

Association Between Cerebral Shape and Social Use of Language in Williams Syndrome

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Williams syndrome (WS) is a neurogenetic disorder resulting from a hemizygous microdeletion at band 7q11.23. It is characterized by aberrant development of the brain and a unique profile of cognitive and behavioral features. We sought to identify the neuroanatomical abnormalities that are most strongly associated with WS employing signal detection methodology. Once identified with a Quality Receiver Operating Characteristic Curve (QROC), we hypothesized those brain regions distinguishing subjects with WS from controls would be linked to the social phenotype of individuals with this disorder. Thirty-nine adolescents and young adults with WS and 40 typically developing controls matched for age and gender were studied. The QROC identified a combination of an enlarged ventral anterior prefrontal cortex and large bending angle of the corpus callosum to distinguish between WS and controls with a

sensitivity of 85.4% and specificity of 75.0%. Within the WS group, bending angle significantly correlated with ventral anterior prefrontal cortex size but not with other morphometric brain measures. Ventral anterior prefrontal size in subjects with WS was positively associated with the use of social engagement devices in a narrative task assessing the use of social and affective language. Our findings suggest that aberrant morphology of the ventral anterior prefrontal cortex is a pivotal contributing factor to the abnormal size and shape of the cerebral cortex and to the social-affective language use typical of individuals with WS.

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INTRODUCTION

Williams syndrome (WS) is caused by a ~1.6 Mb chromosomal microdeletion at band 7q11.23 (Bayes et al., 2003). The microdeleted region consists of ~28 genes. The estimated incidence of WS is up to 1 in 7500 live births (Stromme et al., 2002). The syndrome is a multisystem disorder manifested by a wide range of medical disorders (Pediatrics, 2001) and the majority of people with WS have cognitive deficits, with IQs

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typically in the mild to moderate range of mental retardation.

Neuroanatomical Profile of WS

Social behavior in WS may involve interaction of several factors including social cognition and social desire, regulation of emotions and disinhibition [Bellugi et al., 2007; Porter et al., 2007]. Two key brain networks are putatively involved in shaping social behavior. The first is the ventral circuit monitoring social cognition that includes the amygdala, anterior cingulate, superior temporal gyrus (STG) and mediadorsal nucleus of the thalamus [Adolphs, 2001; Bachevalier and Loveland, 2006]. The amygdala processes multimodal sensory information and retrieves socially relevant knowledge by analyzing the emotions of facial expressions [Adolphs, 2001; Bachevalier and Loveland, 2006]. The social information processed in the amygdala is transferred to the orbitofrontal cortex where social responses and behaviors are selected [Adolphs, 2001]. The second brain network regulating social behavior is the striatal-thalamocortical loop. This network is in charge of behavioral inhibition and includes prefrontal regions—the orbital and lateral cortices and anterior cingulate [Middleton and Strick, 2002].

Research accumulated in recent years has begun to delineate the neuroanatomical abnormalities occurring in individuals with WS. Overall brain volume in WS is decreased by about 10%, which is particularly attributable to reductions in parietal and occipital lobe volumes [Meyer-Lindenberg et al., 2004; Reiss et al., 2004]. Regions that are relatively increased in gray matter volume in WS include the ventral prefrontal cortex, STG, amygdala, and posterior vermis of the cerebellum [Schmitt et al., 2001a,b; Meyer-Lindenberg et al., 2004; Reiss et al., 2004, 2000]. In addition to volumetric abnormalities, the shape of the cerebrum is different in WS. The decreased parieto-occipital lobe volumes relative to frontal volumes are thought to lead to a more flat bending angle of the corpus callosum and cerebrum in WS compared to typical controls [Schmitt et al., 2001a].

The Social Phenotype

People with WS are often described as being “overly friendly” and “gregarious” showing enhanced social interest in others, hypersensitivity to others’ feelings, and a strong affiliative drive. Yet they have pronounced difficulties in making friendships [Jones et al., 2000; Mervis and Klein-Tasman, 2000; Doyle et al., 2004]. An increased interest in social interactions is one of the most salient phenotypic features of the syndrome that is evident from infancy and extends into adulthood [Davies et al., 1998; Jones et al., 2000; Meyer-Lindenberg et al., 2006]. The gregariousness of individuals with WS is accompanied by social disinhibition even

towards people they objectively do not consider approachable [Frigerio et al., 2006].

