Longitudinal investigation of cognition, social competence, and anxiety in children and adolescents with Turner syndrome

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Abstract

Turner syndrome (TS), a common neurogenetic disorder caused by complete or partial absence of an X chromosome in females, is characterized by distinct physical, cognitive, and social-emotional features. Girls with TS typically display average overall intellectual functioning with relative strength in verbal abilities and weaknesses in visuospatial processing, executive function (EF), and social cognition. This study was designed to better understand longitudinal trajectories of cognitive and social-emotional domains commonly affected in TS. Participants included 57 girls with monosomic 45,X TS and 55 age- and verbal-IQ matched girls who completed behavioral, child-report, and parent-report measures across four timepoints. Group differences in visuospatial processing, EF, social cognition, and anxiety were assessed longitudinally. Potential effects of estrogen replacement therapy (ERT) were assessed cross-sectionally on an exploratory basis. The TS group showed poorer performance on measures of visuospatial processing, EF, and social cognition, but not anxiety, compared to controls throughout childhood and adolescence. There were no significant group differences in the trajectory of skill development over time. Exploratory analyses within the TS group revealed that girls who were receiving ERT showed better performance on measures of overall IQ, expressive vocabulary, and visuospatial processing compared to those not receiving ERT. Consistent with existing literature, weaknesses in visuospatial processing, EF, and social competence among girls with TS persisted throughout childhood and adolescence. Exploratory analyses suggest that ERT may help improve some aspects of cognitive function in TS, although other pre-existing, nonhormonal differences between the two TS subgroups may alternatively explain these findings, given our study design. Future studies are needed to examine potential impacts of ERT on cognitive and social-emotional development in TS.

Keywords: cognition; visuospatial processing; executive function; social cognition; children; adolescents; puberty; estrogen; Turner syndrome

Introduction

Turner syndrome (TS) is a common neurogenetic disorder caused by complete or partial absence of an X chromosome in females (Bondy, 2007). This disorder occurs in approximately 1 in 1,800 to 2,000 live births and is characterized by a distinct physical, cognitive, and psychosocial profile (Fechner, 2020). Physical features include short stature, cardiovascular abnormalities, and endocrine issues related to ovarian dysgenesis, such as estrogen deficiency, amenorrhea, and infertility (Fechner, 2020). Individuals with TS generally display overall IQ in the average range with relative strength in verbal abilities and weaknesses in visuospatial processing and executive function (EF) (Rovet, 1993; Hong et al., 2009). TS-associated difficulties with tasks involving attention (Green, 2015; Russell et al., 2006), processing speed (Bender et al., 1993), arithmetic skills (Mazzocco, 2009; Baker & Reiss, 2016), motor function (Nijhuis-van der Sanden et al., 2007), and social cognition (Hong et al., 2014) may also impact educational and occupational outcomes (Downey et al., 1991).

Visuospatial problems are considered a core cognitive weakness in TS throughout the lifespan. Relative to verbal/language skills, individuals with TS show poorer performance on measures of visual construction (Murphy et al., 1994), design copying (Waber, 1979), mental rotation (Rovet & Netley, 1982), part-whole perception (Silbert et al., 1977), nonverbal reasoning (Murphy et al., 1994), visual discrimination (Silbert et al., 1977), and visual-motor integration (Lewandowski et al., 1985). These weaknesses typically emerge in early childhood and persist into adulthood (Downey et al., 1991) with the possible exception of perceptual judgment, which approximates typically developing peers in late adolescence (Romans et al., 1998).

More recent studies have focused on EF in TS. EF refers to a set of interrelated, higher-order mental processes necessary for self-regulation, initiation of goal-directed behavior, and adaptation to novel situations, including inhibition, set shifting, working memory, planning, organization, and problem solving (Diamond, 2013). Findings regarding working memory impairments in TS are robust, while results for other EFs are less conclusive (Romans et al., 1997). A meta-analysis of EF in children and adolescents with TS confirmed significant impairments with small effect sizes for inhibitory control, medium effect sizes for cognitive flexibility, and large effect sizes for working memory, organization, planning, and problem solving (Mauger et al., 2018). Although the longitudinal trajectory of EF has not been extensively studied in TS, adolescence/puberty is an important time for the development of EF in typically developing individuals.

