Supplementary Material

Altered microstructure within social-cognitive brain networks during childhood in Williams syndrome

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Supporting Materials and Methods

TBSS: all white matter pathways

Tract based spatial statistics (TBSS) was used to investigate structural alterations within all white matter pathways within the brain (Nichols & Holmes, 2002). All analyses were corrected for multiple comparisons (family-wise error [FWE]) and used thresholdfree cluster enhancement (TFCE) (Smith & Nichols, 2009) with default parameters. In order to aid in the interpretation of between group differences in FA, subsequent analysis of RD, AD and ADC were restricted to loci where significant between group differences in FA were observed. All between-group comparisons were conducted while age was entered as a covariate.

Correlations with age: TBSS and Atlas Based Analysis

We performed a series of analyses designed to investigate the association between age and DTI metrics within the IFOF, UF and the fusiform gyrus, amygdala, hippocampus and medial orbitofrontal gyrus. TBSS was used to test for significant associations between age and each DTI metric (FA, RD, AD and ADC) within the IFOF and UF, within each group independently (WS and TD controls). TBSS was also used to test for significant differences between groups in the (slopes) association between age and each DTI metric. All TBSS correlational analyses were corrected for multiple

comparisons (family-wise error [FWE]) and used threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009).

SPSS software (Version 18) was used to test for significant associations between age and each DTI metric (FA, ADC), within the fusiform gyrus, amygdala, hippocampus and medial orbitofrontal gyrus, within each group independently (WS and TD controls). This software was also used to test for significant differences between groups in the (slopes) association between age and each DTI metric. All analyses used a statistical threshold of $p < .05$.

Atlas-Based Analysis: Other ROIs

We performed an exploratory analysis designed to investigate between group differences in DTI metrics (FA and ADC) within other brain regions known to be functionally and/or structurally abnormal in WS. These regions included the superior parietal lobule (Boddaert, et al., 2006; Eckert, et al., 2005), insula (Cohen, et al., 2010; Jabbi, et al., 2012) and cingulate (Campbell, et al., 2009; Reiss, et al., 2004). The superior parietal lobule, insula and cingulate ROIs were selected from the JHU_MNI_single-subject atlas (Oishi, et al., 2009). SPSS software (Version 18) was used to test for significant between group effects using a statistical threshold of $p < .05$.

Supporting Results

TBSS: all white matter pathways

Results of the TBSS analysis are presented in **Table S1** and **Figure S1**. These results are consistent with findings within white matter ROIs (IFOF and UF). The finding of both increased and decreased ADC within the cingulum may be representative of crossing fibers in this region.

Supporting Table 1.

FA	WS > TD	white matter pathway
	left	ATR
		cingulum
		thalamus
	right	IFOF
		UF
		ILF
		ATR
		cingulum
		thalamus
RD	TD > WS	
	left	ATR
		cingulum
		thalamus
	right	IFOF
		UF
		ATR
AD	WS > TD	
	left	ATR
		cingulum
		thalamus
	right	IFOF
		UF
	TD > WS	
	left	ILF
		ATR
ADC	WS > TD	
	left	cingulum
	TD > WS	
	left	ILF
		ATR
		cingulum

Table S1. Pathways where significant ($p < .05$ corrected) between group differences (WS vs. TD controls) were observed. FA: Fractional anisotropy; RD: Radial diffusivity; AD: Axial diffusivity; ADC: Apparent diffusion coefficient; WS: Williams syndrome; TD: Typically developing; ATR: Anterior thalamic radiation; IFOF: inferior fronto-occipital fasciculus, UF: Uncinate fasciculus, ILF: Inferior longitudinal fasciculus.

Supporting Figure 1.

