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Original Paper

Sex Differences in the Association between Cortical Thickness and Children's Behavioral Inhibition

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Abstract

Aim*: To investigate sex differences in the association between cortical thickness and behavioral inhibition of 9-10 years old American children.* ***Materials and methods****: This cross-sectional investigation used data from the Adolescent Brain Cognitive Development (ABCD) study. Baseline ABCD data of 10249 American children between ages 9 and 10 were analyzed. The independent variable was cortical thickness measured by structural brain magnetic resonance imaging (sMRI). The primary outcome, behavioral inhibition, was measured based on the behavioral inhibition system (BIS), and behavioral approach system (BAS). Sex was the moderator. Age, race, ethnicity, socioeconomic status indicators, and intracranial volume were covariates.* ***Results****: In the overall sample, high cortical thickness was not associated with behavioral inhibition in children. Sex showed a statistically significant interaction with cortical thickness's effect on children's behavioral inhibition, net of all confounders. The interaction indicated a statistically stronger positive effect of high cortical thickness on male behavioral inhibition compared to female children.* ***Conclusion****: Cortical thickness is a determinant of behavioral inhibition for male but not female American children. Male but not female children show better behavioral inhabitation at higher levels of cortical thickness.*

Keywords

behavioral inhibition, children, cortical thickness, sex, MRI

1. Background

The Depue and Iacono (1989) and Gray (1990) behavioral activation/inhibition system (BIS/BAS) model integrates biological and environmental factors to explain motivated behaviors. In this view, the Behavioral Activation System (BAS) controls motivation for reward (Aluja & Blanch, 2011; Basharpoor, Molavi, Barahmand, & Mousavi, 2013; Y. Li, Xu, & Chen, 2015; Scholten, van Honk, Aleman, & Kahn, 2006). This system is sensitive to cues of reward and avoidance of punishment (Merchan-Clavellino, Alameda-Bailen, Zayas Garcia, & Guil, 2019; Schiltz et al., 2018). This system reflects reward sensitivity, fun-seeking, and desire (Aluja & Blanch, 2011). The Behavioral Inhibition System (BIS), which is mainly inhibitory and regulatory, controls impulses and withdraws behaviors. The BIS aims to inhibit actions that may generate negative emotions such as disgust, fear, and anxiety (J. A. Gray, 1990). These systems explain how cues predict behaviors such as substance use, eating, sex, and risk-taking (Domen et al., 2019; Hatzenbuehler, Wieringa, & Keyes, 2011; Schiltz et al., 2018).

At a biological level, the cerebral cortex is mainly responsible for multiple functions, including but not limited to behavioral inhibition (Shackman, McMenamin, Maxwell, Greischar, & Davidson, 2009). As such, the cerebral cortex's maturation and development would be associated with higher behavioral inhibition (Shackman et al., 2009), which is necessary for avoiding high-risk behaviors (Domen et al., 2019; Hatzenbuehler et al., 2011; Schiltz et al., 2018). High cortical thickness, an indicator of cortical development, predicts lower-risk behaviors and higher behavioral inhibition (Domen et al., 2019; Hatzenbuehler et al., 2011; Schiltz et al., 2018).

The cerebral cortex may, however, differently correlate with behavioral inhibition of males and females (Li et al., 2014). This is based on the observation that males and females may differ in behavioral correlates of neural circuits. For example, socioeconomic status (SES) indicators and parenting may have differential effects on males' and females' brain structures and functions (Wierenga et al., 2018). Although Javanbakht et al. (2016) and Kim et al. (2019) found opposite results (larger effects of household income on brain function of female than male children), most studies (Whittle et al., 2014; McDermott et al., 2019) have shown that males may be more sensitive than females to environmental inputs such as SES and parenting. Similar to the differential vulnerabilities of males and females to SES and parenting (Javanbakht et al., 2016), sex differences may exist in the impact of various proxies of brain development on behaviors such as behavioral inhibition (Li et al., 2014). However, the direction of these sex differences is not yet clear. Thus, more research is needed on the topic.

