Functional Neuroanatomy of Spatial Orientation Processing in Turner Syndrome

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Turner syndrome (TS), a neurogenetic disorder characterized by the absence of one X chromosome in a phenotypic female, is frequently associated with visuospatial impairments. We investigated the neural mechanisms underlying deficits in spatial orientation processing in TS. Thirteen subjects with TS and 13 age-matched typically developing controls underwent neuropsychological assessments and were scanned using functional MRI while they performed easy and difficult versions of a judgment of line orientation (JLO) task. Controls and subjects with TS activated parietal-occipital regions involved in spatial orientation during the JLO task. However, activation was significantly less in the TS group. Control subjects responded to increased task difficulty by recruiting executive frontal areas whereas subjects with TS did not activate alternate brain regions to meet increased task demands. Subjects with TS demonstrate activation deficits in parietal-occipital and frontal areas during the JLO task. Activation, and possibly deactivation, deficits in these areas may be responsible for the visuospatial deficits observed in females with TS.

Keywords: fMRI, JLO, spatial orientation, Turner syndrome

Introduction

Turner syndrome (TS) is usually the result of a sporadic chromosomal nondisjunction causing complete or partial absence of an X chromosome in a phenotypic female (45X). This neurogenetic disorder is one of the most common sex chromosome aneuploidies, occurring in ~1 of every 2500 live births (Lippe, 1990). Turner syndrome is associated with a well-described physical phenotype that includes short stature, webbed neck, low-set ears, broad shield-like chest with widely spaced nipples, infertility and gonadal dysgenesis as well as diminished estrogen, progesterone and secondary sexual production. Cognitively, individuals with TS typically possess normal overall IQ but demonstrate a discrepancy between verbal (VIQ) and performance IQ (PIQ). PIQ is consistently decreased in individuals with TS whereas VIQ tends to be within normal limits (Garron, 1977; Swillen *et al.*, 1993).

Neuropsychological studies have demonstrated that subjects with TS show impaired performance on visuospatial tasks, including problems with spatial/perceptual cognition, visual memory, and visual motor integration. Increased impulsivity, decreased attention and problems with executive functioning also have been reported in TS (Waber, 1979; Pennington *et al.*, 1985; Romans *et al.*, 1998; Lippe, 1990). Results from these and other cognitive studies led to early hypotheses that spatial/perceptual impairments in persons with TS are localized to the parietal lobe and executive dysfunction to the prefrontal cortex (Waber, 1979; Money and Alexander, 1966; Pennington *et al.*, 1985).

Volumetric neuroimaging studies have been used to characterize the neuroanatomical correlates of visuospatial and executive function deficits in TS. Murphy *et al.* demonstrated decreased volume in the right parietal/occipital cortex in TS (Murphy *et al.*, 1993). Similarly, we showed a proportional decrease in gray matter in the right posterior parietal lobe of girls with TS (Reiss *et al.*, 1995). Further, in a study of prepubertal 10 year old monozygotic twins discordant for X monosomy, we reported decreased proportions of gray matter volumes in the left and right parietal and right occipital cortices in the affected twin (Reiss *et al.*, 1993). In addition to these volumetric studies, two positron emission tomography (PET) studies showed decreased glucose metabolism in the parietal and occipital lobes bilaterally in individuals with TS (Clark *et al.*, 1990; Murphy *et al.*, 1997). None of these imaging studies reported a direct correlation between parietal morphology or function and measures of cognitive performance.

In a previous study aimed at characterizing the link between neuroanatomical deficits and impaired performance on spatial cognition tasks, we used functional magnetic resonance imaging (fMRI) to investigate differences in brain activation in individuals with TS during a working memory task (Haberecht *et al.*, 2001). Our findings indicated that subjects with TS had impaired visuospatial working memory and, compared to control subjects, showed significantly decreased activation in the inferior parietal lobe, a region known to play a role in spatial encoding and working memory storage mechanisms. However, no activation differences between the control and TS groups were observed in the superior parietal lobe (SPL), a brain region known to contribute to intact spatial orientation processing. These results led us to inquire whether, in addition to impaired visuospatial memory, performance deficits in visuospatial orientation in TS would also be associated with differences in brain activation profiles in the superior parietal region.

