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Surface-Based Morphometry Reveals Distinct Cortical Thickness and Surface Area Profiles in Williams Syndrome

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Morphometric investigations of brain volumes in Williams syndrome (WS) consistently show significant reductions in gray matter volume compared to controls. Cortical thickness (CT) and surface area (SA) are two constituent parts of cortical gray matter volume that are considered genetically distinguishable features of brain morphology. Yet, little is known about the independent contribution of cortical CT and SA to these volumetric differences in WS. Thus, our objectives were: (i) to evaluate whether the microdeletion in chromosome 7 associated with WS has a distinct effect on CT and SA, and (ii) to evaluate age-related variations in CT and SA within WS. We compared CT and SA values in 44 individuals with WS to 49 age- and sex-matched typically developing controls. Between-group differences in CT and SA were evaluated across two age groups: young (age range 6.6–18.9 years), and adults (age range 20.2–51.5 years). Overall, we found contrasting effects of WS on cortical thickness (increases) and surface area (decreases). With respect to brain topography, the between-group pattern of CT differences showed a scattered pattern while the between-group surface area pattern was widely distributed throughout the brain. In the adult subgroup, we observed a cluster of increases in cortical thickness in WS across the brain that was not observed in the young subgroup. Our findings suggest that extensive early reductions in surface area are the driving force for the overall reduction in brain volume in WS. The age-related cortical thickness findings might reflect delayed or even arrested development of specific brain regions in WS.

Key words: Williams syndrome; brain topography; brain development; structural MRI

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INTRODUCTION

Williams syndrome, is a specific genetic disorder caused by a deletion of 26–28 genes on chromosome 7q11.23 [Stromme et al., 2002; Pober, 2010]. Consequently, individuals with Williams syndrome demonstrate a unique cognitive profile with strengths in selected language skills and weaknesses in visuo-spatial skills [Mervis et al., 2000], and overall mild-to-moderate intellectual disability [Meyer-Lindenberg et al., 2006]. Individuals with Williams syndrome often show appetitive social behavior toward others with particularly increased affinity to faces [Mervis and Klein-Tasman, 2000; Martens et al., 2008]. This well-replicated cognitive and behavioral profile has sparked much research focused on brain structure and function in individuals with this condition with the goal of discovering associations among deleted genes, brain changes and cognition.

Previous imaging studies of William syndrome include assessment of brain volumes from structural MRI (sMRI) as a main outcome measure [Jackowski et al., 2009]. These studies established several consistent differences between individuals with

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Williams syndrome and healthy controls. Total gray matter volume is 11–13% smaller in William syndrome compared to controls [Reiss et al., 2000, 2004; Schmitt et al., 2001] and white matter volume is 20% smaller in Williams syndrome compared to controls [Reiss et al., 2000; Thompson et al., 2005]. Frontal and temporal regions are relatively preserved, compared to disproportionately decreased parietal and occipital cortices, as measured by deformation-based [Chiang et al., 2007] and voxel-based morphometry [Reiss et al., 2004]. This structural alteration of the posterior cerebrum of individuals with Williams syndrome leads to unusual shape of the adult brain [Schmitt et al., 2001].

Surface-based morphometry, a relatively new methodology that can be used to analyze more fine-grained features of the brain, has become available in the time since many initial Williams syndrome imaging studies were reported. This methodology measures two constituent parts of cortical gray matter volume: cortical thickness (CT) and surface area (SA), both of which are considered highly heritable [Panizzon et al., 2009; Chen et al., 2013] yet genetically distinguishable features of brain morphology [Pontious et al., 2008]. In addition, CT and SA have specific spatial features, which do not strictly follow traditional anatomical regions defined on the basis of sulcal-gyral structure or neural function [Rash and Grove, 2006]. Little is known about the independent contribution of CT and SA to volumetric differences that are specific to Williams syndrome. Recently, Meda et al. [2012] compared CT and SA between 31 adults with Williams syndrome and 50 typically developing controls using a surface-based methodology. This study used measured SA and mean CT in association with automated sulcal-gyral parcellation implemented in the FreeSurfer software suite [Desikan et al., 2006]. Thus, this method constrains the results to cortical regions predefined by a priori anatomical maps. No studies [Thompson et al., 2005; Luders et al., 2007; Jackowski et al., 2009; Fahim et al., 2012; Meda et al., 2012] have yet utilized the FreeSurfer-based vertex-by-vertex surface-based approach to investigate how CT and SA are distributed across the entire cortex in Williams syndrome without constraining the analysis to predefined regions of interest (ROIs). Thus, in this study we sought to add to the literature on Williams syndrome brain anatomy by using such a surface-based approach to evaluate differences in CT and SA spatial distribution across the cortex between Williams syndrome and controls.

Most previous research on brain anatomy in Williams syndrome has been conducted in adults, and few studies have included children and adolescent cohorts. To the best of our knowledge, structural imaging studies of children and adolescents to date have included 15 or fewer individuals with Williams syndrome. In spite of small cohorts, these investigations of pediatric populations point to reductions in gray matter volumes in occipital and parietal lobes in Williams syndrome [Boddaert et al., 2006; Campbell et al., 2009] similar to that reported in the adult population, and increased gray matter volumes in frontal and temporal regions [Campbell et al., 2009]. Fahim et al. [2012] recently compared CT and SA between 10 children with Williams syndrome and 12 typically developing controls (age range 2.3–14.6 years), and found an overall preservation of CT and reductions in SA. Although a picture of brain structure in children and adolescents with Williams syndrome has begun to emerge, little is known about the developmental trajectories of brain anatomy in Williams syndrome overall, and specifically of CT and SA. Recent literature demonstrates that the two determinants of cortical volumes, CT and SA, undergo dynamic changes in the child and adolescent period [Raznahan et al., 2011]. Characterizing these brain determinants in individuals of different ages has the potential to better inform the field about the developmental timing of the effects from the genetic deletion associated with Williams syndrome on the brain.

