Left Lateralized Sexual Dimorphism in Cortical Thickness in Autism

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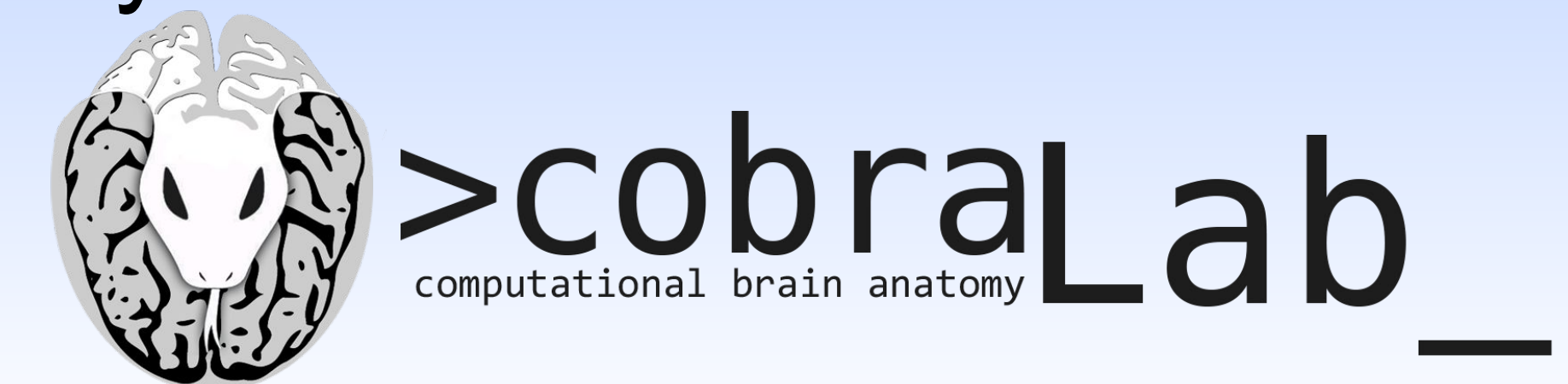
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Introduction

Individuals with autism spectrum disorder (ASD) have been shown to have abnormal developmental trajectories of the cerebral cortex. Some studies have shown cortical thickness (CT) to be increased in individuals with ASD compared to typical controls, yet results have been inconsistent. These findings have largely been based on male-dominant samples, despite reported differences in behavioural profiles and symptom severity between sexes, and little research has examined sex differences in altered cortical development in ASD. This study aims to identify the differences in cortical thickness between males and females with ASD, relative to healthy controls.

Methods

1. Subjects and demographics
MRI data from 296 subjects (23 females with ASD, 38 female controls, 115 males with ASD, and 120 male controls, age 6-30) were analysed, using a subset of the Autism Brain Imaging Data Exchange. Due to the disproportionate number of males in the dataset and different MRI acquisition, we included in our analysis only the 3 sites with the largest number of female subjects that used a Siemens Magnetom scanner.

2. Image and Statistical analysis
CT was estimated using the CIVET pipeline, and multiple linear regression were conducted at 40,962 CT vertices per hemisphere, to model the diagnosis by sex interaction, accounting for the age as a covariate. Correction for multiple comparisons were done using FDR.

