706
VPT	0.042	0.001	−0.001 to 0.004	0.63	0.797	0.027	~0	−0.003 to 0.004	0.38	0.706
HI	0.019	~0	−0.002 to 0.006	1.02	0.797	0.032	~0	−0.001 to 0.001	1.56	0.357
Model 2										
LPT	0.006	~0	−0.002 to 0.002	0.14	0.886	0.038	~0	−0.001 to 0.002	0.85	0.596
VPT	0.071	−0.002	−0.002 to 0.006	0.83	0.648	0.049	0.001	−0.003 to 0.005	0.53	0.599
HI	0.016	~0	−0.001 to 0.001	0.79	0.648	0.036	~0	−0.001 to 0.001	1.64	0.303
Model 3										
LPT	0.006	~0	−0.002 to 0.002	0.12	0.901	0.037	0.001	−0.001 to 0.003	0.78	0.875
VPT	0.029	0.001	−0.004 to 0.005	0.32	0.901	0.005	~0	−0.004 to 0.004	0.05	0.959
HI	0.034	~0	−0.001 to 0.001	1.29	0.495	0.035	0.001	0 to 0.001	2.09	0.093
HI * LPT	−0.005	~0	−0.001 to 0.001	−0.14	0.901	−0.017	~0	−0.001 to 0.001	−0.39	0.875
HI * VPT	−0.189	−0.002	−0.004 to −0.001	−2.84	0.025	−0.206	−0.002	−0.003 to −0.001	−2.87	0.02
L Superior Longitudinal Fasciculus						R Superior Longitudinal Fasciculus				
Model 1										
LPT	−0.008	~0	−0.001 to 0.001	−0.19	0.853	0.001	~0	−0.002 to 0.002	0.03	0.978
VPT	−0.028	~0	−0.003 to 0.002	−0.37	0.853	−0.022	~0	−0.003 to 0.003	−0.27	0.978
HI	−0.014	~0	−0.001 to 0.002	−0.64	0.853	0.007	~0	−0.001 to 0.001	0.31	0.978
Model 2										
LPT	0.002	~0	−0.002 to 0.002	0.04	0.968	0.021	~0	−0.001 to 0.002	0.44	0.691
VPT	0.038	~0	−0.003 to 0.004	0.38	0.968	0.067	0.001	−0.002 to 0.005	0.67	0.691
HI	−0.016	~0	−0.001 to 0.001	−0.67	0.968	0.009	~0	−0.001 to 0.001	0.4	0.691
Model 3										
LPT	~0	~0	−0.002 to 0.002	−0.01	0.995	0.011	~0	−0.002 to 0.002	0.22	0.95
VPT	0.008	~0	−0.004 to 0.004	0.08	0.995	0.037	0.001	−0.003 to 0.004	0.35	0.95
HI	−0.022	~0	−0.001 to 0.001	−0.72	0.79	−0.002	~0	−0.001 to 0.001	−0.06	0.95
HI * LPT	0.04	~0	0 to 0.001	0.87	0.79	0.045	~0	0 to 0.001	0.97	0.853
HI * VPT	−0.103	−0.001	−0.002 to 0	−1.33	0.79	−0.074	~0	−0.002 to 0.001	−0.95	0.853

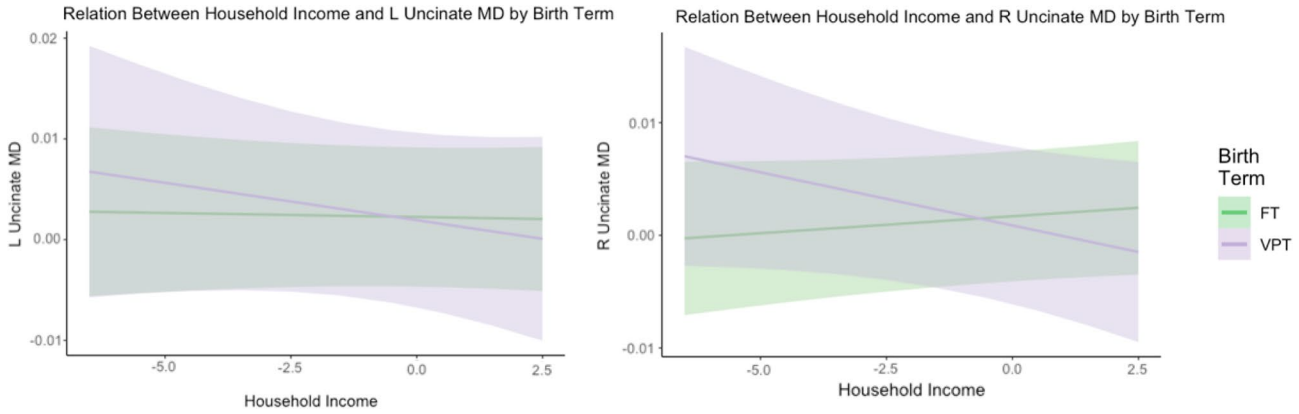

Fig. 4 Interaction of household income and uncinate MD by birth term. FT full term, VPT very preterm 95% confidence intervals

studies that have examined the relation between preterm birth and subsequent cognitive/academic performance [2, 8, 34]. Finally, the study used a large sample that was broadly representative of the population of the U.S., increasing the likelihood that the study findings are generalizable.