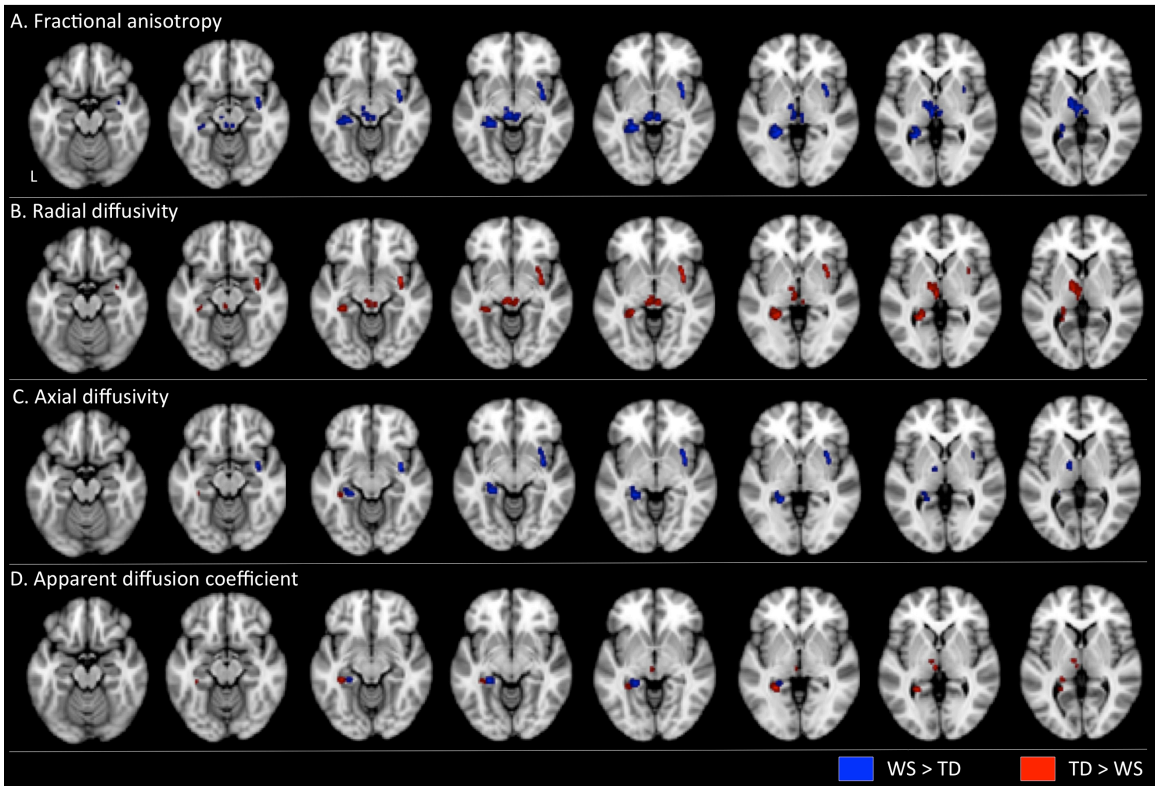

Figure S1. Areas within all white matter pathways that exhibit differences between Williams syndrome (WS) and typically developing (TD) controls in diffusion tensor imaging metrics as measured by tract-based spatial statistics (TBSS), with age entered as a covariate. Areas corresponding to significant differences in fractional anisotropy (A), radial diffusivity (B), axial diffusivity (C) and apparent diffusion coefficient are overlaid on a standardized T1 template (Montreal Neurological Institute). Areas that were higher in WS as compared to TD are displayed in blue; areas that were higher in TD as compared to WS are displayed in red. L = Left.

Correlations with age: TBSS and Atlas Based Analysis

Results of the correlational analysis using TBSS are presented in **Figure S2A**. Results of the correlational analysis within the Atlas-Based ROIs are presented in **Figure S2B**.

Supporting Figure 2.