| Characteristic	All Sites (n=296)	NYU (n=175)	UCLA (n=71)	YALE (n=50)	Test statistic with df (p value)			
					NYU vs UCLA	UCLA vs YALE	NYU vs YALE	ASD vs TD
Diagnosis								
ASD	138	75	40	23	X^2 (df=2) = 3.6978 (p = 0.1574)			
Ctl	158	100	31	27				
Sex								
Female (total)	61	36	10	15	X^2 (df=2) = 4.5426 (p = 0.1032)			
Male (total)	235	139	61	35				
F-ASD	23	10	6	7				X^2 (df =1) = 2.0242 (p = 0.1548)
F-Ctl	38	26	4	8	X^2 (df = 6) = 9.8565 (p = 0.1308)			
M-ASD	115	65	34	16				
M-Ctl	120	74	27	19				
Age, mean (SD)	13.98 (4.75)	14.60 (5.72)	13.27 (2.34)	12.82 (2.90)	t(df=234.97)= 2.59 (p=0.010)	t(df=90.98)= 0.92 (p=0.359)	t(df=162.45)= 3.00 (p=0.003)	t(df=289.01)= -1.59 (p=0.113)
ADOS Gotham Severity Score	6.88 (2.01) (*NA=26)	7.09 (2.11) (*NA=22)	6.31 (2.04) (*NA=4)	7.26 (1.60)	t =1.76 (p=0. 081)	t =-2.00 (p=0. 050)	t= -0.376 (p=0. 708)	NA