1.1 Aims

This study compared male and female 9-10 years old American children for cortical thickness effects on behavioral inhibition. While high cortical thickness was expected to be associated with smaller behavioral inhibition, this effect was more salient for females than males. In line with past research (Whittle et al., 2014; McDermott et al., 2019), males may show a higher vulnerability to environmental inputs but lower vulnerability to neural and brain structures such as cortical thickness. In line with previous research, sex-specific neural correlates of behavioral inhibition were plausible (Y. Li et al., 2014).

2. Materials and Methods

2.1 Design

This cross-sectional study was a secondary analysis of existing data. We borrowed data from the Adolescent Brain Cognitive Development (ABCD) study (Alcohol Research: Current Reviews Editorial, 2018; Casey et al., 2018; Karcher, O'Brien, Kandala, & Barch, 2019; Lisdahl et al., 2018; Luciana et al., 2018). The ABCD is a national children's brain development study with broad diversity based on race, ethnicity, sex, and SES (Alcohol Research: Current Reviews Editorial, 2018; Auchter et al., 2018).

2.2 Sample

Participants were recruited from multiple cities across various states in the US. This sample was enrolled through the US school system. The recruitment catchment area of the ABCD, which was composed of 21 participating sites, encompasses over 20% of the entire United States population of 9-10-year-old children. The ABCD applied a carefully designed sampling and recruitment process across various sites, described elsewhere (ABCD; Alcohol Research: Current Reviews Editorial, 2018; Asaad & Bjarkam, 2019; Auchter et al., 2018; Beauchaine, 2020; Buscemi et al., 2018; Casey et al., 2018; Dick et al., 2019a, 2019b, 2019c; Exuperio et al., 2019; Feldstein Ewing et al., 2018; Fine et al., 2019; J. C. Gray, Schvey, & Tanofsky-Kraff, 2019; Hoffman, Howlett, Breslin, & Dowling, 2018; Lisdahl et al., 2018; Lynch et al., 2019; Michelini et al., 2019; Werneck et al., 2018), to ensure that the sample is random and representative. Such local randomization efforts yielded a final overall ABCD sample that is a close approximation of national sociodemographic factors. These sociodemographic factors include race and ethnicity, age, sex, SES, and urbanicity. The SES target in the ABCD has two sources: 1) the American Community Survey (ACS) and 2) annual 3rd and 4th-grade school enrollment. A full description of the ABCD sample and sampling is published here (Garavan et al., 2018). The first is a large-scale survey of approximately 3.5 million households conducted annually by the US Census Bureau. The second data is maintained by the National Center for Education Statistics (NCES), affiliated with the US Department of Education. This study included 10249 non-twin 9-10 years old children who had data on income and behavioral inhibition. Children from any race or ethnicity were included.

2.3 Process

Brain Imaging. To calculate cortical thickness and intracranial volume, structural MRI (sMRI) was used. As described elsewhere (Hagler et al., 2019), brain imaging in the ABCD study is based on the following three 3 tesla (T) scanner platforms: Philips Healthcare (Philips, Andover, Massachusetts, USA), GE Healthcare (General Electrics, Waukesha, WI, USA), and Siemens Healthcare (Siemens, Erlangen, Germany).The MRI devices generated T1-weighted and T2-weighted brain images that were carefully harmonized, a detailed process explained here (Casey et al., 2018). These images were processed and corrected for gradient non-linearity distortions to reduce bias due to variation in imaging sites (Jovicich et al., 2006). The ABCD has available pre-processed structural data that are available in the data set. These measured are calculated based on T1- and T2-weighted images that adjust and maximize the relative position and orientation of mutual information across images (Wells III, Viola, Atsumi, Nakajima, & Kikinis, 1996). The ABCD has performed intensity non-uniformity correction using tissue segmentation and sparse spatial smoothing. Images have been resampled with 1-mm isotropic voxels into rigid alignment within the brain atlas. These volumetric measures were constructed using FreeSurfer software, version 5.3.0 (Harvard University). The ABCD study has also corrected topologic defects using procedures described elsewhere (Fischl, Liu, & Dale, 2001; Ségonne, Pacheco, & Fischl, 2007) Images in the ABCD study have undergone surface optimization (Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999) and nonlinear registration to a spherical surface-based atlas (Fischl et al., 1999).