In this investigation, subjects completed a judgment of line orientation (JLO) task during high-resolution fMRI scans to characterize spatial orientation processing in TS and to more closely examine parietal contributions to this component of spatial cognition. The JLO is a well-established visuospatial task that tests an individual's ability to assess angular orientation of lines. Posterior parietal lesions, most often occurring in the right hemisphere, are known to disrupt JLO performance (Benton *et al.*, 1983). Several behavioral studies have shown impaired JLO performance in subjects with TS (Reiss *et al.*, 1995; Mazzocco, 1998; Romans *et al.*, 1998); however, the neural substrates of these deficits are not known. We hypothesized that, when compared to control subjects, individuals with TS would show impaired JLO task performance, and that

activation differences associated with these impairments would be localized to the superior parietal lobe. Subjects were given easy and difficult versions of a JLO task to investigate the effect of increasing task difficulty on activation differences between TS and control subjects.

Materials and Methods

Subjects

All potential subjects were interviewed and screened by telephone for assessment of medical and psychiatric history. Documentation of X monosomy on standardized karyotype was obtained from the diagnosing physician or facility. Growth hormone and estrogen replacement status were determined. All 13 subjects with TS had received growth hormone and only three subjects had started estrogen replacement therapy. Thirteen right-handed subjects with TS (ages 7–18 years; mean 12.6 years) and 13 right-handed typically developing control subjects (ages 7–20 years, mean 14.5 years, matched for VIQ to the TS group) participated in the study after giving written informed consent. All subjects received neurocognitive assessments and underwent fMRI scanning. The human subjects committee at Stanford University School of Medicine approved the protocols used in this study.

Neuropsychological Assessment

The Wechsler Adult Intelligence Scale-III (Wechsler, 1991) was administered to participants over 17 years of age, and the Wechsler Intelligence Scale for Children-III (Wechsler, 1997) was administered to participants between 6 and 17 years. The JLO test (Benton *et al.*, 1983) was administered to all participants outside the scanner in its typical form to assess spatial reasoning skills.

Functional Imaging of the JLO Task Design

The scanner-based JLO task consisted of rest, experimental (E) and control (C) epochs in the following order: Rest–E–C–E–C–E–C–Rest–E–C–E–C–E–C –Rest. Thus, there were three rest epochs, six experimental epochs, and six control epochs in each task. Two levels of difficulty were presented for the experimental epochs. The first three experimental epochs were less difficult (i.e. 'easy' task) and the last three were more difficult. Each rest epoch lasted 30 s, during which subjects passively viewed a blank screen. Control (or 'baseline') epochs began with a 4 s display of the instructions 'judge if colors match'. Experimental epochs began with a 4 s display of the instructions 'judge if line orientations equal'. Each baseline and experimental epoch consisted of 10 stimuli presented for 500 ms each, with a 1500 ms interstimulus interval.

For the easy level of the experimental epoch, five lines appeared in the shape of a protractor. Two of the lines were yellow and three were purple. Two lines appeared above the protractor in an angle resembling the angle of the two yellow lines in the protractor. The task required that the subject compare the angles of the two sets of yellow lines; and if the orientation of the sets of lines were identical, the subject would respond with a button press. (Subjects were instructed to withhold response if the orientation is not equal). In the difficult trials, the protractor consisted of 11 lines. For the baseline epoch, subjects were instructed to respond only when the color of the lines above the protractor matched the colors of the protractor. The number of appropriate responses (button presses) was comparable for the different conditions.

fMRI acquisition

Images were acquired on a 1.5 T GE Signa scanner with Echospeed gradients using a custom-built whole-head coil that provides a 50% advantage in signal-to-noise ratio over that of the standard GE coil. A custom-built head holder was used to minimize head movement. Eighteen axial slices (6 mm thick, 1 mm skip) parallel to the anterior and posterior commissure covering the whole brain were imaged with a temporal resolution of 2 s using a T_2^* weighted gradient echo spiral pulse sequence (T_R = 2000 ms, T_E = 40 ms, flip angle = 89° and 1 interleave) (Glover and Lai, 1998). The field of view was 240 mm and the effective in-plane spatial resolution was 3.75 mm. To aid in localization of functional data, high resolution T_1-weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence with the following parameters was used: T_R = 35 ms; T_E = 6 ms; flip angle = 45°; 24 cm field of view; 124 slices in coronal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9 mm spatial resolution.

