Reduced parietal and visual cortical activation during global processing in Williams syndrome

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Several lines of investigation suggest that individuals with Williams syndrome (WS), a neurodevelopmental disorder of well-characterized genetic etiology, have selective impairments in integrating local image elements into global configurations. We compared global processing abilities in 10 clinically and genetically diagnosed participants with WS (eight females, two males; mean age 31y 10mo [SD 9y 7mo], range 15y 5mo–48y 4mo) with a typically developed (TD) age- and sex-matched comparison group (seven females, one male; mean age 35y 2mo [SD 10y 10mo], range 24y–54y 7mo) using functional magnetic resonance imaging (fMRI). Behavioral data showed participants with WS to be significantly less accurate ($p<0.042$) together with a non-significant trend to be slower than the TD comparison group while performing the global processing task. fMRI data showed participants with WS to possess reduced activation in the visual and parietal cortices. Participants with WS also showed relatively normal activation in the ventral occipitotemporal cortex, but elevated activation in several posterior thalamic nuclei. These preliminary results largely confirm previous research findings and neural models implicating neurodevelopmental abnormalities in extended subcortical and cortical visual systems in WS, most notably dorsal-stream pathways.

See end of paper for list of abbreviations.

Williams syndrome (WS) is a rare genetic condition caused by a contiguous 1.6 megabase microdeletion on the long arm of chromosome 7q11.23.[1] The absence of this genomic segment results in a syndromic constellation of neuroanatomical, behavioral, and cognitive phenotypes.[2] Within the cognitive domain, individuals affected by WS typically exhibit an uneven pattern of strengths and weaknesses. Widely documented are impairments in visual-spatial and global-processing, problem-solving, and mathematical abilities.[2,3] Despite mild to moderate mental retardation,* WS is also characterized by a relative proficiency in verbal expressiveness, musicality, social reciprocity, and face-processing skills.[2,4] Together, these studies parallel the neuroanatomical profile associated with WS and support the theory that affected individuals possess deficits in engaging the dorsal 'occipitoparietal' stream, while possessing relatively preserved functioning of the ventral 'occipitotemporal' stream pathways of visual cortical processing.[5–11]

Several converging lines of evidence suggest that individuals with WS show a prominent impairment in tasks that require global processing (i.e. the integration of individual, local-image features into perceptually global-wholes). On classic block-construction tasks, most individuals with WS show profound deficits in correctly assembling blocks into globally coherent configurations,[12,13] and perform poorly when reconstructing hierarchically organized figures.[3] This phenomenon also extends to copying and freehand drawing abilities, where affected individuals frequently demonstrate an over-attention to detail, coupled with fragmented global configurations,[14] and to non-motor tasks involving visual search and visual perceptual grouping of local images.[15,16] Despite the robustness of these findings, no study has directly examined the neural systems that underlie global processing deficits in WS.

In the present study, we used a non-verbal global processing task to examine further the dorsal-stream deficits in individuals with WS while they underwent functional magnetic resonance imaging (fMRI). In accordance with previous neuroanatomical and behavioral findings, we hypothesized that individuals with WS would exhibit reduced accuracy and slower response latencies for global processing compared with a typically developed (TD) comparison group. We expected these differences to reflect a decreased blood oxygenation-level-dependent (BOLD) response in regions associated with global-attention and visual-spatial processing, most notably the parietal cortex, an important node in dorsal-stream processing. We further reasoned that early visual areas (e.g.V1) would exhibit reduced activation, reflecting the aberrant neuropathology in this region.

Method

PARTICIPANTS

Twelve right-handed individuals with WS (10 females, two males) were recruited by the Laboratory for Cognitive Neuroscience at the Salk Institute, CA, USA. Two of these participants were later excluded from the analyses owing to poor task performance and excessive head-movement during the scan (more than 3mm). The remaining 10 participants (eight females, two males) had a mean age of 31 years 10 months (SD 9y 7mo; range 15y 5mo–48y 4mo). Genetic diagnosis was established using fluorescent in situ hybridization (FISH) probes for elastin (ELN), a gene consistently found in the

*UK usage: learning disability.

microdeletion associated with WS.[1] In addition, all participants exhibited the medical and clinical features of the WS phenotype, including the cognitive, behavioral, and physical profile.[2]

The TD adult comparison group consisted of eight healthy, right-handed participants (seven females, one male; mean age 35y 2mo [SD 10y 10mo], range 24y–54y 7mo), matched for chronological age, who were recruited through advertisements within the local community. Each participant was deemed asymptomatic and screened for a history of psychiatric or neurological problems.[17] Cognitive functioning was assessed using the Wechsler Intelligence Scale Revised for Children[18] (<16y) and the Wechsler Adult Intelligence Scale – Revised[19] (≥16y). Both scales assessed Verbal IQ (VIQ), Performance IQ (PIQ), and Full-scale IQ (FSIQ; Table I). All participants gave written, informed consent before participation. All procedures complied with the guidelines of the human subjects committee at Stanford University School of Medicine.