Social Use of Language in WS

Language abilities in WS are sharply bifurcated. The grammatical proficiency is significantly impaired in individuals with WS and commensurate to the cognitive deficits associated with the syndrome. Social use of language is unique in individuals with the syndrome [Bellugi et al., 2000]. Language can be analyzed at the level of grammatical proficiency or alternatively in terms of the use of language in discourse and narrative. Reilly et al. [2004] investigated the development of grammatical mastery and the social use of language in children with WS, using narratives as a context, they coded for grammatical complexity and correctness. To control for length, proportions were created using the total number of clauses as the denominator (see Materials and Methods Section). Children with WS syndrome were found to produce many fewer grammatically correct clauses than normal controls, reflecting their grammatical deficiencies. The same narratives were also coded for the use of social evaluative language. Social evaluative language refers to lexically conveyed affect and sociability, or language that reflects the narrator’s attitude or perspective. Evaluative devices are linguistic tools used to attribute emotions or motivations to characters in the story, build suspense, and maintain audience involvement and interest [Berman and Slobin, 1994]. Examples include: emphatics, intensifiers (e.g., *really*, *very*, and *so*), character speech, direct quotes, and sound effects. An added category of evaluative devices termed “audience hookers,” defined as devices to capture and maintain the listener’s attention, was developed to characterize language functions salient in WS. Using Reilly Evaluation Coding System (RECS) [Reilly et al., 1998], it was found that in contrast to their grammatical performance, the WS group used significantly more evaluative language than controls [Losh et al., 2000; Reilly et al., 2004; Bellugi et al., 2007] (see Fig. 1a and b). Thus, in WS there is a sharp bifurcation between proficiency with linguistic structure (mastery of morpho-syntax) and the social affective use of language (evaluation).

The excessive use of social affective language in WS compared to other groups has now been shown in a series of studies:

- (a) Excessive evaluative language has been identified across different ages in WS from childhood through late adolescence [Reilly et al., 1990, 2004; Losh et al., 2000].
- (b) Abnormal social evaluation seems specific to WS. WS exhibit significantly higher use of social language in comparison to normal controls and other neurodevelopmental disorders individuals