The JLO task was programmed using PsyScope (Cohen *et al.*, 1993) on a Macintosh® (Apple Computer, Cupertino, CA) computer. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a 'CMU Button Box' microprocessor (http://poppy.psy.cmu.edu/psyscope) connected to the Macintosh. Stimuli were presented visually at the center of a screen using a custom-built magnet compatible projection system (Resonance Technology, CA).

Image Preprocessing

Images were reconstructed by inverse Fourier transformation for each of the 120 time points into 64 × 64 × 18 image matrices (voxel size 3.75 × 3.75 × 7 mm). Imaging data were pre-processed using Statistical Parametric Mapping (SPM99) (http://www.fil.ion.ucl.ac.uk/spm). Images were corrected for movement using least-squares minimization without higher-order corrections for spin history, and normalized to stereotaxic Talairach coordinates (Talairach and Tournoux, 1988). Images were then resampled every 2 mm using sinc interpolation and smoothed with a 4 mm Gaussian kernel to decrease spatial noise.

Statistical analysis

Statistical analysis was performed on individual and group data using the general linear model and the theory of Gaussian random fields as implemented in SPM99. This method takes advantage of multivariate regression analysis and corrects for temporal and spatial autocorrelations in the fMRI data (Friston *et al.*, 1995). Activation foci were superposed on high-resolution T_1-weighted images and their locations interpreted using known neuroanatomical landmarks.

A within-subjects procedure was used to model all the effects of interest for each subject. Individual subject models were identical across subjects (i.e. a balanced design was used). Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high-pass filter (0.5 cycles/min) applied to the fMRI time series at each voxel. A temporal smoothing function (Gaussian kernel corresponding to dispersion of 8 s) was applied to the FMRI time series to enhance the temporal signal-to-noise ratio.

Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure. This model estimates the error variance for each condition of interest across subjects, rather than across scans (Holmes and Friston, 1998) and therefore provides a stronger generalization to the population from which data are acquired. In the first stage, contrast images for each subject and each effect of interest were generated as described above. In the second stage, these contrast images were analyzed using a general linear model to determine voxel-wise *t*-statistics. One contrast image was generated per subject, per effect of interest. A one-way *t*-test was then used to determine group activation for each effect. TS and control subjects were compared using an unpaired *t*-test. Finally, the *t*-statistics were normalized to *Z* scores, and significant clusters of activation were determined using the joint expected probability distribution of height and extent of Z scores (Poline *et al.*, 1997), with height ($Z > 1.67$; $P < 0.05$) and extent ($P < 0.05$) thresholds. Contrast images were calculated using within subject design for the following comparisons: easy JLO-baseline and difficult JLO-baseline. For between group comparisons, the following contrasts were used: [Control (easy-baseline)] – [TS (easy-baseline)]; [TS (easy-baseline) – Control (easy-baseline)]; [Control (difficult-baseline)] – [TS (difficult-baseline)]; and [TS (difficult-baseline)] – [Control (difficult-baseline)].

Results

Neuropsychological Assessment

Table 1 presents a summary of the neuropsychological data for both groups. Visual inspection of IQ data indicated that they were not normally distributed and therefore Mann–Whitney tests were used to determine between group differences. The full-scale IQ (FSIQ) and VIQ scores were not significantly different between the groups. Therefore, none of the subsequent analyses were corrected for FSIQ. However, as expected, PIQ scores of the subjects with TS were significantly lower than controls ($U = 27$, $P = 0.002$). One-way ANOVA indicated that subjects with TS performed significantly lower on the JLO neuropsychological test compared with control subjects: $F(1,22) = 9.4$, $P = 0.005$ (a JLO score was not available for one control subject).

fMRI Behavioral Performance

Behavioral performance (number correct) on the JLO scanner version was compared within and between the two groups (Table 1). Visual inspection showed that the behavioral performance data were not normally distributed. Wilcoxon signed-rank tests indicated that, as expected, subject performance on the difficult task was significantly lower than the easy task in both the TS [$Z = -5.78$, $P = 0.000$] and the control group [$Z = -6.48$, $P = 0.000$]. Mann–Whitney analyses indicated that TS subjects performed similarly to control subjects on the easy JLO task ($P = 0.20$) but were significantly less accurate on the difficult version ($U = 29.5$, $P = 0.012$). Behavioral data did not record for one subject with TS and one control subject. Reaction time on correct trials was normally distributed and repeated-measures ANOVA indicated no significant main effect of diagnosis or diagnosis by task difficulty interaction. In other words, individuals with TS were not significantly slower than control subjects in responding to the easy or difficult JLO task. Reaction time did not record for one control subject and two subjects with TS.