To help reduce the potential problem of hyperacusis, auditory allodynia, and anxiety in participants with WS, each was provided with a professionally produced video introduction to the scanning procedures and a CD with samples of the MRI sounds. Before the scan, participants with WS were prepared for the experiment using a standardized MRI preparation protocol, which included a full MRI simulation, and motion evaluation (http://spnl.stanford.edu/participating.mri_prep/intro.html). Research staff also worked with each participant to ensure that they were capable of attending to, understanding, and performing the tasks in the scanner.

EXPERIMENTAL STIMULI AND PROCEDURES

In the study, 72 experimental and 72 control stimuli were randomly presented. Experimental stimuli were either a large concentric triangle or square consisting of smaller triangles or squares; stimulus size was 5cm×5cm. The control stimuli consisted of a large, single-lined triangle or square of the same dimensions. To ensure equal hemispheric input, the left peripheral, right peripheral, and foveal visual fields were equally exposed to the stimuli. The stimuli were modeled on classic Navon images,[20] where, for example, a large letter is made up of smaller letters. However, because participants with WS typically show proficient verbal abilities, we used non-linguistic hierarchical stimuli. Further, task-switching confounds (e.g. increases in demand for cognitive control) between the comparison group and experimental conditions were minimized by using a blocked-design.[15,21]

The task was presented in a single 6.24 minute session. Stimuli were presented in a blocked fMRI paradigm. The task consisted of three rest epochs, six experimental epochs (E), and six control epochs (C) in the following order: rest–E–C–E–C–E–C– rest–E–C–E–C–E–C–rest. Each rest epoch lasted 24s, during which participants passively viewed a blue screen, with the word 'REST' and a fixation cross presented at the center of the screen. Experimental and control epochs lasted 26s and consisted of 12 randomly alternating stimuli. Stimuli were presented for 750ms each, with a 1250ms interstimulus interval. A fixation cross was presented for 2000ms at the beginning of each epoch, and task instructions were simultaneously presented at the bottom of the screen reminding the participants to attend to the 'BIG' triangles and squares. For experimental and control epochs, participants were instructed to attend to and identify the global aspects of the stimuli (i.e. big triangles and squares) and to press button 1 if a 'BIG' square appeared, or button 2 if a 'BIG' triangle appeared. Each participant was assessed at the end of the

Table I: Demographic and neuropsychological characteristics of patients with Williams syndrome (WS) and healthy comparison individuals

Participants	*Sex*	*Handedness*	*Age, y:m*	*Verbal IQ*	*Performance IQ*	*Full-scale IQ*
WS patients						
1	M	Right	25:7	68	60	63
2	F	Right	31.10	71	59	64
3	F	Right	40:4	69	73	69
4	F	Right	15:5	60	52	52
5	F	Right	31:8	71	67	68
6	F	Right	48:4	89	72	80
7	M	Right	30:11	66	67	65
8	F	Right	30:8	77	68	72
9	F	Right	41:0	71	79	74
10	F	Right	22:2	74	59	66
Mean	–	–	31:10	71.6	65.6	67.3
SD	–	–	9:7	7.6	8.1	7.5
Comparison group						
1	F	Right	33:6	121	120	124
2	F	Right	48:1	87	112	100
3	M	Right	24:0	132	100	117
4	F	Right	54:7	122	119	124
5	F	Right	36:2	120	114	119
6	F	Right	25:2	109	112	112
7	F	Right	28:8	119	114	118
8	F	Right	31:1	98	98	99
Mean	–	–	35:2	113.5	111.2	114.2
SD	–	–	10:10	14.7	8.1	9.8

scan and asked specific questions about how they performed the tasks.

