

Abnormal Prefrontal Cortex Function during Response Inhibition in Turner Syndrome: Functional Magnetic Resonance Imaging Evidence

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Background: *Turner syndrome (TuS) arises from the partial or complete absence of one X chromosome. Although neuropsychological studies report impaired attentional function and response inhibition in TuS, the neural correlates of these cognitive problems are unknown.*

Methods: *Eleven female subjects with TuS and 11 individually matched normal control subjects were imaged using functional magnetic resonance imaging while performing a Go/NoGo task.*

Results: *Groups did not differ on accuracy or reaction time; however, the TuS group activated more in the bilateral superior and middle frontal gyri than control subjects. Control subjects did not activate more than the TuS group in any region.*

Conclusions: *These findings suggest that female subjects with TuS compensate for executive dysfunction via recruitment of additional prefrontal cortex regions involved in inhibition, attention, and working memory, functions necessary for successful performance of Go/NoGo tasks. Elucidating brain function in TuS will advance our understanding of the influence of X-chromosome genes on neurodevelopment and brain function and contribute to planning future intervention strategies.* Biol Psychiatry 2003;53:107–111 © 2003 Society of Biological Psychiatry

Key Words: Turner syndrome, functional magnetic resonance imaging, inhibition, prefrontal cortex

Introduction

Turner Syndrome (TuS), which results from the complete or partial absence of one X chromosome, occurs in approximately 1 in 2500 births. In addition to a variable physical phenotype, individuals with TuS typically demonstrate impairments in visuo-spatial processing, memory,

motor function, executive function, and attention (e.g., Ross et al 2000a). The specific mechanism leading to these deficits is unknown but is thought to arise directly from genetic haploinsufficiency (insufficient dosage of gene product from a region of the X chromosome that escapes inactivation; Bishop et al 2000) and/or secondary estrogen deficiency (Ross et al 2000a). Atypical cortical organization and brain morphology has been reported in TuS (Reiss et al 2000) and may play a role in neurocognitive deficits in TuS. The most common anatomical finding is the presence of smaller parietal and occipital lobe volumes (Murphy et al 1993; Reiss et al 1995).

Despite ample evidence of executive dysfunction in TuS on cognitive tasks thought to involve frontal regions, there is little evidence for anatomical abnormalities in the prefrontal cortex. Among possible explanations is that executive dysfunction may arise from aberrant frontal-parietal connections, thereby creating neurofunctional, rather than morphologic, anomalies in frontal regions. Functional magnetic resonance imaging (fMRI) provides a unique opportunity to investigate this hypothesis. Results from two fMRI studies of individuals with TuS have recently been reported. Both studies found evidence to suggest impaired frontal-parietal connections on tasks of visuo-spatial working memory and visuo-spatial orientation processing (Haberecht et al 2001); however, studies using tasks known to reliably and primarily activate the prefrontal cortex are warranted to further investigate the neurofunctional basis of executive dysfunction in TuS.

In the present study, we used fMRI to investigate brain activation related to executive function and inhibitory control. We hypothesized that female subjects with TuS would make more errors of commission and omission on a Go/NoGo task than control subjects, based on neuropsychological evidence of impaired inhibitory control in TuS (Murphy et al 1994; Romans et al 1998; Skuse et al 1997; Williams et al 1991). We also hypothesized that female subjects with TuS would show aberrant brain activation compared to control subjects, particularly in the prefrontal cortex, because the Go/NoGo task is known to consistently activate prefrontal regions (Casey et al 1997; Garavan et al 1999; Liddle et al 2001; Menon et al 2000).

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Methods and Materials

Participants included 11 monosomic female subjects with TuS and 11 age-matched healthy control female subjects (mean age 14.03 years, SD = 4.89). The protocol was described to all participating subjects and parents, and written consent was obtained under protocols approved by the Institutional Review Board (IRB) of Stanford University. Intellectual functioning was assessed with the Wechsler Intelligence Scale for Children, Third Edition or the Wechsler Adult Intelligence Scale, Third Edition.

Experimental Task

The experiment consisted of a 30-sec rest epoch, 12 alternating 26-sec epochs of Go and Go/NoGo conditions, followed by a 30-sec rest epoch. During both conditions, letters were presented every 2 sec. In the Go/NoGo condition, subjects responded with a key press to every letter except “X” (presented on 50% of the trials), to which they were instructed to withhold response. In the Go condition, subjects responded with a button press to every letter (no “X’s” were presented). Errors of omission, errors of commission, and reaction time to correct trials during the experimental condition were recorded.

Data Acquisition

Images were acquired on a 1.5-T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI) with Echosped gradients using a custom-built, whole-head coil (Hayes and Mathias 1996). Eighteen axial slices (6-mm thick, 1-mm skip) parallel to the anterior and posterior commissures, covering the whole brain, were imaged with a temporal resolution of 2 sec using a T2*-weighted, gradient echo, spiral pulse sequence (time to repetition [TR] = 2000 msec, time to echo [TE] = 40 msec, flip angle = 89°, and 1 interleave) (Glover and Lai 1998). The field of view (FOV) was 240 mm, and the effective in-plane spatial resolution was 4.35 mm. To aid in localization of functional data, a high-resolution, T1-weighted, spoiled gradient-recalled acquisition in the steady state (GRASS), three-dimensional MRI sequence with the following parameters was used: TR = 35 msec; TE = 6 msec; flip angle = 45°; 24 cm FOV; 124 slices in coronal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm.