Brain Activation

Whole brain analyses were performed on control and TS groups during the JLO task. As an initial step in understanding brain activation associated with the JLO, we first contrasted the experimental condition with the control condition for each of the groups. Between-group contrasts were then examined.

Table 1
Group means and standard deviations on behavioral measures

	Turner	*n*	Control	*n*
FSIQ	102 ± 22	13	116 ± 14	13
VIQ	113 ± 21	13	115 ± 13	13
PIQ	91 ± 18	13	110 ± 12*	13
Reaction time	1479 ± 276	11	1443 ± 184	12
Easy JLO	23 ± 9	12	28 ± 3	12
Difficult JLO	14 ± 4	12	18 ± 5*	12
Neuropsychological JLO	16 ± 10	13	25 ± 4*	12

Reaction time is shown in milliseconds.
FSIQ, full-scale IQ score; VIQ, verbal IQ score; PIQ, performance IQ; JLO, judgment of line orientation (JLO is shown as number correct).
*Significant at $P = 0.01$ for Control > Turner.

Within-group Analyses

Control Group

When the easy JLO epoch was compared to the baseline epoch, significant activation was observed in the inferior parietal lobule (IPL) extending into the superior parietal lobule (SPL). The activation was bilateral but more extensive in the right hemisphere. Additionally, significant activation occurred in the right and left middle occipital gyrus (MOG) and superior occipital gyrus (SOG). During the difficult JLO epoch, the control group again showed significant activation in the IPL, SPL, MOG and SOG, but to a greater extent. They additionally recruited frontal brain regions, specifically, inferior, middle and superior gyri (IFG, MFG, SFG) as well as motor and sensory cortices (Table 2, Fig. 1).

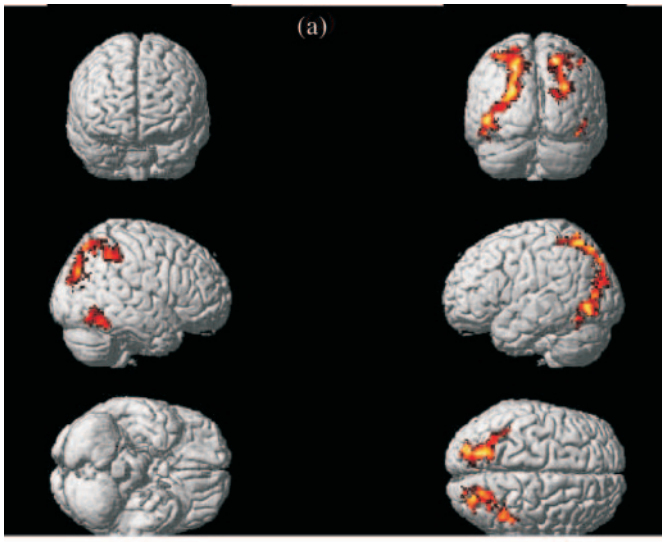
TS Group

Subjects with TS did not show significantly greater activation for the easy JLO task compared to the baseline task at the 0.05 level. When the significance threshold was empirically lowered to 0.1, the TS group showed activation in expected parietal and occipital areas (i.e. IPL, SPL, MOG and SOG — see Table 2, Fig. 2). On the difficult JLO task, the TS group demonstrated significant activation bilaterally in the IPL extending into the SPL and also in the inferior occipital gyrus (IOG), MOG and SOG (Table 2, Fig. 2).

