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Atypical Functional Brain Activation During a Multiple Object Tracking Task in Girls With Turner Syndrome: Neurocorrelates of Reduced Spatiotemporal Resolution

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Abstract

Turner syndrome is associated with spatial and numerical cognitive impairments. We hypothesized that these nonverbal cognitive impairments result from limits in spatial and temporal processing, particularly as it affects attention. To examine spatiotemporal attention in girls with Turner syndrome versus typically developing controls, we used a multiple object tracking task during functional magnetic resonance (fMRI) imaging. Participants actively tracked a target among six distracters or passively viewed the animations. Neural activation in girls with Turner syndrome during object tracking overlapped with but was dissimilar to the canonical frontoparietal network evident in typically developing controls and included greater limbic activity. Task performance and atypical functional activation indicate anomalous development of cortical and subcortical temporal and spatial processing circuits in girls with Turner syndrome.

Turner syndrome occurs in approximately 1 in 2,500 live births and results from the complete or partial deletion of an X chromosome in a phenotypic female. Physical characteristics associated with the deletion include heart and cardiovascular abnormalities, decreased stature, webbed neck, shield chest, hearing and vision difficulties, gonadal dysgenesis, infertility, and diminished secondary sex characteristics (Loscalzo, 2008).

The Turner syndrome neuropsychological profile is characterized by impairments in executive function, increased impulsivity, and decreased attention (Pennington, Bender, Puck, Salbenblatt, & Robinson, 1982; Waber, 1979). Full Scale IQ and Verbal IQ (Ratcliffe, Butler, & Jones, 1991; Robinson, Bender, Linden, & Salbenblatt, 1990; Stewart, Bailey, Netley, & Park, 1990) are, however, within the average range but with lower Performance IQ than that found for typically developing girls (Rovet, 1993; Temple, 1996). Girls with Turner syndrome demonstrate significant impairments in visuospatial and spatial memory tasks (Mazzocco, Singh Bhatia, & Lesniak-Karpiak, 2006) as well as poor math and numeracy skills (Bruandet, Molko, Cohen, & Dehaene, 2004; Rovet, Szekely, & Hockenberry, 1994; Temple, 1994, 1996). There is also some evidence of impairments in temporal processing (e.g., Silbert, Wolff, & Lilienthal, 1977). Elucidating the neurological correlates of these numerical and spatial

memory impairments has typically been focused on the frontoparietal and frontostriatal networks (Haberecht et al., 2001; Kesler, Menon, & Reiss, 2006).

We have suggested that understanding the origin of numerical impairments in girls with Turner syndrome (and other neurodevelopmental disorders associated with impairments in spatial, temporal, and numerical processing) requires a greater focus on the foundational components of the developing system required to develop even basic mathematical skills (Simon, 2008; Simon, Takarae et al., 2008). As have other investigators, we also posit that numerical competence is based on cognitive competencies related to spatial and object cognition (Ansari & Karmiloff-Smith, 2002; Mazzocco et al., 2006; Simon, 1997, 1999; Simon, Wu, et al., 2008). Typical development of attentional competencies, which depend on frontoparietal networks in healthy individuals, results in an array of abilities, including object detection and individuation, attention and orientation to objects based on internally derived search paths and external spatial cues, engaging and disengaging from objects, and eventually orienting attention within internal representational structures (Corbetta & Shulman, 2002; Dehaene, Piazza, Pinel, & Cohen, 2003). Therefore, we have also proposed that atypical attentional development, likely associated with changes to the frontoparietal network, is a foundational problem from which spatial, temporal, and numerical impairments likely cascade. Our research group has shown this account to be consistent with the developmental profile of children with chromosome 22q11.2 deletion syndrome (22q11.2DS), who share many of the spatiotemporal and numerical impairments seen in Turner syndrome (Simon, Bearden, McDonald-McGinn, & Zackai, 2005; Simon, Bish et al., 2005).

Kesler and others (2006) had girls with Turner syndrome and typically developing controls perform simple and more complex arithmetic during a functional magnetic resonance imaging (fMRI) scan. Females in these groups did not differ in performance and shared similar activation in the frontoparietal regions in response to the arithmetic task. However, during simple, two-operand arithmetic, the Turner syndrome group apparently recruited more frontoparietal resources, as suggested by greater amounts of activation in the left dorsolateral and ventrolateral prefrontal cortex, the supramarginal gyrus, and the premotor cortex. As computation demand increased with the more complex three-operand task, girls with Turner syndrome showed less activation than did controls in these areas. Also distinct from the typically developing group, there was greater activation in the anterior cingulate in the Turner syndrome group during the simple arithmetic task. Given that performance on the tasks did not differ, Kesler and colleagues (2006) posited that individuals with Turner syndrome have engaged other neural systems involved with working memory, attention, and language to assist with successful task completion.

Haberecht and others (2001) administered a 1-back and 2-back working memory task during an fMRI scan. This task tests ability to both hold information in memory while also manipulating it to generate new results. This so-called "N-back" task requires participants to indicate whether a target visual stimulus is in the same location as the previously viewed one (i.e., one step back) or the same location as the stimulus prior to the last one viewed (i.e., two steps back). Girls with Turner syndrome performed more poorly than did controls. However, for girls with Turner syndrome, performance did not decline in association with task load. Furthermore, in the 2-back but not the 1-back task, girls with Turner syndrome had less blood oxygen level dependent (BOLD) activity compared to controls in the dorsolateral prefrontal cortices (DLPFC), caudate nucleus, and the inferior parietal lobes. A shift from greater activation in the supramarginal gyri (SMG) measured in the Turner syndrome versus the typically developing groups during the 1-back task disappeared in the 2-back task. The authors suggested that activation differences did not reflect performance but rather efficiency and processing speed of visuospatial information and load on working memory, which they further linked to impairments in executive function and memory associated with Turner syndrome.