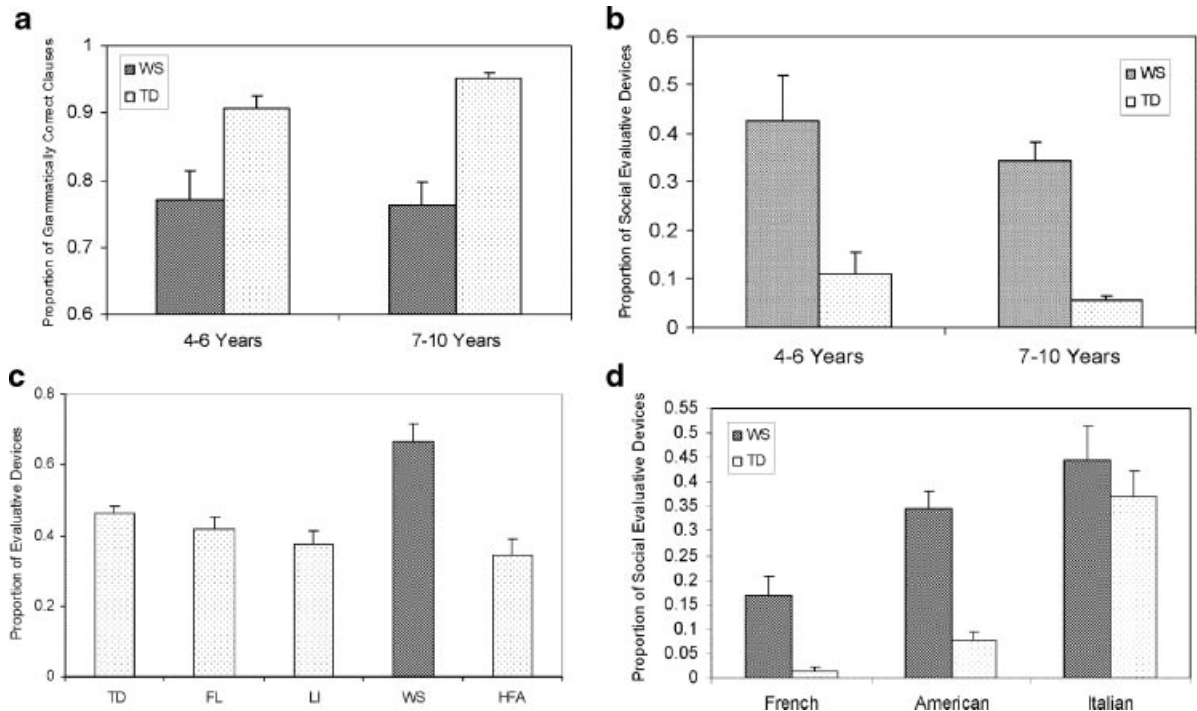


FIG. 1. In comparison to typically developing controls (TD), WS show grammatical impairment in morphosyntax (**Panel a**), yet exhibit consistently higher use of social affective language (**Panel b**). WS also exhibit significantly higher use of social language than TD subjects, subjects with early focal lesions (FL), language impairment (LI), and high functioning autism (HFA; **Panel c**). Abnormally high use of social affective language is characteristic in WS compared with normal controls from three different cultures (**Panel d**). Adapted with permission from Reilly et al. [2004, 2005a].

with focal brain lesions, language impairment and high functioning autism [Reilly et al., 2004; Järvinen-Pasley et al., 2008] (see Fig. 1c)

- (c) Excessive social language is characteristic of WS in other discourse genres compared to other groups, not only in narratives, but also in picture description, biographical interviews and dyadic conversation [Bellugi et al., 1999].
- (d) Evaluative language is significantly higher in WS than controls across different languages and widely different cultures (France, Italy, USA), indicating the genetic predisposition for social affiliation in WS [Reilly et al., 2005a,b; Zitzer-Comfort et al., 2007] (see Fig. 1d).

Summary

The purpose of the present study was to advance our understanding of the relation between neuro-anatomical abnormalities and hypersocial behavior in WS. Since a wide variety of brain regions are aberrant in WS, it is difficult to know which of these regions are most strongly associated with particular aspects of the cognitive and behavioral phenotype. We decided to focus on the use of atypical social and affective language in WS, as this is a salient and replicable phenotypic characteristic of the syndrome. We predicted that brain regions that most sensitively and specifically distinguish individuals with WS from controls would also significantly

correlate with this aspect of the social phenotype. To test this hypothesis, we first employed signal detection method to identify those brain regions that are most strongly associated with WS, and then we evaluated the association of these regions with a specific measure of social use of language.

MATERIALS AND METHODS

Sample

Participants included 39 young adults with WS and 40 age and gender matched typically developing controls. The clinical characteristics of the study sample are presented in Table I. All participants with WS were recruited and evaluated at the Salk Institute as part of a comprehensive multidisciplinary research program project (HD 330113). Controls were recruited at both the Salk Institute and Stanford University. Participants with WS were confirmed

TABLE I. Clinical Characteristics of Study Subjects

	Williams syndrome	Controls
Mean age (SD)	30.3 (8.4)	27.5 (7.4)
Males/females	18/21	16/24
Mean full-scale IQ (SD)	69.6 (7.2)	
Mean verbal IQ (SD)	72.8 (6.8)	
Mean performance IQ (SD)	68.5 (7.7)	
Mean SED scores (SD)	0.61 (0.17)	

to have a deletion of chromosome 7q11.23 that included the elastin gene, using multicolor fluorescence in situ hybridization and met diagnostic criteria for WS based on phenotypic features according to the WS Diagnostic Score Sheet [Pediatrics, 2001]. IQ was assessed in 37 of 39 individuals with WS using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [Wechsler, 1997].

The typically developing control subjects had no history of major psychiatric, neurological, or cognitive impairment. All behavioral data were acquired within 1 year from scan acquisition time. The institutional review boards of both Stanford University and Salk Institute approved the research protocols. All participants and, if appropriate, their parents or guardians provided informed written consent for the study.