Table 2
Within-group results indicating significant brain activation during the JLO task

	P value (corrected)	No. of voxels	*Z* score	Peak location (Talairach coordinates)	
Control group					
Easy-baseline	<0.0001	1744	4.67	–44, –78, 4	left and right inferior and superior parietal lobules, inferior, superior and middle occipital gyri
	0.002	756	3.96	22, –67, 55	
	0.031	502	3.58	36, –43, 41	
	0.006	645	3.37	44, –70, –10	
Difficult-baseline	<0.0001	10 791	5.12	–40, –79, 8	left and right inferior and superior parietal lobules, middle and superior occipital gyri
	<0.0001	2510	4.46	30, –71, 52	
	0.001	839	4.26	4, 7, 53	
	<0.0001	1780	4.09	–24, –2, 44	
TS group					
Easy-baseline ($P < 0.05$)	none				
($P < 0.1$)	0.018	1292	3.72	34, –77, 8	right and left superior parietal lobule, middle, inferior and superior occipital gyri
	0.017	1307	3.59	–42, –79, 4	
Difficult-baseline	<0.0001	4790	4.07	32, –46, 54	right and left inferior and superior parietal gyri, inferior, middle and superior occipital gyri

Thresholds: height ($Z > 1.67$; $P < 0.05$) and extent ($P < 0.05$).



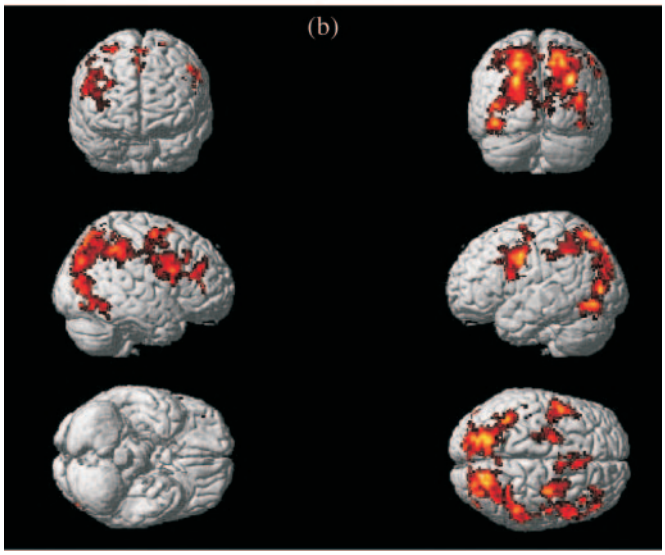
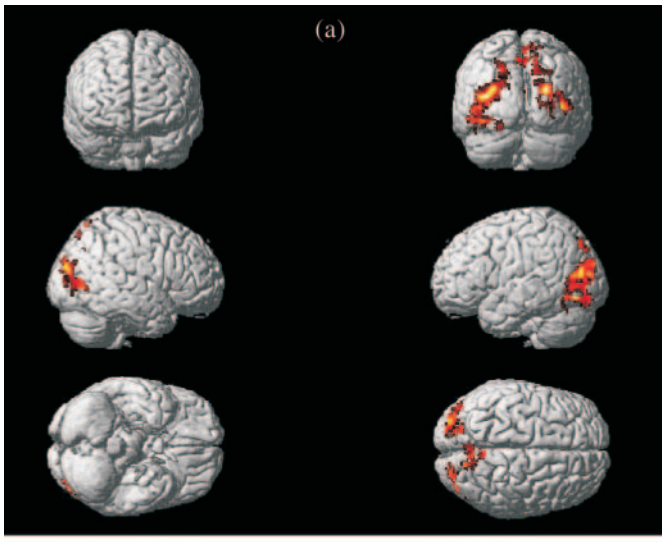


Figure 1. (*a*) During the easy JLO task, control subjects demonstrated significant brain activation in the right and left IPL extending into the SPL as well as right and left MOG, and SOG. (*b*) During the difficult JLO task, control subjects showed increased activation again in the parietal-occipital areas and also recruited IFG, MFG, cingulate, motor and sensory cortices to meet the increased task demands.