Our research group has suggested that the foundation for many of the same spatial and numerical cognitive impairments experienced by females with Turner syndrome lies in the resolution and, thus, capacity of mentally represented spatial and temporal information. We further linked that resolution to the output of processes involved with visual attention. This account has been developed based on findings from research on 22q11.2DS but because we have demonstrated very strong overlap between spatial and numerical impairments in that disorder and Turner syndrome (Simon, Takarae et al., 2008), we are fairly confident that a similar account will explain impairments in Turner syndrome. Using the analogy of a digital camera, much as a one megapixel digital camera cannot represent information captured by a ten megapixel digital camera with the same degree of detail, we hypothesized that attentional resolution of spatial and temporal representations is reduced in these disorders. This reduced resolution, which Simon (2008) called “spatiotemporal hypergranularity,” creates crowding among representational elements and, thus, reduces accuracy and increases discrimination thresholds in ways consistent with the data characterizing spatiotemporal and numerical impairments found in children with 22q11.2DS and Turner syndrome.

Alvarez and Franconeri (2007), Cavanagh (2004), and Cavanagh and Alvarez (2005) have shown that multiple object tracking tasks can provide an accurate assay of spatiotemporal capacity and resolution in adults. Therefore, we decided to adopt this task to investigate the neural correlates of attentional impairments in girls with Turner syndrome compared to typically developing controls. Multiple object tracking tasks require an individual to simultaneously monitor the position of several moving targets among a field of moving distracters. Such tasks test the deployment and maintenance of attention to a set of targets over space and time. Several investigators have established the limitations of typically developing adults, specifically on capacity (number of items tracked), space (size of the tracking field), and time (both speed and length of tracking period; reviewed by Cavanagh and Alvarez, 2005). Recognizing that cognitive processes theoretically determining multiple object tracking performance likely change during development, Trick et al. (2005) created a child's version of the multiple object tracking task and demonstrated that the capacity limitation was age dependent as predicted.

Functional imaging studies of multiple object tracking show widespread neural activations in typically developing adults (Culham, Cavanaugh, & Kanwisher, 2001; Jovicich et al., 2001). However, we are unaware of functional imaging during multiple object tracking tasks in children. Areas associated with the frontoparietal attentional network (Corbetta, 1998) showed increased BOLD signal in positive linear relationship to the number of items tracked. Thus, the areas responding to attentional load could be distinguished from areas associated with other aspects of the task, such as inhibiting eye movements. We hypothesized that girls with Turner syndrome would be less accurate overall on the multiple object tracking task than would typically developing girls, especially when required to track more items. However, we also hypothesized that even when performance did not differ between girls with Turner syndrome and typically developing controls, the former group would demonstrate anomalous neural activation in the typical frontoparietal network compared to age- and gender-matched controls, likely due to differences in functional circuitry. These patterns of neural activation in the Turner syndrome group will help elucidate neurocorrelates of spatiotemporal resolution and memory capacity impairments in the Turner syndrome population.

Method

Participants

This study was approved by the Institutional Review Boards of the Children's Hospital of Philadelphia, Thomas Jefferson University, and the University of California, Davis. Parental consent and child assent was obtained for all participants: 21 girls with Turner syndrome (*M*

age = 10.5 years, range = 7.67 to 14.75, $SD = 32.36$ months) and 21 typically developing girls (M age = 10.58 years, range = 7 to 13.67, $SD = 27.43$ months) recruited through clinics at Thomas Jefferson University in Philadelphia as part of a larger ongoing study. The 45, X karyotype status of all participants with Turner syndrome was confirmed by karyotype analysis, and mosaicism was an exclusionary criterion. The groups did not differ in socioeconomic status (SES) ($M_s = 52.68$ and 52.56 for Turner syndrome group and typically developing group, respectively), $t(35) = 0.045$, $p = .96$, using Hollingshead's (1975) four factor index. SES data were not available for 2 of the girls with Turner syndrome and 2 of the typically developing girls.

We tested all participants, with the exception of one typically developing control, using the Wechsler Intelligence Scale for Children, Version 4–WISC-IV (Wechsler, 2003). As a group, girls with Turner syndrome had lower Full Scale IQs (Turner syndrome $M = 96$, $SD = 13.89$ vs. typically developing $M = 110$, $SD = 10.32$), $t(39) = -3.64$, $p < .01$; lower Processing Speed Scale scores (Turner syndrome $M = 90$, $SD = 12.49$ vs. typically developing $M = 103$, $SD = 12.00$), $t(39) = -3.43$, $p < .001$; and Perceptual Reasoning Scale scores (Turner syndrome $M = 96$, $SD = 15.73$ vs. typically developing $M = 112$, $SD = 12.24$), $t(21) = -5.21$, $p = .004$, than typically developing girls as measured using the WISC-IV. The groups did not differ on Verbal Comprehension scores (Turner syndrome $M = 103$, $SD = 11.94$ vs. typically developing $M = 107$, $SD = 13.37$), $t(39) = -0.92$, $p = .37$.

A number of participants were excluded from the analysis for having no multiple object tracking response data and no fMRI scans ($n_s = 2$ Turner syndrome; 1 typically developing) or excessive motion (using a liberal threshold of ≥ 3 mm given that this was a pediatric population of which half experienced atypical development) during the fMRI scan ($n_s = 6$ for each group). Following exclusions, data from 11 girls (M age = 11.58 years, range 7.67 to 14.75, $SD = 29.20$ months) with Turner syndrome and 13 typically developing girls (M age = 10.83 years, range 6.75 to 13.67, $SD = 27.43$ months) are reported in this study. The groups did not differ with respect to age, $t(22) = .34$, $p = .73$, and all participants but one typically developing girl was right-handed.