In this study, we used a cross-sectional, case control design, to evaluate differences in CT and SA spatial distribution across the cortex between individuals with Williams syndrome ($n = 44$) and controls ($n = 49$). Based on previous studies [Thompson et al., 2005; Luders et al., 2007; Fahim et al., 2012; Meda et al., 2012], we predicted that overall CT would be increased and SA would be reduced in Williams syndrome compared to healthy, age- and sex-matched controls. Furthermore, from a developmental perspective, we sought to evaluate differences in CT and SA between Williams syndrome and controls across two age groups: youth (age range 6.6–18.9), and adults (age range 20.2–51.5). Basing on previous studies of youth [Fahim et al., 2012] and adults [Thompson et al., 2005; Meda et al., 2012] with Williams syndrome, we hypothesized that group differences in CT would become more prominent with development.

METHOD

Participants

The study reports on data collected from participants with Williams syndrome and from typically developing controls (Table I). A 7q11.23 deletion for all Williams syndrome participants was confirmed using fluorescent in situ hybridization (FISH) testing. Each participant with Williams syndrome exhibited the clinical features of the Williams syndrome phenotype, including cognitive, behavioral, and physical profiles [Martens et al., 2008].

Participants with Williams syndrome were recruited via advertisements through national agencies, physicians within local clinics, and advertisement on the Stanford University School of Medicine website. Typically developing controls were recruited through local print media and parent networks. Exclusion criteria for all groups included premature birth (gestational age under 34 weeks), known diagnosis of a major psychiatric disorder, including psychotic or mood disorders, or current neurological disorder including seizures, and any contraindications for a Magnetic Resonance Imaging (MRI) scan. Participants in this study partially overlap with participants reported in previous studies from our laboratory [Reiss et al., 2004; Thompson et al., 2005; Haas et al., 2009, 2014a,b]. Written informed consent and/or assent were obtained from each participant's legal guardian and participant. This study was approved by the Stanford University Administrative Panel on Human Subjects in Medical Research.

Cognitive Assessment

All participants underwent cognitive evaluation conducted by trained psychologists using the age-appropriate versions of the WISC-III or WASI [Wechsler, 1991, 1999] (Table I).

TABLE I. Demographics

	Whole group			Child and adolescents			Adults		
	Controls	Williams	*P*-value	Controls	Williams	*P*-value	Controls	Williams	*P*-value
n	47	44		24	20		23	24	
Male/female	28/19	27/17	NS	15/9	15/5	NS	13/10	12/12	NS
Age range (years)	6.7–50.8	6.6–51.5		6.7–19.0	6.6–19.8		20.2–50.8	20.7–51.5	
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age	22.1 (11.3)	23.8 (11.5)	NS	13.2 (3.9)	13.9 (4.3)	NS	31.5 (8.4)	31.9 (8.2)	NS
FSIQ	114.1 (11.3)	61.7 (12.4)	<0.001	113.0 (11.2)	56.0 (14.7)	<0.001	115.7 (11.5)	66.5 (7.6)	<0.001
VIQ	112.9 (12.8)	69.8 (12.8)	<0.001	111.7 (13.6)	68.0 (16.7)	<0.001	115.1 (11.5)	71.3 (8.5)	<0.001
PIQ	111.3 (12.1)	62.8 (10.2)	<0.001	110.3 (11.2)	59.9 (13.2)	<0.001	113.2 (13.8)	65.1 (7.9)	<0.001

FSIQ, full scale intelligence quotient; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient.

Image Acquisition

Participants underwent behavioral training in a mock MRI scanner prior to their actual scan to desensitize them to the appearance and sounds of an MRI environment and help prevent motion-related artifacts. Images were collected on a 3T GE Signa scanner (Lucas Center of Radiology, Stanford University) using a custom transmit-receive quadrature RF head coil. Coronally oriented T1-weighted MR images were acquired using fast spoiled gradient recall (FSPGR) parameters: repetition time (TR) = 5.9–6.6 ms; echo time (TE) = 1.5–1.6 ms; inversion time (TI) = 300 ms, flip angle = 15°; field of view (FOV) = $220 \times 176\,mm^2$; matrix size = 256×256; pixel size = $0.859 \times 0.859\,mm^2$; number of excitations = 3; and slice thickness = 1.5–1.7 mm (adjusted for brain size in anterior/posterior direction to prevent wraparound artifacts).

Morphometric Analysis

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer 5.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). All scans were preprocessed using the "New Segment" bias field correction method (Chapter 25, http://www.fil.ion.ucl.ac.uk/spm/doc/spm8_manual.pdf) available with SPM8 (http://www.fil.ion.ucl.ac.uk/spm) before entering the FreeSurfer pipeline. The technical details of the FreeSurfer procedures used are extensively described in prior publications [Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2002b, 2004]. Briefly, the FreeSurfer software pipeline removes non-brain tissue, segments the subcortical white matter and deep gray matter volumetric structures [Fischl et al., 2002a], preforms intensity normalization [Sled et al., 1998], does tessellation of the surface generated at the gray matter—white matter boundary, does automated topology correction [Segonne et al., 2007] and aligns the cortical surface and sulci of every subject using a surface registration method to FreeSurfer average subject "FSAverage" [Fischl et al., 1999]. Surface definition follows intensity gradients to optimally place the gray–white and pial surfaces at the location where the greatest shift in intensity defines the transition to another tissue class [Dale et al., 1999; Fischl and Dale, 2000]. Two trained editors visually inspected the gray–white and pial surfaces, and when needed, performed appropriate manual corrections as per the FreeSurfer Tutorial (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial). All image editors were trained to achieve inter-rater reliability of $\geq$0.95 (intraclass correlation coefficient) for editing regions of interest using gold-standard datasets developed in our laboratory.