2.4 Measures

Cortical thickness and intracranial volume. The variables cortical thickness and intracranial volume were both borrowed from the ABCD data release 2.0. While cortical and subcortical regions were parcellated and labeled with a surface-based atlas classification based on various brain regions of interest (ROI), we only used overall cortical thickness and overall intracranial volume.

Behavioral inhibition. Conceptualized based on Gray (1990) and Carver's model of the reinforcement sensitivity theory (RST), BIS reflects mainly inhibitory and regulatory behaviors (controls impulses and withdraws high-risk acts). The BIS aims to inhibit actions that may generate negative emotions such as disgust, fear, and anxiety. This variable was treated as a continuous measure where a higher score was indicative of higher behavior inhibition. Behavioral inhibition has shown an inverse association with high-risk behaviors such as substance use and impulsivity (Akhmetova & Slobodskaia, 2014; Anastasio et al., 2019; W. Li, Zhang, Xiao, & Nie, 2016).

Sex. Sex, 1 for males and 0 for females, was a dichotomous variable. This variable was the effect modifier.

*Ag*e. Parents reported the age of the children. This variable was a continuous variable in months.

Race. Race, a self-identified variable, was a categorical variable: Black, Asian, Other/Mixed, and White (reference group).

Ethnicity. Ethnicity was also a self-identified variable and a categorical variable: Hispanic vs. non-Hispanic (reference category).

Parental education. Parental education was asked using this item: "What is the highest grade or level of school you have completed or the highest degree you have received?" Responses ranged from 1 to 21, with one indicating the lowest and 21 indicating the highest educational attainment.

Parental marital status. The household's marital status was a dichotomous variable: married = 1 and non- married = 0.

Household income. Household income was measured using this item: "What is your total combined household income for the past 12 months? This should include income (before taxes and deductions) from all sources, wages, rent from properties, social security, disability and veteran's benefits, unemployment benefits, workman". Responses included less than $50,000; $50,000 -$100,000; and $100,000 or more.

2.5 Data Analysis

Data Exploration and Analysis Portal (DEAP), which is based on the R package, was used for our statistical analyses. To conduct our multivariable analyses, two mixed-effect regressions were performed (Table 1).

Table 1. Model Formula

Model 1

bisbas_ss_bism_sum ~ smri_thick_cort.desikan_mean + smri_vol_subcort.aseg_intracranialvolume + race.4level + sex + high.educ.bl + married.bl + age + household.income.bl + hisp

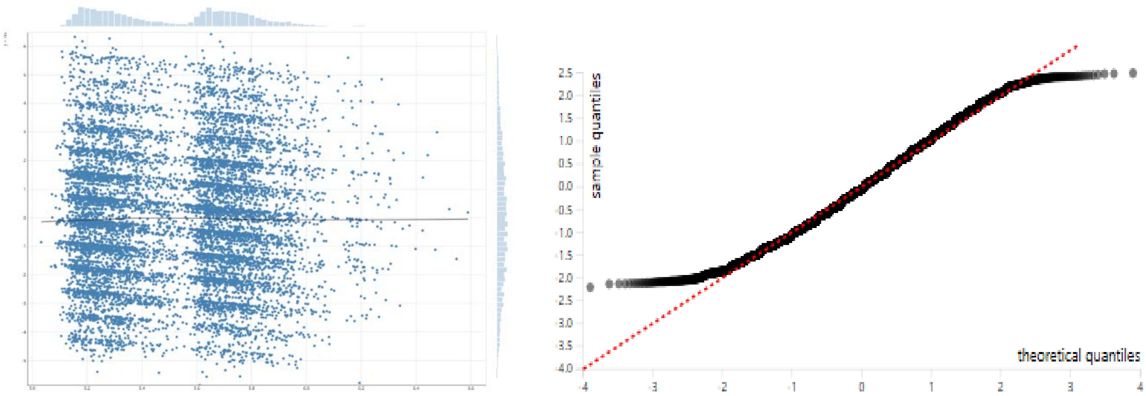
Random: ~ (1|abcd_site/rel_family_id)