The profile of WISC-IV scores for the groups made up of the nonexcluded participants showed that girls with Turner syndrome still had lower Full Scale IQs (Turner syndrome $M = 96$, $SD = 18$ vs. typically developing $M = 110$, $SD = 11$), $t(21) = -2.39$, $p = .026$, and lower Processing Speed Scale scores (Turner syndrome $M = 88.36$, $SD = 14.40$ vs. typically developing $M = 105.42$, $SD = 13.17$), $t(21) = -2.97$, $p = .007$, than typically developing girls. Also, as in the larger sample, the groups did not differ on Verbal Comprehension (Turner syndrome $M = 102.54$, $SD = 15.66$ vs. typically developing $M = 109.67$, $SD = 15.22$), $t(21) = -1.11$, $p = .28$.

Of the participants who were included in the final analyses, Perceptual Reasoning scores did not differ between groups (Turner syndrome $M = 98.73$, $SD = 17.60$ vs. typically developing $M = 110.42$, $SD = 10.54$), $t(21) = -1.95$, $p = .064$. The excluded participants in both groups did not differ on any of the IQ measures from the included participants, $p_s > .1$, nor did the included and excluded participants differ in age for either group, $p_s > .1$. Demographics of the participants who were included in the fMRI analysis are summarized in Table 1.

Multiple Object Tracking Task

As items require continuous processing, multiple object tracking tasks are inherently active and, therefore, ideal for block design functional imaging studies of spatiotemporal maintenance of attention. The multiple object tracking task presented was a variation of the “Catch the Spies” task, which was developed for children and described by Trick et al. (2005). To facilitate their motivation, we asked participants to play a game in which they must help space explorers by

identifying planets with hidden aliens. Participants then trained on a simple, progressive version of the task.

Seven planets were presented to a participant on a black field of 770 by 770 pixels. Planets were 58 by 58 pixels in size. The planets moved randomly about, independently of one another at 2 pixels per frame in both the horizontal and vertical direction. They changed their motion vector with a per frame probability of .005 or they repelled each other; when they were within 5 pixels of each other, their chance of changing direction was increased to .5. Frame rate was set at 60 frames per s. Planets could collide with each other or with the field boundary, but they could not overlap each other or cross the field boundary. In the center of the field, an 8 by 8 pixel square fixation point appeared.

During passive viewing, participants simply watched the 7 planets move. During active viewing, participants were cued to follow either 1 or 3 planets on any given trial; the remainder functioned as distracters. Active trials began with 1 or 3 bitmaps of aliens positioned above the target planet(s) for 1 s. In the first s, the words *Track Aliens* replaced the fixation point in the center of the field and then by a 1-s animation of the aliens shrinking down behind the target(s). During the third s, the target(s) flashed and after a 1-s pause, random motion began and lasted for 16 s. Afterwards, all planets stopped and a question mark appeared over one of them. Participants had 2 s to respond with an affirmative button press if the question mark designated a target (i.e., a planet behind which an alien had hidden). During the last 2 s, feedback text ("Oops!" or "Right!") appeared in the center of the viewing screen, depending on the child's response. Passive trials were similar to active trials, except that during the first s the words *Watch Planets* appeared instead of the fixation point. Because there were no targets, the motion was preceded by a static image of planet objects for a total of 4 s before motion started. After motion, objects stopped and remained still for 4 s. Figure 1 is a schematic example of a three-target trial. Each child completed 2 runs of the 12 trials and was randomly assigned to start with either a one-target block or a three-target block in the following order of presentation: numbers represent targets per trial–3-1-0-3-1-0-3-1-0-3-1-0 or 1-3-0-1-3-0-1-3-0-1-3-0.

Image Acquisition

All MRI scans were acquired at Thomas Jefferson University using a Philips 3.0T whole-body clinical MRI system (Achieva, Philips Medical Systems, Best, The Netherlands) equipped with a Quasar Dual high performance gradient system capable of on-axis (x, y, and z) peak gradient of 80 mT/m and 200 mT/m/ms slew rate, and a 8-channel sense head coil. We acquired fMRI scans in an axial orientation (AC-PC aligned) using a single-shot gradient echo EPI sequence sensitized to the BOLD contrast (repetition time (TR)/echo time (TE)/flip angle (FA) = 2s/29ms/90°, 37 interleaved slices of 3.44 mm thickness, zero interslice gap, 3.44 mm × 3.44 mm in-plane resolution). Each fMRI scan lasted 7 min 12 s, collecting a time series of images of 216 time points. Three dummy acquisitions, lasting 6 s, preceded the imaging data acquisition for the purpose of stabilizing magnetization. A task/stimulation used a block design, and each epoch lasted 36 s. High resolution anatomical images in sagittal view were acquired using a three-dimensional (3D) T1-weighted (T1WI) magnetization prepared rapid gradient-echo (MP-RAGE) sequence (Mugler III and Brookeman, 1990) (TR/TE/FA = 6.4 ms/3.2 ms/812ms/8°, 1 mm³ isotropic voxels, 170 contiguous slices of 1 mm thickness, acquisition time = min 25 s). For the purpose of across scan image registration, the orthogonal axis of the 3D sagittal T1WI anatomical scan was aligned with the BOLD scans so that axial T1WIs aligned with the BOLD images could be readily reconstructed from the original sagittal T1WIs.

Immediately following the MRI scanning session, all MRI images in Philips proprietary image format (i.e., ".par" files that contain recorded imaging parameters, and ".rec" files that contain pixel values) were transferred from the MRI scanner console computer to a computer in the

third author's MRI Lab. In addition, MRI images of the participants in DICOM format were archived to DVD. Images were sent electronically to the University of California at Davis (UCD) using an internet-based encrypted software service where transfer of images is immediate. All images are stored at both TJU and UCD for retrieval. Both laboratories at TJU and UCD have the same software to read the Philips proprietary image format and have successfully exchanged fMRI and MRI images.

Acquired images were then transferred to a workstation preprocessed and analyzed using Brain Voyager QX version 1.10 (Brain Innovation B.V., Maastricht, The Netherlands) at UCD. The functional data sets were temporally corrected for interleaved slice acquisition, 3D-motion corrected, realigned, smoothed using a Gaussian kernel to 6 mm, and normalized to Talairach space (Talairach & Tournoux, 1988). High-resolution T1-weighted 3D anatomical MRI data sets were transformed into Talairach space, used for coregistration, and averaged to generate a composite image that was created using all 24 anatomical data sets.

