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To modulate or not to modulate: Differing results in uniquely shaped Williams syndrome brains

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Voxel based morphometry (VBM) studies of Williams syndrome (WS) have demonstrated remarkably consistent findings of reduced posterior parietal gray matter compared to typical controls. Other WS VBM findings have been inconsistent, however. In particular, different findings have been reported for hypothalamus and orbitofrontal gray matter regions. We examined a sample of 8 WS and 9 control adults and show that the hypothalamus and orbitofrontal cortex results depend on whether the images undergo Jacobian modulation. Deformation based morphometry (DBM) analysis demonstrated that major brain shape differences between the groups accounted for the Jacobian modulated gray matter findings. These results indicate that cautious interpretations of modulated gray matter findings are warranted when there are gross shape and size differences between experimental groups. This study demonstrates the importance of methodological choices towards understanding a disorder like WS, but also highlights the consistency of parietal lobe, orbitofrontal, and midbrain findings for this disorder across methodologies, participants, and research groups.

Introduction

VBM has been used to characterize the neurobiology of various disorders, development, aging, gender differences, training, and exceptional talents (Draganski et al., 2004; Good et al., 2001; Kwon et al., 2004; Luders et al., 2004; Wilke et al., 2003) The popularity of VBM stems from (1) the opportunity to examine all of the voxels representing the cerebrum, (2) faster data collection and analysis compared to manual methods, (3) local specificity for gray or white matter findings that may be lost in large regional volume manual measures, and (4) integration with fMRI or DTI results for greater insight into a question of interest. There are many different methodological choices that can be made in pre-processing images for VBM analyses that depend on the question or group of images that are examined. These choices can impact study outcomes and the likelihood that results from studies of the same population will replicate when different pre-processing choices are made. VBM studies of Williams syndrome (WS) represent one example where different results have been reported between studies (Meyer-Lindenberg et al., 2004; Reiss et al., 2004). We present evidence that these different results reflect different methodological choices.

WS occurs when ~28 genes are deleted on the long arm of Chromosome 7 (Korenberg et al., 2000; Tassabehji et al., 2005). This deletion has widespread developmental effects that include atypical facial features, cardiac and gastrointestinal anomalies, glucose intolerance, hypertension, strabismus and sensorineural hearing loss (Cherniske et al., 2004; Korenberg et al., 2003). The deletion also affects development of visuospatial systems (Atkinson et al., 1997), sparing systems important for object recognition (Landau et al., 2005); and is associated with hyper-sociability (Doyle et al., 2004). Neuroimaging studies of WS have largely focused on the visuospatial and social-emotional problems in affected individuals with the goal of identifying impaired neural systems associated with the ~28 gene deletion.

The WS brain has a unique structural profile that seems to parallel the unique WS cognitive and behavioral profile. The 8% to 18% decrease in posterior cortex white matter and gray matter produces a characteristic brain shape that is easily differentiated

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from typical brains (Reiss et al., 2004; Schmitt et al., 2001a,b; Thompson et al., 2005). Two VBM studies from different research groups have shown that this decrease in posterior cortex volume is focused in posterior portions of the intraparietal sulcus bilaterally (Meyer-Lindenberg et al., 2004; Reiss et al., 2004). These findings are consistent with decreased superior parietal lobule volume (Eckert et al., 2005b) and decreased intraparietal sulcus depth in people with WS compared to controls (Kippenhan et al., 2005).

The two VBM studies of WS also reported results that were inconsistent. In particular, Meyer-Lindenberg et al. (2004) observed decreased hypothalamus and orbitofrontal gray matter in people with WS compared to controls, where as Reiss et al. (2004) observed increased orbitofrontal gray matter in people with WS compared to controls. The Meyer-Lindenberg and Reiss studies differed in their sample size (14 WS vs. 40 WS, respectively), the cognitive ability of the WS subjects (high functioning vs. "typically" functioning), MRI scan orientation (axial vs. sagittal), the normalization strategy (linear and non-linear vs. linear only), the choice of template (study specific vs. MNI template), segmentation (study specific a priori maps vs. MNI template a priori maps), the smoothing kernel (10 mm vs. 8 mm), and whether the images were Jacobian modulated or not (yes vs. no).