Impairments in social cognition and communication have also been described in TS. Previous studies report difficulties with recognition of emotional faces (Hong et al., 2014) and aberrant eye gaze processing (Elgar et al., 2002; Mazzola et al., 2006). Social communication challenges may be related to neurocognitive deficits in attention, extrapersonal space perception, and theory of mind (Hong & Reiss, 2012). Taken together, these deficits potentially negatively impact peer relationships in childhood (Hong et al., 2011). Adult women with TS experience higher incidence of self-perceived impairment in social competence (Lagrou et al., 2006), which could contribute to anxiety about social functioning. Although there is no clear increase in prevalence of anxiety and affective disorders in TS (Avdic et al., 2021), several studies have shown increased self-reported symptoms of generalized anxiety, social anxiety, depression, and low self-esteem compared to same-aged peers (Boman et al., 2001; Lagrou et al., 2006).

The cognitive-behavioral phenotype described above is likely a unique constellation of genetic (e.g., haploinsufficiency for gene(s) on X chromosome), hormonal (e.g., reduced estrogen and androgen production), and environmental influences (e.g., educational opportunities, impact of medical issues such as short stature and hearing loss on social interactions). Current standard of care for girls with TS includes initiation of estrogen replacement therapy (ERT) at 11-14 years of age to induce puberty, maintain secondary sex characteristics, attain peak bone mass, and normalize uterine growth. Preliminary evidence suggests that ERT may improve some cognitive weaknesses in TS including processing speed, motor function, nonverbal memory, and verbal memory in pre-pubertal girls (Ross et al., 2000; Ross et al., 1998).

Additionally, Ross and colleagues (1996) found that self-esteem, psychological well-being, and parental report of behavioral problems improved for pre-pubertal TS girls who received ERT. Although few, if any, studies have examined influences of ERT on social cognition in TS, animal studies implicate estrogen as an integral component to social behavior more broadly (Choleris et al., 2006; Phan et al., 2011), and higher estrogen levels during the menstrual cycle have been associated with better performance on social information processing (Gasbarri et al., 2008; Yamazaki & Tamura, 2017) and working memory (Hampson & Morley, 2013) tasks among adult women without TS. Accordingly, a secondary aim of our study is to begin exploring the potential impact of ERT on cognitive and social-emotional challenges in TS. This study is the first of its kind to follow a large sample of girls with TS in the pre-pubertal/estrogen and post-pubertal/estrogen age ranges, between 6 and 16 years of age, over time.

We conducted a large-scale longitudinal study of cognitive and social-emotional development in girls with monosomic TS (45,X monosomy) relative to an age-, sex-, and verbal IQ-matched control group. Our *a priori* hypothesis was that the TS group would show poorer performance on measures of visuospatial processing, EF, social cognition, and anxiety across all ages. Secondarily, we explore possible effects of exogenous estrogen replacement therapy (ERT) within the TS group by performing a cross-sectional comparison of age-matched TS subgroups who were or were not receiving ERT. We hypothesized that girls in the ERT group would show better performance on neuropsychological measures of visuospatial processing, EF, and social cognition as well as reduced anxiety compared to the group without ERT. This study was designed to build upon existing literature by considering longitudinal trajectories of cognitive and social-emotional domains affected in TS. Further, our exploratory analyses offer a preliminary opportunity to advance knowledge of how estrogen and puberty may influence brain development and neuropsychological functioning in adolescent girls. Results may inform timing of ERT initiation in young girls with TS. To the best of our knowledge, this is the first study of its kind to investigate these measures in girls with TS spanning the pubertal timeframe.