Statistics

We performed statistical analyses using the R Project for Statistical Computing (R) (http://www.r-project.org). Unpaired *t*-tests were used to compare age and IQ scores between Williams syndrome and control groups. Difference in sex was assessed using Chi-square tests. ANCOVA was used to first compare the total cortical volume between groups, controlling for age and sex.

Once cortical models are completed, FreeSurfer calculates GMV, WMV, and SA of the gray–white boundary and mean CT for each hemisphere. These values were used for whole-brain analysis for the control and Williams syndrome groups. In typical FreeSurfer analyses, brain surfaces for each hemisphere are parcellated into 34 distinct regions based on gyral and sulcal structure [Fischl et al., 2004; Desikan et al., 2006]. While this approach is extensively used in analyses of neuroanatomy, it is limited by restricting the outcome measures to predefined anatomic regions that do not necessarily follow aberrations in brain structure associated with genetic variation such as that associated with Williams syndrome. To overcome this limitation, we used the single-binary application Query, Design, Estimate, Contrast (QDEC) implemented in FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis_freeview) for the between-group comparison of cortical surface and thickness. A cross-subject general linear model (GLM), fit at each vertex, was used to test group-wise differences in surface measures between individuals with Williams syndrome and controls, while controlling for age and sex. To determine the absolute difference in CT and SA between the groups as well as the differences in CT and SA relative to total brain volume, we performed analyses both with and without total brain volume as a covariate. Continuous covariates (age and total brain volume) we centered at the mean.

To correct for multiple comparisons, a Monte-Carlo simulation with 10,000 iterations and vertex-wise threshold of $P < 0.01$ [Ly et al., 2012; Strawn et al., 2014]. For illustration purposes, the results were mapped onto an averaged FreeSurfer template.

Low IQ scores are intrinsic to Williams syndrome status. Thus, as expected, there was a significant IQ difference between the groups with no overlap in the distribution of scores (Table I). Therefore, as assumptions of independence between IQ and group status could not be assumed, IQ was not used as a covariate in analyses of SA or CT [Wildt and Ahtola, 1978; Miller and Chapman, 2001; Dennis et al., 2009]. In support of this approach, exploratory QDEC analyses indicated no significant or trend-level associations between CT/SA and IQ scores within groups (P's = n.s.).

RESULTS

Demographic and Cognitive Measures

There were no significant differences in age or sex between the groups (Table I). As expected, the neurotypical group scored significantly higher than the Williams syndrome group for FSIQ, PIQ, and VIQ (Table I).

Whole-Brain Analyses

Total cortical volume, gray matter volume, white matter volume, total subcortical volume, and total ventricle volume were all significantly smaller in individuals with Williams syndrome than controls while controlling for age and sex (all P's < 0.0001). These measures were not significantly different after controlling for total brain volume in addition to age and sex (Table II). Total SA was significantly smaller in Williams syndrome than in typically developing controls ($P < 0.0001$), whereas mean CT was significantly larger in Williams syndrome than in typically developing controls while controlling for age and sex ($P = 0.0002$). SA and CT measures were still significantly different between groups after controlling for total brain volume in addition to age and sex (Table II).

Vertex-Wise Analysis of Surface Area

Whole sample. Vertex-wise analyses yielded significant differences between Williams syndrome and control groups after controlling for age and sex. Individuals with Williams syndrome had smaller SA in most brain regions, bilaterally (P's ≤ 0.0001). However, in several regions, no differences were detected between the groups (Fig. 1). These regions included the temporal-parietal junction, the posterior aspect of the insula, precuneus and anterior aspect of inferior temporal, and fusiform gyrus (all bilateral). Controlling for total brain volume in addition to age and sex, vertex-wise analyses also yielded significant differences between the Williams syndrome and control groups in specific brain regions. Specifically, individuals with Williams syndrome were observed to have smaller SA in the bilateral anterior insula and superior parietal, precentral and lingual regions on the right and fusiform, inferior parietal and caudalmiddlefrontal regions on the left.

TABLE II. Presents the Results of Whole-Brain Analysis for Control and Williams Syndrome Groups

	Controls		Williams			
	Mean	SD	Mean	SD	% Difference	*P*-value*
Total brain volume	1,242.77	98.76	1,031.59	90.78	−17.0	<0.0001
Gray matter volume	515.99	44.73	435.55	46.06	−15.6	NS
White matter volume	476.57	50.95	382.67	46.57	−19.7	NS
Subcortical volume	198.99	18.66	172.83	20.22	−13.1	NS
Total ventricle volume	15.4	6.93	9.16	3.89	−40.5	NS
Total surface area	1,729.08	127.91	1,407.88	117.17	−18.6	<0.001
Mean cortical thickness	2.66	0.1	2.74	0.1	2.6	<0.001

For each measurement, except cortical volume, we compared between groups using ANCOVA, with brain measurement as the dependent variable, diagnosis as the independent variable and age, gender and total brain volume as covariates; volumes are expressed in cm^3, surface in cm^2, and thickness in mm.
*Bonferoni corrected.

