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Aberrant Parietal Cortex Developmental Trajectories in Girls With Turner Syndrome and Related Visual–Spatial Cognitive Development: A Preliminary Study

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Abstract

Turner syndrome (TS) arises from partial or complete absence of the X-chromosome in females. Girls with TS show deficits in visual–spatial skills as well as reduced brain volume and surface area in the parietal cortex which supports these cognitive functions. Thus, measuring the developmental trajectory of the parietal cortex and the associated visual–spatial cognition in TS may provide novel insights into critical brain-behavior associations. In this longitudinal study, we acquired structural MRI data and assessed visual–spatial skills in 16 (age: 8.23 ±2.5) girls with TS and 13 age-matched controls over two time-points. Gray and white matter volume, surface area and cortical thickness were calculated from surfaced based segmentation of bilateral parietal cortices, and the NEPSY Arrows subtest was used to assess visual–spatial ability. Volumetric and cognitive scalars were modeled to obtain estimates of age-related change. The results show aberrant growth of white matter volume (P =0.011, corrected) and surface area (P =0.036, corrected) of the left superior parietal regions during childhood in girls with TS. Other parietal sub-regions were significantly smaller in girls with TS at both time-points but did not show different growth trajectories relative to controls. Furthermore, we found that visual–spatial skills showed a widening deficit for girls with TS relative to controls (P =0.003). Young girls with TS demonstrate an aberrant trajectory of parietal cortical and cognitive development during childhood. Elucidating aberrant neurodevelopmental trajectories in this population is critical for determining specific stages of brain maturation that are particularly dependent on TS-related genetic and hormonal factor.

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Keywords

longitudinal; parietal lobe; turner syndrome; visual–spatial

INTRODUCTION

Turner syndrome (TS), a genetic disorder occurring in 1 in 2,000 females [Stochholm et al., 2006], arises from the complete or partial absence of an X-chromosome in females. The cognitive phenotype associated with TS includes relative strengths in verbal ability and relative weaknesses in visual–spatial abilities and executive function in the context of overall normal intellectual function [Kesler, 2007; Hong et al., 2009].

Girls with TS are at significant risk for visual–spatial deficits [Hong et al., 2009]. During childhood, impairment in visual–spatial cognition can lead to considerable difficulties with spatial ability (e.g., block construction, puzzle assembly, and directional sense), visualization (e.g., part-whole perception and visual discrimination), and visuomotor ability (e.g., design copying and visuomotor integration) [Rovet, 2004]. Functional brain imaging studies have found that during visual–spatial and arithmetic tasks, individuals with TS show abnormal activation profiles of the parietal and frontal cortices [Haberecht et al., 2001; Molko et al., 2003; Kesler et al., 2004, 2006; Hart et al., 2006; Beaton et al., 2010; Bray et al., 2011, 2013]. Specifically, in a visual–spatial task (Judgment of Line Orientation), young girls and adolescents with TS showed lower activation of parietal cortices [Kesler et al., 2004]. Moreover in girls with TS, increased task difficulty did not lead to recruitment of executive frontal areas as observed in age-matched controls.

Previous structural imaging findings from cross-sectional studies show consistent differences in parietal–occipital regions between participants with TS and controls across the lifespan. Specifically, structural MRI (sMRI) studies have found reduced gray matter in bilateral parietal–occipital cortices in children, adolescents and adults with TS relative to controls [Murphy et al., 1993; Reiss et al., 1995; Brown et al., 2004; Lepage et al., 2013]. A recent cross-sectional study investigated developmental neuroanatomy in TS by comparing two age cohorts, children and adolescent girls with TS, to age-matched control groups [Lepage et al., 2013]. This study used automated segmentation and surface-based morphometry to assess cortical surface area (SA) and mean cortical thickness (CT) as well as gray matter volumes (GMV) and white matter volumes (WMV). In the parietal lobe, postcentral and precuneus regions showed reduced bilateral GMV, WMV, and SA in girls with TS for both children and adolescents, while reduced bilateral GMV, WMV, and SA of the superior parietal areas were observed only for the TS adolescent cohort. These results point to critical periods when the trajectory of brain development in TS begins to diverge from that seen in typically developing controls. These critical periods may represent “windows of opportunities” for evaluation and treatment. Further, elucidating the development of the parietal cortex in TS may provide biomarkers for follow-up or intervention, such as cognitive visual–spatial and math skills training [Kesler et al., 2011]. However, all morphometric studies to date have used a cross-sectional study design as a

basis of longitudinal inferences, which not only limits the ability to detect developmental changes, but also can lead to inferential errors [Kraemer et al., 2000].

In this study, we used a prospective, longitudinal design to investigate the anatomical development of the parietal cortex and its association with visual–spatial cognition in young girls with TS and age-matched controls. For this preliminary study, children from a larger cross-sectional study were invited for a follow-up assessment 1 year after their baseline assessment. To overcome the limitation of a small sample size we chose the parietal cortex as our a priori region of interest due to the robust differences in structural and functional imaging between TS and typical controls. Our objectives were to determine whether subregions of the parietal lobe in girls with TS show aberrant development during childhood, and to investigate whether changes in cognitive skills associated with the parietal cortex would parallel aberrant neuro-anatomical development.

