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Morphometry of corpus callosum in Williams syndrome: shape as an index of neural development

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Abstract Brain abnormalities in Williams syndrome (WS) have been consistently reported, despite few studies have devoted attention to connectivity between different brain regions in WS. In this study, we evaluated corpus callosum (CC) morphometry: bending angle, length, thickness and curvature of CC using a new shape analysis method in a group of 17 individuals with WS matched with a typically developing group. We used this multimethod approach because we hypothesized that neurodevelopmental abnormalities might result in both volume changes and structure deformation. Overall, we found reduced absolute CC cross-sectional area and volume in WS (mean CC and subsections). In parallel, we observed group differences regarding CC shape and thickness. Specifically, CC of WS is morphologically different, characterized by a larger bending angle and being more curved in the posterior part. Moreover, although CC in WS is shorter, a larger relative thickness of CC was found in all callosal sections. Finally, groups differed regarding the association between CC measures, age, white matter volume and cognitive performance. In conclusions, abnormal patterns of CC morphology and shape may be implicated in WS cognitive and behavioural phenotype.

Keywords Corpus callosum · MRI · Neurodevelopment · Williams syndrome

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Introduction

Williams syndrome (WS) is a rare genetically determined neurodevelopmental disorder with an estimated prevalence of 1 in 7,500 live births (Strømme et al. 2002) and is caused by a hemideletion on chromosome 7q11.23 (Ewart et al. 1993). Associated with this genotype, WS patients display an unusual cognitive phenotype, characterized by intellectual disabilities with a distinctive neuropsychological profile, with peaks and valleys of abilities. Specifically, severe impairments in visuo-spatial cognition coexist with a relative preservation of face recognition, language and narrative skills (Bellugi et al. 2000). One of the most striking features of individuals with WS is their distinct social-affective profile, characterized by high sociability, disinhibition, over-friendliness (Bellugi et al. 1999; Klein-Tasman and

Mervis 2003) and strong empathy (Klein-Tasman and Mervis 2003).

This cognitive/behavioural phenotype has also been associated with several neuroanatomic changes, including volumetric and morphological changes, as well as abnormal asymmetry patterns (Sampaio et al. 2008; Holinger et al. 2005; Chiang et al. 2007). Importantly, brain alterations in individuals with WS also involve white matter abnormalities (Hoeft et al. 2007; Marenco et al. 2007). Specifically, corpus callosum (CC), the major white matter fiber bundle responsible for homotopic and heterotopic interhemispheric connections (Paul et al. 2007), has also been studied in this syndrome. Fibers of the CC are implicated in a wide range of cognitive abilities, such as binocular coordination skills (Johansen-Berg et al. 2007), visual attention (Hines et al. 2002), processing speed (Schulte et al. 2005), reading and intelligence (Luders et al. 2007b), and comprehension of syntax and linguistic pragmatics (Paul et al. 2007). Of note, all of these cognitive functions have been found to be affected in WS (Karmiloff-Smith et al. 2003). Previous studies that have analyzed the CC in WS reported morphologic abnormalities and volumetric reductions, particularly in the posterior component of CC (Luders et al. 2007a; Schmitt et al. 2001a, b; Tomaiuolo et al. 2002). Specifically, midsagittal CC area and midline length were found to be reduced in WS, with absolute reductions of whole CC being more pronounced in the posterior part of CC (splenium and isthmus), even when relative volumes were compared (Schmitt et al. 2001a, b). In addition, the CC is reported to be shorter and with a larger bending angle in WS than in typically developing individuals (Luders et al. 2007a; Schmitt et al. 2001b; Tomaiuolo et al. 2002).

Of note, the majority of these studies have used Witelson's geometric classification of callosal regions (Witelson 1989) and only volumetric measurements have been included. However, recent reports, based on tractography analysis, propose new landmarks for defining callosal sections, which provide a better description of CC with respect to the microstructure level of this brain region (Hofer and Frahm 2006), when comparing with geometric-based divisions.

The current study is the first to provide a detailed characterization of CC using a tractography-assisted white matter segmentation approach and a new shape analysis method. We used this multimethod approach because we hypothesized that neurodevelopmental abnormalities might involve both volume change as well as deformation of structure. In addition, taking into account that CC exhibits a continuous growing pattern during adolescence, in parallel to other white matter brain regions (Giedd et al. 1999a, b; McLaughlin et al. 2007), we studied the associations between CC, age and white matter volumes, as well as between cognitive and callosal measures.