We present results that indicate the modulation step, modifying the signal intensity of a voxel by how much it was expanded or contracted during the process of warping the voxel into standardized coordinate space, can account for the different hypothalamic and orbitofrontal findings reported by these two studies. This study (1) highlights the consistent anatomical findings in WS, particularly for posterior parietal cortex, across research groups and WS samples, (2) raises cautions about interpretations of gray matter differences in VBM studies where there are also significant brain shape differences, and (3) demonstrates statistically unique orbitofrontal findings from the parietal lobe findings.

Methods

Participants

Eight adults with WS (4 females, 4 males; mean age 31.0 ± 12.3 years) and 9 typical control adults (6 females, 3 males; mean age 28.8 ± 11.0 years) were included in the present study. These participants were recruited for a series of functional imaging experiments (Mobbs et al., submitted for publication; Mobbs et al., 2004). Three of the WS participants were included in the Reiss et al. (2004) VBM study. Genetic diagnosis of the WS participants was established using florescent in situ hybridization (FISH) probes for elastin (*ELN*) (Korenberg et al., 2000). With the exception of one person with WS, all participants wrote with their right hand. All of the participants were native English speakers and gave written informed consent before participation. All experimental procedures complied with the standards of the human subjects committee at Stanford University School of Medicine.

MRI protocol

Coronal brain scans for each subject were acquired using a GE-Signa 1.5 T scanner at Stanford University (General Electric, Milwaukee, Wisconsin). The images were acquired using the following 3D volumetric radio frequency spoiled gradient echo pulse sequence parameters: TR = 35 ms, TE = 6 ms, flip angle = 45°, NEX = 1, matrix size = 256 × 192, field of view = 24 cm, slice thickness = 1.5 mm, 124 contiguous slices.

VBM Pre-processing and analyses

The "optimized" VBM pre-processing procedure used for this study was consistent with the Meyer-Lindenberg et al. (2004) protocol (Good et al., 2001) and SPM2 was used for image pre-processing and statistical analysis (http://www.fil.ion.ucl.ac.uk/spm/spm2.html). Group specific templates were created for this study from the images of 42 people with WS and 40 controls who participated in the Reiss et al. (2004) VBM study. The a priori gray matter, white matter, and CSF image templates from each group were used to segment the original T1 images. The segmented gray matter images were then normalized, using 12 parameter affine and 16 iteration non-linear transformations, to the 82 image WS and control a priori gray matter template. The spatial normalization parameters from the gray matter normalization were applied to the original T1 images. These normalized T1 images were segmented using the 82 image WS and control a priori gray matter, white matter, and CSF templates. The normalized and segmented gray matter images, Jacobian modulated and unmodulated, were then smoothed with a 12-mm kernel (Salmond et al., 2002). We chose to use group specific templates to replicate the Meyer-Lindenberg et al. (2004) template choice, which was based on the idea that a group specific template would improve the normalization of the WS images. While this approach may improve the normalization of images to the same standardized space and the validity of the statistical analyses, particularly for the 3 WS adults who also participated in the Reiss et al. (2004) study, replication studies using standard templates may generate different results because of differences in the degree of warping during normalization between our group specific template and standard templates.

Gray matter values for unmodulated images are typically referred to as gray matter density. The term density indicates that cortical thickness and/or white matter volume averaging in a particular area influences the size of the gray matter values. Gray matter values for Jacobian modulated images are referred to as gray matter volume. Gray matter volume reflects the influence of regional volumes on the size of the gray matter values, as well as cortical thickness and/or volume averaging.