Model 2

bisbas_ss_bism_sum ~ smri_thick_cort.desikan_mean + smri_vol_subcort.aseg_intracranialvolume + race.4level + sex + high.educ.bl + married.bl + age + household.income.bl + hisp + smri_thick_cort.desikan_mean * sex

Random: ~ (1|abcd_site/rel_family_id)

In our models, behavioral inhibition was the outcome. Cortical thickness was the predictor. We controlled for race, ethnicity, age, parental education, parental employment, parental marital status, and intracranial volume. Sex was the moderator. Both mixed-effects regression models were estimated in the overall/pooled sample. *Model 1*, the main effect model, was estimated in the absence of the cortical thickness by sex interaction term. *Model 2 (the interaction model)* added an interaction term between sex and cortical thickness. Both models adjusted for the nature of the data (observations were nested to families to sites). Regression coefficient (b), SE, and p-values were reported for each model. We also ruled out multi-collinearity between study variables and tested the distribution of residuals. Figure 1 shows residuals and also quantiles of observed and theorized variable (outcome).



a) Residuals of the model

b) Quantiles

Figure 1. Testing the Assumpptions of Our Regression Models

2.6 Ethical Aspect

For this study, we used a fully de-identified data set. As such, this study was exempted from a full Institutional Review Board (IRB) review. However, the main study protocol, the ABCD, was approved by the IRB at the University of California, San Diego (UCSD), and several other institutions. Participants signed consent or assent, depending on their age (Auchter et al., 2018).

3. Results

3.1 Descriptives

Table 2 depicts the summary statistics of the pooled/overall sample and also by sex. The current analysis was performed on 10249, 9-10 years old children from which 52.3% were male (n = 5358), and 47.7% were female (n = 4891). Males and females did not differ in race, ethnicity, parental education, household income, and family structure. Males had lower levels of behavioral inhibition. Males also had less cortical thickness. Males, however, had larger intracranial volume.

Table 2. Descriptive Statistics Overall and by Sex

Characteristic	Level	All	Female	Male	p
		n = 10249	n = 4891	n = 5358	
		Mean (SD)	Mean (SD)	Mean (SD)	
Child Age		118.97 (7.47)	118.80 (7.44)	119.13 (7.49)	0.024
Behavioral Inhibition		5.52 (2.83)	5.76 (2.82)	5.30 (2.82)	< 0.001
Mean Cortical Thickness (mm2)		2.77 (0.11)	2.78 (0.11)	2.77 (0.11)	< 0.001
Intracranial Volume (mm3)		1515686.80 (149269.99)	1448156.74 (127716.34)	1577330.98 (140609.34)	< 0.001
		n (%)	n (%)	n (%)	
Race	White	6824 (66.6)	3214 (65.7)	3610 (67.4)	0.296
	Black	1480 (14.4)	731 (14.9)	749 (14.0)	
	Asian	220 (2.1)	111 (2.3)	109 (2.0)	
	Other/Mixed	1725 (16.8)	835 (17.1)	890 (16.6)	
Hispanic	No	8315 (81.1)	3976 (81.3)	4339 (81.0)	0.707
	Yes	1934 (18.9)	915 (18.7)	1019 (19.0)	
Parental Education	< HS Diploma	373 (3.6)	187 (3.8)	186 (3.5)	0.626
	HS Diploma/GED	845 (8.2)	392 (8.0)	453 (8.5)	
	Some College	2633 (25.7)	1238 (25.3)	1395 (26.0)	
	Bachelor	2709 (26.4)	1290 (26.4)	1419 (26.5)	
	Post Graduate Degree	3689 (36.0)	1784 (36.5)	1905 (35.6)	
Household Income	< 50K	2939 (28.7)	1423 (29.1)	1516 (28.3)	0.641
	> =50K& < 100K	2940 (28.7)	1401 (28.6)	1539 (28.7)	
	> =100K	4370 (42.6)	2067 (42.3)	2303 (43.0)	
Married Family	No	3113 (30.4)	1523 (31.1)	1590 (29.7)	0.112
	Yes	7136 (69.6)	3368 (68.9)	3768 (70.3)	