We predicted absolute volumetric CC reduction in WS in parallel to atypical morphological patterns, when compared to typically developing individuals. We expected that these differences were more prominent in anterior and posterior CC regions.

Method

Participants

In this study, seventeen participants (7 males), diagnosed with WS (age 19.29 ± 6.29; age range 11–34 years; mean Full Scale IQ: 47.87 ± 7.86; range 40–62) were compared with 17 typically developing individuals (TD 6 males; age 21.29 ± 7.07; age range 11–34 years; mean Full Scale IQ: 109.54 ± 12.00; range 90–127). There was no group differences with respect to age ($t(32) = -0.87$, $p > 0.05$), although they differed in mean Full Scale IQ ($t(26^{1}) = -18.07$, $p < 0.001$). Participants with WS were recruited at the Genetic Medical Institute (Portugal) and the Genomic Foundation in Galicia (Spain). WS diagnoses were made by fluorescent in situ hybridization for confirmation of elastin gene deletion (Ewart et al. 1993). Controls were typically developing individuals with no evidence of psychiatric, neurological disorder or cognitive impairment. Taking into account evidence that CC morphology may be distinctly different in left handed individuals with WS than in left handed TD controls (Martens et al. 2012), all participants from the WS group were right handed, according to the Edinburgh handedness inventory (Oldfield 1971)—some of these participants were also involved in a EEG study (Pinheiro et al. 2010). One participant from the TD group was left handed, but was we decided to include him in the analysis because there is previous evidence showing the absence of significant differences between right and left handers when comparing callosal thickness (Luders et al. 2010, 2011). The Ethical Board approved this study and written informed consent was obtained prior to enrolment from all participating individuals and/or their parents (when individuals were age under 18 years or had a legal representative).
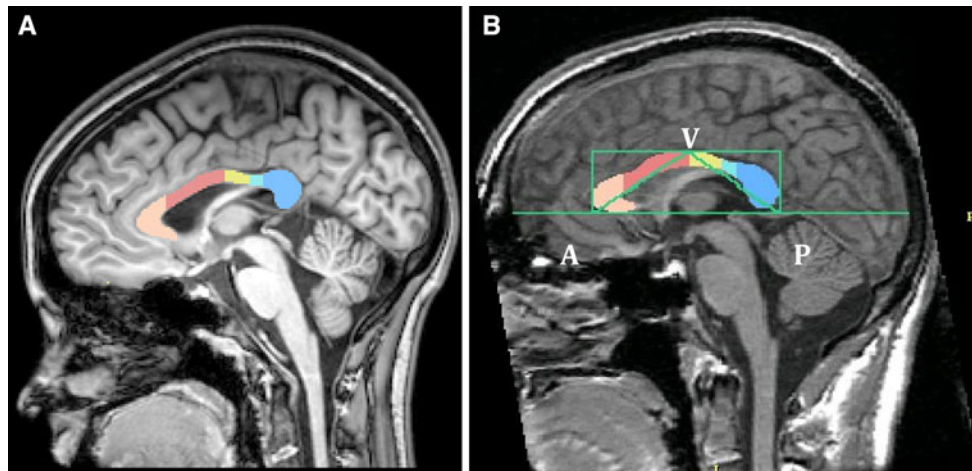
Cognitive assessment

To assess general cognitive functioning, participants were administered the Wechsler Intelligence Scales (Wechsler 1991, 1997).

MRI acquisition and processing

MRI images were obtained on a 1.5-T General Electric system (GE Medical Systems). The scan acquisition protocol

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[1] FSIQ was not available for two participants in TD group.

Fig. 1 a CC sections segmentation, **b** CC length (*A–P*) and bending angle: *A* anterior, *P* posterior, *V* vertex

consisted of contiguous 1.5-mm slices of the whole brain. Coronal T1 (SPGR), TE = 5 ms, TR = 35 ms, 256 × 192 matrix, 1.5 mm thickness and an axial PD/T2 (TE = 30 ms, TR = 3,000 ms) sequence were aligned. Images were aligned using the line between the anterior and posterior commissures and the sagittal sulcus to correct head tilt and were also resampled to make voxels isotropic (sides measured 0.9375 mm). Then, an atlas-based expectation maximization (EM) segmentation program separated raw MR data into cerebrospinal fluid (CSF), gray matter and white matter volumes (Pohl et al. 2007) and total intracranial volume (ICV) was computed as the sum of white matter, gray matter and CSF volumes. The individual volume of CC regions was calculated using the 3D slicer software for segmentation (http://www.slicer.org/).