METHODS

Participants

Of 21 girls with TS and 19 neurotypical girls recruited, 16 TS and 13 neurotypical girls had usable scans at both time-points and were included in the reported analyses. Of these 29 participants, two (one with TS and one control) who were under the lower age limit (5 years of age) for the NEuroPSYchological assessment (NEPSY) Arrows subtest [Korkman et al., 1998] were not given the test. One participant with TS who was older than the upper limit (12 years of age) for the Arrows subtest (14.3 years old at time-2) was given the test, and data were used only for analysis of raw data. Participants with TS were recruited through the national Turner Syndrome Society and the Turner Syndrome Foundation, a local network of physicians, and advertisement on the Stanford University School of Medicine website. Control participants were recruited through local print media and parent networks. Exclusion criteria for both groups included premature birth (gestational age under 34 weeks), low birth weight (less than 2,000 g), known diagnosis of a major psychiatric or current neurological disorder including seizures, and any contraindications for an MRI scan. Girls with TS exhibiting mosaic or uncommon structural karyotypes (e.g., 45X/46XX, ring X, isochromosome, deletion) were excluded. Only participants demonstrating a verbal intelligence quotient (VIQ) within the typical range (70–130) were included in the present study. The local Institutional Review Board of the Stanford University School of Medicine approved this study and informed written consent was obtained from a legal guardian for all participants, as well as written assent from participants over 7 years of age. Participants with usable MRI scans at two different time-points were included in the final longitudinal analyses (16 TS, 13 controls). Twelve girls with TS at time-1 and 10 at time-2 were using growth hormone (GH) therapy. Participants with TS had not started estrogen replacement therapy except for one participant who began three weeks before her time-2 assessment. This participant was included in the analysis.

MRI

Participants underwent behavioral training in a mock MRI scanner prior to their actual scan to desensitize them to the appearance and sounds of an MRI environment and help prevent

motion-related artifacts. Imaging data were acquired at the Stanford University Lucas Center for Medical Imaging. Magnetic resonance images were collected between 2006 and 2011 on a Signa HDxt 3.0 T whole-body MR system (GE Medical Systems, Milwaukee, WI) using a standard birdcage headcoil. A fast spoiled gradient recalled (FSPGR) echo pulse sequence was employed to obtain a high-resolution anatomical brain image for each participant (124 coronal slices, repetition time [TR]/echo time [TE] =6.4/2 msec, inversion time [TI] =300 msec, flip angle =15°, number of excitations (NEX) =3, field of view (FOV) =22 cm ×22 cm, matrix =256 ×256, 1.5 mm thickness, acquisition time =14 min 43 sec). Structural MRI datasets were collected from all recruited participants at time-1 and time-2. All images were manually inspected and rated separately by two raters (T.G. and K.F.) for image quality and in ambiguous cases the final decision for exclusion was reviewed with an expert rater (M.M. R.). Eighteen scans were found to be unusable because of artifacts likely induced by participant motion, blood flow, or wraparound artifact (unusable scans: TS =10; control =8). The remaining usable scans consisted of 29 scans at each time-point collected 0.9 years (11 months) to 1.8 years (mean interval 1.2 ±0.2 years) after the first scan.

Morphometric Analysis

The analyses focused exclusively on regions comprising bilateral parietal cortices. Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer 5.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). All scans were preprocessed using bias field correction methods available with SPM8 (http://www.fil.ion.ucl.ac.uk/spm) before using the FreeSurfer pipeline. The technical details of the FreeSurfer procedures used are extensively described in prior publications [Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2002, 2004]. Briefly, surface definition follows intensity gradients to optimally place the gray–white and pial surfaces at the location where the greatest shift in intensity defines the transition to another tissue class [Dale et al., 1999; Fischl and Dale, 2000]. Two editors (T.G. and K.F.) visually inspected the gray–white and pial surfaces, and when needed, performed appropriate manual corrections as per the FreeSurfer Tutorial (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial). All image editors are trained to achieve inter-rater reliability of ≥0.95 (intraclass correlation coefficient) for volumetric regions of interest using gold-standard datasets developed in our laboratory. These datasets were selected to exemplify FreeSurfer errors that are typically encountered during processing and were taken from neurotypical participants as well as individuals with TS, 22q11.2 deletion syndrome, fragile X syndrome and autism. The participants were between 7.6 and 48.3 years of age and data were acquired using 1.5 and 3T GE scanners and several pulse sequences, including the sequence used for this study. Two highly experienced FreeSurfer users edited these images and the final gold-standard datasets were defined by a consensus of six senior lab members (including P.M., M.M.R., and A.L.R.).