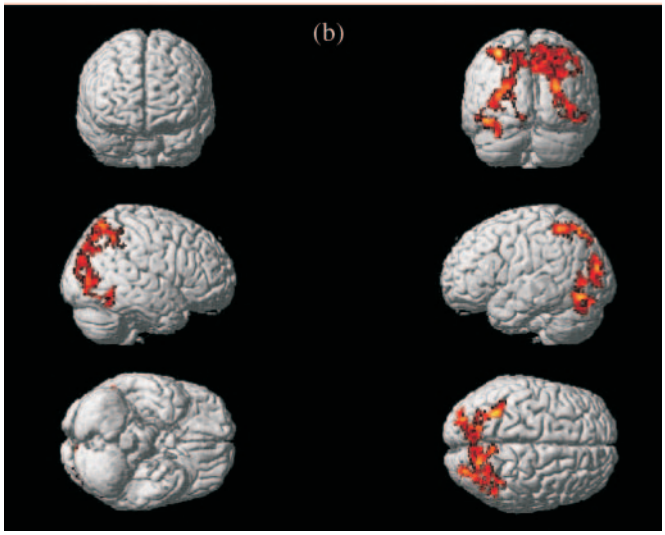


Figure 2. During the easy JLO task, TS subjects did not demonstrate any significant activation at the a priori threshold of $P < 0.05$. (*a*) However, when the threshold was lowered to 0.1, activation occurred in the IPL, SPL, MOG and SOG. (*b*) During the difficult JLO task, subjects with TS demonstrated significant activation in the right and left IPL extending into the SPL. They also demonstrated significant activation in the MOG, SOG and IOG.

Between-group Analyses

Control Group Minus TS Group

On the easy JLO task, control subjects showed greater activation in the right motor and sensory cortices (i.e. pre- and post-central gyri), right cingulate gyrus and right IPL extending into the SPL. On the difficult task, control subjects showed greater activation bilaterally in the IFG, MFG, SFG, the cingulate, motor and sensory cortices, IPL, SPL, MOG and SOG. These differences remained even after covarying for difficult task performance (Table 3, Fig. 3).

TS Group Minus Control Group

The TS group did not show greater activation compared to the control group during the easy JLO task. On the difficult JLO task, subjects with TS demonstrated significantly greater activation in the medial frontal lobe, the SFG, caudate, putamen, cingulate, superior and middle temporal gyri (STG, MTG) and the precuneus (Table 3, Fig. 4).

Discussion

From the perspective of behavioral performance, both groups showed an expected decrease in accuracy on the difficult JLO task compared to the easy JLO task. Subjects with TS were significantly less accurate than control subjects on the difficult version of the JLO task. However, their performance on the easy JLO task was comparable to that of control subjects. Subjects with TS were not significantly different from controls in reaction time on correct trials, suggesting that neither impul-

Table 3
Between-group results indicating significant brain activation during the JLO task

	P value (corrected)	No. of voxels	Z score	Peak location (Talairach coordinates)	
Control-TS					
Easy JLO	0.024	598	3.22	42, –32, 28	pre and post central gyri, right cingulate, right inferior and superior parietal lobules
	<0.0001	1035	3.17	36, –37, 33	
Difficult JLO	<0.0001	4913	4.67	–24, –2, 42	right and left inferior, middle and superior frontal gyri, pre and post central gyri, inferior and superior parietal lobules, middle and superior occipital gyri
	<0.0001	5109	4.25	2, 25, 37	
TS-Control					
Easy JLO	none				
Difficult JLO	<0.0001	3035	4.7	2, –32, 29	medial frontal lobe, superior frontal gyrus, caudate, putamen cingulate, superior and middle temporal gyri, precuneus
	<0.0001	1236	4.4	0, 54, –4	
	<0.0001	1379	3.87	–53, –20, –14	

Thresholds: height ($Z > 1.67$; $P < 0.05$) and extent ($P < 0.05$).