IMAGE ACQUISITION

Images were acquired on a 1.5T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI, USA) with echospeed gradients using a custom-built, whole-head coil. Eighteen axial slices (6mm thick, 1mm skip) parallel to the anterior and posterior commissures, covering the whole brain, were imaged with a temporal resolution of 2s using a T_2*-weighted, gradient echo, spiral pulse sequence. To aid in localization of functional activation, a high-resolution, T_1-weighted, spoiled gradient-recalled, three-dimensional MRI sequence was obtained.[6]

IMAGE ANALYSIS

Images were reconstructed by inverse Fourier transform, for each of the 192 time points, into 64×64×18 image matrices (voxel size 3.75mm×3.75mm×7mm). fMRI data were then analyzed using statistical parametric mapping (SPM99; http://www.fil.ion.ucl.ac.uk/spm). Briefly, images were corrected for movement and spatially normalized to stereotaxic Talairach coordinates.[22] We used the non-linear spatial (stereotaxtic) transformation methods, as implicated in SPM,[21] to account for any gross volume differences in the WS group. For each participant, a *T*-score image was generated for each contrast of interest (i.e. global minus control condition) using a general linear model (described in detail elsewhere[6]). Significant clusters of activation were determined using the joint expected probability of height ($z>1.96$, $p<0.05$) and extent ($p<0.05$) of *z*-scores, yielding a cluster-wise significance level of $p=0.05$, after correction for multiple comparisons.

To address the nature of activation patterns in participants with WS, we examined the correlation between trial accuracy and FSIQ using regions of interest generated at the whole-brain level. The group analysis was conducted using *z*-scores derived from the individual participant analysis, as described above. The percentage of voxels, in each cluster of interest, with $z>1.96$ ($p<0.05$) was determined for each contrast. An alpha level for significance of $p<0.05$ (two-tailed) was used.

Results

NEUROPSYCHOLOGICAL DATA

FSIQ scores for the WS group (mean 67.3 [SD 7.5]) were significantly lower than for TD comparison group (114.2 [9.8], $p<0.001$). VIQ and PIQ scores followed a similar trend for the WS (VIQ 71.6 [7.6], PIQ 65.6 [8.1]) and TD groups (VIQ 113.5 [14.7], PIQ 111.2 [8.1], $p<0.001$; Table I).

BEHAVIORAL DATA

Participants with WS were less accurate (66.7% [SD 14.7]) than TD comparison group (85.6% [19.7]; $t^{16}=-2.262$; $p<0.042$; Fig. 1). Response times (RTs) showed participants with WS to be slower (1031.3ms [172.7]) than the comparison group (937.7 [89.7]), albeit not reaching a level of significance ($t^{16}=1.484$; $p<0.160$). Because of the large disparity in FSIQ, we conducted correlations to determine if performance was driven by IQ. For the WS group, no correlation was found between IQ and the global task RT (Pearson's product moment: $r=-0.082$, $p<0.821$) or accuracy ($r=0.463$, $p<0.178$). The TD group also showed no correlation between performance and IQ (RT: $r=-0.484$ $p<0.224$; or accuracy: $r=0.454$, $p<0.238$). No significant difference in RT or accuracy was found when incongruent and congruent global images were compared ($p<0.05$).

fMRI DATA

Participants with WS showed activation in the bilateral lingual gyrus (LG; Brodmann's area [BA] 18), spreading, via ventral aspects of the occipotemporal junction (encompassing the fusiform gyrus [FuG; BA 37]), to the inferior temporal gyrus (ITG). Activation also was seen in the right (R) ventrolateral

Table II: Voxel coordinates in Talairach space and associated *z*-scores showing BOLD differences within and between groups ($p<0.05$ corrected)[a]

Regions	*p*	*z-score*	*Peak Talairach coordinates*			*IQ correlations*	*Performance correlations*
			X	*Y*	*Z*		
Williams syndrome (WS) group							
Left FuG, ITG, cerebellum	<0.046	4.06	–44	–68	–4	–0.35	–0.25
Right IFG, MFG, DLPFC (BA 44/8/9)	<0.001	3.95	48	10	26	–0.16	–0.05
Bilateral LG (BA 18)	<0.005	3.87	–4	–62	–2	0.28	–0.04
Typically developed (TD) group							
Bilateral cerebellum, cuneus, LG, FuG, SPL, SOC (BA 17/18/19/7)	<0.001	4.77	–14	–71	–13	0.28	–0.099
WS minus TD group							
Right MFG, precentral gyrus, left thalamus (BA 8/9)	<0.040	3.85	28	29	43	–0.14	–21
Right insula, IFG, thalamus, caudate, HIPP, PHG (BA 43/47/45)	<0.001	3.54	30	9	–14	–0.16	0.18
Precentral gyrus, right OFC (BA 6/4)	<0.001	3.48	55	0	28	–0.04	0.19
TD minus WS group							
Left cuneus, MOC, IOC, bilateral LG, right FuG, (BA 17/18/19)	<0.001	3.63	28	–77	8	–35	–02