FIQ, mean (SD)	107.3 (16.07)	110.9 (15.07)	103.6 (12.17)	99.54 (20.19)	t=3.96 (p<0. 001)	t=1.28 (p=0.203)	t=3.71 (p<0. 001)	t=-3.26 (p=0. 0012)
ASD	104.0 (17.45)	107.9 (16.78)	102.9 (13.28)	93.43 (21.60)	t=1.75 (p=0. 084)	t= 1.90 (p=0. 067)	t= 2.94 (p=0. 006)	NA
Ctl	110.1 (14.21)	113.2 (13.28)	104.6 (10.71)	104.7 (17.68)	t = 3.67 (p<0. 001)	t= -0.024 (p=0. 98)	t=2.32 (p=0. 026)	NA

Results
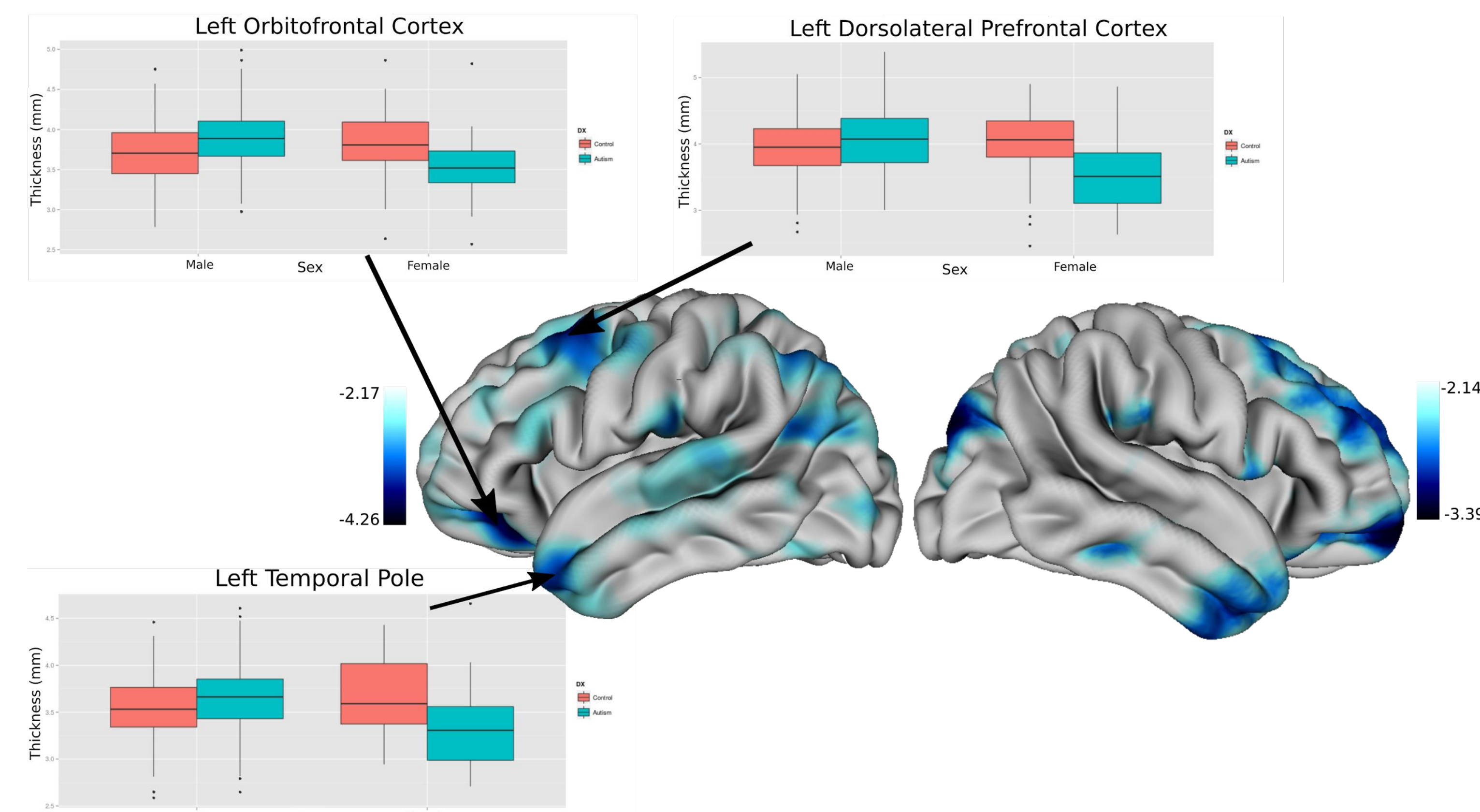
Figure1. A diagnosis by sex interaction for cortical thickness was observed in the left orbitofrontal cortex, left dorsolateral prefrontal cortex and left temporal pole, and survived 10% FDR, with the orbitofrontal cortex also surviving 5% FDR. This interaction was significant in the same areas in the right hemisphere only at 15% FDR, indicating a possible left lateralisation of the sex differences.
Colour bars for the left and right hemispheres show the range of t-values displayed, from the FDR threshold to the minimum calculated value.