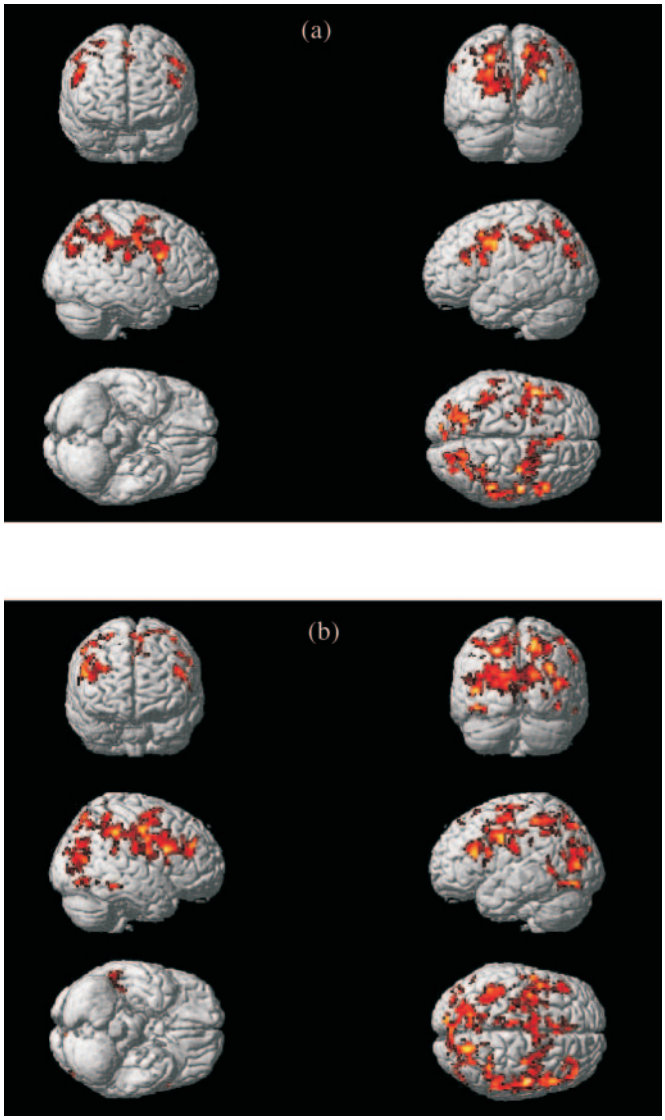


Figure 3. Between group comparisons indicated that, during the difficult JLO task, (*a*) controls demonstrated significantly greater activation in IFG, SFG, MFG, cingulate, motor and sensory cortices, IPL, SPL, MOG and SOG; and (*b*) These differences remained even after covarying for JLO performance.

sivity nor slowed cognitive processing affected task performance or brain activation results.

Functional MRI data presented in this study provide evidence that both TS and control subjects use functionally interconnected regions of the parietal and occipital lobes to process simple spatial orientation information. Although activation in the TS group was observed to be less robust during the easy JLO task, both groups tended to activate a similar topography of parietal and occipital regions. These findings are consistent with other neuroimaging studies of spatial processing in typically developing individuals (Fink *et al.*, 2000; Ng *et al.*, 2000; Podzebenko *et al.*, 2002; Sack *et al.*, 2002). As expected, control subjects showed increased activation in visuospatial areas (i.e. parietal and occipital) in response to the increased demands of the difficult JLO task. Additionally, control subjects recruited executive planning and organizational areas (i.e. frontal regions) to compensate for the increased task difficulty. A similar pattern of increased brain activation in response to increasing task demand has been demonstrated in other studies involving typically developing individuals (Fu *et al.*, 2002; Rivera *et al.*, 2002).

JLO-associated brain activation in subjects with TS appeared to occur in an inefficient manner. While TS subjects recruited the appropriate visuospatial processing regions during the easy JLO task, it was to a significantly lesser extent compared to control subjects. In fact, activation in the TS group did not reach initial significance thresholds during the easy JLO task. These data are consistent with our previous study showing significantly decreased parietal lobe volumes in individuals with TS (Reiss *et al.*, 1995), suggesting a structure–function association. During the difficult JLO task, subjects with TS showed significant activation in the parietal-occipital visuospatial areas but again to a more limited extent compared to controls. Further, unlike controls, they did not recruit prefrontal executive systems to meet the increased task demands. Our previous study involving working memory function in TS also demonstrated that, compared to controls, subjects with TS did not increase brain activation to meet increased task demands (Haberecht *et al.*, 2001).

Our findings suggest a complex relationship between spatial orientation processing and frontal lobe function. Control subjects recruited IFG, MFG and motor-sensory regions during the difficult JLO task. Thus, in contrast to data derived from patients with acquired brain lesions (Benton *et al.*, 1983), our findings point to the dorsolateral prefrontal cortex for executive function of visuospatial processing. However, subjects with TS did not demonstrate activation of similar prefrontal cortical regions. Frontal activation deficits in the TS group were preserved even after covarying for task performance.

