Brain Development in School-age and Adolescent Girls: Effects of Turner Syndrome, Estrogen Therapy and Genomic Imprinting

Supplementary Information

Supplementary Methods

Tissue Probability Maps

The location of GM/WM/CSF at each voxel will vary by age; therefore, tissue probability maps were constructed based on the average age of the total study population (approximately 11 years). Standard SPM tissue probability maps are based on adult reference data. Therefore, in this study, specific tissue probability maps were generated to produce an appropriate reference map for child data.

Voxel-Based Morphometry

An initial image normalization to a standard MNI152 template produced GM and WM images from the age specific tissue probability maps. Partial Volume Estimation, a feature of the Computational Anatomy Toolbox, accounted for mixed tissue classes within voxels that resulted in partial volumes of pure tissue for each voxel (1).

Supplementary Results

Post-hoc Analysis

In a post-hoc analysis, we also examined the group of girls with TS who initiated estrogen after study entry. These girls did not receive estrogen at the first MRI visit, but later initiated estrogen prior to the second MRI visit. We, therefore, tested for differences in volume change between girls who initiated estrogen status after study entry and girls who did not change estrogen status. The girls

who changed estrogen status (TS E- to TS E+) showed a similar trajectory to the girls with TS E+. However, this group was underpowered (n=9) to detect a statistically significant effect.

Exploratory, post hoc unpaired t-tests conducted for gray matter, white matter and total intracranial volumes at each time point (Table 1) did not show significant between-group differences (all p's >.10).