The current study also has several limitations. The data regarding PTB and pregnancy rely on parent retrospective report. Thus, it is possible that some of the information that parents provided is not completely precise. Future research should aim to gather medical and birth records when possible, to corroborate parent reports. Second, although the data was collected across multiple timepoints, a stronger cause for causation could be made with more timepoints. Future studies should aim to repeat measures across at least three timepoints to make a more definitive case for causality. Third, it is possible that the inclusion criteria for the study excluded LPT or VPT children who had more evidence for brain or cognitive disruptions, since frank brain trauma, autism spectrum disorders severe enough to preclude participation in standard schooling, and other neurological disorders were exclusion criteria for the ABCD study.

It is also worth noting that the current study did not explicitly explore whether there were associations between PTB and other cognitive processes (e.g., working memory, processing speed, long term memory encoding). Several studies have demonstrated working memory deficits in individuals born preterm [16, 39, 55]. Other studies have found evidence of more global effects of PTB on cognition [36]. It is probable that the current study's findings represent a component of a broader system of implications of PTB. Post hoc exploratory analyses were conducted in order to gain preliminary insight as to whether the effects observed could be more specific to IC. These exploratory analyses examined PTB's influence on changes in performance on the pattern comparison task (an index of processing speed) and the picture vocabulary knowledge task (an index of receptive vocabulary knowledge that is correlated with general intelligence) [25]. These exploratory analyses indicated that PTB was not associated with changes in picture vocabulary knowledge, but it was associated with changes in performance on the pattern comparison task within the VPT group. The results of these supplementary analyses are suggestive of some specificity for PTB's relation to general information processing. Prior literature corroborates these findings [1, 10, 47, 48]. Further studies are needed to determine whether preterm birth is related to change in other executive function tasks over time within the ABCD sample.

Conclusion

This study has crucially demonstrated that PTB is significantly related to deficits in IC task performance, reduced FA, and increased MD in executive function-implicated brain regions. It has also demonstrated the particular vulnerability of individuals born preterm in lower SES households when it comes to IC. Although we did not find evidence that brain structure moderated the relationships of PTB to IC task performance, this work adds to the growing body of evidence linking PTB to attentional/inhibitory deficits and highlights the need to consider the socioeconomic circumstances of youth when trying to understand long-term outcomes for youth born prematurely.

Summary

Prior research has robustly demonstrated that preterm birth (PTB) is associated with increased risk for developmental delays and greater difficulty with executive function processes such as inhibitory control (IC) [1, 28, 45; 59; 63). PTB has also been demonstrated to be more common in financially impoverished contexts. This is especially concerning, because past studies have suggested that children

born preterm may be particularly vulnerable to their external environments (Montagna & Nosarti, 2016). The current study sought to further elucidate the potential influence of SES on children born preterm by first examining the relations between PTB and IC-implicated brain volumes, white matter tract integrity, and task performance within an ABCD Study participant sample. Crucially, a moderating effect of SES on the relation between PTB and IC-implicated brain volumes, white matter tract integrity, and task performance was also tested.

The sample consisted of 2,899 ABCD Study participants who were grouped into very preterm (VPT), late preterm (LPT), and full term (FT). Mixed effects models examined the relation between PTB and subsequent performance on an IC task, prefrontal gray matter volume in dorsal lateral prefrontal cortex (dlPFC) and ventral lateral prefrontal cortex (vlPFC), and white matter fractional anisotropy (FA) and mean diffusivity (MD) in uncinate fasciculus (UF), cingulum (CB), and superior longitudinal fasciculus (SLF). Household income was examined as a moderator.

The results demonstrated that LPT was significantly associated with less improvement in IC task performance over time after controlling for relevant covariates. LPT was associated with decreased FA in left UF, while VPT was associated with decreased FA in left CB. Further, results indicated that SES moderated the relation between VPT and both CB FA and UF MD. Taken together, the current study's findings underscore the relation between PTB and IC processes. Notably, the observed moderation of SES on VPT's relation to white matter integrity provides compelling evidence that preterm children within more impoverished environments are at particular risk for attenuated IC development.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10578-023-01531-y.

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Authors Contribution RL Taylor generated hypotheses, conducted the analyses, wrote the main manuscript, and prepared tables and figures. DMB provided guidance in conducting statistical analyses. CER, CDS, and DMB thoroughly reviewed initial hypotheses and written manuscript and offered suggestions for edits.

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Data availability Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development[SM] (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9–10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

Declarations

Conflict of Interest The authors have no financial, non-financial, or other conflicts of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Washington University in St. Louis (201708123).

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