Once cortical models are completed, brain surfaces for each hemisphere are parcellated into 34 distinct regions based on gyral and sulcal structure [Fischl et al., 2004; Desikan et al., 2006]. Free-Surfer calculates GMV, WMV, and SA of the gray–white boundary and mean CT for each parcellated region. For WMV a 5 mm distance constraint from the gray-white boundary was applied as implemented in FreeSurfer. This process results in labeling of gyral WM and avoids inclusion of WM from the centrum semiovale and periventricular regions

[Salat et al., 2009]. Five parcellated parietal cortex subregions are included in the analyses: inferior parietal, postcentral, precuneus, superior parietal and supramarginal.

Cognitive Assessment

Participants were administered cognitive assessments appropriate for their age at both time-points [Wechsler, 2002, 2003]. For two study participants (one with TS and one control) cognitive assessments were not available at time-2. Visual–spatial ability was assessed using the developmental NEPSY Arrows subtest [Korkman et al., 1998]. This test involves judging line orientation by choosing which arrows point directly at a target.

Statistical Analysis

For demographic and cognitive data, independent two-tailed *t*-tests were used to assess differences between groups. Total brain volume was defined as total brain cortical tissue volume (http://surfer.nmr.mgh.harvard.edu). All data were examined for normality to confirm the assumptions of the parametric statistics. A cross-sectional analysis was performed at each time-point using an analysis of covariance (ANCOVA) model with group (TS vs. control) as a between-group factor; regional volume, SA, or mean CT as the dependent variable; and age and total brain volume as covariates. All regions showing significant differences between TS and controls for at least one time-point were used as primary outcome variables for the longitudinal analyses. For the longitudinal analyses of brain development, we employed analysis of covariance (ANCOVA) with group (TS vs. control) as a between group factor; delta (time-2 measurements –time-1 measurement) of regional volume, SA, or mean CT as the dependent variable; and total volume, SA, or mean CT at time-1, age, interval between scans, and total brain volume as covariates. For the longitudinal analysis multiple comparisons were controlled using the false discovery rate (FDR) [Benjamini and Hochberg, 1995]. The FDR threshold was applied separately to the results for each characteristic (GMV, WMV, SA, and mean CT) in order to avoid possible correlations between different characteristics for the same region. The reported longitudinal analysis results were considered statistically significant only if they passed both the significance threshold of $P < 0.05$ for ANCOVA in a single region and the FDR threshold $P < 0.05$ for multiple comparisons.

For the cognitive outcomes, we employed an ANCOVA with the change in the age-normed Arrows scores as the dependent variable, and group and VIQ as covariates. One participant was out of age range for standardized Arrows subtest score at time-2, thus, a similar analysis was performed with raw data scores by also including age as a covariate.

RESULTS

Demographic and Cognitive Measures

There was no significant difference in age between groups at either time-point ($P \geq 0.70$ for both) (Table 1) or in time elapsed between scans (TS 1.2 ±0.3 years and control 1.1 ±0.2 years, $P = 0.26$). As expected, the control group scored significantly higher for all IQ measures (all P's ≤0.008) and for the NEPSY Arrows subtest (all P's ≤0.002) at both time-points.

Total Gray and White Matter Results

As expected based on previous research [Raznahan et al., 2010; Lepage et al., 2013], total brain volume, total GMV and WMV, total SA, and mean CT of the whole brain were comparable between groups at both time-points. ANCOVA analysis for brain development did not reveal significant group differences in the developmental trajectories of total brain volume, GMV and WMV, SA, or mean CT of the whole brain.

Region of Interest Differences at Time 1 and Time 2

Figure 1 shows the significant differences between TS and controls at each time-point. The TS group showed significantly smaller regional brain sizes at both time-points including left postcentral WMV and SA; left precuneus WMV and SA; left superior parietaland supramarginal GMV and SA; right precuneus SA and right superior parietal GMV, WMV, and SA. Regions that were significantly smaller in girls with TS at time-1 only included the left postcentral and left precuneus GMV, right precuneus WMV. At time-2, group differences approached significance for these regions as well. Left superior parietal WMV was significantly smaller in girls with TS at time-2 only. Right inferior parietal mean CT was significantly larger in TS at time-1 and left precuneus mean CT was significantly larger in TS at time-2.

Region of Interest Trajectories (Change From Time 1 to Time 2)

Trajectories of left superior parietal WMV ($F = 11.76$, $P = 0.011$ corrected) and SA ($F = 9.59$, $P = 0.036$ corrected) showed significant group effects on change from time-1 to time-2 such that these measures were observed to show significantly smaller increases in size in TS relative to controls (Figs. 2 and 3). GMV trajectories in this region showed similar, though not statistically significant group differences ($P = 0.082$). While the right superior parietal region was smaller for TS than controls at both time-points, we did not observe a significant group effect on change from time-1 to time-2 after FDR correction.