Materials and Methods

Data were collected as part of a longitudinal study examining the interaction between genes, brain development, and behavior in children and adolescents with TS and their age-, sex-, and verbal IQ-matched peers. Participants in the TS group were recruited through pediatricians, pediatric endocrinologists, and medical geneticists as well as local and national chapters of the Turner Syndrome Society of the United States and the Turner Syndrome Foundation. Diagnosis of monosomic TS was confirmed for each participant in the TS group by karyotype analysis. Participants in the control group were recruited through newspaper and internet advertisements.

A total of 112 participants (at first timepoint, N_{Turner}=57, mean age=10.5, range=6.3-16.0; $N_{control}$=55, mean age=10.2, range=6.9-14.2) were recruited and underwent a battery of standardized neuropsychological assessments once a year for up to four years. A total of 267 visits were completed across four timepoints. Each participant and their parent/guardian completed a Tanner staging form, and each child underwent physical exam to assess pubertal status at each timepoint. We found high intraclass correlation coefficients (ICC) for Tanner staging across self, parent, and physician ratings ($ICC_{Tanner\ Breast}$=0.96 and $ICC_{Tanner\ Genital}$=0.94, see **Table S1** in Supplemental Materials). Within the TS group, the physician also completed a medication questionnaire with parent/guardian of each participant to document if the participant was receiving growth hormone or ERT. The majority of individuals in both groups were White (TS=87.1%, control=69.7%), with smaller proportions of Black participants (TS=0.8%, control=2.5%). The inter-quartile range (IQR) of household income was slightly higher in the control group (IQR=$100,000-$200,000) compared to the TS group (IQR=$75,000-150,000). English was the primary language spoken for all participants.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees (Stanford University Institutional Review Board) on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Prior to participation, informed consent was obtained from the parent or guardian, and informed assent was obtained from each participant. Trained assessors supervised by a licensed psychologist administered and scored all neuropsychological assessments. The battery included but was not limited to measures of intellectual functioning, visuospatial processing, EF, social cognition, and anxiety. To assess a broad range of core areas commonly impacted in TS, we employed the following standardized behavioral, parent-report, and child-report assessments:

Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV), Wide Range Assessment of Visual Motor Abilities (WRAVMA), Developmental NEuroPSYchological Assessment, Second Edition (NEPSY-2), Behavior Rating Inventory of Executive Function (BRIEF), Social Responsiveness Scale (SRS), and Revised Children's Manifest Anxiety Scale, Second Edition (RCMAS-2). For each participant, one parent completed the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) to obtain a parental IQ estimate.

For our outcome variables, we selected widely used assessments within domains commonly impacted in TS including visuospatial processing, EF, social cognition, and anxiety as well as domains commonly preserved in TS including verbal abstraction and vocabulary. A complete list and description of all subtests can be found in **Table S2** in Supplemental Materials. Based on our group's previous findings and results from other studies, we selected the following subtests within each domain for analysis on an *a priori* basis:

(1) Verbal abilities: WISC-IV Verbal Composite Index (VCI), Vocabulary, and Similarities

(2) **Visuospatial processing:** WISC-IV Block Design and Matrix Reasoning, WRAVMA Drawing, NEPSY-2 Arrows and Picture Puzzles

(3) **Executive function:** WISC-IV Letter-Number Sequencing, NEPSY-2 Inhibition and Inhibition/Switching, BRIEF Global Executive Composite

(4) **Social cognition:** NEPSY-2 Affect Recognition and Theory of Mind (Verbal), SRS Cognition, Communication, Motivation, and Awareness