Image Acquisition and Processing

All participants were scanned with a General Electric 1.5 Tesla Signal Scanner (GE Imaging Systems, Milwaukee, WI) located at one of three sites: University of California, San Diego Medical Center Magnetic Resonance Imaging Institute; Scripps Clinic, San Diego; or Stanford University as previously described [Reiss et al., 2004]. In all cases, sagittal brain images were acquired with the same three-dimensional (3D) volumetric radio frequency spoiled gradient echo pulse sequence using the following scan parameters: repetition time, 24 ms; echo time, 6 ms; flip angle, 45° ; slice thickness, 1.2 mm; field of view, 24 cm; and matrix size, 256×192 for 124 contiguous slices. Data processing steps were conducted following a well-established protocol [Reiss et al., 1998] included removal of non-brain tissues from the images, correction of equipment related image artifacts, and separation (segmentation) of tissue components (gray, white, CSF).

Volumetric Measures

Each brain was positionally normalized to make it parallel to the plane defined by the anterior and the posterior commissures. The brain tissue was subdivided based on Talairach parcellation method into the four cerebral lobes, subcortex, and brainstem on the basis of stereotaxic atlas template [Talairach and Tournoux, 1988; Reiss et al., 1998; Kates et al., 1999]. The cerebellum was manually segmented.

Four subregions of prefrontal gray matter (dorsal, mid-superior, mid-inferior, and ventral-anterior) were obtained using previously described methods [Reiss et al., 2004; Schoenemann et al., 2005]. Briefly, the prefrontal cortex was defined as all frontal cortical gray matter lying anterior to a coronal plane intersecting the most anterior point of the genu of the corpus callosum [Schoenemann et al., 2005]. The inferior subdivision of the prefrontal parcellation corresponds to the ventral anterior prefrontal cortex

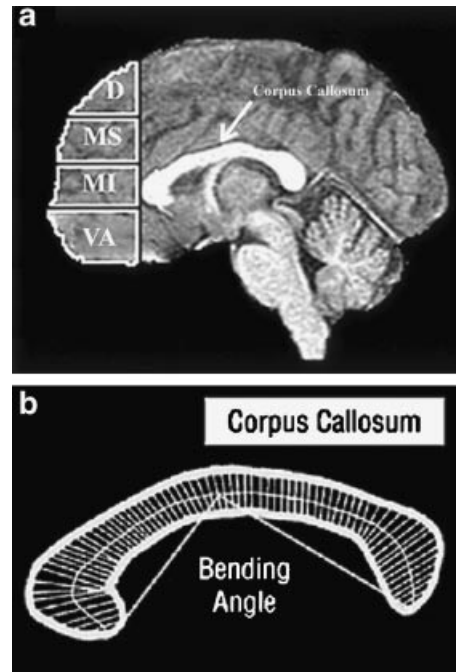


FIG. 2. **Panel a:** shows the subdivisions of the prefrontal cortex. The prefrontal cortex was defined as the part of the cortex lying anterior to a coronal plane intersecting the most anterior point of the genu of the corpus callosum. The prefrontal cortex was then subdivided by three axial planes parallel to a line passing through the anterior and posterior commissure. Each axial plane was determined at the same location for each participant after fitting a proportional (Talairach) grid system to the normalized brain. The prefrontal parcellation yielded four prefrontal subregions: D, dorsal, MS, middle-superior, MI, middle-inferior, VA, ventral-anterior. **Panel b:** The bending angle of the corpus callosum is the angle created by lines connecting the most anterior and posterior points of the corpus callosum with the midline of the corpus callosum.

(VAPFC, Fig. 2a). In a similar manner, the cingulate gyrus was subdivided into four components corresponding to inferior, dorsal-anterior, middle, and posterior segments [Reiss et al., 2004].

Trained research assistants, following detailed protocols, delineated additional regions of interest (ROI) volumes manually. The ROI variables included the volumes of the hippocampus and amygdala [Kates et al., 1997], thalamus [Chang et al., 2005] the gray matter volume of the STG [Kesler et al., 2003], and the bending angle of the corpus callosum [Schmitt et al., 2001a] (Fig. 2b). Raters were blind to subject diagnosis, gender, and other subject characteristics; inter-rater reliabilities for volumes of manually drawn ROIs were above 0.90 as calculated by the intraclass correlation coefficient.