Cognitive Trajectories

Having established that parietal cortical regions develop at a different rate in TS, we investigated whether cognitive development of associated cognitive abilities was also aberrant. At time-1 and time-2, girls with TS demonstrated significantly lower age-normed Arrows scores than controls (Table 1). There was a significant group effect on change from time-1 to time-2 of NEPSY age-normed Arrows scores ($F = 12.14$, $P = 0.002$). Increasing deviation of scores in the TS group compared to controls was observed. In order to assess if visual–spatial performance in TS actually decreased with age or just improved at a slower rate compared to controls we performed the same analysis with Arrows subtest raw scores. The results demonstrated a slower rate of increase in visual–spatial performance between time-1 and time-2 in the TS group ($n = 15$) compared to controls ($n = 12$; Fig. 4). A significant group by time effect for NEPSY Arrows raw scores was also observed when including age as a covariate ($F = 15.94$, $P = 0.001$). Thus, like parietal cortical trajectories, performance on the NEPSY Arrows task follows an aberrant developmental course in TS.

DISCUSSION

This investigation is the first longitudinal study to examine trajectories of change in morphometric measurements of parietal cortex subregions in individuals with TS. Our results point to divergent longitudinal developmental trajectories in the superior parietal cortex during childhood and early adolescence. In particular the trajectory of brain development of left superior parietal WMV and SA in girls with TS significantly diverges from controls over a 1-year period. Further, left superior parietal GMV, WMV, and SA were all significantly reduced in size for girls with TS compared to controls at the second time-point.

Morphometric differences of the parietal cortex are one of the most replicated findings in TS across a broad range of age groups; children 4–11 years [Marzelli et al., 2011; Lepage et al., 2013], children and adolescents [Reiss et al., 1995; Brown et al., 2002, 2004] and adults [Murphy et al., 1993; Molko et al., 2003, 2004; Cutter et al., 2006]. As expected, we observed that the TS cohort had consistently reduced volume at both time-points for many regions including left postcentral and left precuneus WMV and SA, and right superior parietal GMV, WMV, and SA, suggesting these differences arise earlier in childhood or in the prenatal period. No differences in mean CT were detected for most subregions studied, except in the right inferior parietal and left precuneus areas. These findings are in line with previous observations of mean CT from children and adolescents with TS [Lepage et al., 2013]. Our longitudinal results suggest that aberrant brain development of specific parietal subregions in TS continues into late childhood, a finding likely associated with previously demonstrated structural abnormalities of the parietal lobe in this condition. As all previous studies have been cross-sectional rather than longitudinal in design [Murphy et al., 1993; Reiss et al., 1995; Molko et al., 2003, 2004; Brown et al., 2004; Lepage et al., 2013] or included different age cohorts imaged on different scanners [Lepage et al., 2013], these novel results add important knowledge to our understanding of brain development in TS.

It is known that dynamic changes in the parietal cortex occur during typical development, where gray and white matter volumes follow distinct developmental trajectories during childhood [Lenroot and Giedd, 2006]. While white matter volume in the parietal cortex increases linearly throughout childhood, gray matter volumes (including related constructs of SA and CT), follow an “inverted U” non-linear developmental trend [Giedd et al., 1999; Raznahan et al., 2011]. When combined with our longitudinal design, previous observations of developmental trajectories of the parietal cortex in neurotypical children are relevant to our findings. Specifically, we observed significant between-group differences in WMV and SA trajectories, while there were no significant group differences for GMV and mean CT. For WMV, which is expected to increase linearly, our two time-point linear model captured age-related differences between groups. For SA, that is known to follow a more complex, non-linear growth trajectory, we also observed between-group differences in developmental trajectories. This finding suggests that changes in SA during this period are sufficiently robust to be detected using a linear model. However, a linear model might not be sufficient to capture growth trajectories in parietal GMV. GMV is the product of its underlying components, SA and CT [Panizzon et al., 2009], each of which follow independent and distinct growth trajectories in neurotypical controls [Raznahan et al., 2011]. It is noteworthy

that previous cross-sectional studies observed increases in mean CT compared to controls in adults with TS [Raznahan et al., 2010], but not in children and adolescents with TS [Lepage et al., 2013]. Thus it is possible that aberrant developmental trajectories of CT occur in TS later in development than the participant ages studied here or, if present, are not adequately distinguished with a linear model.

With respect to the right and left hemispheres, we found significant differences in developmental trajectories of the left, but not the right, superior parietal lobe. Moreover, right superior parietal GMV, WMV, and SA were significantly smaller at both time-points. It is possible that changes in the right side arise earlier in development as recent observations from neurotypical controls show that at least for SA, the left hemisphere lags behind the right during early adolescence [Schanck et al., 2014].

With respect to developmental trajectories of superior parietal SA, our results suggest a failure to reach the maximal SA of the superior parietal lobe in TS. In neurotypical children, maximal cortical surface area is achieved between 8 and 10 years of age [Raznahan et al., 2011; Schanck et al., 2014]. In our group of girls with TS, visual inspection of the data (Fig. 3) show regional SA loss between two time-points for several girls with TS that appear to drive the overall group differences. These girls with TS might demonstrate early decrease in SA, expected only later in development. We observed changes in WM in the same manner as that observed for SA, that is, regional WM loss between two time-points (Fig. 2). This finding is surprising given that total brain WM increases in a linear manner throughout childhood and adolescence [Giedd and Rapoport, 2010]. Several factors might contribute to our results. First, since the WM parcellation scheme is an extension of cortical parcellation procedures in the FreeSurfer pipeline, the amount of WM labeled is largely associated with the amount of SA labeled for that region. Thus, both scalars are expected to change in the same manner (Figs. 2 and 3). Second, as implemented in FreeSurfer, we measure only WM proximal to the cortical regions, which contains afferent and efferent fibers associated with the superior parietal cortical region [Salat et al., 2009] and not total brain WMV (for which no differences in developmental trajectories were detected). Third, the observed decrease in WM might particularly reflect changes in WM adjacent to the superior parietal cortical region, a region that, together with the inferior parietal areas, are highly associated with visual–spatial cognition, impaired in TS [Kesler et al., 2004]. Finally, our results are aligned with previous comparisons of separate cross-sectional samples of children and adolescents with TS, which found consistent differences in superior parietal SA between groups and group-by-age interaction for superior parietal WMV [Lepage et al., 2013].