Data Analysis

Images were corrected for movement using least-square 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 was performed on individual and group data using the general linear model and the theory of Gaussian random fields using SPM99 (Wellcome Institute of Cognitive Neurology, London, UK). A within-subject procedure was used to model all the effects of interest for each subject. Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each

Table 1. Descriptive Data on Dependent Variables of Interest and IQ

	Female Subjects with TuS	Control Subjects
Verbal IQ	111.55 (23.33)	114.73 (13.51)
Performance IQ	95.27 (14.38)	114.91 (11.77)
Full-scale IQ	104.27 (19.95)	116.09 (13.45)
Errors of Commission	5.64 (5.61)	4.00 (2.79)
Errors of Omission	2.91 (5.80)	1.64 (2.54)
Reaction Time to Correct Go Trials	601.33 (113.24)	558.86 (117.99)

Data are presented as mean (SD). IQ, intelligence quotient; TuS, Turner syndrome.

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 sec) was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Effects of interest were defined for each subject with the relevant contrasts of the parameter estimates. For each of these contrasts, a corresponding contrast image was also generated. Voxel-wise *t* statistics were normalized to *Z* scores to provide a statistical measure of activation independent of sample size. 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 ($Z > 2.33$; $p < .01$) and extent thresholds ($p < .05$).

Results

Wechsler Intelligence Quotient Scales

The full-scale intelligence quotient (IQ) scores of the female subjects with TuS did not significantly differ from those of control subjects [$t(20) = 1.63$, ns]; however, an examination of group differences between verbal (VIQ) and performance IQ (PIQ) scores revealed that, as expected, subjects with TuS had lower PIQ scores than control subjects [$t(20) = 3.51$, $p < .01$]. Verbal IQ scores were not significantly different [$t(20) = .39$, ns]. Table 1 shows means and standard deviations for IQ and behavioral variables.

Behavioral Analyses

Independent-samples *t* tests were conducted on the errors of omission [$t(20) = .66$, ns], errors of commission [$t(20) = .87$, ns], and reaction time to correct trials during the experimental condition [$t(20) = .86$, ns] variables. No significant group differences emerged for these variables.

Brain Activation

Female subjects with TuS showed greater activation than female control subjects in the dorsal regions of the left and

Table 2. Brain Areas That Showed Significant Activation during the NoGo Compared with the Go Condition

Activated Region	No. of Voxels	Z Max	Peak Locations
Turner Group Minus Control Group			
Left Superior/Middle Frontal Gyrus (BA 6/8)	571	3.25	–24, 26, 44 –20, 26, 54 –6, 30, 54
Right Superior/Middle Frontal Gyrus (BA 6/8)	823	3.22	26, 22, 54 16, 40, 42 38, 24, 42

For each significant cluster ($p < .05$), region of activation, number of voxels activated, maximum Z score, and location of peak (Talaraich coordinates) are shown. BA, Brodmann's area.

right superior frontal gyri (SFG; Brodmann's area [BA]6/8) and middle frontal gyri (MFG; BA6/8) on the NoGo compared with Go contrast (Table 2, Figure 1).

Compared with female subjects with TuS, female control subjects did not show greater activation associated with the NoGo condition for any brain region.

Discussion

Contrary to our prediction, the two groups did not differ in terms of accuracy or reaction time on the Go/NoGo task; however, in association with their comparable behavioral performance, female subjects with TuS showed significantly greater bilateral brain activation in the NoGo condition compared to control subjects, primarily in the dorsal regions of the SFG and MFG (BA6/8). Thus,

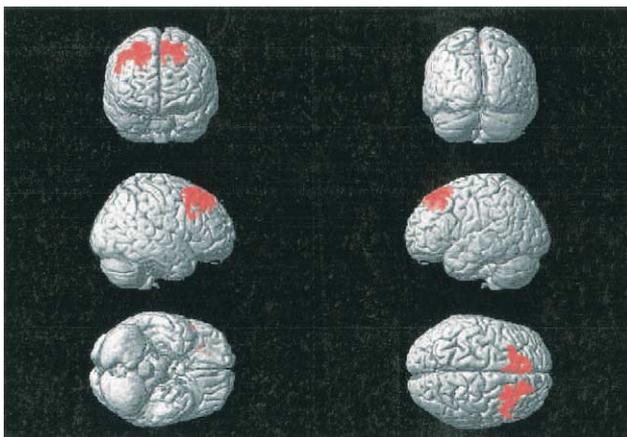


Figure 1. Brain regions in which female subjects with Turner syndrome show significantly more activation than typically developing female subjects for the experimental (NoGo) minus control (Go) condition (i.e., left and right superior and middle frontal gyri).