Social Use of Language

Twenty-five participants with WS (11 females, 14 males, mean age 29.3 ± 9.5 and mean FSIQ 69.8 ± 7.1) completed an assessment of social cognition using a narrative task that has been previously used and described in studies of individuals with WS [Reilly et al., 1990, 2004; Losh et al., 2000]. There is no overlap between the subjects

evaluated for language in the current study and previous reports on language in WS. In this narrative task, subjects are presented with the 24-page wordless picture book "Frog, where are you?" [Mayer, 1969], and asked to tell the story to the experimenter. The narrations were video- and audio-taped; they were then transcribed, according to the Child Language Data Exchange System (CHILDES), a system that transcribe the oral stories of participants to written transcriptions [MacWhinney, 2000].

The stories were then coded using the coding scheme which was designed to assess both grammatical proficiency, and use of evaluative language [Reilly et al., 1998]. Stories were first coded for length as measured by number of propositions; a proposition is defined as a verb and its arguments; semantically, a proposition corresponds roughly to a single event. Each clause in a complex sentence was considered to represent one event, and therefore, one proposition. To control for varying story lengths, the number of propositions in a story was used as a denominator for the additional analyses. Morphological errors were tallied and categorized by type as were the frequency and types of complex syntax recruited. Proportions were created for all measures. Transcription and coding was conducted by two independent trained researchers and reliability was at or above 90%.

For this project, we were especially interested in the use of social evaluative language. Evaluative language is defined as elements within the story that convey the narrator's perspective on events [Labov and Waletzky, 1967]. One type of evaluative language is social engagement devices (SED); these include phrases that add interest, serving to attract and maintain the listener's attention, e.g., sound effects, intensifiers, *very*, *so* and character speech, such as, "*The boy said, 'Oh, little froooggie, where have you gone?'*" Additional evaluative devices include inferences about characters and events, character motivation, and the narrator's level of certainty concerning events. According to Labov's definition, all stories include evaluation. In this study, we were particularly interested in the degree to which the WS participants used social versus other types of evaluative devices. Thus, each participant received proportion score (SED), which was calculated by dividing the number of social evaluations by the total number of evaluative devices.

The Quality Receiver Operating Characteristic Curve (QROC) Analysis

The QROC [Kraemer, 1992; Kiernan et al., 2001; O'Hara et al., 2002; Salmond et al., 2002; Gothelf et al., 2008] version 4.19 (<http://mirecc.stanford.edu>) was applied to identify the brain regions that most sensitively and specifically distinguished subjects

with WS from controls. For this analysis, we included brain regions that have been reported by our group or others to be abnormal in subjects with WS [Schmitt et al., 2001a,b; Meyer-Lindenberg et al., 2004; Reiss et al., 2004; Meyer-Lindenberg et al., 2005b]. The gray matter volumes of the following regions were included in the QROC analysis: ventral and dorsal-anterior prefrontal regions, dorsal-anterior cingulate, parietal and occipital lobes, STG, cerebellum, amygdala, hippocampus, and thalamus. The bending angle of the corpus callosum also was included [Schmitt et al., 2001a].

These brain measures were entered as independent variables, and the binary outcome measure was group status (WS vs. controls). To statistically account for the smaller overall brain size of subjects with WS, all brain variables entered into the analysis, besides the bending angle, were adjusted using linear regression, with total cerebral tissue as the independent variable, and each of the brain regions as the dependent variable. The unstandardized residual value of each region derived from these analyses was then entered into the QROC. The QROC searched all independent variables, values representing adjusted brain volumes and their associated cutpoints, and identified those that had the optimal balance between sensitivity and specificity for distinguishing between WS and controls. Once the optimal variable and associated cutpoints were identified, the strength of the cutpoint for the chosen variable was compared to the random probability by using a stopping rule of a $P < 0.001$ in a 2×2 Chi-square test. If the variable passed this "test," the sample was divided into two subgroups, above and below the cutpoint. The QROC analysis was then restarted, independently, for each of these two subgroups. The procedure again examined every remaining variable and associated cutpoints to see if either group could be further differentiated. The resulting outputs were given as a decision tree (see Fig. 3). The QROC procedure stopped when it