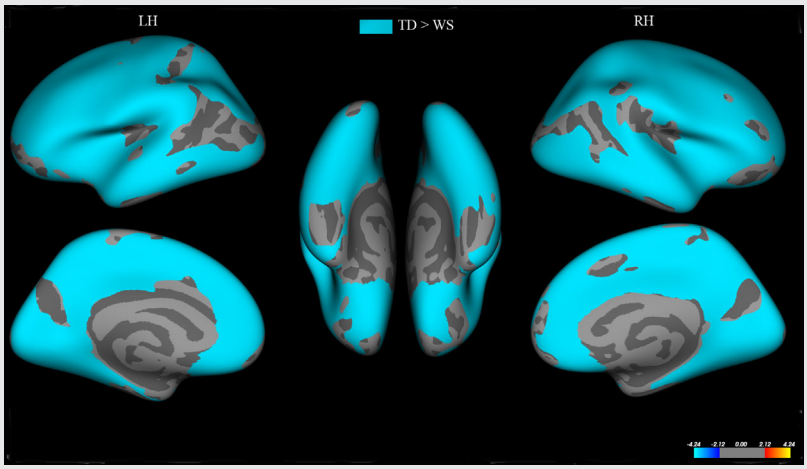

FIG. 1. Vertex-wise analysis of surface area in Williams syndrome (WS) (youth + adult) compared to the typically developing controls (TD). Note: LH, left hemisphere; RH, right hemisphere. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

Limited increases in SA were observed in bilateral precuneus and posterior insula in the right hemisphere (P's < 0.05).

Developmental analysis. Our large sample size enabled us to further examine separately a youth subgroup and an adult subgroup (Table I). For these analyses of SA, the results were largely similar to those observed in the entire group. In both the youth and the adult subgroup, individuals with Williams syndrome had smaller SA compared to controls in most brain regions bilaterally (all P's ≤ 0.0001). In the youth group, 60% (39,563 mm^2/65,416.6 mm^2) of left hemisphere (and 60.5% (37,197 mm^2/65,020.7 mm^2) of the right hemisphere SA was reduced in Williams syndrome; in the adult group 79% (51,653 mm^2/65,416.6 mm^2) of left hemisphere and 80% (51,925 mm^2/65,020.7 mm^2) of right hemisphere SA was reduced in Williams syndrome. Thus, comparisons between Williams syndrome and controls for both the youth and adult subgroups yielded a similar pattern of results, such that the majority of the total brain SA was reduced in Williams syndrome.

Vertex-Wise Analysis of Cortical Thickness

Whole sample. In contrast to the general pattern of reductions in SA in Williams syndrome compared to controls, CT analysis showed a specific pattern of (mostly) increases in Williams syndrome compared to controls. Specifically, significant differences in thickness were observed in 18 cortical regions, 17 of which showed increases and 1 decrease, in Williams syndrome compared to controls (P's < 0.01, corrected). Figure 2 shows the location of these clusters on the cortical surface and Table III provides more detailed information regarding these clusters. Increases in Williams syndrome compared to controls were primarily observed in bilateral medial orbitofrontal and superior frontal cortices, the bilateral dorsal stream, specifically in the superior parietal and the postcentral cortices, in the bilateral anterior and dorsal parts of the superior temporal gyri, and several regions within the temporal-parietal junction. Increased CT of Broca's area (brodmann area 44-left pars opercularis and 45-left pars triangularis) was observed in Williams syndrome as compared with controls. In addition, a region of decreased CT was observed along the caudal part of the left fusiform gyrus in Williams syndrome compared to controls. After controlling for total brain volume in addition to age and sex, significant increases in CT were still observed in bilateral superior temporal and superior frontal regions and precuneus on the right (P's < 0.02).

Developmental analysis. We found the same overall pattern of Williams syndrome-related increases in CT relative to controls in both the youth and adult subgroups. However, in the youth cohort, differences were observed mostly in frontal regions and the postcentral gyrus bilaterally. In contrast, Williams syndrome-related increases in CT in the adult group were more widespread, with spread into parieto-occipital and temporal regions. Also, Williams syndrome-related decrease in CT was observed in the left fusiform gyrus, in the same location as in the whole sample analysis as described in Tables III and IV, Figure 3.

DISCUSSION

In this study, we sought to investigate the topography of specific constituents of gray matter volume, CT and SA in a large cohort of individuals with Williams syndrome. Overall, we found a pattern of increases in CT, and a pervasive decrease in SA with few unaffected regions in Williams syndrome compared to controls. Given that SA is more closely related to gray matter volumes [Winkler et al., 2010], these findings are in line with previous results from sMRI studies of Williams syndrome showing a substantial reduction in brain volumes of affected individuals [Reiss et al., 2000, 2004; Schmitt et al., 2001]. Our results are also potentially pertinent to developmental aspects of CT and SA, providing clues as to