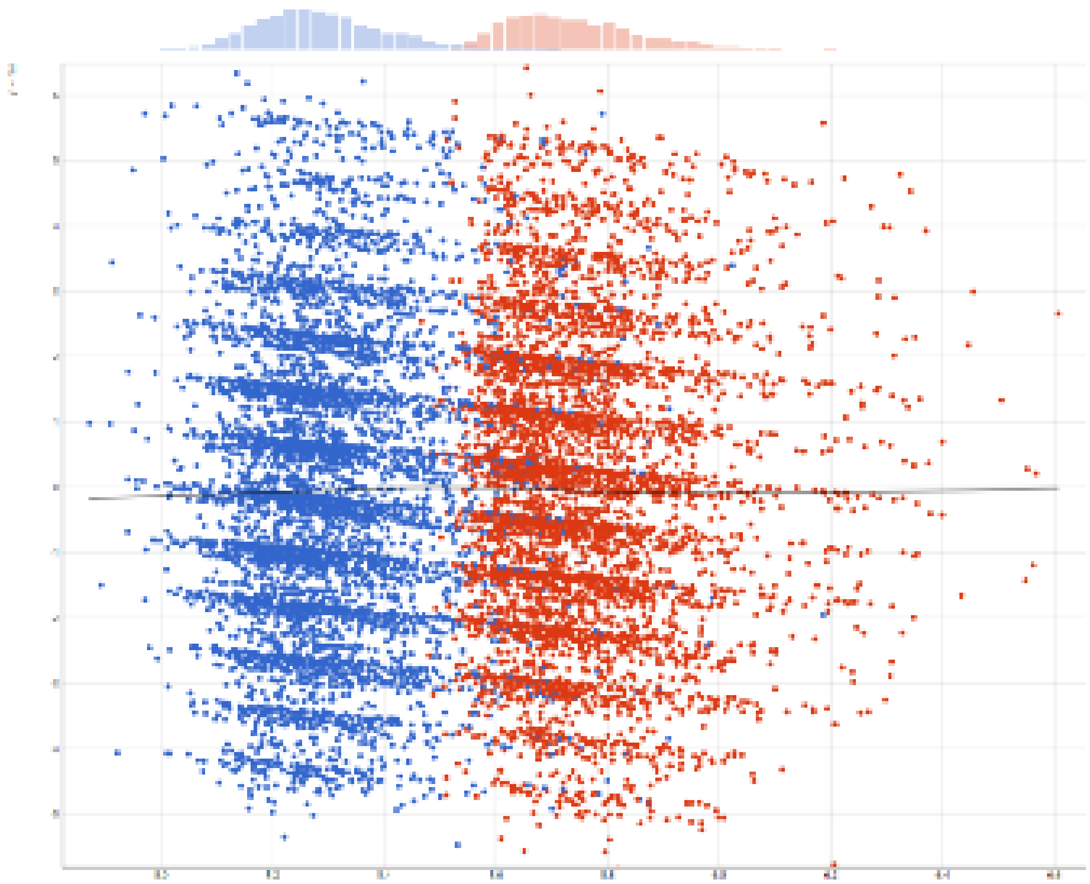
Table 3 depicts the results of two mixed-effects regression models in the pooled/overall sample. *Model 1* did not show an association between cortical thickness and behavioral inhibition overall. *Model 2*, however, showed an interaction between sex and cortical thickness on behavioral inhibition, suggesting a larger positive association between cortical thickness on behavioral inhibition for males than females.