Autism vs Typical Development in Females
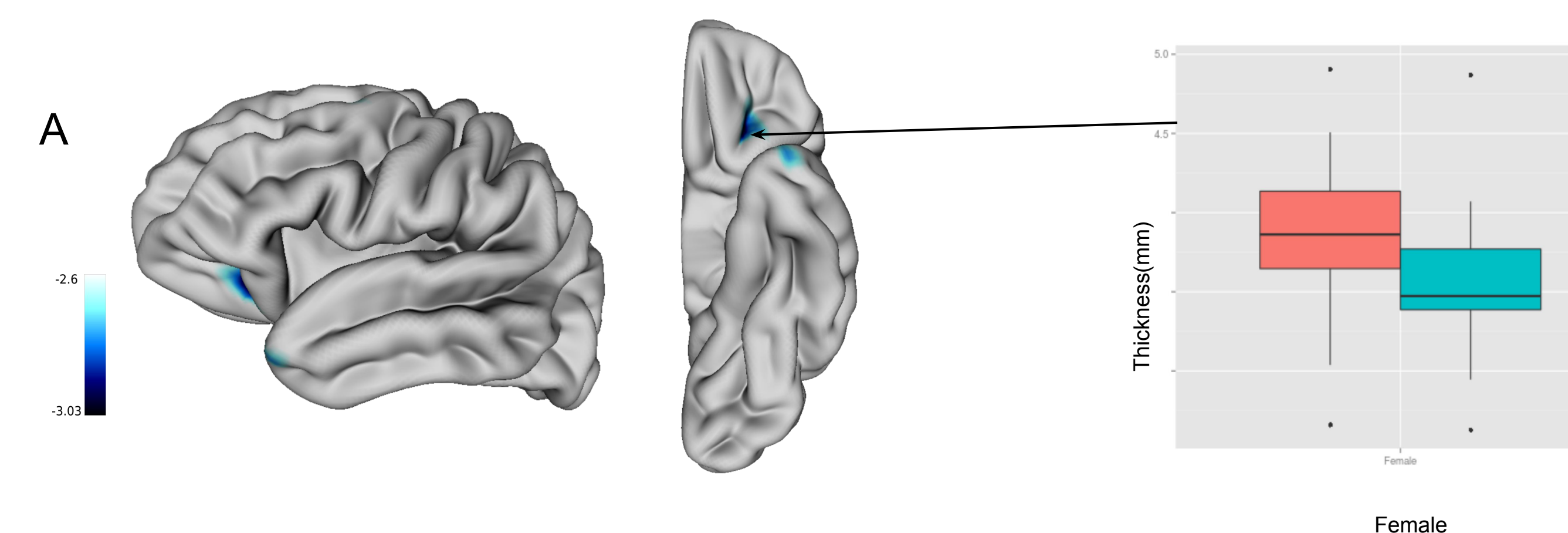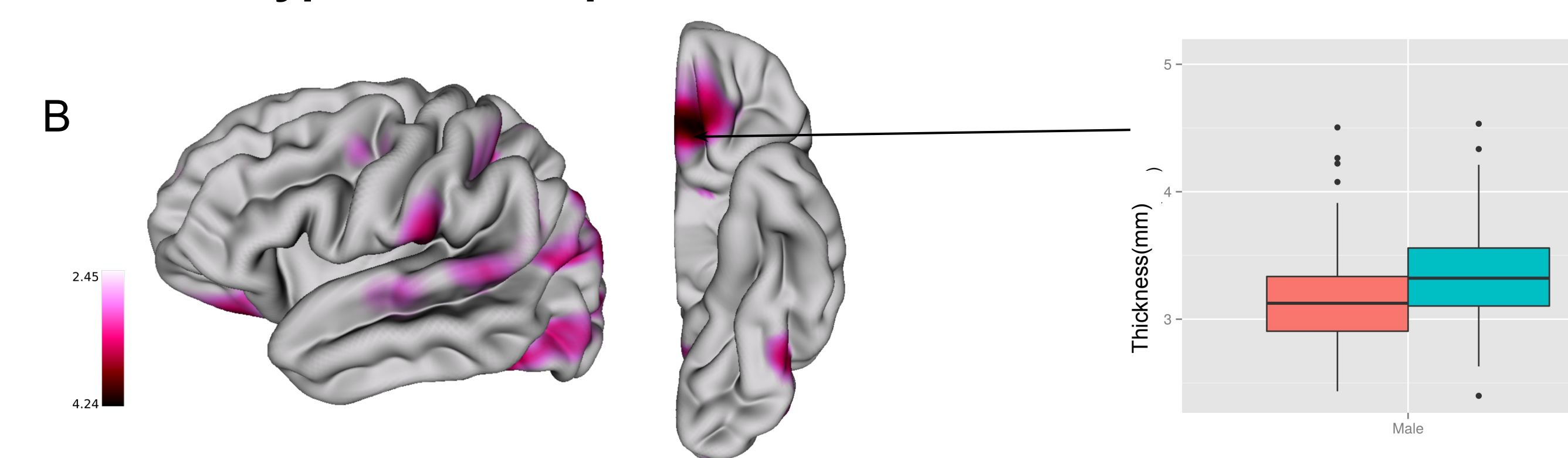