(5) **Anxiety:** RCMAS-2 Physiological Anxiety, Worry, and Social Anxiety

To test our primary *a priori* hypothesis that the TS group would show poorer performance on neurocognitive measures and elevated scores on anxiety measures, we employed linear mixed effects (LME) modeling in SPSS 26. LME is optimally suited for modeling

longitudinal data, as it accommodates multilevel fixed and random-effects to account for within-subject data and does not require timepoints be matched between participants (Raudenbush and Bryk, 2002). We utilized standardized scores generated by each assessment to determine whether age-normed cognitive metrics may or may not change in TS over time, particularly as a result of reduced estrogen during the pubertal timeframe, is a key time for brain development. We used a random intercept model allowing for variation across participants in terms of their baseline, separately for the TS and control groups for each outcome variable. Our choice of using linear trends is based on likelihood ratio test results, which showed little improvement in model fit by adding a quadratic growth term to allow for nonlinear trends. We conducted analyses centered at 8, 11, and 14 years of age to assess group differences at specific pubertal stages of interest. We included terms for group, age, and age by group in the model to assess possible group differences and differences in trajectory over time. To control for inflated Type I errors due to testing multiple outcomes, we applied false discovery rate (FDR) correction for the number of variables within each domain.

We completed post-hoc sensitivity analyses using child VCI in the model for each outcome to determine if differences in verbal IQ were driving group differences across domains given the possible link between verbal IQ and cognitive functioning across other domains. Similarly, we then included parent IQ (WASI-II FSIQ) in the model given possible association between parent IQ and child outcomes to determine if group differences in outcomes held.

For our secondary, exploratory analyses, we performed a cross-sectional comparison within the TS group to assess possible differences in outcomes based on ERT status. We selected a subgroup of participants within the TS group to create approximately age-matched groups of participants currently receiving ERT and not currently receiving ERT (N_{ERT}=22, mean age=13.0,

range=10.3-16.0, $N_{no\ ERT}$=23, mean age=11.8, range=10.5-14.8). All participants receiving ERT were treated by their own pediatric endocrinologist in a clinically appropriate manner per standard of care treatment. We compared these subgroups using independent samples t-tests for each outcome variable from the initial analyses as well as additional measures of interest within our battery. Given the exploratory, hypothesis-generating nature of these analyses, we did not correct for multiple comparisons.

Results

Prior to modeling, we visually inspected the distribution of data for each outcome variable across timepoints. All data were normally distributed for both groups, with a general trend of lower performance for the TS group across each neuropsychological measure. We then produced scatter plots showing group means and standard deviations for each outcome variable at each age. Similarly, we saw a clear distinction between groups, with a similar trajectory of scores across age for both groups. There were no apparent outliers in either group.

For our primary analyses (i.e., verbal abilities, visuospatial processing, executive functioning, social cognition, and anxiety domains) comparison of linear and quadratic models using the likelihood ratio test revealed that adding a quadratic growth term did not improve the fit. Thus, we conducted mixed effects modeling assuming a linear trend over time allowing for random intercept. The results of longitudinal mixed effects modeling are presented in **Table 1**, where we show the estimated group differences, significance values, and effect sizes for each subtest when the model was centered at 8, 11, and 14 years of age (see **Table S3** in Supplemental Materials for longitudinal mixed effects modeling results for additional variables).

Table 1 shows that when the longitudinal model was centered at 8 years of age (i.e., when we would expect the majority of participants in both groups have not yet experienced pubertal

onset), there were no significant group differences for any subtests within the verbal (*p*-values ranging from .054 to .619) or anxiety (*p*-values ranging from .848 to .933) domains. As predicted, there were significant group differences for all subtests within the visuospatial ($p<.001$ for all subtests), EF ($p=.001$ or $<.001$ for all subtests), and social cognition (*p*-values ranging from <.001 to .025) domains (See **Fig 1** for actual longitudinal data for measures within the visuospatial domain, **Fig 2** for measures within the EF domain, and **Fig 3** for measures within the social cognition domain). Table 1 also shows that, across subtests within these three domains, the TS group showed lower scores on performance-based measures and elevated scores on parent-report measures, reflecting greater impairment. At 11 years of age (i.e., when we would expect some participants in the control group and few participants in the TS group have experienced pubertal onset), there were significant group differences for all subtests within the visuospatial ($p<.001$ for all subtests), EF ($p<.001$ for all subtests), and social cognition ($p<.001$ for all subtests) domains. Additionally, there were significant group differences in verbal IQ (VCI, $p=.001$) and Vocabulary subtest ($p=.002$) scores. At 14 years of age (i.e., when we would expect majority of participants have experienced pubertal onset for both groups, either naturally or with ERT), there were significant group differences for all subtests within the verbal (*p*-values ranging from .001 to .010), visuospatial ($p<.001$ for all subtests), EF (*p*-values ranging from <.001 to .004), and social cognition (*p*-values ranging from <.001 to .026) domains.