The growth trajectories of the parietal cortex in TS observed here suggest two possible, related biological mechanisms. First, the observed aberrant growth trajectories may stem from genetic, non-hormonal factors. Studies in humans and mice show that X-linked genes have higher expression in the brain relative to other tissues [Nguyen and Disteche, 2006a,b]. Girls with TS suffer from haploinsufficiency of genes on the X-chromosome, leading to putative reduced expression of these genes in the brain. Based on their findings in adults with TS, Raznahan et al. [2010] suggested that haploinsufficiency of X-chromosome genes may differentially impact cortical folding (measured by SA) and dendritic pruning (measured by mean CT) [Raznahan et al., 2010], a hypothesis that is also consistent with

findings that SA and mean CT appear influenced by distinct genetic mechanisms [Panizzon et al., 2009]. Taken together, our results suggest that haploinsufficiency of X-chromosome genes may have longitudinal effects on cortical folding over the time frame studied here.

A second potential biological mechanism is that observed differences in brain structure and cognitive development may be due to hormonal effects occurring even before puberty. Typically developing girls are exposed to low levels of estrogen in utero and during childhood [Janfaza et al., 2006], while girls with X-monosomy have gonadal (ovarian) dysgenesis in early development, resulting in a significantly different pattern of exposure to sex hormones. Estrogen replacement therapy to induce puberty and the development of secondary sexual characteristics in individuals with TS is usually started at age 12 [Bondy and Turner Syndrome Study, 2007], which is beyond the age range of the girls in our study. A study of 7- to 9-year-old girls with TS examined the influence of early low-level estrogen replacement therapy on cognitive abilities (verbal and spatial memory, language and attention), and found improved spatial memory compared to placebo treatment [Ross et al., 2000]. Thus, the presence of prepubertal estrogen may affect the development of visual–spatial ability in this critical developmental window. To the best of our knowledge no study has examined the effect of early low-level estrogen on brain anatomy in TS. Thus, it is possible that in addition to haploinsufficiency for X-chromosome genes, prepubertal deficits in estrogen adversely affect brain and cognitive development in young girls with TS.

With respect to visual–spatial cognition, the NEPSY Arrows subtest was used to assess ability to judge line orientation, a component of visual–spatial cognition [Korkman et al., 1998]. Our study is the first to demonstrate significant differences in line orientation abilities for girls with TS relative to controls at an early age (mean =8.23 years). Previous cross-sectional studies utilizing the Judgment of Line Orientation task [Benton et al., 1978] found that the performance of individuals with TS varied according to age. While no differences from typical controls were observed in children (6.0–10.9 years) and young adolescents (11.0–14.9 years) with TS [Ross et al., 1995], reduced performance was observed in older adolescents (13.0–16.9 years) and young adults with TS [Romans et al., 1998]. The finding of early deficits in line orientation ability in our sample but not in previous studies of children with TS may be explained by the exclusion of participants from our cohort with partial X-monosomy and mosaicism, who perform better in visual–spatial tasks [Ross et al., 1995].

The longitudinal design used in the current study revealed a slower rate of increase in visual–spatial performance between time-1 and time-2 in the TS group. Thus, the results of the present study provide a potential link between the previous cognitive performance results in adults by showing that the gap in visual–spatial abilities between girls with TS and healthy controls widens during childhood, and this change in cognitive abilities is paralleled by growth of the left superior lobe during childhood. Furthermore, the left superior parietal cortex is associated with spatial coding and location discrimination of objects [Corbetta et al., 1995; Owen et al., 1996; Corbetta and Shulman, 1998]. Deficits in superior parietal cortical (along with inferior parietal) activation were found in individuals with TS compared to neurotypical controls during a line orientation task [Kesler et al., 2004] and a multiple object tracking task [Beaton et al., 2010], but not during a visuo-spatial working memory

task where deficits in activation are localized to the supramarginal gyrus [Haberecht et al., 2001]. Thus, the results provide a potential developmental link between brain and behavior by showing that the gap in visual–spatial abilities and in volumes of associated brain regions widens during childhood between girls with TS and neurotypical controls. Finally, elevated brain activation was observed in the precuneus [Haberecht et al., 2001; Beaton et al., 2010] and right superior parietal lobe [Beaton et al., 2010] in females with TS compared to neurotypical controls during tasks involving visuo-spatial abilities. It was suggested that these findings may represent less efficient spatial processing. We observed increases in mean CT in right inferior parietal (at time-1) and left precuneus (at time-2). Increases in CT were observed in other neurogenetic syndromes such as Williams syndrome [Meda et al., 2012; Thompson et al., 2005] and 22q11.2DS [Jalbrzikowski etal.,2013] in regions that relate to syndrome-specific cognitive and behavioral phenotypes. Taken together, increased CT may represent aberrant cortical maturation that is associated with inefficient neural processing. Such inefficiencies in neural processing during visuo-spatial tasks might be expressed as increased functional activation observed in TS compared to neurotypical controls.