Regions of interest definition

Measurement of the corpus callosum

The sagittal slice that included the clearest view of the corpus callosum, aqueduct, tectum, septum pellucidum, and falx, was chosen as the midsagittal slice. This slice and two slices laterally on each side (*N* = 5 slices) were manually segmented, and volume of the entire corpus and the five CC subsections (number of voxels) was calculated for each of the five slices, using 3D slicer software (Frumin et al. 2002).

Measurement of CC subregions

Although the majority of studies subdivide CC according to Witelson's geometric classification (Witelson 1989), other proposals performing DTI-based CC subdivisions, suggest new landmarks for defining callosal sections (Hofer and Frahm 2006). Thus, for this study, CC was segmented based on a classification method of five vertical CC partitions

(Hofer and Frahm 2006), which provides a better description of CC at the connectivity and microstructural level of this brain region. Specifically, region I connects prefrontal areas; region II contains fibers that connect premotor and supplementary motor areas; region III is composed by fibers that connects to primary motor area; region IV connects primary sensory areas in parietal and temporal lobes; and region V encompasses fibers that connect parietal, temporal, and occipital lobes (Hofer and Frahm 2006). Specifically, i.e. five vertical CC partitions were segmented along the midline between the most frontal (*A*) to the most posterior (*P*) points in five slices (see Fig. 1a).

Global shape measures

We extracted two measures to describe the overall shape of the midsagittal section of the CC. First, the midline length was computed in the midsagittal slice as the distance between the most anterior (*A*) and posterior (*P*) points of CC. Second, the bending angle was measured as described previously (Tomaiuolo et al. 2002). Briefly, in the midsagittal slice, a horizontal line was drawn at the most inferior level of CC, the most anterior (*A*) and posterior (*P*) part of CC on this line was labeled. Then, the bounding box of CC was drawn as a rectangle and a third landmark (*V*) was placed on the superior line of the rectangle at the midpoint between (*A*) and (*P*). The distance [AP] is the midline length, and the angle (AVP) is the so-called bending angle—see Fig. 1b.

Skeletal shape analysis

A two-dimensional skeleton of the CC was extracted in the mid-sagittal slice. Two landmarks were positioned at the anterior and posterior tips of CC and the algorithm of Bouix and Siddiqi (2005) was used to extract the 2D

skeleton by "peeling" layers of the object until only the central line remained. This line was then smoothed and parametrized by arc length by fitting a cubic smoothing spline to the data. The result is a 2D curve composed of 100 equally spaced vertices on the curve (see Fig. 2a). This process makes it possible to compare directly the specific location along a skeleton across individuals as they all have identical parametrization. At each vertex the distance from the skeleton to the boundary of the midsagittal CC (we call this measure thickness), as well as the curvature of the skeletal line are recorded.

Data analysis

All volumetric, bending angle, midline length and volume data met the criteria for using parametric tests, including normality and variance homogeneity. Thus, group differences were analyzed with the Student's t test. Taking into account that groups were matched on chronological age, intracranial volume (ICV) was used as covariate in all computations, with the exception of CC length variable, where we opted to use age and anterior–posterior length of cerebrum in the midsagittal slice (as we considered this to be a better morphological variable to control for this measure). Thus, MANCOVAs were performed, using CC measures as dependent variables, with diagnosis as fixed effects (WS and typically developing subjects), and ICV volume as covariate. A $p < 0.05$ was assumed to denote significant difference. Effect sizes were reported for group comparisons.

For skeletal shape differences, we measured the following quantities at each vertex along the skeletal curve: curvature, distance from the vertex to the boundary (thickness), and thickness normalized by the area of the CC midsagittal section. The mean of each of these values was computed over each population at each vertex and compared using a non-parametric permutation test (Good 2005). Given the large number of vertices on the curve and the small sample size, the resulting p values were corrected for multiple comparisons using the false discovery rate (FDR) at the 5 % level (Nichols 2003).