When we examined the entire sample longitudinally, there were significant age effects for Block Design and SRS Awareness. However, these were no longer significant after correction for multiple comparisons. Similarly, we did not observe significant group differences in the trajectory of skill development over time (p-values ranging from .080 to .995). In other

words, once the trajectory was established for each group, it did not change significantly over time, and the initial robust group differences persisted over time.

When we added child VCI to the model for our sensitivity analyses, all subtests that initially showed significant group differences remained significant at $p<.05$ (FDR corrected). When we added parental IQ into the model, all subtests that initially showed significant group differences remained significant at $p<.05$ except for Similarities and Theory of Mind.

For our secondary, exploratory analyses, we compared ERT and non-ERT groups cross-sectionally. The results are presented in **Table 2** with *p*-values and 95% confidence intervals for each overall and subdomain score (no adjustment for multiple testing). There was a general trend for better performance in the ERT group, on average, across measures of verbal abilities, visuospatial processing, and EF. Group differences reached statistical significance for overall intellectual functioning (FSIQ), overall perceptual reasoning (PRI), and all visuospatial measures except Rey-O Copy and Matching. There were no significant group differences within the EF, social cognition, or anxiety domains.

Discussion

This investigation is the first large-scale longitudinal study examining trajectories of cognitive and social-emotional development in children and adolescents with TS, encompassing a time period before, during, and after pubertal onset. As predicted, girls with TS showed poorer performance on measures of visuospatial processing, EF, and social cognition compared to same-aged peers throughout childhood and early adolescence. Discrepant performance was evident in early childhood (by 8 years old) and followed a similar trajectory as the control group throughout puberty. The TS group continued to build skills in these areas at a similar pace as typically developing girls, but the gap in performance remained given initial deficits. When we

secondarily examined potential effects of ERT cross-sectionally within the TS group, girls currently receiving ERT demonstrated higher overall IQ and higher performance on measures of expressive vocabulary and visuospatial processing. These secondary results highlight the need to further examine potential effects of ERT on cognition, social functioning, and anxiety in adolescents and young adults with TS.

Visuospatial weaknesses are one of the most replicated findings in TS across a broad range of age groups. Our findings are consistent with literature demonstrating that visuospatial weaknesses persist beyond childhood, into adolescence and adulthood in TS (e.g., Ross et al., 2002). Specifically, the TS group consistently achieved lower scores than controls on measures of visual construction, perceptual reasoning, figure copying, perception of part-whole relationships, and judgment of line orientation with medium to large effect sizes. There were no age effects or differences in trajectory between groups. The stability of visuospatial weaknesses in TS before and after pubertal onset suggests that they may be more closely linked to genetic or other nonhormonal factors. Neuroimaging studies have found an association between visuospatial and EF difficulties and structural, functional, and biochemical abnormalities in frontal-parietal regions in TS (e.g., Kesler et al., 2004; Holzapfel et al., 2006; Lepage et al., 2011). In addition, Zinn and colleagues (2007) found that visuospatial and perceptual deficits in TS may map to genes located at Xp22.3. Haploinsufficiency of multiple inactivation-escaping X-chromosome genes, combined with other genetic and environmental factors, likely contributes to increased risk for neurodevelopmental differences and cognitive impairments in TS.

With regard to EF, the TS group consistently demonstrated worse performance on measures of working memory, inhibition, and cognitive flexibility as well as parental report of overall EF abilities compared to same-aged peers, with medium to large effect sizes across tasks.