The results of our study may hold particular relevance for designing future treatments for young girls with TS. Cognitive interventions in girls 7–14 years with TS have been associated with improvement in visual–spatial skills [Kesler et al., 2011]. The plasticity of brain development during childhood combined with findings that girls with TS have diverging visual–spatial abilities during this time frame suggests that there may be critical neurodevelopmental periods for cognitive or hormonal interventions in TS. In particular, there is a possibility that combining cognitive intervention targeting visual–spatial cognition with estrogen treatment before the age of 12 years may be beneficial.

Strengths and Limitations

Although preliminary, the data presented here offer novel insights into parietal lobe development and associated cognitive functions in girls with TS. We found aberrant developmental trajectories in the parietal lobe during childhood relative to controls. We also discovered that related cognitive functions, that is, visual–spatial skills, follow aberrant developmental trajectories over this time period. This study provides a developmental framework that links distinct brain regions and related cognitive functions with haploinsufficiency of X-chromosome genes and prepubertal sex hormone deficiency. Our study was limited by the use of a two time-point design and use of a linear model, though it is known that GMV, SA, and CT all demonstrate “inverted U” non-linear development. Also, the age ranges of the children in our sample spanned childhood through adolescence, including the period between 8 and 10 years of age, which is a particularly dynamic period during which GMV, SA, and CT reach peak levels in typical development. This underscores the need for larger longitudinal neuroimaging studies during this developmental period that appropriately account for the possibility of non-linear developmental trends.

In conclusion, we present the first longitudinal neuroimaging study of children with TS. These findings suggest that the age at which disorder-specific therapeutic interventions are introduced in individuals with TS may be a critical factor in determining response to

intervention. The divergent developmental trajectories observed in distinct brain regions also introduce the possibility that neuroimaging might be used to define TS-specific biomarkers. Based on our results for the parietal lobe, we believe that larger and longer longitudinal neuroimaging studies can establish novel imaging biomarkers for assessment and treatment of girls with TS.

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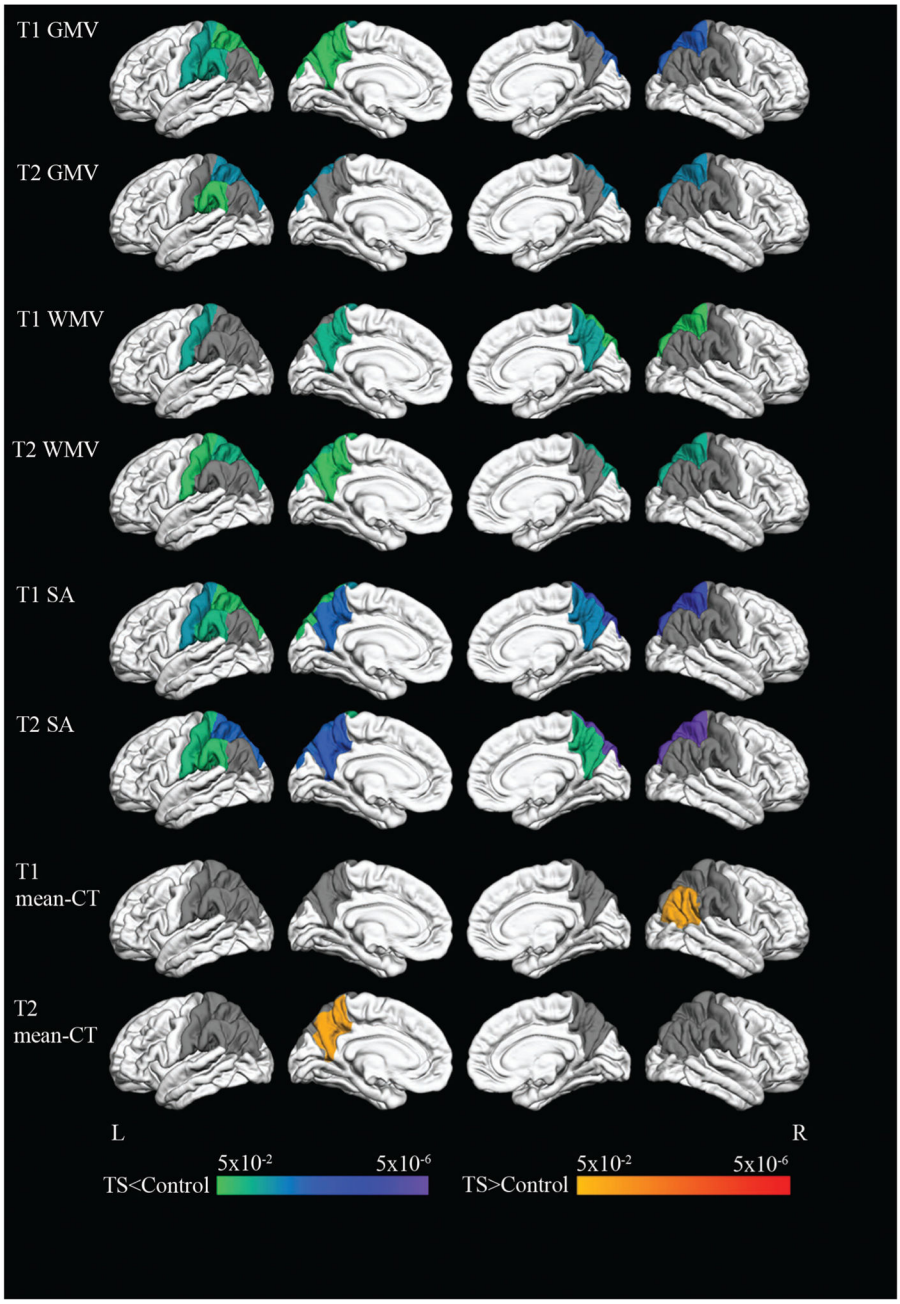