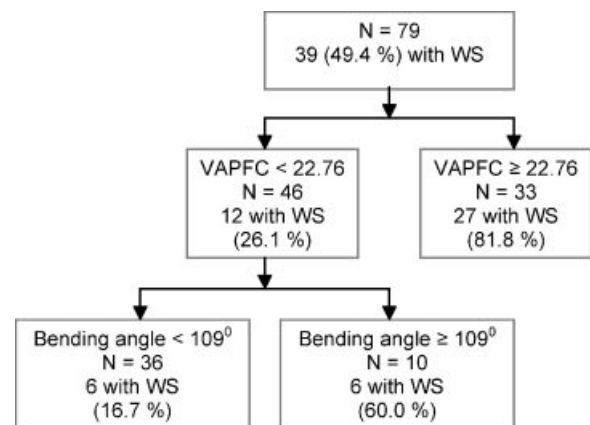


FIG. 3. Quality Receiver Operating Characteristic Curve (QROC) showing the brain regions that best distinguish between subjects with WS and controls.

hit the stopping rule, and/or when a subgroup was too small for further analysis [Kraemer, 1992; Kiernan et al., 2001; O'Hara et al., 2002; Salmund et al., 2002].

RESULTS

Brain Regions That Distinguish Williams Syndrome

As illustrated in Figure 3, from a total of 79 subjects, 39 (49.4%) had WS and 40 (51.6%) were controls. At the first level of the QROC, the adjusted gray matter volume of the VAPFC was identified as the most optimal variable that distinguished between WS and controls, with a cut point of 22.76 cm^3 . Of the 33 subjects with $\text{VAPFC} \geq 22.76$, 27 (81.8%) were from the WS group; whereas of the 46 subjects with $\text{VAPFC} < 22.76$ only 12 (26.1%) had WS. Alternatively, 27 of 39 subjects with WS (69.2%) and only 6 of 40 TD controls (15.0%) had large VAPFC. A univariate analysis of covariance (ANCOVA) with VAPFC as the dependent variable, group (WS vs. controls) as fixed factor and total cranial tissue as a covariate confirmed a robust difference in VAPFC volumes between groups ($25.6 \text{ cm}^3 \pm 5.1 \text{ cm}^3$ for WS vs. 17.1 ± 4.6 for controls, $t = 5.6$, $P < 0.0001$, effect size = 1.8).

Among those with $\text{VAPFC} < 22.76$ (left side of Fig. 3), the next optimal variable to divide the sample was the bending angle, with a cutpoint of 109° . The end result of the QROC partition yielded three groups: (1) $\text{VAPFC} \geq 22.76 \text{ cm}^3$, 81.8% of whom were from the WS group; (2) $\text{VAPFC} < 22.76 \text{ cm}^3$ and bending angle $\geq 109^\circ$, 60.0% with WS; (3) $\text{VAPFC} < 22.76 \text{ cm}^3$ and bending angle $< 109^\circ$, only 16.7% with WS. The combination of large VAPFC or small VAPFC and large bending angle had 85.4% sensitivity and 75.0% specificity in distinguishing WS from controls.

Social Use of Language

In this study, we investigated the extent to which the WS participants used social versus other types of evaluative devices. Each participant received a score reflecting the proportion of SED to the total evaluation score. The mean SED score of the WS group was 0.62 ± 0.17 , with no gender differences ($t = 0.96$, $P = 0.34$). To contextualize these results, we also coded Frog story narratives from additional sample of 40 TD young adults also recruited from the area of Salk Institute and Stanford University. The TD controls were matched for age (27.6 ± 7.2 years) and gender (20 males and 20 females) to the WS group. As is typical of narratives, both populations used significant amounts of evaluations in their stories. However, the two groups differed in the distribution of social versus other types of evaluation. As seen in Figure 4, the proportion of SED was

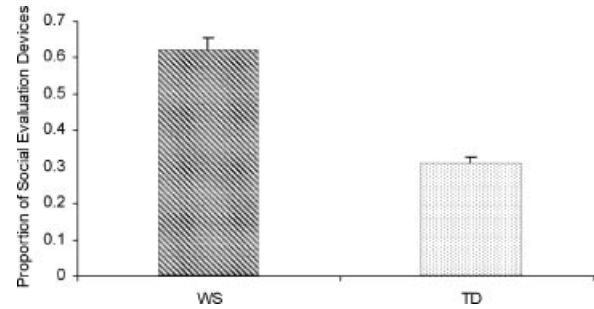


FIG. 4. Proportion of social evaluation devices (SED) was significantly higher in the Williams syndrome (WS) group compared to typically developing controls (TD).

significantly higher in the WS group (0.61 ± 0.17) than in the TD control group (0.31 ± 0.10 , $t = 8.0$, $P < .0001$, effect size = 2.2).