MRI Statistical Analyses

Statistical analyses were completed two ways. Because group sizes were fairly small (11 and 13 participants in Turner syndrome and typically developing groups, respectively) and because we were aware of some degree of variation in the pattern of activations seen, we first examined BOLD signal at every voxel with a fixed effects (FFX) general linear model (GLM). The FFX GLM assumes consistency of the experimental effect across participants and that the multiple object tracking task will elicit that same BOLD signal response in everyone. Averaging the BOLD responses within groups and then comparing the groups is advantageous in that it increases detection power and allows for inferences related to the sample. FFX GLM is limited in that it does not allow for inferences about the population at large. Also, extreme individual's responses can skew results because activations are averaged for each group. Although more conservative and requiring larger sample sizes, the random effects general linear model (RFX GLM) allows for population inferences where there are no assumptions made regarding individual's BOLD responses to the task. (For an accessible review see Huettel, Song, and McCarthy, 2004.)

We first used FFX GLM and then the more conservative RFX GLM. This was largely possible because a large amount of BOLD signal was evident using FFX GLM, despite the relatively small number of participants in each group. Because the two groups of girls could be equated in terms of behavioral performance when tracking just one target, single-target tracking and passive viewing were set as the explanatory variables accounting for differences in BOLD signals within and between groups.

We constructed activation maps that identified clusters of activity associated with the peak differences in activation both between groups (one target minus passive) and within groups (one target vs. passive) within an anatomically defined whole-brain mask. We corrected contrasts for multiple-comparisons using the false discovery rate (FDR), set at $p = .05$, methodology described elsewhere (Genovese, Lazar, & Nichols, 2002). The FDR method is less conservative than a Bonferroni correction and does not eliminate any and all false positives. In summary, the FDR method controls the proportion of errors among those tests for which the null hypothesis is rejected (represented in the Statistical Parametric Map [SPM] by active voxels) rather than controlling for the proportion of errors for which the null hypothesis is true (represented in the SPM as inactive voxels). Each voxel was 2 mm^3 , and voxel clusters were thresholded to 50 voxels or greater. Peak activation voxels and average statistical value for the region is reported using the FFX GLM for within and between groups and RFX GLM for between groups.

Results

Functional MRI Behavioral Performance

Due to the block design of our experiment, we believed it was important to equalize performance between the groups to allow us to explore differences in neural activation during the tracking task that are attributable to differences in the groups and not as a result of the girls with Turner syndrome being unable to do the task at a beyond chance level. Performance below chance in combination with lost imaging data due to motion and other image artifacts led us to focus on the within- and between-group differences comparing the one-target and passive blocks. Given equal performance between groups, we can make interpretations of neural activation differences associated with differential developmental trajectories that may underlie spatiotemporal and numerical cognitive impairments seen in females with Turner syndrome.

Groups did not differ in mean reaction times to indicate whether a target planet hid a cartoon alien during the one-target task (Turner syndrome $M = 3,265$ ms, $SD = 53$; typically developing $M = 3,272$ ms, $SD = 50$), $t(28) = 0.09$, $p > .9$, or three-target task (Turner syndrome $M = 3,274$ ms, $SD = 266$; typically developing $M = 3,293$ ms, $SD = 210$), $t(28) = 0.22$, $p > .8$, blocks. Mean error rates did not differ between the Turner syndrome and typically developing groups on the one-target blocks (Turner syndrome mean error = 0.16, $SD = 0.15$; typically developing mean error = 0.10, $SD = 0.10$), $t(28) = -1.21$, $p > 0.1$, but mean error rates were greater in the Turner syndrome (0.31, $SD = 0.13$) versus the typically developing (0.16, $SD = 0.15$) groups in the three-target blocks, $t(28) = -2.99$, $p < .01$.

Within Groups Analysis One Target Versus Passive Viewing

As shown in Figure 2 and Table 2, when contrasting the one-target versus passive tasks, we found that the typically developing controls demonstrated significant activation (warm colors) in the predicted canonical areas (e.g., Culham et al., 2001; Culham & Kanwisher, 2001; Jovicich et al., 2001) of both the left and right superior parietal lobules (SPL) and extending bilaterally into the postcentral gyri (PCG), the inferior parietal lobules (IPL), cuneus and precuneus, the postcentral (PCS), and interparietal sulci (IPS), the left and right middle frontal gyri (MidFG) extending into the precentral sulci, the right medial frontal gyrus (MedFG), and the left anterior cingulate sulcus (ACS) extending into the medial surface of the superior frontal gyrus (SFG). Regions of greater activation in response to the passive task within the typically developing group are shown in Table 2 but not shown in Figure 2.

As shown in Figure 3, activation within the Turner syndrome group (warm colors) in the one-target versus passive tasks produced some of the canonical network of activations seen in the typically developing girls, but significant differences were also evident. As in the typically developing group, there was strong activation (not shown) in the left and right SPL extending into the precuneus and cuneus. However, girls with Turner syndrome did not produce the activations in the IPL seen in the typically developing group. Also dissimilar to the typically developing group, the Turner syndrome group demonstrated activation in the right parahippocampal gyrus and right orbital gyrus; the right pulvinar and the occipital cuneus and precuneus. Regions of greater activation in response to the passive task within the Turner syndrome group are shown in Table 2 but are not shown in Figure 3.

Fixed-Effects Between Groups Analysis

As listed in Table 3, greater activation was evident in the typically developing group versus the Turner syndrome group contrasting the one-target tracking and passive viewing tasks in the left and right SPL and extending bilaterally into the IPS, the left middle temporal gyrus (MTG), the left and right MidFG, left parahippocampal gyrus, right posterior cingulate gyrus (PCG), the right MedFG, right precentral gyrus, the right parahippocampal gyrus, and the left

and right occipital lingual gyrus extending into the collateral sulcus and the medial occipitoemporal gyrus bilaterally.