Jacobian determinant images were also created from the spatial normalization parameters for DBM (Ashburner et al., 1998). These images were not smoothed because this representation of the normalization displacement field is inherently smooth. The Jacobian determinant images represent the transformations necessary to move a voxel in the native space image to a corresponding voxel in a template image. More generally, they reflect the local expansions and contractions necessary to fit the native space image to the template image. Because this information is used to modulate the images, DBM analyses were performed to determine if areas of group differences from the VBM analyses coincided with areas of DBM group differences. Common VBM and DBM findings might indicate that the VBM findings are a consequence of brain shape differences rather than differences in the amount of gray matter because gross shape information (the displacement) was used to alter the signal

Table 1
Unmodulated gray matter group comparison results

	Cluster size	*t*-score	*X*	*Y*	*Z*
Controls > WS					
Left intraparietal sulcus[a]	41	5.43	−20	−68	42
Right intraparietal sulcus[a]	47	5.34	28	−76	26
Left inferior semilunar lobule (Left inferior cerebellar hemisphere)	222	4.46	−14	−76	−54
Right isthmus/superior colliculus[b]	45	4.27	8	−34	−6
WS > Controls					
Left inferior frontal sulcus	79	6.26	−38	38	12
Left retrosplenial cortex[b]	135	5.66	−14	−44	18
Right cerebellar tonsil	73	5.57	8	−50	−46
Right putamen/claustrum/insula	312	5.47	30	−16	8
Right inferior frontal gyrus (pars triangularis)	47	4.98	46	18	16
Left fusiform gyrus[b]	110	4.85	−36	−66	−12
Left superior semilunar lobule (left inferior cerebellar hemisphere)[b]	82	4.58	−20	−76	−38
Left orbitofrontal gyrus[b]	49	4.54	−26	34	−18
Right orbitofrontal gyrus[a]	49	4.35	26	48	−16
Left superior occipital gyrus	18	4.34	−18	−78	24
Left cerebellar tonsil	18	4.24	−10	−52	−48
Left putamen/claustrum[b]	10	4.06	−30	−12	10
Right angular gyrus	10	4.00	40	−54	28
Right superior semilunar lobule (right inferior cerebellar hemisphere)[b]	10	3.87	16	−76	−36

†Observed only in the Meyer-Lindenberg study.
[a] Observed in Meyer-Lindenberg et al. (2004) and Reiss et al. (2004) studies.
[b] Observed only in the Reiss study.

intensity of the gray matter during the modulation procedure. It should be noted that DBM is a gross measure of deformation and is less sensitive than VBM for detecting local anatomical differences.

Analysis of variance (ANOVA) was used for the VBM and DBM comparisons. A statistical threshold of $P < 0.001$ was used rather than a more conservative family wise error corrected threshold. This statistical threshold was used because we had a priori hypotheses regarding the location of group differences based on previous VBM findings and because this study did not have the sample size power of the Reiss et al. (2004) study. Results that were consistent with the Meyer-Lindenberg and Reiss studies are

Table 2
Jacobian modulated gray matter group comparison results

	Cluster size	*t*-score	*X*	*Y*	*Z*
Control > WS					
Left intraparietal sulcus[a]	456	8.19	−20	−68	42
Right intraparietal sulcus[a]	417	6.92	28	−76	30
Hypothalamus[b]/basal forebrain/caudate/anterior temporal and hippocampus	2420	6.02	6	2	0
Left cingulate sulcus, marginal ramus[c]	86	5.91	−16	−40	50
Right medial temporal (uncus)	176	5.49	14	−14	−30
Left superior parietal gyrus[b]	297	5.32	−8	−64	70
Isthmus/superior colliculus/pulvinar[b]	338	4.90	12	−34	−8
Left inferior cerebellar hemisphere (inferior semilunar lobule)	288	4.72	−6	−82	−52
Left post-central gyrus	37	4.38	−18	−28	62
Right superior parietal gyrus[c]	83	4.32	6	−72	64
Left anterior inferior temporal gyrus	25	4.28	−42	−8	−48
Right post-central gyrus[c]	32	4.28	22	−36	54
Right anterior inferior temporal gyrus	24	4.21	20	14	−40
Right anterior superior temporal gyrus (medial)	14	4.16	24	−84	14
Left posterior thalamus/caudate	6	3.87	−18	−26	18
Left isthmus[c]	8	3.82	−18	−28	−10
WS > Controls					
No significant differences					