We analyzed the developmental trajectories of callosal regions, performing a correlational analysis between age, CC and CC subsections volume [ICV was not correlated with age in WS ($r = -0.33$, $p < 0.05$) and TD ($r = -0.35$, $p < 0.05$)]. Correlational analyses between Verbal IQ (VIQ), Performance IQ (PIQ), Full Scale IQ (FSIQ), Factorial Indexes (Processing Speed and Perceptual Organization) and general measures of CC (length and volume) were performed for both groups separately (controlling for age effects). Additionally, we performed a correlational analysis between volumes of the different regions of CC (I, II, III, IV and V sections) and IQ measures—VIQ, PIQ and

FSIQ. The Fisher r-to-z transformation was used to assess the significance of the difference between two correlation coefficients observed in both groups.

Results

Global shape indices

We found no group differences regarding the bending angle, although a trend towards a larger angle in WS ($M = 112.87 \pm 8.25$) when compared with TD ($M = 108.93 \pm 5.19$) could be observed ($t(32) = 1.67$, $p = 0.11$). However, when ICV volume was used as covariate, a significant group effect emerged ($F(1,32) = 5.59$, $p < 0.05$), with WS showing an increased CC angle. The absolute midline CC length was also significantly reduced in WS ($t(32) = -3.04$, $p < 0.01$) and when anterior–posterior distance of cerebrum in the midsagittal line was computed as covariate ($F(1,32) = 4.83$, $p < 0.05$).
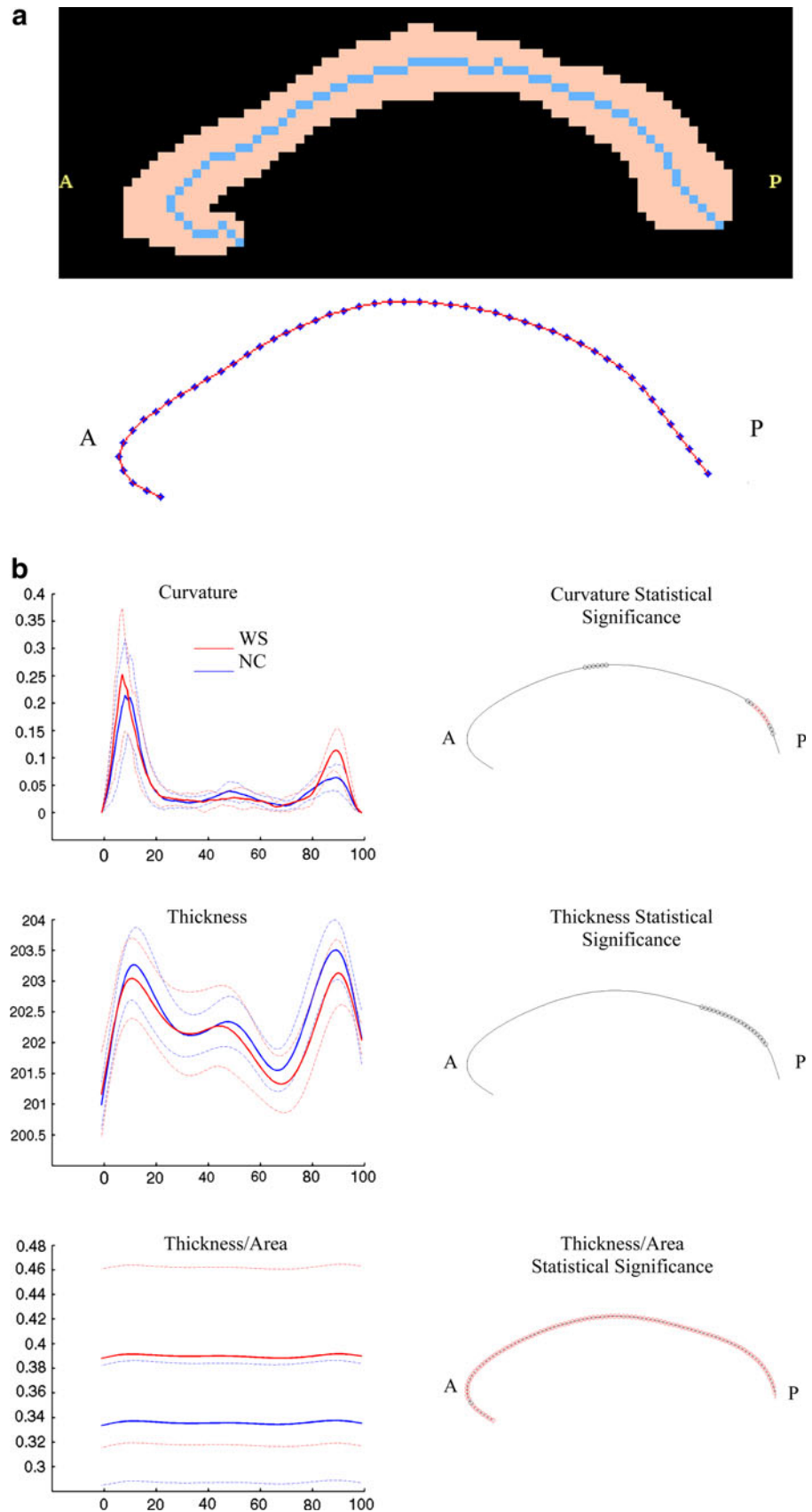
CC volume indices