FIG. 1.

Results of parietal lobe analysis comparing girls with Turner syndrome (TS) and controls at time-1 and time-2. The rows of the figure (top to bottom) correspond to gray matter volume (GMV), white matter volume (WMV), surface area (SA), and mean cortical thickness (mean CT). Regions comprising bilateral parietal cortices were colored in dark gray. For subregions in which significant differences between groups were detected we used a log based color scale. The color scale was generated from the negative log of the *P* value due to the large range of *P* values (e.g., the negative log (*P*) of 0.05 =1.3). In cases where the subregion size for TS was significantly smaller than that of the controls a cool color palette

was used, and in cases where the TS subregion size was larger than that of the controls, a warm palette was used.

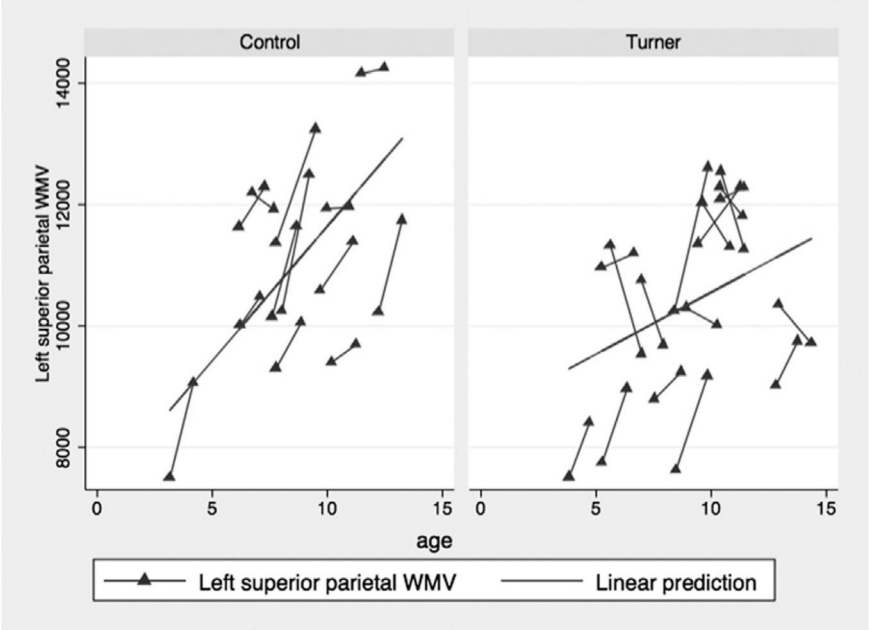

FIG. 2.

Longitudinal change in the raw FreeSurfer measurements of left superior parietal white matter volume (WMV) across time-points for controls and Turner syndrome. A regression line estimating the overall trend of the data was added for illustration purposes.