[a] Observed in Meyer-Lindenberg et al. (2004) and Reiss et al. (2004) studies.
[b] Observed in the Meyer-Lindenberg study.
[c] Observed in the Reiss study.

Table 3
Modulated VBM ANCOVA results, covarying for the eigenvariate from the midbrain DBM (shape) difference

	Cluster size	*t*-score	*X*	*Y*	*Z*
WS > Controls					
Left[a] and right retrosplenial cortex	1039	7.44	−8	−44	20
Right cerebellar anterior lobe/tonsil/biventer lobule[a]	1694	6.29	18	−68	−30
	8	3.87	44	−48	−32
Left middle temporal gyrus	103	5.52	−44	−46	0
Left superior occipital gyrus	117	5.38	−14	−80	24
Left inferior temporal gyrus	248	4.62	−54	−56	−24
Right orbitofrontal gyrus[a]	50	4.46	32	40	−22
	10	3.89	20	46	−14
Left claustrum/insula[a]	78	4.45	−30	−20	16
Right middle temporal gyrus	22	4.26	48	−42	−8
Right superior occipital gyrus	10	4.18	20	−74	24
Left orbitofrontal gyrus[a]	69	4.17	−24	40	−22
Left inferior occipital gyrus	6	4.01	−36	−74	0
Left cerebellar tonsil	14	4.00	−14	−44	−44
Left superior temporal sulcus	8	3.97	−40	−30	2
Right post-central gyrus[a]	7	3.96	54	−24	28

[a] Observed in the Reiss et al. (2004) study.

labeled in Tables 1, 2 and 3. Caution should be used interpreting positive findings from this study that were not observed in the Meyer-Lindenberg or Reiss studies.

Analysis of covariance (ANCOVA) also was used to examine gray matter volume differences that were independent of differences related to the group differences in deformation. A principal eigenvariate obtained from the DBM analysis was used as the covariate in the VBM ANCOVA (Eckert et al., 2005a; Lawrie et al., 2002). This eigenvariate, representing variance that each participant contributed to the DBM group difference, was from anatomical regions that exhibited inconsistent group differences in gray matter between the Meyer-Lindenberg et al. (2004) and Reiss et al. (2004) VBM studies. The goal of this analysis was to control for gross modulation effects on gray matter volume and confirm that the inconsistent gray matter findings between Meyer-Lindenberg et al. (2004) and the Reiss et al. (2004) could be attributed to modulation. This analysis also demonstrated the statistical independence of the parietal lobe group differences from the orbitofrontal group differences.

Results

Unmodulated VBM

Table 1 and Fig. 1 present the results for areas where controls had significantly more gray matter density than the WS group. In particular, there were group differences in areas that corresponded to the posterior branch of the intraparietal sulcus/superior parietal lobule bilaterally. There were no differences in the hypothalamus. Table 1 and Fig. 1 also present areas where people with WS had significantly higher gray matter density than the controls. In particular, there were group differences in areas that corresponded to the orbitofrontal cortex bilaterally.