Similar to other domains tested, we did not see age effects or group differences in the trajectory of EF skill development over time. Taken together, these findings suggest that the core weaknesses in visuospatial processing and EF may be primarily related to genetic or other nonhormonal influences.

Consistent with existing literature documenting social problems in TS, we found significant group differences in affect recognition, theory of mind, and parental ratings of social cognition, social communication, social awareness, and social motivation with medium to large effect sizes. The TS group consistently demonstrated poorer performance on a behavioral task requiring the child to recognize the emotion expressed in photographs of children's faces. Interestingly, the TS group demonstrated poorer performance on a verbally mediated theory of mind task during which participants were required to articulate others' perspectives and infer other's feelings based on pictures of hypothetical scenarios. This finding is consistent with prior investigations showing more subtle deficits in verbal tasks involving visual or executive processes (Hong et al., 2009). Similarly, parents in the TS group consistently rated their children as having greater difficulty with understanding the meaning of tone of voice or facial expressions, understanding humor, maintaining a reciprocal conversation, conveying their own thoughts and feelings in conversations, using facial expressions appropriately, and showing awareness of others' thoughts and feelings compared to parents of typically developing controls. Difficulties with understanding others' perspectives in social situations may relate to underlying cognitive deficits in theory of mind.

When considering the trajectory of social skill development, we anticipated that the TS group would have more discrepant abilities (i.e., more pronounced deficits and more elevated scores) over time, as social demands increase during adolescence. During this time, relationships

become more complex, and peers become a more significant source of social and emotional support. However, we did not observe age effects or differences in trajectory aside from SRS Social Awareness, which no longer reached statistical significance once we corrected for multiple comparisons. It is possible that parents of girls with TS have modified their expectations for social behavior or provided more support to ease social interactions over time, resulting in less elevated concerns. Future studies should incorporate direct behavioral measures of social interaction or behavioral ratings from teachers to minimize potential bias resulting from parental reporting.

We also observed significant group differences in parental rating of social motivation throughout our age range, with the TS group showing greater impairment. This is discrepant from our group's previous findings with a smaller, younger (pre-estrogen) sample (Hong et al., 2011). The items that load onto SRS-2 Social Motivation capture not only the child's tendency to join group activities and seek social interaction with others, but also her self-confidence in social situations, comfort in separating from caregivers, and tenseness in social situation, which may be indicative of social anxiety. Furthermore, this subdomain is sensitive to both anxiety and autism characteristics in non-TS populations (Briot et al., 2020) because it captures both social anxiety symptoms and social dysfunction or reticence without anxiety. We suspect that the observed group differences in this subdomain in our study are partly reflective of increased social anxiety within the TS group. This is consistent with previous studies suggesting increased social anxiety in TS (Boman et al., 2001; Lagrou et al., 2006). Future longitudinal studies should include parental report of social anxiety symptoms in addition to social competence.

Contrary to expectations, we did not find significant group differences in self-reported physiological anxiety, worry, or social anxiety. Both group means fell in the low normal range

for all three anxiety domains across all timepoints and followed a similar trajectory over time. In light of parental report of decreased social motivation in girls with TS, the lack of group differences in self-reported social anxiety suggests that future studies should include a combination of self, parent, and clinician report of anxiety symptoms as well as direct physiological measures of autonomic nervous system function.

Also contrary to expectations, we observed significant group differences in overall verbal comprehension abilities and vocabulary when our model was centered at 11 and 14 years of age with medium effect sizes. Significant group differences in verbal abstraction skills occurred at 14 years of age. Although the group difference in trajectory did not reach statistical significance, our findings imply that the gap between the TS group and controls may widen during adolescence. Future longitudinal studies should extend the age range into later adolescence in young adulthood to clarify the nature and outcome of this cognitive trajectory.