Association Analyses of Cerebral Shape

The QROC identified enlarged VAPFC and bending angle of the corpus callosum as key components of the morphological brain phenotype in WS. As flattening of the bending angle in WS may be secondary to focal changes in both anterior and posterior parts of the brain, we tested the hypothesis that the bending angle variable would be significantly correlated with other morphological measures used in this study. In particular, since morphology of both the VAPFC and parieto-occipital cortex are abnormal in WS [Meyer-Lindenberg et al., 2004; Reiss et al., 2004], both brain regions potentially contribute to the flattening of the bending angle. Bending angle was significantly correlated with VAPFC ($r = 0.36$, $P < 0.05$), but not with occipital ($r = -0.17$, $P = 0.28$), nor with parietal ($r = 0.29$, $P = 0.07$) lobe volumes. In the control group, there were no significant correlations between the bending angle and any of these three measures ($P > 0.1$).

Association Between Social Evaluation Device Scores and VAPFC Size

To test the hypothesis that the VAPFC would be associated with the social phenotype of WS, specifically use of social evaluative language, we compared SED scores of the WS subgroup with large VAPFC ($\geq 22.76 \text{ cm}^3$, $n = 17$) and the WS subgroup with small VAPFC ($< 22.76 \text{ cm}^3$, $n = 8$). The subgroup with large VAPFC had significantly higher SED scores than the subgroup with small VAPFC (0.67 ± 0.16 vs. 0.50 ± 0.15 , $t = -2.5$, $P < 0.05$, effect size = 1.1). There was also a significant positive medium to large correlation between adjusted VAPFC volume and SED scores of the WS group ($r = 0.50$, $P < 0.01$).

To evaluate whether, in addition to VAPFC, other brain regions significantly contributed to the variability of SED scores in the WS group, we conducted a linear regression with several brain regions chosen as

predictors based on the literature indicating the importance of these regions for social regulation [Adolphs, 2001; Bachevalier and Loveland, 2006]. The brain regions chosen were the adjusted volumes of the amygdala and STG, in addition to adjusted VAPFC volume. FSIQ scores were entered as additional predictor. Only adjusted VAPFC volume significantly predicted SED scores ($\beta = 0.50$, $P = 0.03$), whereas amygdala volume ($\beta = -0.17$, $P = 0.42$), STG volume ($\beta = 0.11$, $P = 0.53$) and FSIQ scores ($\beta = 0.03$, $P = 0.90$) did not.

DISCUSSION

Using QROC analysis, we identified the VAPFC and bending angle of the corpus callosum as measures that distinguish individuals with WS from typically developing controls with moderately high sensitivity and specificity (85.4% and 75.0%, respectively). We also showed that a unique aspect of WS social phenotype, the use of enhanced social language, positively correlates with the size of the VAPFC in WS.

The data presented here are in line with previous studies of brain morphology in WS using a variety of image analysis methods. Results from these studies indicate the existence of aberrant cortical morphology and shape in individuals with WS including increased gyrification [Gaser et al., 2006], increased cortical thickness [Thompson et al., 2005], and folding abnormalities [Van Essen et al., 2006]. Interestingly, the VAPFC region is among the most prominent morphological abnormalities emerging from brain imaging studies focused on WS [Meyer-Lindenberg et al., 2004; Reiss et al., 2004; Gaser et al., 2006; Van Essen et al., 2006].

In a previous study, it was found that the bending angle of the corpus callosum is larger (flatter) in WS compared to typically developing controls [Schmitt et al., 2001a]. In the present study, we found a significant association between the bending angle of the corpus callosum and VAPFC volume, but not with other morphological measures. It is possible, however, that we would have detected other significant correlations if more fine-grained measures of posterior brain morphology were available. The association between the bending angle and VAPFC suggests that aberrant development of the most anterior parts of the cortex contributes to abnormal bending of the cerebrum in WS as well as to prominence of the VAPFC cortical region as defined in the present study.