Modulated VBM

Table 2 and Fig. 2 present results for areas where controls had significantly more gray matter volume than the WS group. There were many group differences, including throughout the parietal

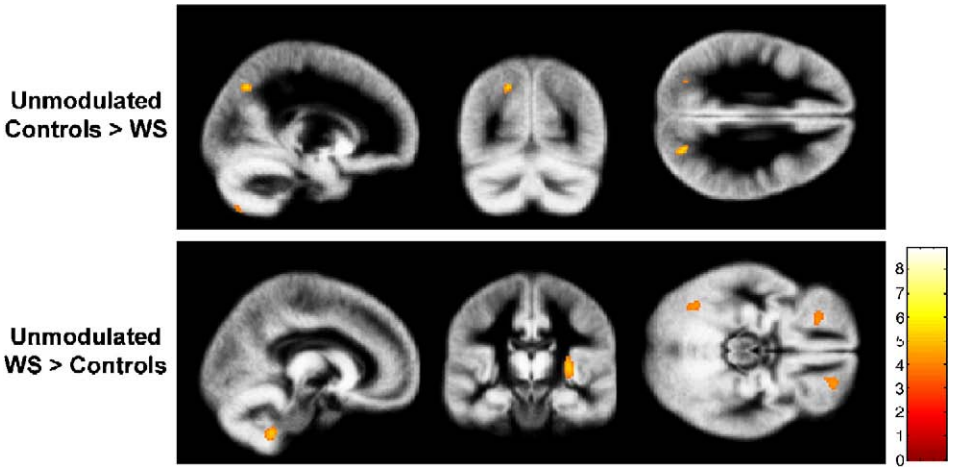

Fig. 1. VBM ANOVA results for unmodulated gray matter areas where controls had more gray matter density than WS (top) and WS had more gray matter density than controls (bottom) ($P < 0.001$, uncorrected). Results are overlaid on the unsmoothed WS and control gray matter template. The color bar represents the range of *t*-scores.

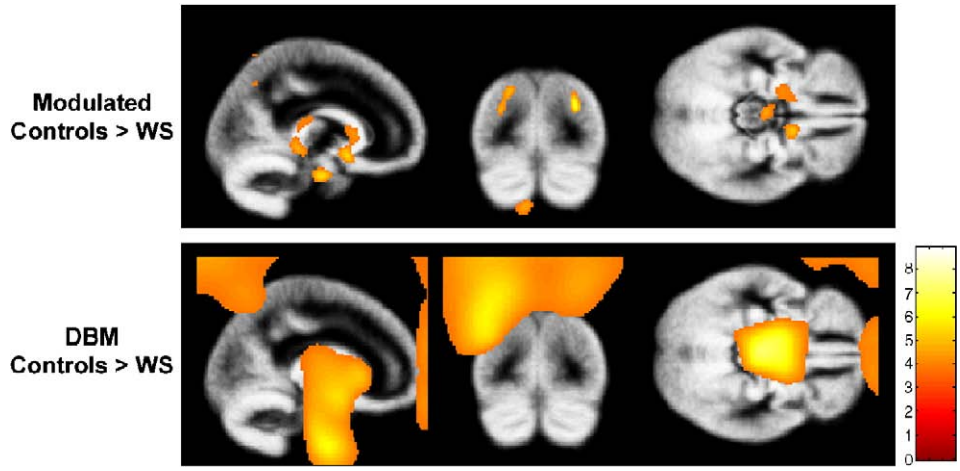

Fig. 2. VBM ANOVA results for modulated gray matter areas where controls had more gray matter volume than WS (top). DBM ANOVA results are also presented to show areas where control brain images had to be reduced in size to fit to the study specific template in comparison to the WS brain images (bottom). Note that the modulated VBM differences correspond to areas that were different in gross shape and size between the groups. Results are overlaid on the unsmoothed WS and control gray matter template. The color bar represents the range of *t*-scores.

lobes and along the intraparietal sulcus. There was also significantly reduced hypothalamic and orbitofrontal/posterior gyrus rectus gray matter volume in WS compared to controls. There were no cortical or subcortical areas where individuals with WS had more gray matter volume than controls.