[a]Only clusters with a significance value of $p<0.05$ corrected for whole brain are reported. Stereotaxic coordinates as in Talairach and Tournoux[22] atlas space. BOLD, blood oxygenation-level-dependent; FuG, fusiform gyrus; ITG, inferior temporal gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal cortex; BA, Brodmann's area; LG, lingual gyrus; SPL, superior parietal lobe; SOC, superior occipital cortex; HIPP, hippocampus; PHG, parahippocampal gyrus; OFC, orbital frontal gyrus; MOC, middle occipital cortex; IOC, inferior occipital cortex.

prefrontal cortex, encompassing the inferior frontal gyrus (IFG; BA 44), the medial frontal gyrus (MFd; BA 8/9), and the dorsolateral prefrontal cortex (DLPFC). Closer examination of sub-peaks revealed activation in the right insula (BA 22) and right hippocampus (HIPP; Fig. 2a). In comparison, the TD comparison group had a large cluster peaking in the left cerebellum. This cluster also extended dorsally to the bilateral LG and FuG (BA 18/37), primary visual cortex (BA 17,18,19), bilateral intrapariatal sulcus (IPs), right supramarginal gyrus, and the right cerebellum (Fig. 2b).

Between-group analysis demonstrated greater activation in participants with WS compared with the TD comparison group, in the right MFd (BA 8/9), extending to the left thalamus and the right precentral gyrus (BA 6). Significantly increased activation in participants with WS was seen in the HIPP and parahippocampal gyrus (mostly right lateralized), right LG, insula, thalamus, superior temporal gyrus (BA 22), middle temporal gyrus, orbital frontal cortex, middle frontal gyrus, superior frontal gyrus, and medial aspects of the precuneus (PCu). The opposite contrast (i.e. TD minus WS participants) revealed one robust peak activation cluster that encompassed the left cuneus (BA 19), bilateral LG, proceeding dorsally to the superior parietal lobe and PCu. Together, these clusters encapsulated the primary and secondary visual cortices (BA 17, 18, 19; Fig. 2c, d). No significant correlation was found between activation and either IQ or performance accuracy in the WS group.

Discussion

To our knowledge, this study is the first to examine directly the neural systems that underlie global processing abilities in WS. Our behavioral data showed participants with WS to be less accurate and marginally slower than the comparison group. The fMRI data showed participants with WS to possess distinct decreases in parietal and visual cortical activation, while also demonstrating relativity preserved activation in the occipitotemporal cortex. An unexpected finding was the increased posterior thalamic activation in the WS group, encompassing the lateral geniculate nucleus (LGN) and pulvinar, regions known to have important subcortical connections with both dorsal and ventral stream structures. Further, the WS group also possessed increased right DLPFC activation, which may reflect greater task difficulty and corresponding 'effort'.

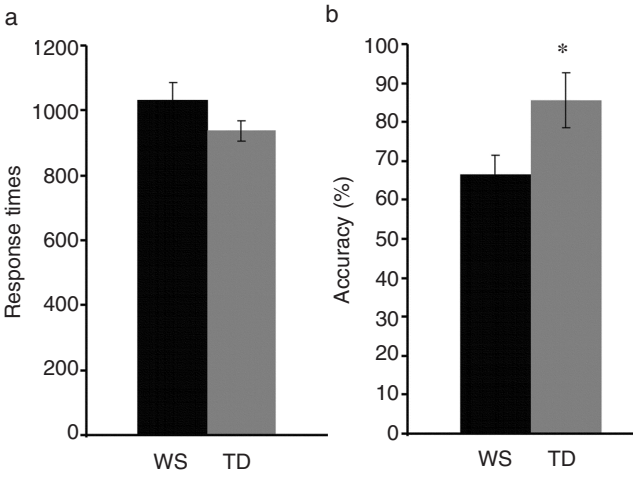

Figure 1: *Behavioral performance including (a) response times and (b) accuracy for Williams syndrome (WS) and typically developed (TD) groups and trials (SEM). Although no significant difference was found in response times, those with WS were significantly less accurate (*two-tailed t-test $p<0.05$).*