Overall, the cerebral cortex of individuals with WS is reduced in size in its posterior pole and increased in size in its anterior pole. There is increasing evidence that anterior/posterior patterning of cortical development is determined by differential gene expression [Grove and Fukuchi-Shimogori, 2003]. Haploinsufficiency of one or several genes that are

within the WS deletion region may result in the observed unbalanced development of the cerebral cortex of affected individuals. One such candidate gene is the *FZD9*, related to the *WNT* gene family, which are involved in the anterior/posterior patterning of the cortex.

The QROC analysis indicated that the VAPFC is a strong distinguishing characteristic of individuals with WS. Abnormal morphology and function of the orbitofrontal cortex in WS has been identified in several brain imaging studies [Meyer-Lindenberg et al., 2004; Meyer-Lindenberg et al., 2005a; Van Essen et al., 2006]. The orbitofrontal cortex, which partially overlaps with the VAPFC region defined here, is a pivotal part of the ventral circuit that monitors social cognition and regulates emotional states and behavior [Bachevalier and Loveland, 2006].

Interestingly, we found that the volume of the VAPFC was positively associated with the use of social language of individuals with WS, but not with general cognitive functioning (IQ scores). Somewhat surprisingly, the amygdala and STG regions were not identified by the QROC as strongly distinguishing between WS and controls. Furthermore, it was also only the VAPFC and not the volume of the amygdala or STG that was significantly associated with the abnormal use of social language in individuals with WS.

Social behavior in WS is characterized by a strong drive towards social interaction. Social drive is regulated by prefrontal regions and in particular by the medial OFC (Roberts et al., 2004). Cognitive studies of WS suggest that social behavior of individuals with WS is similar to that of patients with acquired frontal lobe injuries [Porter et al., 2007]. Like patients with acquired frontal lobe injuries there seems to be dissociation in WS between “knowing” and “doing” in the social domain. For example, both WS and frontal-injured patients know that strangers should not be approached but yet indiscriminately approach strangers [Porter et al., 2007]. We believe that the dissociation in WS between “knowing” and “doing” in social contexts is attributed to their deficits in inhibitory capacity. Frontostriatal dysfunction during response inhibition in WS was recently reported [Mobbs et al., 2007]. Disinhibition in WS is also consistent with abnormal development of the orbitofrontal cortex that partially overlaps with the VAPFC region defined here. Thus, our results associating VAPFC volume with social use of language in WS provide further support for the important role of prefrontal cortex abnormalities in shaping the social phenotype of WS.

In the present study, we utilized a signal detection method (QROC) that has rarely been used in imaging studies. As this study shows, QROC was instrumental in the identification of specific brain measures that are most closely associated with WS. This was

especially important since in WS there are a myriad of structural changes in the brain. Using the QROC we were able to identify the VAPFC, and consequently to elucidate its association with the use of social language in WS. The QROC also addresses limitations of traditional parametric statistical analyses commonly used in analyzing brain-imaging data. For example, using logistic regression for analysis of brain imaging data does not allow for identifying higher order interactions and does not provide cutpoints for determining sensitivity and specificity [Kiernan et al., 2001]. As such, QROC should be considered as a potentially useful tool in future neuroimaging studies.

Our findings raise the possibility that aberrant neurodevelopment of the ventral anterior region of the prefrontal cortex is an important factor contributing to the unique cerebral morphology of individuals with WS, as a consequence of haploinsufficiency of genes from the deleted region. The results of the present study also suggest that the abnormal morphology of the VAPFC may be associated with the hypersocial language of individuals with WS. However, we cannot conclude from our data if the association between VAPFC size and social language is specific to WS, or also occurs in TD subjects and other group of patients.

Limitations

Because the VAPFC measure in our study was derived from an atlas-based parcellation using dividing planes, the size of this brain region is likely to reflect cortical shape characteristics as well as actual volume. The VAPFC is comprised mainly of the OFC, but includes also the gyrus rectus and small portion of the inferior frontal cortex. Future brain-behavior studies should focus on the structure and function of sub-components of this region, including the gyrus rectus and orbitofrontal cortex, and their association with measures of social cognition, emotion and behavior.

The association between VAPFC volume and SED scores identified in our study was relatively robust and VAPFC volume predicted 28% of SED scores. However, it should be acknowledged that the multiple statistical testing employed in our study is a limitation and results should be replicated in future studies. Of note, the SED scale used has yet no standard norms. Additional limitation of the present study is the comparison group which included typically developing subjects and not matched IQ subjects.

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