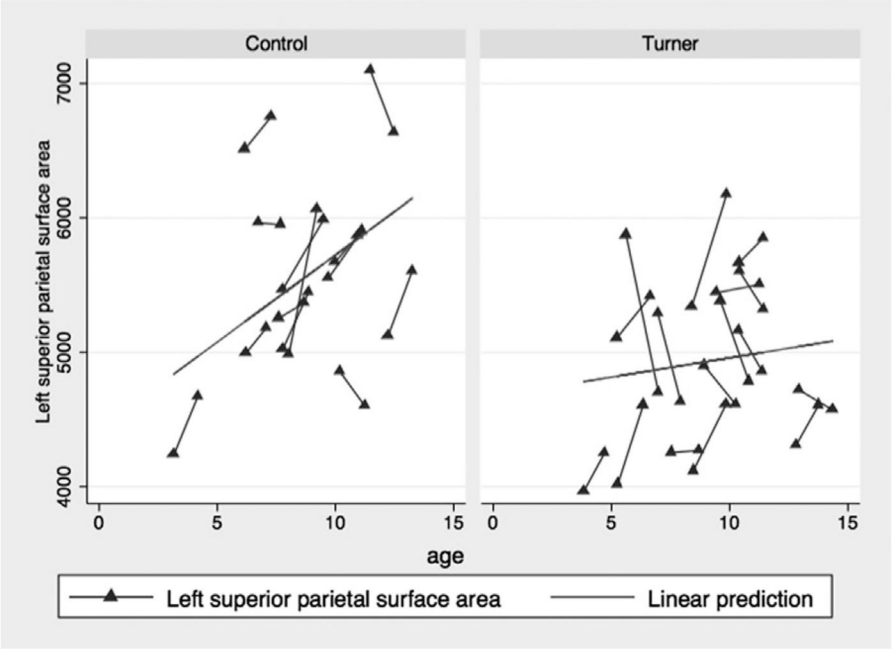

FIG. 3.

Longitudinal change in the raw FreeSurfer measurements of left superior parietal surface area across time-points for controls and Turner syndrome. A regression line estimating the overall trend of the data was added for illustration purposes.

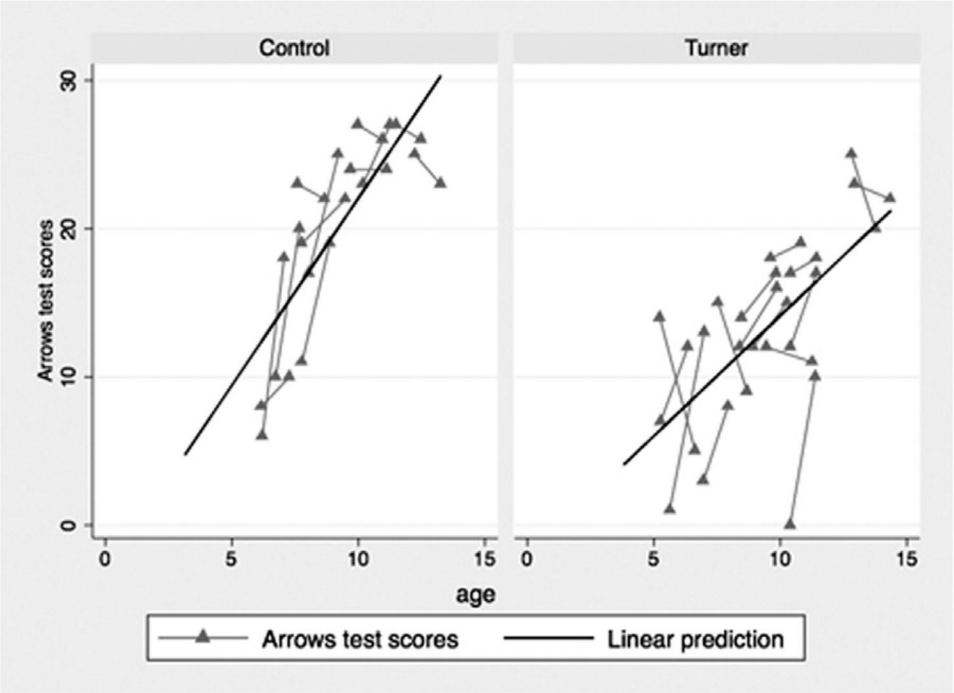

FIG. 4.

Longitudinal change in the raw Arrows subtest score measuring visual–spatial skills across time-points for Turner syndrome and controls. A regression line estimating the overall trend of the data was added for illustration purposes.

TABLE 1

Demographic and Cognitive Measures

	Time 1			Time 2		
	Control (n =13)	**Turner (n =16)**	***P*-Value**	**Control (n =13)**	**Turner (n =16)**	***P*-Value**
Age	8.23 (2.5)	8.51 (2.7)	NS	9.34 (2.5)	9.73 (2.7)	NS
FSIQ	120.1 (9.0)	88.7 (14.9)	<0.001	120.3 (13.3)[a]	90.5 (16.5)[b]	<0.001
PIQ	118.0 (6.2)	85.5 (15.8)	<0.001	119.8 (11.9)[a]	89.7 (16.7)[b]	<0.001
VIQ	118.2 (14.6)	100.0 (16.0)	0.004	119.8 (15.2)[a]	102.9 (16.7)[b]	0.012
Arrows (NEPSY)	10.2 (2.3)	6.75 (3.0)	0.002	10.7 (1.9)	5.6 (2.6)[b]	<0.001
Growth hormone	—	12			10, 3U	
Estrogen	—	0			1, 1U	

FSIQ, full-scale intelligence quotient; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient; NEPSY, a developmental NEuroPSYchological Assessment; NS, not significant; Growth hormone, number of participants reporting current or past usage; U, Unknown.

[a] n =12.

[b] n =15.