In support of our hypothesis, we found reduced activation in important dorsal-stream structures including the inferior and superior parietal cortices. This finding is supported by studies showing increased parietal lobe gyrification in the right hemisphere in WS,[24] structural impairment,[7,8,25] decreased intraparietal sulci depth,[24] larger cell size, and greater cellular density in BA 7 (Hollinger et al. 2002, unpublished). A recent study by Meyer-Lindenberg et al. also demonstrated reduced gray matter density and reduced BOLD signal in a region adjacent to the IPs while individuals with WS performed a square completion task. In the same study, post-hoc connectivity analysis showed reduced connectivity in regions known to constitute the dorsal-stream.[5] In the present study, the TD group, but not the WS group, showed increased activation in the parietal lobe including the precuneus, angular gyrus, and IPs, regions critical in encoding spatially coded material. Interestingly, patients with focal damage to similar portions of the parietal cortex demonstrate some neurological parallels with participants with WS, including visual-spatial deficits[26] and constructional apraxia.[27] Therefore, in light of studies from numerous modalities, our findings support the theory that individuals with WS have specific deficits in parietal lobe functioning.

For the distinct pattern of reduced visual cortical activation, the present study suggests that the dorsal-stream is disrupted early in cortical (or subcortical) visual processing. We have previously shown decreases in visual cortical activation in participants with WS during the performance of a face and eye gaze task.[6] Moreover, structural MRI studies have clearly demonstrated gross gray matter reductions in the occipital lobe of individuals with WS,[7,8] and cytoarchitectonic and histological examinations of the WS brain have revealed abnormal cell size and cell-packing density in the visual cortex (Galaburda et al. 2002, unpublished). Although the exact role of the visual cortex in higher-visual processes remains largely speculative, there is mounting evidence showing that early retinotopically organized areas modulate global processing.[28,29] Also, single-cell recordings of the homologous primate brain have shown the region of V2 to code visually complex stimuli.[30] Given that fMRI may reflect input into regions, it is plausible that back projections into the visual areas are disrupted. An important direction of future studies will be to investigate how important early visual cortical pathology and synaptic connectivity deficits disrupt the propagation of information to, or from, parietal dorsal-stream regions.

An unexpected finding worthy of comment was the WS group's increased modulation of several thalamic nuclei, including the LGN and pulvinar. The two main LGN connections to the primary visual cortex, the magnocellular and parvocellular pathways, correspond with the dorsal and ventral stream respectively.[31] Additionally, the pulvinar, a region implicated in spatial attention and visual imagery,[32,33] projects to caudal portions of the inferior parietal lobule and receives back projections from the IPS.[34] This raises the interesting possibility that dorsal-stream deficits begin early in the corticothalamic pathways. Some support for this hypothesis comes from

research showing the thalamus to be reduced in volume and gray matter density,[7] and that it was overactivated during face and gaze processing[6] in individuals with WS. Thus, a topic of further investigation will be to examine both the feed-forward and feed-backward thalamic connections to the parietal and visual structures in this population.

In the context of the dorsal–ventral stream hypothesis, it is important to mention that participants with WS and the TD comparison group both showed increased activation in the bilateral ventral occipitotemporal cortex encroaching the FuG. This region is of interest as it is known to form a significant portion of the ventral-stream and has recently been shown to be relatively functionally and structurally preserved in WS.[6,8] Indeed, a recent fMRI study of individuals with WS demonstrated normal FuG activity and connectivity during the presentation of faces.[5] However, event-related potential (ERP) studies of individuals with WS found abnormal amplitude in the occipitotemporal cortex while they performed simple illusory contour[35] and face processing tasks,[36] suggesting an abnormal developmental trajectory of the ventral-stream. This is plausible because of evidence showing that both dorsal and ventral streams have intricate interactions.[37] Nonetheless, despite the potential abnormalities in functioning, the ventral-stream is still less significantly disrupted than the dorsal-steam.

Given the exploratory and preliminary nature of the present study, several inherent limitations are evident. The conventional blocked-design paradigm used in this study limited the opportunity to tease apart the effects of visual-field and stimulus incongruence. Knowledge of these two factors would further clarify hemispheric connectivity and visual-field impairments in this disorder. Although we believe that a blocked-design is an acceptable trade-off to confound task switching,[15,19] future studies might use, or integrate, an event-related design. Another prominent limitation is the large differences in IQ between the WS and TD participants. We partly controlled for this problem by assessing whether IQ was correlated with brain activation and performance in the WS group; however, despite the problems,[6] the addition of an IQ-matched group would help to support this premise. Finally, previous studies have shown that immaturity of global processing is defined by decreased lateralization.[38] Although we did not directly test for differences in lateralization, future studies should test this hypothesis.