DBM

The unmodulated VBM results demonstrated increased orbitofrontal and insula gray matter density in WS compared to controls, results that were not present in the modulated VBM analysis. In comparison, the modulated VBM results demonstrated decreased gray matter volume in the hypothalamus and orbitofrontal cortex/posterior gyrus rectus in WS compared to controls, results that were not present in the unmodulated analysis. DBM analyses demonstrate that these differences can be attributed to the modulation step. Fig. 2 shows there were large differences between the groups in how much the midbrain, the remainder of the brainstem, posterior cortex and frontal cortex had to be warped to fit to the template. These differences correspond in location to the decreased hypothalamus and orbitofrontal modulated gray matter results.

The principal eigenvariate from the DBM midbrain and brainstem cluster was used as a covariate in a VBM analysis of covariance (ANCOVA) of the modulated gray matter images. This DBM cluster was selected because it overlapped with anatomical regions that exhibited inconsistent group differences between the Meyer-Lindenberg et al. (2004) and Reiss et al. (2004) VBM studies. This analysis demonstrated that the midbrain and brainstem deformation difference between the groups accounted for all of the modulated VBM ANOVA findings where controls had more gray matter volume than people with WS. Table 3 and Fig. 3 show that controlling for the DBM shape difference also unmasked elevated modulated orbitofrontal cortex gray matter in the WS group compared to controls.

Discussion

The results of this study demonstrate that the choice to Jacobian modulate images during image pre-processing is a likely explanation for discrepant VBM findings reported in studies of WS (Meyer-Lindenberg et al., 2004; Reiss et al., 2004). Specifically, we replicate the Meyer-Lindenberg et al. (2004) hypothalamus finding when images are Jacobian modulated. We also replicate the Reiss et al. (2004) orbitofrontal cortex finding when the images are not Jacobian modulated. These results indicate that the unique WS brain shape and size affects VBM results. This study also highlights the remarkably consistent neurobiological findings for WS.

The WS brain is unusually shaped (Schmitt et al., 2001a,b). This unusual shape is best illustrated by the corpus callosum which is more likely to appear flattened or less concave in mid-sagittal sections compared to typical control adults (Schmitt et al., 2001a,b; Tomaiuolo et al., 2002). The corpus callosum is similarly flattened in animals that have not undergone the dramatic frontal and temporal/parietal growth that occurs in humans. The reduction in parietal and occipital lobe size almost certainly contributes to the unique WS corpus callosum and brain shape.

An unusual brain shape and small brain volume mean that considerable warping is necessary to normalize a WS brain image to a standard template brain image. Like the Meyer-Lindenberg study, we used a template composed of WS and control brain images to minimize the amount of image warping between the WS and control groups and obtain the best possible correspondence between brain regions across the WS and control brain images. Without good alignment of images, the significance of locally specific VBM results is ambiguous because it is not clear whether the same brain regions have been compared.

DBM confirmed that there were large shape/size differences between the groups, despite the use of a study specific template. These shape/size differences help explain why the choice to Jacobian modulate images produced discrepant results between the Meyer-Lindenberg and Reiss studies. Jacobian modulation makes good sense when there are regional differences in brain volume between groups that might be lost during normalization without adjusting for the brain volume differences. In addition, failing to adjust for regional volumetric differences might lead to false positive increases in gray matter density in an experimental group that has regional volume reductions in that region. In the case of unique brain shape and/or gross volume reduction, such

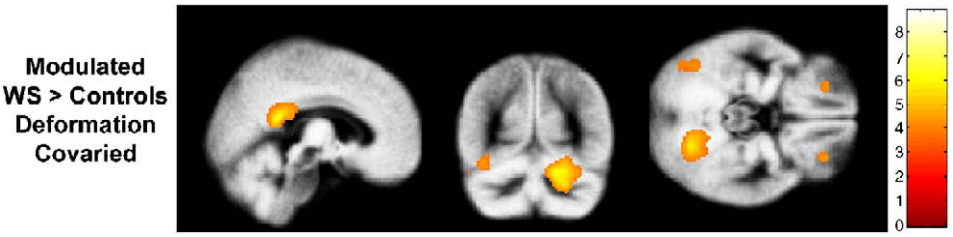

Fig. 3. VBM ANCOVA results for modulated gray matter areas where WS had more gray matter volume than controls after covarying for the midbrain/brainstem shape differences observed in the DBM analysis ($P < 0.001$, uncorrected). Results are overlaid on the unsmoothed WS and control gray matter template. The color bar represents the range of t-scores.