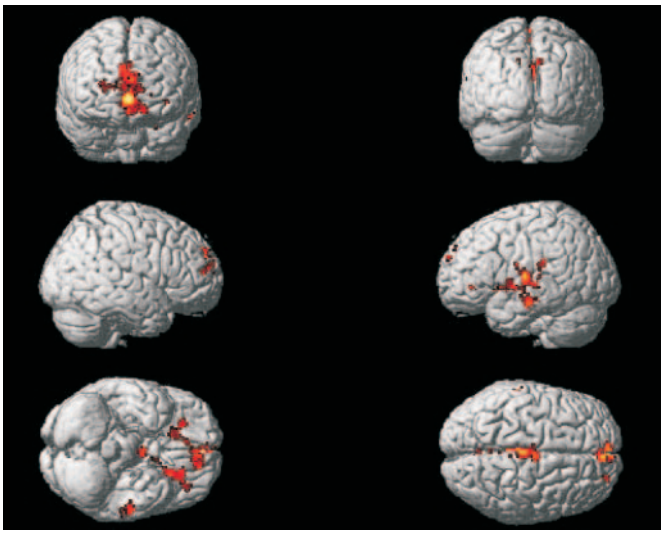


Figure 4. The TS minus Control contrast for the difficult JLO task demonstrated greater activation in the medial aspect of the frontal lobe, SFG, caudate, putamen, cingulate, STG, MTG and precuneus. However, further analyses suggest that these findings likely represent areas of deactivation deficits in the TS group on the difficult JLO or areas of activation deficits in the TS group relative to the baseline color discrimination task.

Subjects with TS showed greater activation relative to control subjects in the medial aspect of the frontal cortex, SFG, caudate, putamen, cingulate, STG, MTG and precuneus during the difficult version of the JLO task. However, these activated areas may actually arise from greater deactivation in control subjects rather than increased activation in TS, given that activation in these areas was not observed during the TS within group analysis of the difficult task. To further explore these findings *post hoc*, activation from the difficult JLO task was subtracted from the baseline task in the control subjects. This contrast demonstrated activation in the same areas (e.g. medial frontal, caudate, STG), suggesting that the between-group difference was actually due to activation in the controls during the baseline task. These brain regions are consistently deactivated during a wide range of cognitive tasks (Shulman *et al.*, 1997). However, it is not clear whether differences in activation actually reflect inhibitory processes during the experimental condition or increased activation related to neural mechanisms during the baseline condition (Shulman *et al.*, 1997; Binder *et al.*, 1999; Fransson *et al.*, 1999). For example, the medial aspect of the frontal cortex is involved in the evaluation of emotional stimuli and its impact on cognitive processes (Raichle *et al.*, 2001). If the observed group difference represents deactivation deficits in the medial aspect of the frontal cortex, females with TS may have more difficulty with dissociating the effect of emotional and cognitive processing during the JLO task.

Alternatively, these areas may be activated in control subjects consistent with making the color discriminations required by the baseline task. For example, frontal activation may be consistent with executive judgment of color similarity, while STG activation may suggest use of verbal strategies such as subvocalizing color names (Binder *et al.*, 2000; Benson *et al.*, 2001; Burton *et al.*, 2001). Control subjects may utilize these brain regions during the baseline task while subjects with TS do not. This would be consistent with the hypothesis of executive dysfunction in TS (Bender *et al.*, 1993; Ross *et al.*, 2000). Additionally, a previous study conducted by our laboratory indicated significantly aberrant STG morphology in individuals with TS (Kesler *et al.*, 2003), a finding that may be associated with activation deficits in this region. Nevertheless, whether reflecting deactivation or activation deficits, these between-group differences further highlight dissimilarities in the profiles of brain activation and possibly, deactivation, during cognitive processing in subjects with TS.

In summary, subjects with TS were significantly impaired on the difficult JLO task compared with control subjects. They demonstrated activation deficits in the parietal-occipital areas, brain regions known to be critically involved in spatial orientation processing, and in the prefrontal cortex, a region thought to mediate more general executive control. This suggests that dysfunction of neural systems underlying both spatial processing and executive function contribute to the JLO deficit observed in girls with TS. Future studies will be needed to further define the role of these cognitive domains in individuals with TS. Additionally, given that subjects with TS were less accurate on the difficult JLO task but similar to controls in reaction time, it is possible that training individuals with TS to take more time on difficult tasks might increase performance accuracy. Alternatively, cognitive rehabilitation in executive functioning also may benefit individuals with TS. Future studies involving potential compensatory cognitive strategies are necessary.

Notes

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