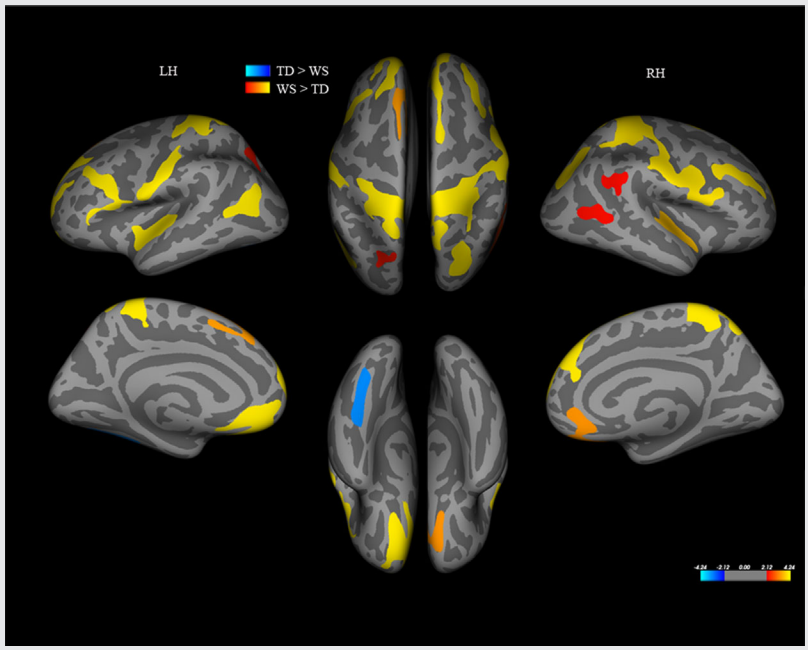

FIG. 2. Vertex-wise analysis of cortical thickness in Williams syndrome (WS) (youth + adult) compared to the typically developing controls (TD). Note: LH, left hemisphere; RH, right hemisphere. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

differential age-related variations of these brain metrics in Williams syndrome. In particular, the effect of Williams syndrome status on CT was mainly observed in the adult subgroup, such that increases in CT were more widespread across the brain than in the youth subgroup. These results suggest widening deviations of CT as individuals with Williams syndrome progress from childhood and adolescence to adulthood. Our finding of decreased CT in Williams syndrome restricted to the inferior temporal lobe surface and fusiform gyrus, is a new and intriguing observation.

The comparison of our findings to previous studies is hindered by many methodological differences. Thompson et al. [2005] used cortical pattern mapping and found increased right perisylvian CT in Williams syndrome. Meda et al. [2012] used FreeSurfer atlas-based sulcal-gyral parcellation [Desikan et al., 2006] and found four regions of increased CT: postcentral gyrus; cuneus; lateral orbital cortex and lingual gyrus, and 21 regions of decreased SA in Williams syndrome compared to controls. These results are in some agreement with our findings, such that scattered increases in CT and overall reductions of SA were found in Williams syndrome compared to controls. Yet, Meda et al. used anatomic gyral defined parcellations [Desikan et al., 2006] to calculate CT and SA scalars. In these anatomic parcellations, CT is averaged within each predetermined brain region. Because the specific genetic influence of the Williams syndrome microdeletion on CT does not necessarily follow such traditional parcellations, this approach might hinder the detection of both discrete and widespread differences such as those observed in our study. In contrast, the vertex-by-vertex approach used in this study provides between group differences in SA and CT that are independent of a priori sulcal-gyral parcellations. Thus, the findings presented here are likely to more accurately represent the neurodevelopmental effects of Williams syndrome status on CT and SA. No differences in CT and widespread reduction in SA were found in a different investigation of 10 children with Williams syndrome using lobar parcellation (frontal, temporal, parietal and occipital lobes) [Fahim et al., 2012]. In this study, power issues, due to small sample size, might explain the absence of CT findings. Nevertheless, fewer regions of CT increases observed in our youth subgroup with Williams syndrome compared to the adult subgroup suggests that findings in Fahim et al. might stem in part from age-related effects. Hence, aberrations in CT in Williams syndrome might be more prominent in the adult brain than the youth brain.

The developmental trajectories of CT in typically developing populations show an increase in early childhood and reduction from mid-childhood to adulthood [Shaw et al., 2008; Raznahan et al., 2011]. Hence, lower CT measurements are expected in older age groups. In contrast, the effect of Williams syndrome status on CT was mainly observed in the adult subgroup, such that increases in CT were more widespread across the brain than in the youth subgroup. Thus, higher CT measurements in the adult subgroup might reflect delayed or even arrested neurodevelopment. Specifically, between-group differences in CT in the superior temporal lobe and insula, fusiform gyrus, Broca's area and along the left superior parietal appeared only in the adult subgroup. These regions generally follow a complex pattern of typical development (i.e., quadratic and cubic curves). Furthermore, CT maturation of the temporal and insular regions occur relatively late in development, with CT peak at 14.9 years for the superior temporal lobe and

TABLE III. Brain Regions Showing Significant Differences in Cortical Thickness Between Williams Syndrome and Typically Developing Controls

Index	Cluster	Change in cortical thickness in WS	Cluster size (mm^2)	Talairach coordinates			*P*-value	Young	Adult
				x	y	z			
LH									
C1	Medial orbitofrontal	⇑	1,599.03	−9.7	37.2	−19.1	0.0001	Yes	Yes
C2	Superior parietal	⇑	423.84	−13.8	−67.1	47.4	0.0261		
C3	Postcentral (superior) extending to the precentral	⇑	2,310.11	−15.1	−29.3	69.8	0.0002	Yes	Yes
C4	Superior frontal (caudal)	⇑	695.57	−11.3	32.7	44.7	0.0008		
C5	Superior frontal (rostral)	⇑	1,643.19	−11.0	62.6	8.9	0.0001		Yes
C6	Superior temporal	⇑	997.85	−50.1	−9.8	−3.4	0.0002		Yes
C7	The junction of the banks, superior and middle temporal and inferior parietal	⇑	878.22	−42.5	−64.5	12.2	0.0001		Yes
C8	Pars opercularis, pars triangularis and caudal part of the rostral middle frontal (Broca's area)	⇑	878.22	−43.4	15.8	19.9	0.0002		Yes
C9	Postcentral (inferior) extending to the precentral	⇑	1,105.02	−56.8	−1.0	10.5	0.0001		
RH									
C10	Fusiform	⇓	668.35	−36.7	−44.8	−15.7	0.0008		Yes
C11	Medial orbitofrontal	⇑	537.62	59.5	−53.0	5.8	0.0074		
C12	Superior parietal extending to inferior parietal	⇑	1,119.89	23.2	−56.6	40.2	0.0001		Yes
C13	Postcentral extending medially to the superior parietal and the precuneus and inferior-rostral to the precentral and parsopercularis	⇑	5,746.34	17.7	−29.6	67.1	0.0001	Yes	Yes
C14	Superior frontal	⇑	1,612.21	17.0	58.4	5.9	0.0001	Yes	
C15	Middle frontal	⇑	945.77	37.8	26.8	28.5	0.0002	Yes	Yes
C16	Superior temporal	⇑	771.56	48.0	−17.4	−0.1	0.0002		Yes
C17	Supramarginal, inferior parietal	⇑	531.86	52.9	−43.2	27.6	0.0078		
C18	Middletemporal, inferior parietal	⇑	537.62	59.5	−53.0	5.8	0.0074		