The Turner syndrome group demonstrated greater activation in the left inferior frontal gyrus extending into the left inferior frontal sulcus and middle frontal gyrus, the left cingulate gyrus, left anterior cingulate, the left middle temporal gyrus extending into the left superior and inferior temporal sulci, part of the right superior parietal lobule abutting apex of the inferior parietal lobe and intraparietal sulcus, right putamen, the left and right anterior cerebellum, the left and right ventral lateral nucleus of the thalamus, the right postcentral gyrus at Brodmann Areas 40 and 3, the left and right amygdalae, and the brainstem.

Random-Effects Between Groups Analysis

As illustrated in Figure 4 and listed in Table 4, random-effects analyses revealed greater activation in the typically developing group (cool colors) in response to the one-target tracking task, overlapping the left and right occipital fusiform and lingual gyri and the declive of the posterior cerebellum and the culmen of the right and left cerebellum.

In the Turner syndrome group (warm colors), greater activation was evident bilaterally in the frontal precentral gyri, the left inferior frontal gyrus extending into the middle frontal gyrus and the inferior frontal sulcus, the left ventral posterior lateral nucleus extending into the medial dorsal nucleus of the thalamus, the left and right putamen, the left cingulate gyrus, the left parietal postcentral gyrus, and the left superior temporal and middle temporal gyri.

Discussion

In an investigation of the neurocognitive foundation of impaired spatiotemporal attention in girls with Turner syndrome, we have shown, for the first time, two differences compared to age-matched typically developing girls. The first is that when using a multiple object tracking task designated to assay the capacity and resolution of spatiotemporal attention, girls with Turner syndrome can track one item over space and time as accurately as do their typical peers, but they are significantly impaired when trying to track three items. We suggest that this finding may indicate one of the foundational causes of the spatial, temporal, and numerical impairments that girls and women with Turner syndrome consistently demonstrate and that impairs their ability to function effectively in a manner consistent with their own verbal abilities and with the nonverbal abilities of their unaffected peers. We have also demonstrated functional brain activation differences between girls with Turner syndrome and typically developing controls during the same task, when performance did not differ between the two groups. This finding suggests that despite their overall relatively high level of functioning, girls with Turner syndrome experience an atypical trajectory in the development of neural circuitry capable of implementing spatiotemporal attentional functions and that this hampers the development of typical levels of competence in this domain and in those that depend on it during development.

Comparing the tracking of one out of seven targets to passive viewing of seven objects within groups, we have replicated findings that attentional focus increased activation in the frontal eye fields and the superior parietal lobules (SPL) and precuneus on the medial aspect of the parietal, with activation extending into the inferior parietal lobules (IPL) (e.g., Culham et al., 2001) and the interparietal sulci (IPS) (e.g., Jovicich et al., 2001) within the typically developing and Turner syndrome groups. Generally, regions of activation are more diffuse in our pediatric sample compared to the adult sample studied by Culham et al. (2001), possibly due to movement within the scanner, a greater ratio of grey to white matter, a propensity to see more white matter activations, and lower BOLD signal-to-noise ratio in children versus adults (Thomason, Burrows, Gabrieli, & Glover, 2005). As reviewed by Casey, Tottenham, Liston, and Durston (2005), cortical function becomes more efficient as the brain matures from

childhood through adolescence and into adulthood. Although brain activations appear more diffuse in the current study, the typically developing group clearly demonstrated a “child version” of the expected canonical spatial-attention and memory networks driven by the multiple object tracking task. Given that the typically developing group shows this predicted pattern of activation, we can make stronger inferences about brain activation differences both within the Turner syndrome group and between typically developing girls and girls with Turner syndrome.

Contrasting Turner syndrome and typically developing groups on the one-target tracking task revealed differences in laterality between the groups with greater left SPL activation in the typically developing group, but greater right SPL activation in the Turner syndrome group in the FFX GLM analysis. However, the group differences did not remain significant in the more stringent RFX GLM analysis. This could be a result of lower detection power stemming from the relatively small sample size or possibly because individuals with more atypical BOLD responses are skewing the Turner syndrome group mean in the FFX analysis. Activation of the SPL is generally associated with spatial coding and location discrimination of objects in typical adults (Corbetta, 1998; Corbetta, Shulman, Miezin, & Petersen, 1993). Laterality in SPL activation has been reported in elderly adults (Otsuka, Osaka, & Osaka, 2008), with greater right SPL activation associated with short-term memory storage during a word span test and greater left SPL associated with executive function during a reading span test. Decreased tissue volumes in the right parietal brain region with increased right occipital volume (Reiss, Mazocco, Greenlaw, Freund, & Ross, 1995) and with decreased right occipital volume (Murphy et al., 1993) have also been associated with poorer visuospatial performance in the Turner syndrome population on tasks such as judgment of line orientation (Reiss et al., 1995). Therefore, greater right SPL activation in the Turner syndrome versus the typically developing group might be indicative of less efficient spatial location processing during the tracking task and could also indicate a reliance on short-term memory strategies and relative impairment in the integration of frontal and parietal circuits. However, given the atypical brain development of the Turner syndrome group, one must be careful about attributing specific locations of brain activations to the functions associated with those areas in typically developing children and adults (Johnson, Halit, Grice, & Karmiloff-Smith, 2002).