When we examined potential effects of ERT cross-sectionally within the TS group, we found significant group differences for IQ, expressive vocabulary, and all but two measures of visuospatial processing, with the ERT group demonstrating better performance. More specifically, the ERT subgroup showed better performance on measures of visual construction, nonverbal reasoning, visual organization, perception of part-whole relationships, judgment of line orientation, and drawing abilities. This is consistent with prior studies documenting positive effects of estrogen on visuospatial processing in adult women without TS (Hampson, 1990). However, we did not see subgroup differences for measures of EF, social cognition, or anxiety. This is somewhat surprising, as ERT may help improve working memory and social processing in other populations including adult women without TS (Gasbarri et al., 2008; Jacobs & D'Esposito, 2011; Hampson & Morley, 2013; Colzato & Hommel, 2014). Taken together, our

findings suggest that ERT may improve aspects of visuospatial processing, but not EF, social cognition, or anxiety in girls with TS. Because our study design is naturalistic and observational rather than a randomized control trial, the subgroups of girls with TS who are and are not receiving ERT in our study may differ for a variety of reasons (i.e., beyond ERT status), which could provide alternate explanations for the subgroup differences. For example, ascertainment bias, medical advocacy, parental medical exposure could impact which children receive ERT. In addition, these exploratory analyses included participants within a limited age range, and it is possible that effects of ERT may be more pronounced after longer exposure to ERT (i.e., during later adolescence and early adulthood). Prospective, randomized clinical trials of ERT in TS with staggered age onset would help clarify the effects of estrogen supplementation on cognitive and social-emotional development. Findings could inform clinical practice regarding the ideal time to initiate ERT in this population, particularly from the standpoints of cognitive-psychosocial function and improved quality of life.

We acknowledge some limitations in this study. Despite our efforts to recruit a racially and ethnically diverse sample, both groups were primarily comprised of White participants. For the longitudinal investigation, some participants did not complete testing at all four timepoints due to attrition. It is possible that individuals/families who were experiencing greater cognitive and social-emotional challenges were more motivated to continue participating in our study to receive additional support and recommendations, which could inflate the observed group differences (i.e., if the TS group in our study performed more poorly than the TS population as a whole). Conversely, it is also possible that families who were experiencing greater cognitive and social-emotional challenges were more likely to drop out of the study due to increased stress interfering with participation in study visits. Therefore, there may be an element of ascertainment

bias despite our efforts to recruit a representative sample of girls with TS. In addition, our secondary-exploratory analysis ERT effects must be interpreted with caution, given that this was a cross-sectional comparison within the TS group with a limited age range of participants, without correction for multiple comparisons. There are many clinical considerations that determine the timing and dosage of ERT (e.g., delaying initiation to allow for maximum effect from growth hormone), which could contribute to neuropsychological outcomes. It is not possible to dissociate potential effects of growth hormone therapy, and thus, growth hormone therapy may have influenced our findings. Future studies should include more detailed information about the timing and dosage of ERT within the TS group.

Conclusions

We conducted a longitudinal study designed to investigate cognitive and social-emotional development in school-aged girls with and without monosomic TS, throughout pubertal stages. As predicted, longitudinal analyses revealed poorer performance for the TS group on measures of visuospatial processing, EF, and social competence throughout childhood and adolescence. We found lower verbal abilities in the TS group relative to controls in early adolescence. Contrary to expectation, we did not observe significantly elevated self-reported anxiety in the TS group. Preliminary investigation of potential ERT effects suggests that estrogen supplementation may play a role in improving visuospatial processing, expressive vocabulary, and overall IQ within the TS group. Future studies (e.g., randomized control trials) are needed to examine potential impacts of ERT on cognitive and social-emotional development in TS.

Acknowledgements: We would like to acknowledge the children and families who generously volunteered their time and energy to participate in our study, as well as the Turner Syndrome

Society of the United States and the Turner Syndrome Foundation for their help with recruiting participants.

Funding Statement: This work was supported by the National Institute of Health (ALR, grant number R01 HD049653/HD/NICHD NIH HHS/United States), the Sharon Levine Foundation, and the Niggeman Family Foundation.

Conflicts of Interest: None.

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