Analyses of CC volumes showed a statistically significant reduction in WS for the entire CC [WS, $M = 2.40 \pm 0.33$; TD $= 2.83 \pm 0.45$; $t(32) = -3,14$, $p < 0.01$, and in all CC subdivisions [section I, $M_{WS} = 0.68 \pm 0.09$; $M_{TD} = 0.77 \pm 0.12$; $t(32)_I = -2.38$, $p < 0.05$; section III, $M_{WS} = 0.23 \pm 0.06$; $M_{TD} = 0.29 \pm 0.05$, ($t(32)_{III} = -2.78$, $p < 0.01$; section IV, $M_{WS} = 0.10 \pm 0.03$; $M_{TD} = 0.13 \pm 0.03$, $t(32)_{IV} = -2.71$, $p < 0.05$; section V, $M_{WS} = 0.71 \pm 0.09$, $M_{TD} = 0.88 \pm 0.13$; $t(32)_V = -4.07$, $p < 0.001$], except for section II ($M_{WS} = 0.67 \pm 0.13$; $M_{TD} = 0.76 \pm 0.15$; $t(32)_{II} = -1.93$, $p = 0.06$). Using MANCOVA to control for the effects of ICV, the group differences remained for total mean CC volume ($F(1,32) = 5.97$, $p < 0.05$) and for the different callosal subsections [$F(1,32)_{II} = 4.94$, $p < 0.05$; $F(1,32)_{III} = 5.06$, $p < 0.05$; $F(1,32)_{IV} = 6.14$, $p < 0.05$; $F(1,32)_V = 5.21$, $p < 0.05$]. No group differences were observed regarding section I [($F(1,32)_I = 2.97$, $p = 0.09$)].

Skeletal line indices

To further evaluate the shape of CC, we analyzed the curvature and thickness along its skeletal curve (Fig. 2b). As thickness is highly correlated with the area of the CC midsagittal section, we also analyzed the thickness normalized by this area. Our results showed significant group differences with respect to skeletal curvature, that is, CC in the WS group was more curved in the posterior part (Fig. 2b). No significant difference in absolute thickness profile (Fig. 2b) was found, but normalized thickness was

Fig. 2 **a** *Top* CC and extracted skeleton. *Bottom* the corresponding smoothed and arc length parametrized skeleton. This example is parametrized with 50 equally spaced vertices (*blue dots*) for display purposes, although in our experiments, we use 100 vertices for better spatial resolution. **b** Statistical analysis along the CC skeleton. On the *left side*, the *x* axis represents the index of 100 vertices equally spaced along the skeleton. The *y* axis is the dependent measure at the corresponding vertex location (*top* curvature, *middle* local thickness, *bottom* local thickness normalized by CC midsagittal area). *Solid lines* represent mean values for each population and *dashed lines* ±1 standard deviation. On the *right side*, the mean skeleton for the entire population is displayed with *black circles* at vertices where the dependent measure leads to a raw $p < 0.05$, and the *red circles* for vertices where the dependent measure leads to a *p* value surviving the multiple comparison correction using FDR. The posterior part of the CC (splenium) shows curvature differences. Unnormalized thickness never survives the multiple correction procedure. Normalized thickness reaches significance over the entire length of the CC skeleton