Conclusions

The inability to modulate visual and parietal areas during global processing suggests that persons with WS possess early visual deficits, which may begin in the LGN and extend to cortical regions (e.g. V1) that, in turn, may disrupt the dorsal-stream pathway processes. This hypothesis is in considerable agreement with morphometric, histological, and ERP studies demonstrating aberrant neural topography along the ventral–dorsal axis. Importantly, other related impairments in WS (e.g. mathematical and visuospatial working memory skills) may also stem from the anomalous development of the pareital lobe. More broadly, the present results offer new insight into

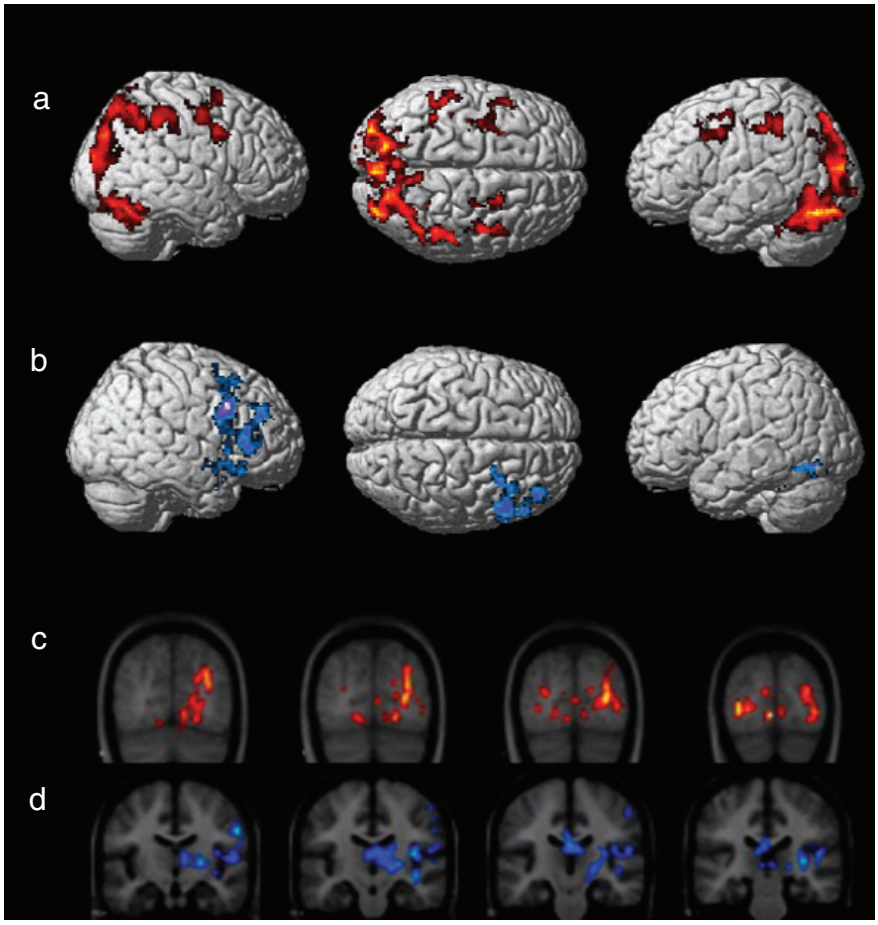

Figure 2: *Surface renderings for (a) typically developed (TD) comparison group and (b) patients with Williams syndrome (WS) showing significant within-group t-maps ($p<0.05$). Note lack of visual and parietal lobe activation in WS group. (c) Between-group coronal slices showing parietal and visual areas activated more by TD comparison group. (d) Slices illustrating increased posterior thalamic activation in WS group.*

the relation between brain functioning and how the aberrant expression of specific genes affects cognitive functioning.

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List of abbreviations

BA	Brodmann's area
BOLD	Blood oxygenation-level-dependent
FuG	Fusiform gyrus
IPS	Intrapariatal sulcus
LGN	Lateral geniculate nucleus
RT	Response times
WS	Williams syndrome