Greater activation of limbic areas was evident in the Turner syndrome group. The ventralmedial prefrontal cortex (vPFCm) has projections to the amygdala (Quirk, Likhtik, Pelletier, & Pare, 2003) and activity in the vPFCm at the time of a fear-inducing stressor has been shown to mediate amygdala-dependent fear conditioning in rodent models (Baratta, Lucero, Amat, Watkins, & Maier, 2008; Quirk et al., 2003). The Turner syndrome group had greater activity in both the vPFCm and amygdalae than the typically developing group during the one-target task. Furthermore, greater anterior cingulate cortex (ACC) was active in the Turner syndrome group than the typically developing group, whereas greater posterior cingulate cortex (PCC) activity was evident in the typically developing versus the Turner syndrome group. Elevated ACC activation has been reported in females with Turner syndrome in association with completing simple arithmetic (Kesler et al., 2006). Increased ACC activity has been shown (in typically developing adults) to be negatively correlated with mental exertion and less efficient practice (Raichle et al., 1994), in anticipation of starting various cognitive tasks (Murtha, Chertkow, Beauregard, Dixon, & Evans, 1996) and during anticipatory anxiety to electric shocks (Straube, Schmidt, Weiss, Mentzel, & Miltner, 2009). Therefore, it is not unreasonable to hypothesize that these unusual activations might reflect an increased level of anxiety and negative emotional state in girls with Turner syndrome while they attempt to perform a task that was designed to challenge a domain of neuro-cognitive function that we believe to be foundational to many of their deepest cognitive impairments.

In both the FFX GLM and RFX GLM analyses, the Turner syndrome group showed elevated activation in the left inferior frontal gyrus (IFG) compared to the typically developing group during the object tracking task. Although the Broca's area in this region is known to be critical for speech production, the left IFG is also involved in response inhibition of motor behavior (Swick, Ashley, & Turken, 2008). Activation of this region in combination with pre- and post-central gyri activations also seen in the Turner syndrome but not typically developing groups may indicate that girls with Turner syndrome may be talking themselves through the tracking task using subvocalizations as a method of proactively preserving short-term memory cues or they may be actively trying to not respond before the allotted times in the task (Delazer et al., 2003; Kesler et al., 2006). Again, attributing functions to brain regions in atypical populations can only still be speculative at best because the structure/function relationships evident to be developing in typical individuals can never be taken as the default assumption, especially when it is relatively safe to assume that those with genetic disorders have never experienced a period of typical brain development.

Neural activation differences in the dorsolateral prefrontal cortical (DLPFC) were evident within the typically developing group contrasting one-target tracking and passive viewing but not within the Turner syndrome group. The DLPFC is critically involved in executive functions that support visual-spatial working memory in typical adults, and decreased activation of the DLPFC has been reported with increasing spatial working memory load in females with Turner syndrome (Haberecht et al., 2001).

Greater activation to the tracking task also appeared in the occipital cuneus bilaterally and the occipital fusiform gyrus (OFG) in the Turner syndrome group but not the typically developing group. Greater activation in the OFG has typically been shown to occur when viewing coherent object motion (Könönen et al., 2003).

The FFX GLM analysis revealed greater activation in the pulvinar in the Turner syndrome group and higher SPL and FEF (corresponding to Brodmann Areas 6 and 8) in the typically developing group. The RFX analysis indicated greater activation in the SPL in the typically developing group and higher activity in the putamen in the Turner syndrome versus the typically developing group. Taken together, this may indicate that a greater portion of the cognitive load associated with the object tracking task is being borne by the developmentally more primitive subcortical system of spatial attention and cognition, whereas in the typically developing group, the cognitive load is carried more by the developmentally advanced frontoparietal network (see Simon, 2008).

We recognize several limitations in this study, most especially the reduction in the number of participants that could be included in the final analyses as a result of excessive head motion and/or performance on the task lower than could be ascribed to chance. Lying still in the MRI scanner can be difficult for adults let alone young children. The difficulties associated with acquiring MRI images in children, especially with special populations, typically relate to anxiety regarding the procedure itself, discomfort and boredom, and difficulty self-regulating behavior mean that there will be some degree of data loss. We reiterate that the groups did not differ with regard to data loss associated with motion ($ns = 6$ in each group). More rigorous tools for reducing head motion through active restraint, such as a bite bar or molded face mask, are likely to contribute to anxiety and discomfort; therefore, we did not use these methods.

We also recognize that contrasting activation and performance across three, two, and one targets, thus increasing task load, would be the optimal experimental design if the girls with Turner syndrome in our sample could be accurate to a level beyond chance. As noted previously, if group performance for the multiple object tracking task is not equitable, it is impossible to attribute group differences in BOLD signal changes to task performance and not

some other process, such as anxiety or frustration. However, we believe that the one versus passive contrast is valid because it identifies areas of the brain involved in actively tracking objects. Culham et al. (2001) also used this contrast to identify which areas of the brain are involved in active tracking of objects. In future studies, researchers could adjust the parameters of the multiple object tracking task to make the task easier for children with Turner syndrome without engendering ceiling performance, and likely minimal cognitive effort, in the typically developing group. Decreasing the speed that targets and distracters move about the screen and lowering the number of distracters could make the task easier for children with Turner syndrome, thus equalizing performance with typically developing children.

In this study, we presented, for the first time, functional brain activation differences in children with Turner syndrome versus typically developing children during a multiple object tracking task. Although children with Turner syndrome were able to complete the object single tracking blocks as well as did typically developing girls, they seem to utilize brain regions somewhat differently than those used by typically developing girls, including subcortical circuits that are more developmentally primitive. Girls with Turner syndrome may also be using alternative strategies for coping with spatial, temporal, and memory information during the multiple object tracking task. These strategies are adequate for relatively simple tasks, such as tracking a single object in a field of distracters, but as cognitive load increases, efficient recruitment of and communication between frontoparietal regions become critical. These inefficient strategies break down when attention and memory load increases, as reflected in much poorer performance by the Turner syndrome group on the three-target tracking component of the multiple object tracking task. We suggest that atypical development neural circuits involved in basic processing of spatial and temporal information in girls with Turner syndrome set the stage for impairments in nonverbal higher order cognitive impairments and typical attention and spatiotemporal competence. Early sources of dysfunction may lie in the alterations in the extent, shape, and patterns of neural connectivity that result in poor handling of spatial-temporal information and/or result in reduced resolution of mental representations of space and time (Simon, 2008).

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Figure 1.