The significant between-group differences in cortical thickness were determined at a significant level of $P < 0.01$. Label C1-18 corresponds with the labels in Table IV. Young and Adult coulombs indicate significant between-group differences in cortical thickness found in the Young and Adults subgroups. We used Desikan et al. [2006] parcellation implemented in FreeSurfer to overlay labels on the brain surface. These labels were used to describe clusters showing significant differences in cortical thickness between groups. LH, left; RH, right.

TABLE IV. Young and Adult Cohorts: Brain Regions Showing Significant Differences in Cortical Thickness Between Williams Syndrome and Typically Developing Controls

Index	Cluster	Change in cortical thickness in WS	Cluster size (mm^2)	Talairach coordinates x	y	z	*P*-value
Young cohort							
LH							
C1	Medial orbitofrontal	⇑	430	−10.4	37.2	−18.9	0.026
	Caudalanteriorcingulate	⇑	485.94	−8.8	16.9	28.1	0.0116
C3	Postcentral	⇑	905.59	−10.3	−36.8	61.2	0.0001
RH							
C13	Postcentral extended caudally to the superior parietal	⇑	1259.43	28.6	−26.4	60.7	0.0001
C13	Postcentral (inferior)	⇑	511.06	59.2	−6.4	26.3	0.0097
	Frontal lobe in the junction of caudalmiddlefrontal, rostralmiddlefrontal and superiorfrontal	⇑	382.77	28.9	26.9	35.8	0.0458
	Superior frontal	⇑	925.3	16.0	55.6	13.2	0.0001
Adult Cohort							
LH							
C1	Medial orbitofrontal	⇑	1,239.23	−9.4	35.9	−19.3	0.0001
C3	Postcentral	⇑	838.47	−16.0	−29.5	69.3	0.0001
C5	Superior frontal (more rostral)	⇑	775.34	−12.7	60.9	10.6	0.0001
C6	Superior temporal	⇑	683.12	−51.3	−11.6	−0.5	0.0009
C7	The junction of the banks, superior and middle temporal and inferior parietal	⇑	432.55	−43.2	−62.7	11.8	0.0223
C8	Parsopercularis and caudal part of the rostral middle frontal	⇑	872.72	−41.7	29.3	21.6	0.0001
RH							
C10	Fusiform	⇓	833.83	−40.2	−62.2	−12.5	0.0001
C12	Superior parietal extended to inferior parietal	⇑	1,085.00	30.4	−73.3	17.9	0.0001
C13	Postcentral extended medially to the precuneus	⇑	1,273.22	17.6	−30.7	65.4	0.0001
C13	Postcentral (inferior)	⇑	647.38	55.7	−8.8	23.7	0.0021
C13	Parsopercularis	⇑	452.82	50.9	5.5	6.9	0.0213
C15	Rostralmiddle frontal	⇑	386.78	36.9	26.9	29.3	0.04860
C16	Superior temporal extended into the tranversetemporal and insula	⇑	1,434.93	46.5	−18.9	−0.9	0.0001

The significant between-group differences in cortical thickness were determined at a significant level of $P < 0.01$. Labels (C) correspond with the labels in Table III. We used Desikan et al. [2006] parcellation implemented in FreeSurfer to overlay labels on the brain surface. These labels were used to describe clusters showing significant differences in cortical thickness between groups. LH, left; RH, right.

18.1 years for the insula [Shaw et al., 2008]. This characteristic of complex, slower maturation in neurotypical brains might explain in part why differences in CT were detected for these regions only in the adult subgroup analysis in our study. In contrast, we detected increases in CT in the postcentral and left medial orbitofrontal gyri in both the youth and adult subgroups in Williams syndrome. These CT increases suggest an early effect of Williams syndrome on cortical development for those regions. Notably, peak CT measured during typical development is early for the postcentral gyrus (8.4 years) and the medial orbitofrontal regions (8.6 years) [Shaw et al., 2008]. In addition, orbitofrontal gyrus CT maturation follows a simple linear decline [Shaw et al., 2008]. These converging findings of early and non-complex maturation of the postcentral and the medial orbitofrontal gyri in the neurotypical brain might explain why we were able to detect increases in CT in our youth subgroup with Williams syndrome. The developmental trajectories of SA in typically developing populations show a mild increase in early childhood and reduction from mid-childhood to adulthood [Raznahan et al., 2011]. Our findings in Williams syndrome show low SA measurements compared to controls in both young and adult subgroups. These findings might indicate an early and continuous effect of Williams syndrome status on SA.