Table 1 Correlations between age, white matter volume and callosal sections

	CC	Section I	Section II	Section III	Section IV	Section V
Age						
WS	$r = 0.34$	$r = 0.06$	$r = 0.35$	$r = 0.39$	$r = 0.48$	$r = 0.26$
TD	$r = 0.49^*$	$r = 0.31$	$r = 0.57^*$	$r = 0.54^*$	$r = 0.63^{**}$	$r = 0.35$
Fisher's Z test	$Z = -0.48$	$Z = -0.69$	$Z = -0.75$	$Z = -0.51$	$Z = -0.58$	$Z = -0.26$
White matter volume						
WS	$r = -0.14$	$r = -0.19$	$r = -0.22$	$r = -0.03$	$r = -0.11$	$r = 0.06$
TD	$r = 0.56^*$	$r = 0.49$	$r = 0.41$	$r = 0.51$	$r = 0.42$	$r = 0.65^{**}$
Fisher's Z test	$Z = -2.05^*$	$Z = -1.93^*$	$Z = -1.74^*$	$Z = -1.57$	$Z = -1.48$	$Z = -1.89^*$

* $p < 0.05$, ** $p < 0.01$

found to be significantly different between groups along the entire skeletal curve (Fig. 2b). These results were similar when we normalized thickness to cerebral tissue volumes (to both white matter and ICV volumes). More specifically, we observed a larger relative thickness of CC in WS, when compared with controls.

Developmental trajectories

Developmental trajectories of callosal regions were analyzed, correlating age with CC and regional sections volume. In the typically developing group, age was positively correlated with the volume of the callosal subregions (with the exception of sections I and V), however, no pattern of correlations between age and callosal measures were found in the WS group. Also, in the typically developing group, CC volume and section V subregion were positively correlated with white matter volume, whereas no correlation was again found in the WS group. Most interestingly, the difference between these correlations (WS vs. TD) was significant for CC, sections I, II and V (see Table 1).

Correlation with cognitive functioning

Partial correlations between general callosal measures (CC volume and midline length) and cognitive performance (FSIQ, VIQ, PIQ and Processing Speed Index) were performed, controlling for the effect of age (see Table 2). Additional correlational analysis were performed between volumes of the different regions of CC (I, II, III, IV and V sections) and IQ measures—see Table 3. Specifically, the results showed that in the typically developing group, the speed of processing index was correlated with CC volume ($r = 0.88$, $p < 0.01$) and with CC length ($r = 0.67$, $p < 0.05$). In addition, VIQ was also correlated with CC length ($r = 0.81$, $p < 0.01$) and with section IV ($r = 0.60$, $p < 0.05$) Again, in this group, a trend was also observed for the association between FSIQ and Length of CC ($r = 0.59$, $p = 0.07$). No correlations were observed in the

WS group and the differences between these correlations (WS vs. TD) were significant for speed of processing index and CC volume and length, FSIQ, VIQ and CC length; as well as for VIQ and sections IV and V.

Discussion

This study is the first to use a multimethod approach to the study of CC, namely a combination of morphometric and shape measures to provide a comprehensive characterization of the CC in WS and relationship with cognitive abilities.

Absolute volumetric reductions of CC (mean CC and subsections) were observed in WS, when compared to typically developing individuals. These results remained after controlling for ICV in all CC measures but region I, and are consistent with previous evidence showing CC absolute and relative volumetric reductions, albeit more prominent in posterior regions (Luders et al. 2007a; Schmitt et al. 2001a, b; Tomaiuolo et al. 2002). The relative preservation of region I (CC region that connects prefrontal areas) is consistent with both neuroanatomical and behavioural data in WS (Capitao et al. 2011a; Chiang et al. 2007). Specifically, a relative preservation of prefrontal, orbitofrontal and anterior cingulate volumes (Chiang et al. 2007) associated with a distinctive social/affective/emotional profile has been illustrated in WS (Porter et al. 2007; Mobbs et al. 2007; Capitao et al. 2011a).