Table 3. Summary of Coefficients on the Effects of Cortical Thickness on Behavioral Inhibition

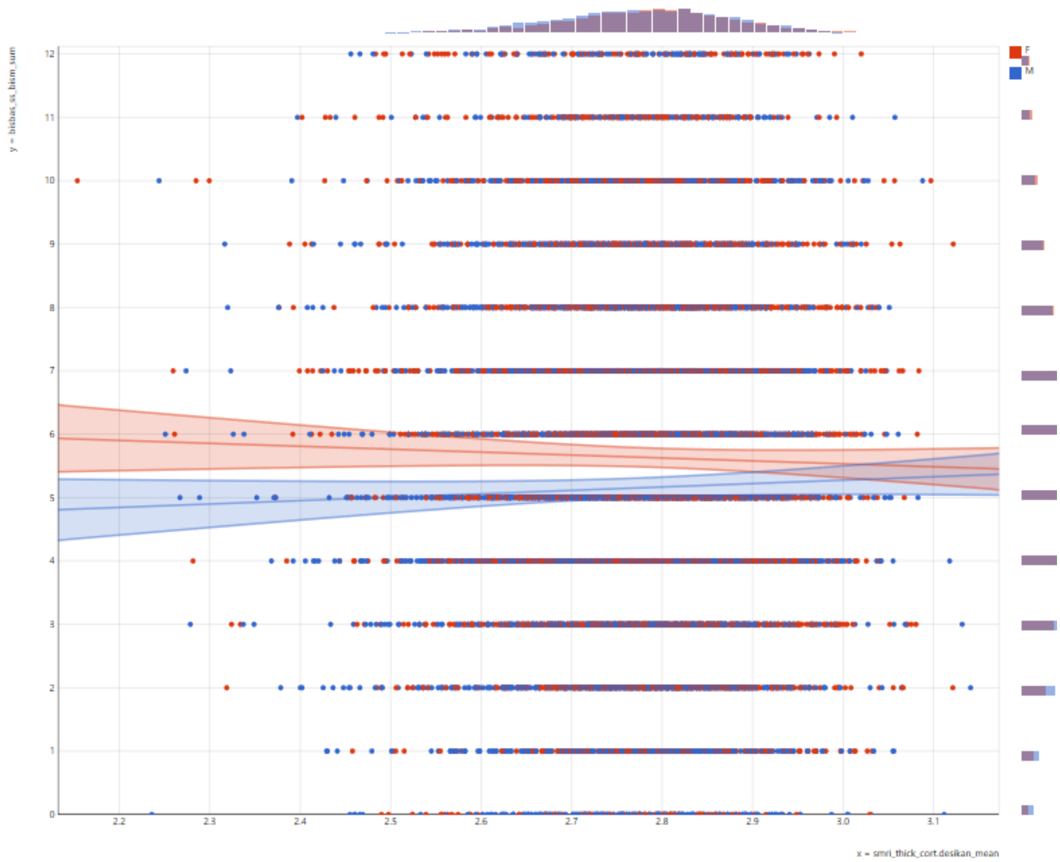
	b	SE	t	p
Model 1				
Mean Cortical Thickness (mm^2)	0.08	0.28	0.28	0.782
Intracranial Volume (mm^3)	0.00	0.00	0.92	0.357
Model 2				
Mean Cortical thickness (mm^2)	-0.46	0.39	-1.18	0.238
Intracranial Volume (mm^3)	0.00	0.00	0.89	0.375
Sex (Male)	-3.25*	1.39	-2.34	0.019
Mean Cortical thickness (mm^2) × Sex (Male)	0.99*	0.50	1.99	0.046