The overall pattern of increased CT and decreased SA in Williams syndrome compared to controls, has been reported in other neurogenetic conditions such as 22q11.2 deletion syndrome [Schmitt et al., 2001], Turner syndrome [Lepage

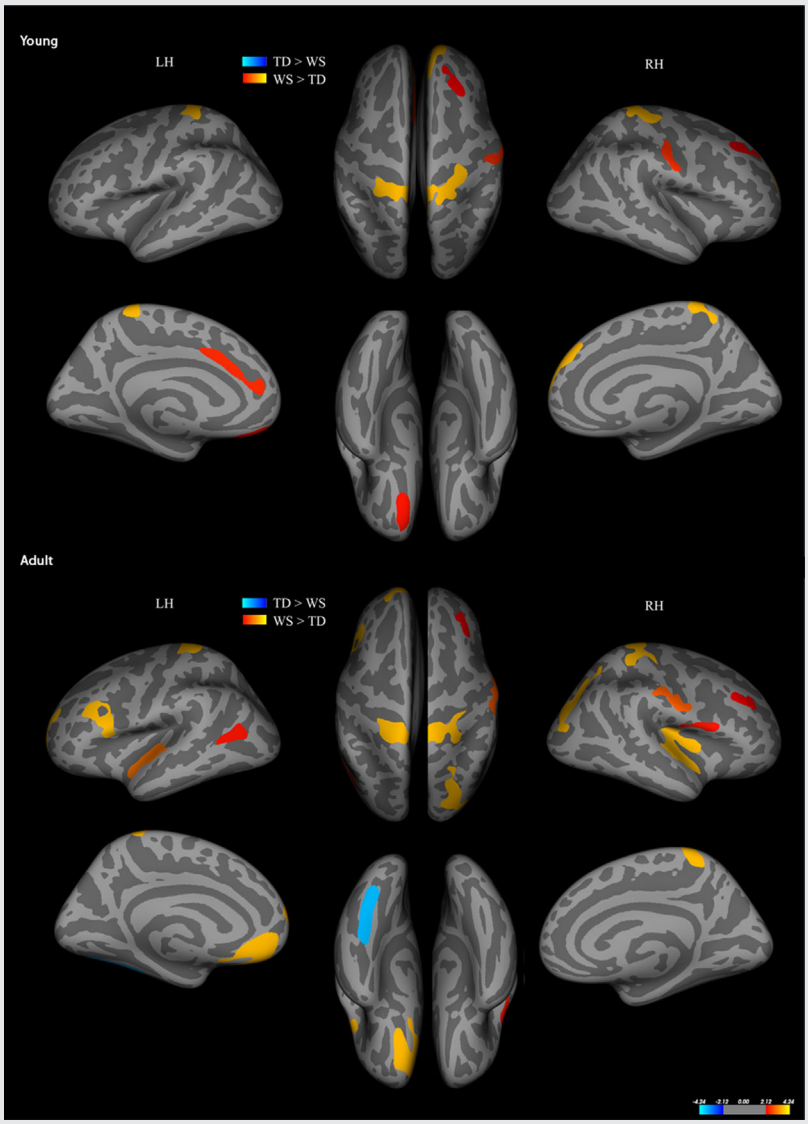

FIG. 3. Vertex-wise analysis of cortical thickness in Williams syndrome (WS) compared to the typically developing controls (TD) in the youth cohort (Top) and adult cohort (Bottom). Note: LH, left hemisphere; RH, right hemisphere. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

et al., 2013] and Down syndrome [Lee et al., 2015]. The observation of increased CT across these conditions might indicate a variety of nonspecific neurodevelopmental effects leading to a similar phenotype, or a specific effect associated with a shared pathophysiological mechanism. Additional longitudinal human studies and examination of animal models are needed to adequately address this issue.

In this study, we observed that the typical Williams syndrome deletion was associated with extensive and widespread effects on SA, while the effect on CT was scattered and non-contiguous across the cortex. A possible explanation for these findings might be associated with the distinct genetic influences that control CT and SA in the human cortex [Panizzon et al., 2009; Rimol et al., 2010; Winkler et al., 2010]. Chen et al. [2012, 2013] compared brain development in neurotypical monozygotic and dizygotic twins to test the effect of genetic factors on SA and CT. The outcomes of these studies provide initial information about the proportion of phenotypic variance (i.e., SA or CT) accounted for by genetic factors. High spatial continuity for genetic influences on SA were observed such that regions within a lobe had higher genetic similarity relative to regions from different lobes. In contrast, genetic influences on CT lacked this within-lobe spatial continuity. Instead, genetic factors affecting CT appeared to operate on distinct and spatial-disconnected cortical regions [Chen et al., 2012, 2013]. The pattern of Williams syndrome genetic effects on CT and SA observed here are consistent with these genetic patterns;

between-group SA differences show spatial continuity while CT differences show uneven distribution, possibly corresponding to functional cortical connectivity patterns.

Another possible mechanism for the pattern of discrete increases in CT and widespread, contiguous decreases in SA between Williams syndrome and control groups is that genes in the deleted region q11.23 of chromosome 7 may contribute more to the development of SA then to CT. The radial unit hypothesis, based on evidence from different mammalian species, including humans, postulate that CT and SA reflect different neurodevelopmental mechanisms in the cortex [Pontious et al., 2008; Rakic, 2009]. SA is thought to be associated with the number of cortical columns and CT is considered to reflect the cell layers within each column and includes diverse neuronal populations [Pontious et al., 2008; Rakic, 2009]. Although there is no direct evidence as yet for an association between specific genes in the Williams syndrome critical region and differential influence on CT or SA, several genes in the deleted region, such as *LIMK1* and *CLIP2*, are extensively expressed in the brain [Hoogenraad et al., 2004]. Also *GTF2I* and *GTF2RD1*, also located in the Williams syndrome critical deleted region, encode transcription factor TFII-I. Deficiency in TFII-I is associated with neural tube defects and microcephaly in mice [Enkhmandakh et al., 2009].