Regional heterogeneity of CC growth is known to occur during development; whereas between 6 and 15 years there is a consistent growth of CC sections connecting temporo-parietal regions, between 7 and 11 years, a rapid focal growth at the callosal isthmus contrasts with the stability of splenium and rostrum (Thompson et al. 2000). This suggests that sharp local increases may not be apparent with conventional volumetric methods but can be pursued with a more detailed shape analysis method. The combination of volumetric data with shape analysis provides a more

Table 2 Correlations between overall CC and cognitive measures

	FSIQ	VIQ	PIQ	Speed of processing index
CC volume				
WS	$r = -0.21$	$r = -0.03$	$r = -0.47$	$r = -0.06$
TD	$r = -0.13$	$r = -0.44$	$r = 0.16$	$r = 0.88$**
Fisher's Z test	$Z = -0.21$	$Z = -1.12$	$Z = -0.89$	$Z = -3.34$***
CC length				
WS	$r = -0.27$	$r = -0.20$	$r = -0.24$	$r = -0.09$
TD	$r = 0.59$	$r = 0.81$**	$r = 0.19$	$r = 0.67$*
Fisher's Z test	$Z = -2.43$***	$Z = -3.38$***	$Z = -1.11$	$Z = -2.29$*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3 Correlations between CC regions and cognitive measures

	FSIQ	VIQ	PIQ
CC section I			
WS	$r = 0.28$	$r = 0.19$	$r = 0.34$
TD	$r = 0.23$	$r = 0.36$	$r = -0.12$
Fisher's Z test	$Z = 0.11$	$Z = -0.37$	$Z = 0.96$
CC section II			
WS	$r = 0.25$	$r = 0.22$	$r = 0.38$
TD	$r = 0.11$	$r = 0.34$	$r = -0.14$
Fisher's Z test	$Z = 0.29$	$Z = -0.26$	$Z = 1.1$
CC section III			
WS	$r = 0.14$	$r = 0.05$	$r = 0.37$
TD	$r = 0.11$	$r = 0.32$	$r = -0.23$
Fisher's Z test	$Z = 0.06$	$Z = -0.57$	$Z = 1.26$
CC section IV			
WS	$r = -0.22$	$r = -0.16$	$r = 0.03$
TD	$r = 0.44$	$r = 0.60$*	$r = 0.13$
Fisher's Z test	$Z = -1.41$	$Z = -1.73$*	$Z = -0.02$
CC section V			
WS	$r = -0.15$	$r = -0.17$	$r = 0.09$
TD	$r = 0.44$	$r = 0.55$	$r = 0.36$
Fisher's Z test	$Z = -1.26$	$Z = -1.70$*	$Z = -0.06$

* $p < 0.05$

powerful tool to detect subtle differences in CC white matter Therefore, we added a shape analysis of CC, which included several parameters, namely the bending angle, CC length, thickness and curvature. We observed a trend for a larger bending angle and lower curvature in the middle of the CC skeleton in WS when compared with typically developing individuals. This indicates an overall "flatter" less convex CC, which is in agreement with previous reports (Luders et al. 2007a; Schmitt et al. 2001a, b; Tomaiuolo et al. 2002). In addition, we found a higher curvature in the posterior part of the CC skeleton, indicating a slightly more convex shape in this area, a result not reported elsewhere. Interestingly, a less curved CC was accompanied by a more curved and premature posterior CC

ending, suggesting abnormal cortico-cortical connections between the parietal and occipital lobes in WS (Meyer-Lindenberg et al. 2004). Indeed, smaller volumes of the parietal and occipital lobes (Eckert et al. 2005; Reiss et al. 2004) together with abnormal gyrification patterns (Gaser et al. 2006; Thompson et al. 2005) and increased cell packing density (Galaburda et al. 2002) in these regions have been associated with one of the most remarkable feature of the WS cognitive profile—their profound deficit in performing visuo-spatial and constructive tasks. In addition, and despite volumetric reductions, a relative increase of CC thickness was observable in WS, which expands previous evidence of small local increases in CC thickness in WS (Luders et al. 2007a).

In agreement with altered CC structure and morphology in WS, a different allometric relationship with age, white matter volume and callosal measures were observed in both groups. Specifically, the absence of an allometric growth between individual subregions of the CC with either white matter volume or age in WS is also a finding in other developmental disorders (Cascio et al. 2006), suggesting a disconnection between CC and white matter. Indeed, a distinct pattern was observed in the typically developing group, where the area of CC was positively correlated with age and total white matter volume. This result confirms the findings of extended growth of CC with age (Giedd et al. 1999a, b; McLaughlin et al. 2007) with white matter volume following the same pattern. Linear increases in white matter with age have been widely reported in typical development (Barnea-Goraly et al. 2005; Giedd et al. 1999a, b; Keshavan et al. 2002; Reiss et al. 1996), indicating that brain circuits become more coherent and myelinated, particularly in areas involved with complex cognitive functions (Barnea-Goraly et al. 2005).