Schematic of a three-target trial in the multiple object tracking task illustrating what the participant sees on the view screen while in the magnetic resonance imaging scanner. The actual presentation background was black but was converted to white for illustration purposes. Trial instructions were either “track aliens” or “watch planets.” Feedback was either “Right!” for a correct trial or “Oops!” for an incorrect trial.

Figure 2.

Fixed-effects general linear model statistical maps of regions of interest generated using a superimposed on a composite average of 24 anatomical coronal T1 image sets normalized into Talairach space, illustrating areas of greater BOLD activity (warm colors) in response to one-target active viewing among six distracters versus passive viewing of seven moving objects for the typically developing group. For illustration clarity, greater BOLD activity to passive viewing versus one-target tracking is not shown. SPS = superior frontal sulcus, SPL = superior parietal lobe, IPL = inferior parietal lobe, FEF = frontal eye field, MT+ = visual motion area; L = left, R = right.

Figure 3.

Fixed-effects general linear model statistical maps of regions of interest generated using a superimposed on a composite average of 24 anatomical coronal T1 image sets normalized into Talairach space, illustrating areas of greater BOLD activity (warm colors) in response to one-target active viewing among six distracters versus passive viewing of seven moving objects for the girls in the Turner syndrome group. For illustration clarity, we do not show greater BOLD activity to passive viewing versus one-target tracking.

Figure 4.

Random-effects general linear model statistical maps of regions of interest generated using a superimposed on a composite average of 24 anatomical coronal T1 image sets normalized into Talairach space, illustrating areas of greater BOLD activity in response to one-target active viewing among six distracters versus passive viewing of seven moving objects in the Turner syndrome group (warm colors) versus the typically developing group (cool colors). Statistical maps illustrating greater group differences in activation in response to passive viewing versus one-target viewing are not shown. Thal = thalamus, cing = cingulate, BA = Brodmann area, L = left, R = right.

Table 1

Participant Characteristics in Final Analysis

Characteristic	<u>Turner syndrome (n = 11)</u>		<u>Typical developing (n = 13)</u>	
	Mean	SD	Mean	SD
Mean age	11.58	–	10.92	–
Full Scale IQ	96	18	110	11
Processing Speed	88	14	110	15
Perceptual Reasoning	99	18	110	11
Verbal Comprehension	103	16	110	15

Note. The Wechsler Intelligence Scale for Children, Version 4 (WISC-IV) was used for scores for participants included in the final analyses. Decimal values were rounded to the nearest whole number.

^aSDs in months.

Table 2**Brain Regions With Significant Activation Differences Within Groups and Contrasting Conditions**

Contrast/Region	No. of voxels	Max <i>t</i> values ^a	Mean <i>t</i> values ^a	Peak location (Tal x, y, z)
Within typical minus one target minus passive				
One target > passive				
Left/right superior parietal lobules (BA7)	97806	11.26	5.38	-23, -63, 52
Left middle frontal gyrus (BA6)	4836	8.86	5.01	-19, -9, 56
Right middle frontal gyrus (BA6)	4828	7.01	4.46	23, -13, 52
Right medial frontal gyrus (BA10)	1608	5.62	4.11	15, 45, 12
Left middle frontal gyrus (BA8)	536	4.60	3.84	-39, 25, 42
Left anterior cingulate gyrus (BA32)	453	4.53	3.77	-17, 41, 8
Passive > one target				
Left middle temporal gyrus (BA21)	3084	-8.46	-4.53	-53, 7, -16
Right inferior temporal gyrus (BA20)	702	-6.83	-4.41	37, -3, -34
Left inferior frontal gyrus (BA46)	1488	-6.67	-4.37	-45, 17, 24
Right medial frontal gyrus (BA10)	1138	-6.48	-4.39	1, 63, 14
Right posterior cingulate gyrus (BA31)	1329	-6.32	-4.40	17, -61, 18
Right frontal precentral gyrus (BA6)	983	-6.09	-4.40	55, -5, 6
Left cingulate gyrus (BA31)	674	-5.92	-4.34	-9, -37, 36
Right frontal precentral gyrus	702	-5.30	-4.07	53, -9, 28
Left sublobar (claustrum)	831	-4.88	-3.95	-37, -21, -2
Left posterior cingulate gyrus (BA30)	855	-4.83	-3.93	-15, -59, 16
Within Turner syndrome minus one target minus passive				
One target > passive				
Right/left parietal lobules/precuneus (BA7)	215137	9.93	4.64	7, -59, 58
Right parahippocampal gyrus (BA35)	531	7.58	4.87	21, -11, -24
Left occipital cuneus (BA18)	1393	6.76	4.33	-15, -83, 14
Left occipital fusiform gyrus (BA19)	923	6.56	4.31	-31, -75, -12
Left posterior cingulate gyrus (BA31)	416	5.50	3.96	-25, -59, 16
Right middle frontal gyrus (BA11)	581	5.49	4.31	31, 37, -14
Left occipital cuneus (BA18)	539	5.45	3.99	-23, -81, 22
Right occipital precuneus (BA31)	1240	4.86	3.71	23, -77, 26
Right thalamus (pulvinar)	630	4.85	3.76	7, -35, 14
Passive > one target				
Right parietal postcentral gyrus (BA3)	838	-5.33	-3.83	53, -9, 42
Right anterior cerebellum (fastigium)	1104	-5.35	-3.99	9, -51, -22
Left occipital cuneus (BA19)	623	-5.95	-3.84	-11, -89, 22
Right middle temporal gyrus (BA39)	2130	-5.99	-4.12	41, -75, 12
Right parietal precuneus (BA19)	413	-6.07	-4.36	37, -67, 42
Right sublobar insula (BA13)	5424	-6.24	-4.30	39, -21, -10
Left inferior frontal gyrus (BA47)	443	-6.32	-4.19	-29, 25, -18
Right superior temporal gyrus (BA22)	618	-6.34	-4.21	59, 3, -2
Left occipital lingual gyrus (BA17)	1050	-7.06	-4.77	-15, -91, 2

Contrast/Region	No. of voxels	Max <i>t</i> values ^a	Mean <i>t</i> values ^a	Peak location (Tal x, y, z)
Right occipital lingual gyrus (BA18)	893	-7.29	-4.65	3, -87, 2
Left parahippocampal gyrus (BA36)	1340	-7.31	-4.79	-29, -21, -20
Right middle frontal gyrus (BA6)	5314	-7.32	-3.76	33, 15, 52
Right occipital lingual gyrus (BA18)	9068	-7.68	-4.57	11, -57, 6
Right inferior frontal gyrus (BA45)	7074	-8.68	-4.77	55, 19, 18

Note. A random effects general linear model (RFX GLM) analysis was used to contrast differences in activation within groups (typical, Turner syndrome) and between conditions and between conditions (passive, one target).