as studies of WS, lesion, or clinical cases with major atrophy, modulation may not be desired because it could have widespread effects on voxel signal intensities. Although the findings of this study appear to be relevant to the behavioral and cognitive impairments in WS and support the use of VBM for grossly atypical brains, the results of VBM studies involving conditions with gross volumetric or brain shape differences between samples may require cautious interpretation.

WS is a unique condition in which there are brain volume reductions and a unique brain shape in comparison to controls. Jacobian modulation could enhance the size of a group difference that is also present in unmodulated VBM analyses (parietal lobe findings) and increase the sensitivity for observing differences that require a larger sample size for unmodulated gray matter analyses (Reiss et al., 2004). However, Jacobian modulation could also introduce gray matter volume effects that may actually reflect a unique gross volumetric and/or brain shape (hypothalamus finding). In this case, DBM can be a valuable tool for determining if VBM findings can be attributed specifically to gray matter differences or whether a more cautious interpretation is warranted.

Orbitofrontal gray matter was increased in WS compared to controls for the unmodulated VBM and the modulated ANCOVA results. In contrast, an orbitofrontal region, consistent in location with the Meyer-Lindenberg orbitofrontal finding, was decreased in WS compared to controls in the modulated VBM results. These results could indicate that orbitofrontal cortex in controls had to be reduced in size to fit to the template and Jacobian modulation increased the gray matter intensity in their orbitofrontal cortex. This notion is consistent with the significant shape and size differences in this region.

There also appears to be theoretical significance for the gray matter finding in WS orbitofrontal cortex. The orbitofrontal finding was statistically independent of the parietal lobe group differences. This result suggests there are genes within the Chromosome 7 deletion influencing anomalous orbitofrontal cortex development that are different from deleted genes influencing reduced posterior parietal cortex volume in WS. The orbitofrontal finding also raises the question as to whether atypical orbitofrontal cortex development influences the unusual social behavior in people with WS. One potential explanation for the unusual social behavior in WS is that people with this disorder fail to visually detect facial affect signals as a consequence of their visual system impairment. Our findings suggest an additional explanation: that the unusual social behavior in people with WS is due to atypical orbitofrontal development. In support of this premise is evidence that orbitofrontal cortex does not participate in the regulation of amygdala responses to threatening faces in WS adults compared to controls (Meyer-Lindenberg et al., 2004).

The modulated and unmodulated VBM findings from this study provide firm support for anomalous development of posterior parietal cortex in WS. This is at least the seventh imaging study to report anomalous posterior parietal development in WS (Eckert et al., 2005a,b; Kippenhan et al., 2005; Meyer-Lindenberg et al., 2004; Reiss et al., 2004; Schmitt et al., 2002; Thompson et al., 2005). In particular, Eckert et al. (2005b) reported that superior parietal lobule volume was more affected in WS than inferior parietal lobule volume compared to controls and Kippenhan et al. (2005) reported reduced WS intraparietal sulcus depth compared to controls. These findings, in conjunction with the VBM findings, suggest that neurons in the superior parietal lobule bank of the intraparietal sulcus are particularly affected in WS. One important question to answer is whether these posterior parietal findings represent a locus for the visual–motor, visual–spatial, selective attention, saccade, and visual-constructive problems in WS (Atkinson et al., 2001; Bellugi et al., 2000; Farran et al., 2003; Frangiskakis et al., 1996; Scerif et al., 2004; van der Geest et al., 2004), or whether they are a consequence of impaired early visual system development (Galaburda et al., 2002).

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