*$p < 0.05$

Figure 2 also shows the association between mean cortical thickness and behavioral inhibition in the pooled/overall sample. Figure 2a did not show an overall association between mean cortical thickness and behavioral inhibition of the children. However, Figure 2b showed differential association by sex, suggesting a larger positive association between mean cortical thickness and behavioral inhibition for males than females.



a) Overall association



b) association by sex (male = blue, female = red)

Figure 2. Association between Mean Cortical Thickness and Behavioral Inhibition

4. Discussion

Our findings showed sex differences in cortical thickness's effect on behavioral inhibition in a national sample of American children. A positive association between cortical thickness and behavioral inhibition is observable for male but not female American children.

Environmental inputs, including parenting and SES, have shown sex-specific effects on brain structure and function (Wierenga et al., 2018). A recent study tested whether biological sex shows any statistical interaction with income on shaping adolescents' brain morphology, cross-sectionally and longitudinally. Overall, income showed effects on the cortical gray matter e including the cortex and sensorimotor processing areas. The effect sizes, however, were larger for males than for fema (King, Dennis, Humphreys, Thompson, & Gotlib, 2020) more extensive. Mcdermott and colleagues also showed a stronger positive association between SES and cortical surface area for males than females (McDermott et al., 2019). Whittle and colleagues in 2014 showed boys' brain structures such as the amygdala and the cortical thinning of the right anterior cingulate to be more sensitive than girls to environmental inputs such as positive caregiving and parenting (Whittle et al., 2014).

Opposite to the studies reviewed above, some research has reported more robust environmental correlates of brain function and structure for females than males. For example, Javanbakht showed SES effects on the amygdala size and function for females but not males (Javanbakht et al., 2016). Kim found that household income was associated with an increased structural brain network efficiency of females but not males aged 6-11 years old (Kim et al., 2019). Thus, although sex differences in brain morphometry and function correlations are frequently reported, the directions of these sex differences are inconsistent (Gur & Gur, 2016).

The complex links between the environment, neurodevelopment, and behaviors may differ by sex (Bock, Wainstock, Braun, & Segal, 2015). Neurodevelopment is sexually dimorphic. While some brain regions develop faster in males, others may develop faster in girls (Dennison et al., 2013; Gur & Gur, 2016; Wierenga, Langen, Oranje, & Durston, 2014). Such sex differences in neurodevelopment (Dennison et al., 2013; Gur & Gur, 2016; Wierenga et al., 2014; Wierenga et al., 2018) and vulnerability to environment (Humphreys et al., 2018; Jaffee, Caspi, Moffitt, Polo-Tomas, & Taylor, 2007; Whittle et al., 2014) may explain our finding.

Research is needed on social, psychological, and biological factors and processes that may explain why boys and girls differ in cortical thickness's effect on behavioral inhibition. Also, not only sex but the intersection of sex, race, place, and class may alter correlates of health and behaviors of children in the US (Chetty, Hendren, Kline, & Saez, 2014). All these complexities require further research.

The major limitation of this study was the cross-sectional design. In this study, we only investigated one brain feature, namely cortical thickness. It is unknown if other brain structures and would show a similar pattern of sex differences or not. There is a need to test sex differences for various ROIs. Future research may also test sex differences in the effects of subcortical structures such as the amygdala, striatum, and hippocampus on behavioral inhibition by sex. Finally, more research is needed on biological processes that explain why cortical thickness differently influences males' and females' behavioral inhibition. It is unknown if sex hormones or cortical and subcortical brain regions' connectivity may explain the observed sex differences in neural correlations of behavioral inhibition.

5. Conclusions

Male but not female children show a positive association between overall cortical thickness and behavioral inhibition. This means that girls with thick and thin cerebral cortex would have similar behavioral inhibition; however, boys with thin cerebral cortex show low behavioral inhibition while boys with thick cerebral cortex show high behavioral inhibition. That means sex and the cerebral cortex thickness interact on behavioral inhibition, a risk factor for a wide range of high-risk behaviors.

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