Finally, callosal measures were positively associated with improved performances in FSIQ, speed of processing and visual attention only in the typically developing group, a result that is in accordance with previous reports (Schulte et al. 2005; Hines et al. 2002), but not observed in our clinical group. Although these results do not allow us to clearly state that CC abnormalities in WS may be associated with cognitive deficits, we have obtained indirect evidence that partially support this hypothesis. First, we observed reduced volumetry and abnormal shape in caudal areas of the CC, brain regions associated with visuo-spatial functioning (Eckert et al. 2005; Meyer-Lindenberg et al. 2004), an important hallmark of WS cognitive architecture. Second, both groups diverge regarding the correlation patterns between callosal measures and IQ, suggesting that this may reflect less inter-hemispheric transfer, affecting visual and verbal information processing in WS. Finally, CC data in a variety of other developmental disorders (e.g. autism, schizophrenia, Tourette's syndrome and developmental delay disorder) reinforces this hypothesis, namely showing an association between callosal measures (shape and size) and certain behavioural, social, language and attention features. For example, an association between callosal thinning (Vidal et al. 2006; Hardan et al. 2009) and clinical features of autism, such as social deficits, repetitive behaviors and sensory abnormalities, have been reported (Hardan et al. 2009). In a different direction, increased CC size and thickness were positively with psychopathic antisocial personality (Raine et al. 2003) and with severity of tics in Tourette's syndrome (Plessen et al. 2004).

The results from this study show evidence of abnormal CC volume, shape and thickness profiles in WS. Together,

this integrated approach is consistent with the fact that morphogenesis changes of the CC are associated with complex mechanical and genetic factors (Van Essen 1997). Interestingly, midline structures are the most vulnerable to the effects of physical and mechanical properties of morphogenetic mechanisms that model shape during brain development (Van Essen 1997; Van Essen and Drury 1997; Van Essen et al. 1998), including the corpus callosum (Lenroot and Giedd 2006). Indeed, previous evidence reporting midline brain regions abnormalities in WS must be considered (Meyer-Lindenberg et al. 2005; Capitao et al. 2011b; Sampaio et al. 2010). Furthermore, WS is a genetic disorder in which several genes are implicated, including FZD3 and FZD9, that are part of *Wnt* signalling pathways involved in convergence and extension control mechanisms (e.g. axon elongation) in mammals (Lindwall et al. 2007). This evidence suggests that deletion of genes within WSCR may play an important role in the mechanisms that model shape and regulate timing of CC axonal growth/migration/pruning in specific developmental growth windows. Specifically, a shorter, curvier, thicker but overall smaller CC in WS may reflect more neuronal aggregation due to greater cell packing densities and/or decreased fiber pruning during development. Indeed, research has shown that callosal axons are eliminated postnatally throughout adulthood (Raine et al. 2003; LaMantia and Rakic 1990) and that extensive postnatal axonal growth of CC (Thompson et al. 2000; Giedd et al. 1999a) is likely due to an increased myelinization of the CC fibers. This CC axon elimination and myelinization can be related to increased synaptic density throughout the cerebral cortex (LaMantia and Rakic 1990; Hardan et al. 2009). and reflect increased inter-hemispheric transfer. Therefore, a possible decreased inter-hemispheric transfer may be associated with cognitive functioning in WS, which is in accordance with other studies showing increased callosal size and abnormal interhemispheric transfer (e.g. Raine et al. 2003).

A limitation of the current study concerns the size of the samples and the fact that all individuals with WS displayed moderate intellectual disabilities. Larger samples will be needed in future studies to allow the generalization of these findings and incorporate new white matter assessment tools like diffusion tensor imaging.

In summary, CC morphometry and shape were evaluated in WS and typically developing individuals. We found group differences regarding absolute and relative volumes and CC shape, suggesting that CC abnormalities may contribute to neurocognitive difficulties in WS, in particular social–emotional and visuo-spatial functioning. Abnormal shape morphology of the CC could help to clarify structural deformities associated with abnormal neurodevelopment processes.

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