female subjects with TuS appear to activate a different or more extensive functional network than control subjects to perform this executive function task. A potential explanation for these findings is that, as a result of X monosomy, the brains of female subjects with TuS are organized differently than those of control subjects. Alternatively, as suggested by recent findings from our laboratory (Tamm et al 2002), the topography and extent of prefrontal regions activated in individuals with TuS performing the Go/NoGo task might be interpreted as being consistent with activation patterns observed in chronologically younger, typically developing control subjects. In this study of typically developing children aged 8–20, younger subjects performed the Go/NoGo task at a level comparable to that of adolescents and young adults while simultaneously recruiting additional prefrontal regions. The question of altered cortical organization versus functional immaturity of brain activation can potentially be addressed with longitudinal studies of children with TuS and an experimental design that incorporates varying levels of task difficulty.

Regardless of the origin of between-group brain activation differences, it is clear that female subjects with TuS activate additional regions of the prefrontal cortex compared with control subjects. Activation in these regions may reflect variable strategies and/or effort necessary to achieve a “normal” performance level. Increased activation in the SFG and MFG in female subjects with TuS during the NoGo condition may reflect greater reliance on functions subserved by these regions. The SFG and MFG are thought to be involved in attention, motor planning, and working memory functions, all integrally related to successful performance of a response inhibition task such as the Go/NoGo. Further, these regions are activated during similar Go/NoGo paradigms (Casey et al 1997; Garavan et al 1999; Kawashima et al 1996; Lee et al 2001; Liddle 2001), although their specific role in inhibition is not completely understood.

Activation of the supplementary motor area may be related to response execution (initiation/suppression of movements; Garavan et al 1999; Rubia et al 2001). The left MFG is thought to play a role in attentional set-shifting during tasks of motor selection (Omori et al 1999), whereas the SFG may be involved in maintaining covert spatial attention (Corbetta 1998) and attentional shifting (Nagahama et al 1999). The left MFG is implicated in nonspatial working memory (Belger et al 1998; Collette et al 1999; D'Esposito et al 1998), and the SFG subserves working memory maintenance functions (Rowe and Passingham 2001; Rowe et al 2000). Thus, it is plausible that female subjects with TuS are relying more on these supplementary functions than control subjects for successful inhibition of a prepotent response in the Go/NoGo task.

The lack of group differences in the behavioral data were somewhat surprising, particularly, because some neuropsychological studies report poorer TuS performance on similar tasks (Romans et al 1998; Ross et al 2002). This may reflect limitations of standard neuropsychological measures, which often measure multiple constructs simultaneously. Our task was designed to illuminate a single process (response inhibition) in a tightly controlled paradigm. Female subjects with TuS performed similarly well as control subjects, and this was not due to a ceiling effect. Perhaps the lack of group differences is due to the fact that the Go/NoGo task is a verbally mediated task. The relatively intact verbal skills of female subjects with TuS may have allowed them to overcome potential performance problems. Further research is warranted to investigate this hypothesis.

It should be noted that female subjects with TuS have reported deficits in working memory (Cornoldi et al 2001; Haberecht et al 2001; Murphy et al 1993) and motor planning (Nijhuis-van der Sanden et al 2000; Ross et al 1996; Salbenblatt et al 1989). Thus, although they can compensate for these deficits on this relatively simple, verbally based task, more complex tasks involving higher working memory load, greater motor planning demands, and more complex cognitive interference may result in poorer performance and perhaps less activation in these regions, owing to inadequate focalization of function (e.g., Haberecht et al 2001).

In an effort to address whether the current findings were confounded by group differences in PIQ or the wide range of ages, despite the groups being individually age-matched, the fMRI and behavioral data were visually examined and subjected to additional analyses covarying for VIQ and age, respectively. Comparable results were obtained, suggesting minimal confounding effects of VIQ and age. Additional exploratory analyses were conducted within the TuS group to investigate potential effects of onset of estrogen supplement treatment at puberty in the TuS group, and the effect of parent of origin for the TuS group. Again, results were unchanged with the exception of parent of origin. Female subjects with TuS of paternal origin had significantly more activation than those of maternal origin in one of the two clusters of significant activation, the right SFG/MFG. This finding is potentially intriguing but requires replication and further analysis, given the small sample size ($n = 5$ and $n = 6$) in the parent-of-origin subgroups.

These results provide new and important evidence of altered prefrontal cortex function in TuS in association with response inhibition. As findings from molecular genetic studies begin to demonstrate the specific role of X-chromosome genes (Ross et al 2000b) and putative epigenetic factors (Brown et al, unpublished data; Skuse et

al 1997) on neurobehavioral phenotypic expression in TuS, the role of these genetic factors in typical brain development and function will become clearer. By explicating intact and aberrant brain activation patterns in TuS and linking these to cognitive abilities, future functional neuroimaging studies also hold promise for contributing to the design of improved interventions in individuals with this important genetic disorder.

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