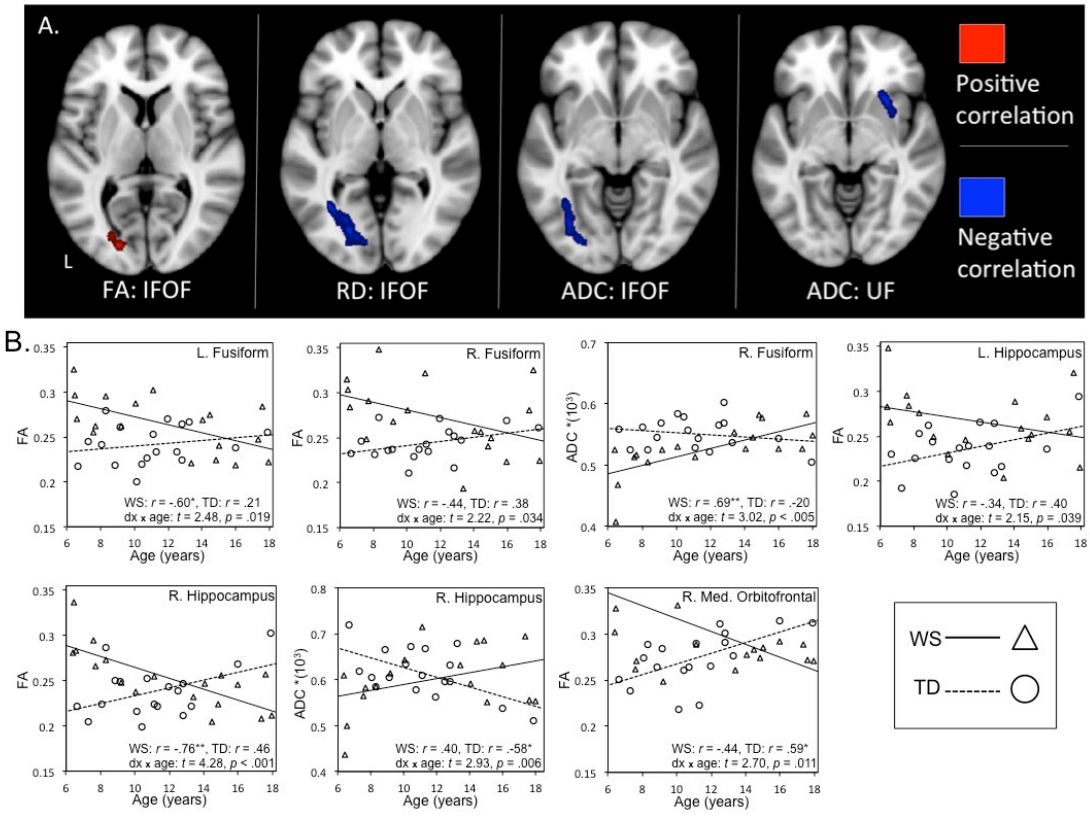

Figure S2. Association between age and DTI metrics within and between groups. **A.** Areas within the IFOF and UF pathways that exhibit significant associations with age within the typically developing (TD) control group as measured by tract-based spatial statistics (TBSS). Areas exhibiting a positive association with age are displayed in red; areas exhibiting a negative association with age are displayed in blue. **B.** Atlas-Based regions of interest exhibiting significant between group differences (WS vs. TD) in the association between age and DTI metrics. FA: fractional anisotropy, ADC: apparent diffusion coefficient, L: left, R: right, **: $p < .005$, *: $p < .05$.

Atlas-Based Analysis: Other ROIs

Results of the between group analysis of DTI metrics within the superior parietal lobule, insula and cingulate ROIs are presented in **Figure S3**. No significant differences in DTI metrics (FA or ADC) were observed within superior parietal lobule, insula and cingulate ROIs (all p's > .10).

Supporting Figure 3.