^a All max *p* values < .0001 (corrected).

^b All mean *p* values < .0001 (corrected).

Table 3

Brain Regions With Significant Activation Differences Between Groups Analyzed Using FFX GLM

Contrast/Region	No. of voxels	Max <i>t</i> values ^a	Mean <i>t</i> values ^b	Peak location (Tal x, y, z)
Typical minus Turner syndrome				
Left superior parietal lobule (BA7)	1032	-7.98	-4.36	-23, -65, 52
Left middle temporal gyrus (BA21/22)	15170	-6.92	-4.38	-37, -57, 2
Left middle frontal gyrus (BA6)	414	-6.04	-4.33	-31, -9, 60
Left parahippocampal gyrus (BA36)	487	-5.86	-4.07	-29, -17, -24
Right middle frontal gyrus (BA6)	1886	-5.79	-4.12	33, 15, 52
Right posterior cingulate (BA29)	874	-5.74	-4.22	13, -43, 6
Right medial frontal gyrus (BA10)	856	-5.67	-4.10	13, 47, 12
Right frontal precentral gyrus (BA4)	735	-5.30	-4.13	51, -7, 44
Right transverse temporal gyrus (BA42)	1032	-5.14	-4.36	63, -17, 8
Right/left occipital lingual gyrus (BA18)	11591	-4.94	-4.52	3, -85, 2
Turner syndrome minus typical				
Left inferior frontal gyrus (BA9)	3396	7.35	4.55	-47, 17, 22
Left frontal precentral gyrus (BA4)	4418	7.16	4.51	-17, -27, 54
Right parahippocampal gyrus (BA35)	14883	7.13	4.42	23, -11, -24
Left cingulate gyrus (BA31)	3282	7.12	4.58	-9, -37, 36
Left middle temporal gyrus (BA21)	407	6.91	3.94	-59, -5, -8
Right lentiform nucleus (putamen)	3582	6.73	4.16	27, -9, 10
Right superior parietal lobule (BA7)	2328	6.43	4.24	29, -53, 38
Left middle temporal gyrus (BA21)	1591	5.53	4.11	-49, 7, -16
Right parietal postcentral gyrus (BA40)	835	5.50	4.23	59, -21, 22
Left anterior cerebellum (culmen)	462	5.31	4.23	-39, -55, -28
Right inferior frontal gyrus (BA47)	666	5.26	4.04	51, 19, -2
Left amygdala	539	5.51	4.42	-24, -9, -8
Right parietal postcentral gyrus (BA3)	520	5.10	4.12	23, -31, 58
Right middle frontal gyrus (BA11)	492	4.98	4.01	27, 35, -14
Right/left brainstem	2380	4.88	6.63	6, -20, -15
Right anterior cingulate gyrus (BA24)	407	4.73	3.94	1, 27, 16
Left parietal precuneus (BA31)	483	4.72	3.92	-11, -59, 20
Right anterior cerebellum (culmen)	462	4.54	4.23	17, -39, -22
Right amygdala	422	4.28	5.23	22, -8, -11

Note. A fixed effects general linear model analysis contrasting differences in activation between conditions (passive, one target) and group (typical, Turner syndrome) was used.

^a All max *p* values < .0001 (corrected).

^b All mean *p* values < .0001 (corrected).

Table 4

Brain Regions With Significant Activation Differences Between Groups Analyzed Using RFX GLM

Contrast/Region	No. of voxels	Max <i>t</i> values ^a	Mean <i>t</i> values ^b	Peak location (Tal x, y, z)
Turner syndrome minus typical				
Left frontal precentral gyrus (BA4)	1411	5.80	4.76	-15, -25, 56
Left inferior frontal gyrus (BA9)	1056	5.27	4.27	-49, 17, 22
Left thalamus (ventral posterior lateral nucleus)	861	4.96	4.38	-13, -15, 8
Right lentiform nucleus (putamen)	799	4.86	4.80	27, -9, 10
Left cingulate gyrus (BA31)	465	4.81	4.57	-9, -37, 36
Left parietal postcentral gyrus	281	4.81	4.71	-31, -31, 60
Left lentiform nucleus (putamen)	162	4.79	4.14	-29, -11, -6
Left superior temporal gyrus (BA41)	130	4.52	3.90	-41, -35, 6
Right frontal precentral gyrus (BA4)	107	4.38	4.02	19, -29, 54
Left middle temporal gyrus (BA21)	58	4.16	4.31	-57, -5, -8
Typical minus Turner syndrome				
Right occipital lingual/fusiform gyrus (BA18/19)	207	-5.00	-4.45	21, -67, -8
Left posterior cerebellum (declive)	394	-4.48	-4.35	-19, -65, -10
Right occipital lingual gyrus (BA19)	103	-4.35	-3.16	31, -69, -2
Right anterior cerebellum (culmen)	162	-4.09	-3.66	1, -57, -20
Left anterior cerebellum (culmen)	62	-4.02	-3.10	-11, -49, -10
Right occipital lingual/fusiform gyrus (BA18/19)	76	-4.02	-2.94	11, -57, 4

Note. We used random effects general linear model RFX GLM analysis to contrast differences in activation between conditions (passive, one target).

^a All max *p* values < .0001 (corrected).

^b All mean *p* values < .0001 (corrected).