Autism vs Typical Development in Males

Figure2. Effect of diagnosis on left CT in females (A) and males (B). Males with ASD showed increased CT compared to male controls whereas females with ASD showed a decrease relative to female controls.
Male results are shown at 10% FDR. Female results did not survive FDR and are shown uncorrected (p=0.0118). Colour bars show the range of t-values displayed, from the FDR threshold to the minimum or maximum calculated value.

Sexual Dimorphism in Typical Development

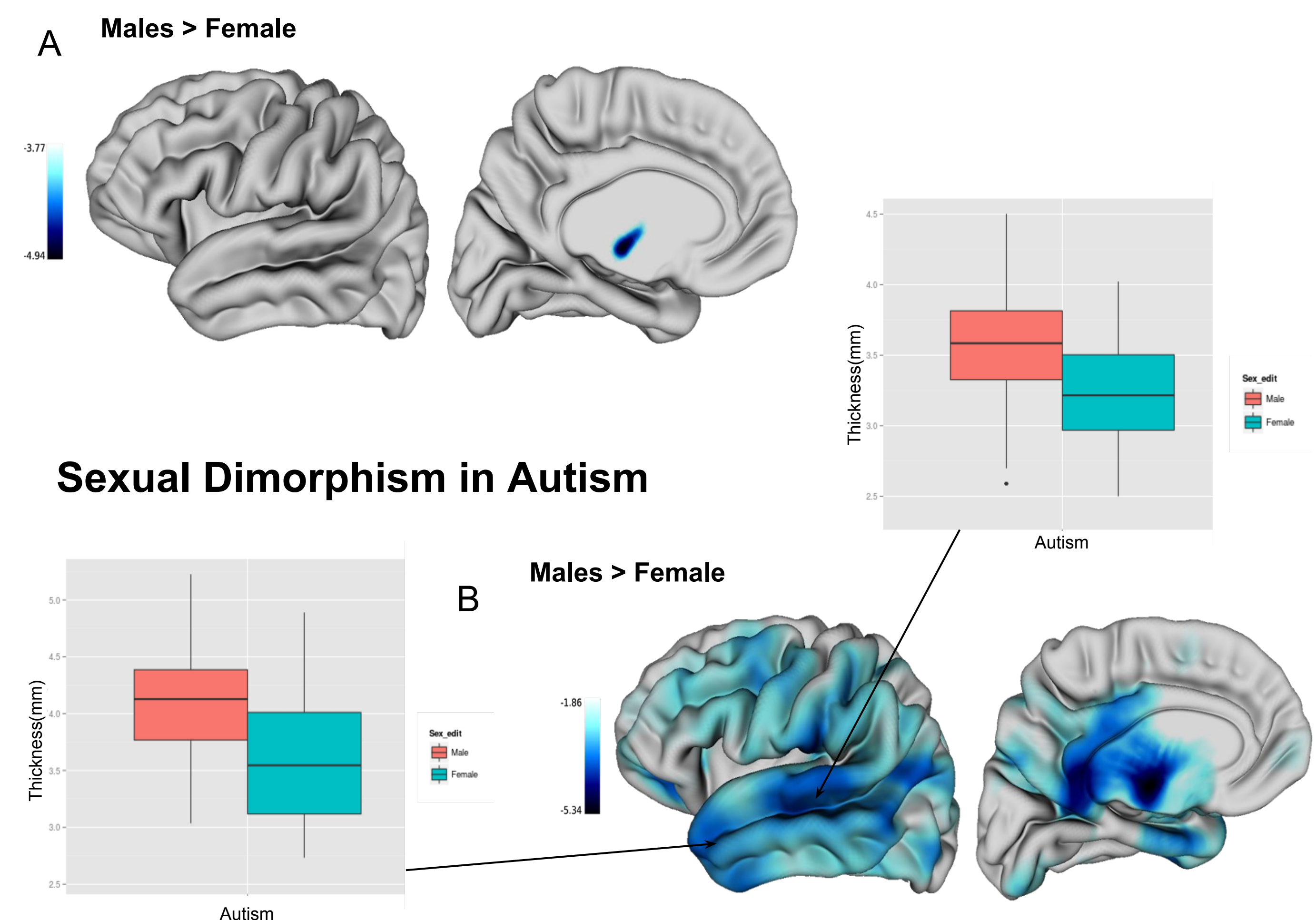### Sexual Dimorphism in Autism

Figure 3. Sexual dimorphism in CT in typical development (A) and ASD (B), at 10% FDR. Males with ASD show increased CT relative to females with ASD while very few differences were observed between male and female controls.
Colour bars show the range of t-values displayed, from the FDR threshold to the minimum calculated value.

Summary

A diagnosis by sex interaction was significant for cortical thickness in the left hemisphere, particularly in the orbitofrontal cortex, with males exhibiting increased cortical thickness compared to typically developing controls, while females showed decreased thickness.

Our results suggest that autism manifests differently in males versus females, and indicate the importance of stratifying by sex when studying the neuroanatomy of autism.

References

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