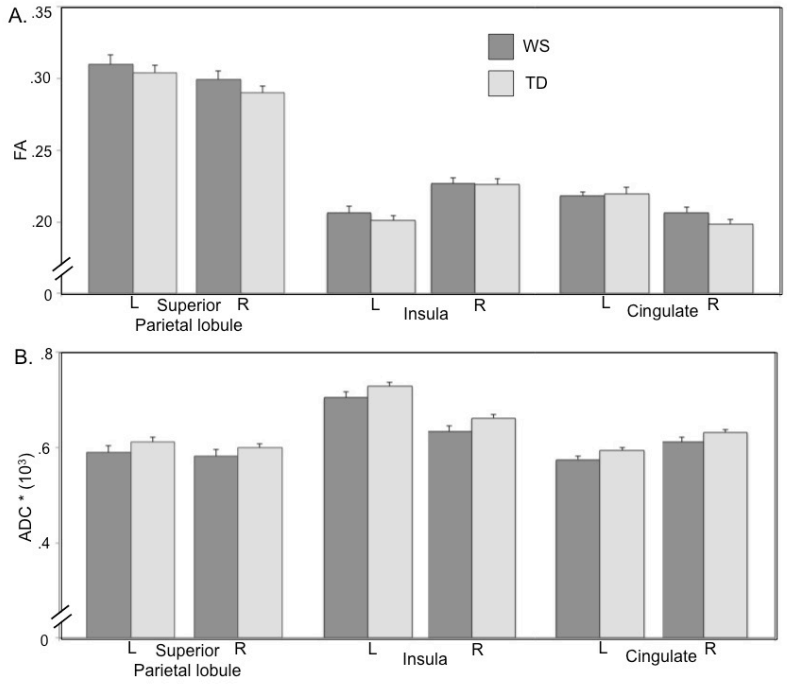

Figure S3. Bar graphs showing diffusion tensor imaging metrics for superior parietal lobule, insula and cingulate ROIs. Data are presented for fractional anisotropy (FA), and for apparent diffusion coefficient (ADC) (B) in WS and TD participants. Error bars represent standard error from the mean.

Supporting References:

Boddaert, N., Mochel, F., Meresse, I., Seidenwurm, D., Cachia, A., Brunelle, F., Lyonnet, S., & Zilbovicius, M. (2006). Parieto-occipital grey matter abnormalities in children with Williams syndrome. *Neuroimage, 30*, 721-725.

Campbell, L. E., Daly, E., Toal, F., Stevens, A., Azuma, R., Karmiloff-Smith, A., Murphy, D. G., & Murphy, K. C. (2009). Brain structural differences associated with the behavioural phenotype in children with Williams syndrome. *Brain Res, 1258*, 96-107.

Cohen, J. D., Mock, J. R., Nichols, T., Zadina, J., Corey, D. M., Lemen, L., Bellugi, U., Galaburda, A., Reiss, A., & Foundas, A. L. (2010). Morphometry of human insular cortex and insular volume reduction in Williams syndrome. *J Psychiatr Res, 44*, 81-89.

Eckert, M. A., Hu, D., Eliez, S., Bellugi, U., Galaburda, A., Korenberg, J., Mills, D., & Reiss, A. L. (2005). Evidence for superior parietal impairment in Williams syndrome. *Neurology, 64*, 152-153.

Jabbi, M., Kippenhan, J. S., Kohn, P., Marenco, S., Mervis, C. B., Morris, C. A., Meyer-Lindenberg, A., & Berman, K. F. (2012). The Williams syndrome chromosome 7q11.23 hemideletion confers hypersocial, anxious personality coupled with altered insula structure and function. *Proc Natl Acad Sci U S A, 109*, E860-866.

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp, 15*, 1-25.

Oishi, K., Faria, A., Jiang, H., Li, X., Akhter, K., Zhang, J., Hsu, J. T., Miller, M. I., van Zijl, P. C., Albert, M., Lyketsos, C. G., Woods, R., Toga, A. W., Pike, G. B., Rosa-Neto, P., Evans, A., Mazziotta, J., & Mori, S. (2009). Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. *Neuroimage, 46*, 486-499.

Reiss, A. L., Eckert, M. A., Rose, F. E., Karchemskiy, A., Kesler, S., Chang, M., Reynolds, M. F., Kwon, H., & Galaburda, A. (2004). An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. *Journal of Neuroscience, 24*, 5009-5015.

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage, 44*, 83-98.