The locations of CT differences between Williams syndrome and controls are intriguing from the concept of alignment between brain structure and function. In typically developing populations, practicing a specific behavior (such as music training) is associated with maturation (cortical thinning) during development in brain regions that subserve this behavior [Hudziak et al., 2014]. A typical behavior in Williams syndrome is the excessive use of language. Thus, one might expect thinning of cortical regions associated with language. Instead, cortical thickening was detected in the current study and others in temporal regions that support language [Thompson et al., 2005]. Furthermore, visual-spatial abilities are known to be severely affected in Williams syndrome [Mervis et al., 2000]. Our results and previous studies [Thompson et al., 2005; Fahim et al., 2012; Meda et al., 2012] show greater cortical thickening in the dorsal visual stream, which supports visual-spatial abilities. Thus, as suggested by Thompson et al. [2005] increases in CT in Williams syndrome may reflect, either or both, attempts to compensate (as in regions that support language) or deficiencies (in visual-spatial abilities). Theoretically, thicker cortex might reflect more processing units and thus attempt to support better function, but also may reflect less efficient neural packing and thus worse function. Early cytoarchitectonic investigation of the brain of one adult with Williams syndrome pointed to increased cell packing density that might support the findings of increases in CT [Galaburda et al., 1994] but these results were not replicated in later investigations. Since our results derive from cross-sectional comparisons, casual effects cannot be determined. Further longitudinal studies might shed light on these processes.

Possible structural–functional associations in Williams syndrome might be considered in light of observed findings in the temporal lobe. In spite of a general deleterious effect on visual-spatial abilities in Williams syndrome, there is an increased tendency of individuals with Williams syndrome to focus on faces compared to controls [Jarvinen-Pasley et al., 2008; Riby and Hancock, 2008, 2009; Doherty-Sneddon et al., 2009]. Our results show that only regions in the inferior aspect of the temporal lobe, along the left fusiform gyrus and mid-fusiform sulcus, show decreased CT compared to controls. This region includes the fusiform face area (FFA), a functional face-selective region in the human brain [Kanwisher et al., 1997; Weiner and Grill-Spector, 2012; Weiner et al., 2014]. The functional extent of the FFA is enlarged in adults with Williams syndrome compared to controls despite a small size of the anatomical region of the overall fusiform gyrus in Williams syndrome [Golarai et al., 2010]. Our finding of reduction in CT within the fusiform gyrus (Fig. 2) is potentially consistent with the previous finding of an atypically large FFA *functional* volume in Williams syndrome and implies a connection between CT maturation (i.e., thinning) and Williams syndrome specific behavior of eagerness for face-to-face interaction [Jarvinen-Pasley et al., 2008].

Limitations and Conclusions

The current study has several limitations that should be noted. Although our cohort allowed us to ask questions about age-related aspects of brain topology in Williams syndrome, its cross-sectional design limits the ability to precisely follow and define developmental trajectories between the groups [Kraemer et al., 2000]. Nevertheless, to the best of our knowledge, it is the first attempt to look at age-related cortical scalars such as CT and SA in this population. The finding of more brain regions with CT increases in Williams syndrome in an adult subgroup compared to a youth subgroup suggests aberrant development of CT during and after childhood and adolescence. Future, longitudinal studies might clarify specific time frames of divergence from typical development. These studies may also provide new information about the relationship between the Williams syndrome cognitive profile and brain development. In addition, the absence of a large sample size for the youth subgroup limits our ability to draw inferences specific for childhood and adolescence.

The issue of covarying for IQ in the analysis of children with developmental disorders has been extensively discussed in the literature: both logical and statistical arguments support an approach to not covary for IQ in the study of such populations [Dennis et al., 2009]. The same argument could support an approach of not covarying for total brain volume in analyses of CT and SA due to colinearity between group status and total brain volume [Reiss et al., 2000, 2004; Schmitt et al., 2001]. In addition, CT is a local cytoarchitectural measure and, when compared on a vertex-by-vertex basis, correction for influences of overall brain volume might not apply. However, SA and CT are both brain measures and thus related to total brain volume. Thus, as recommended by O'Brien et al. [2011], for SA and CT differences between groups we performed analyses with and without total brain volume as a covariate. The results were highly similar indicating little effect of this covariate on our outcomes of interest. Nevertheless, these results should be interpreted with caution due to the colinearity between group status and total brain volume [Dennis et al., 2009].

In conclusion, we utilized advanced structural image processing methods to investigate CT and SA in Williams syndrome without constraining the results to predefined anatomical regions of interest. These genetically and phenotypically independent scalars are important complementary measures, in addition to volume, for

future imaging genetic studies [Winkler et al., 2010]. We demonstrate contrasting effects of Williams syndrome on CT (overall increases) and SA (decreases) compared to controls. We also provide a first look at age-related patterns of CT and SA in Williams syndrome. Our findings suggest that early, extensive reductions in SA are the driving force for overall reduction in brain volume previously described in Williams syndrome [Schmitt et al., 2001; Reiss et al., 2004; Jackowski et al., 2009; Meda et al., 2012]. We also observed increases in CT in Williams syndrome in a more discrete pattern across the brain. These findings are in line with findings in non-Williams syndrome populations suggesting that CT and SA are differentially influenced by genetic and environmental factors [Winkler et al., 2010]. Further, CT age-dependent effects might be associated with brain-behavior interactions, as the unique behavioral phenotype in Williams syndrome might have a significant effect on the developmental trajectory of CT. These important relationships among genes, environment, brain and behavior in Williams syndrome warrant more in-depth investigation, using longitudinal methods to determine causality.

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