Supplementary Reference

1. Khademi A, Venetsanopoulos A, Moody AR (2014): Generalized method for partial volume estimation and tissue segmentation in cerebral magnetic resonance images. *J Med imaging (Bellingham, Wash)*. 1: 014002.
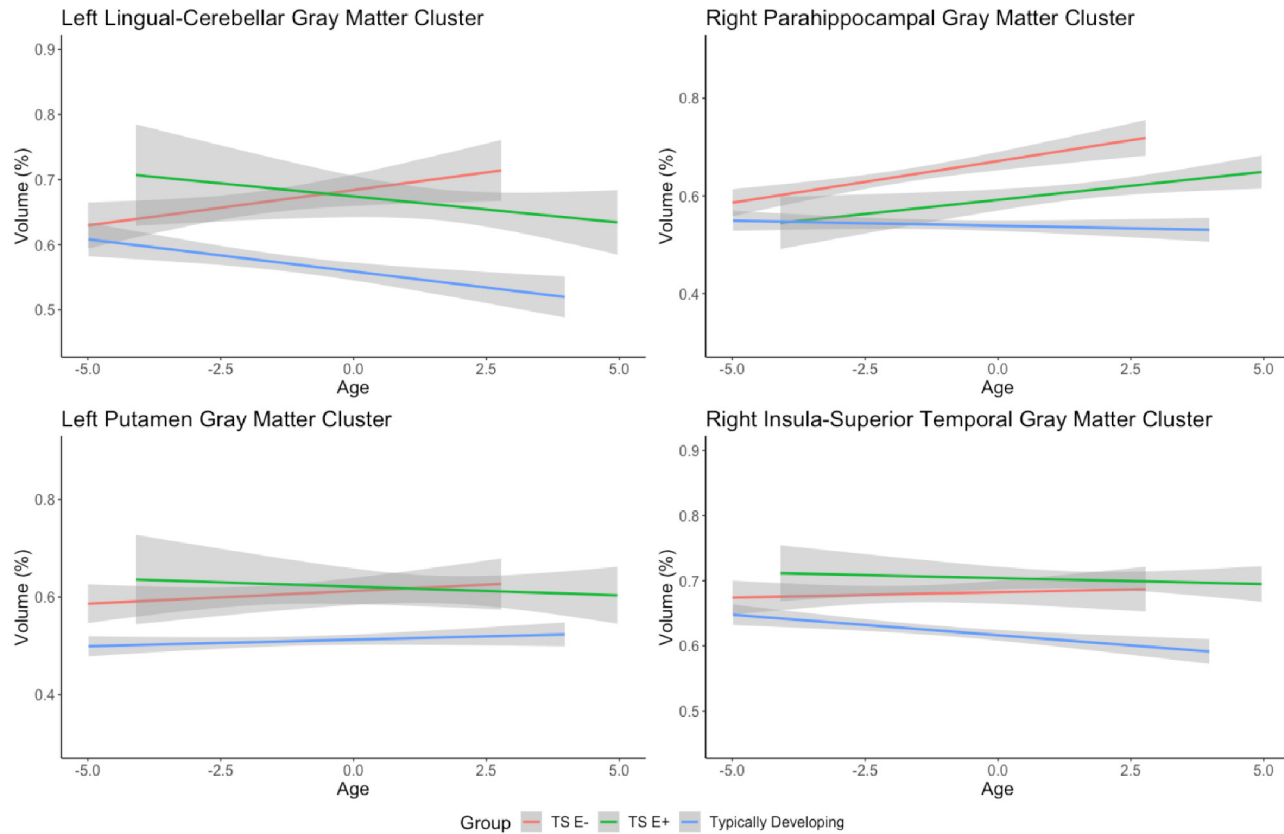
Supplementary Figures
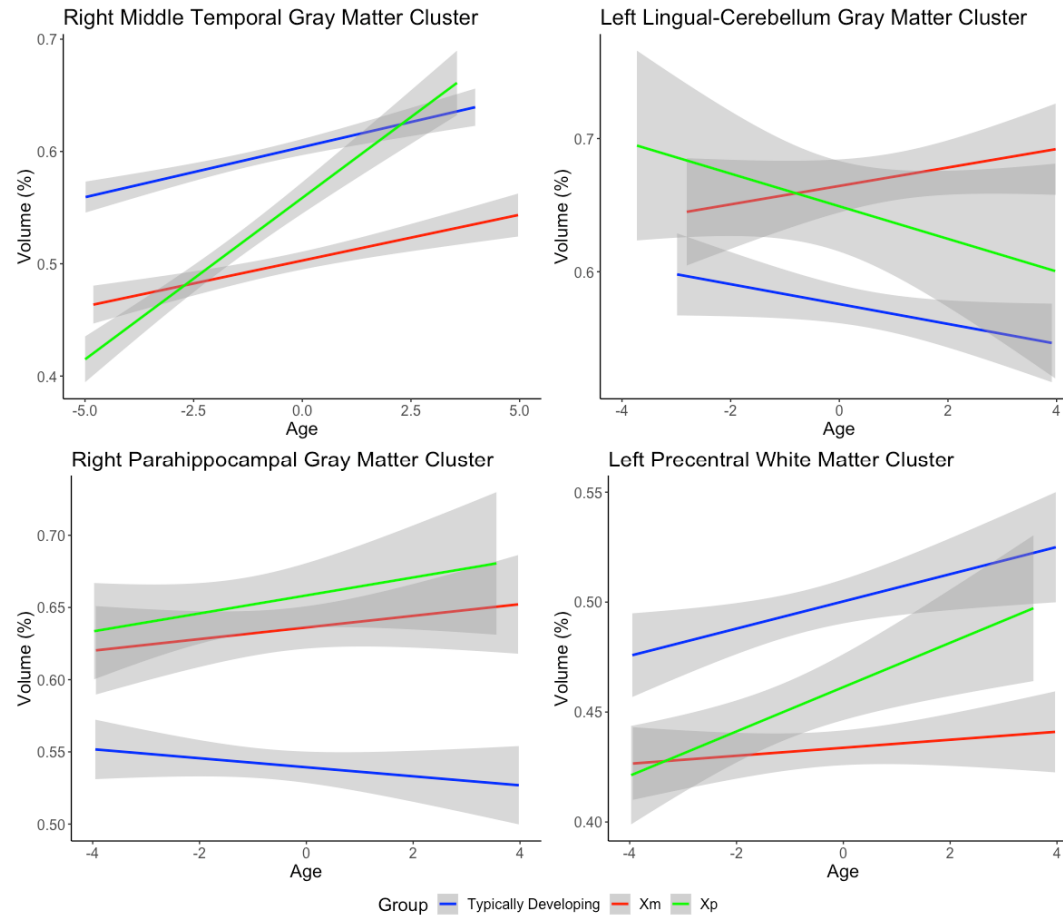
Supplementary Figure S1: Developmental trajectories differ based on parent-of-origin
Average trajectories depict local amount of gray matter in % volume (y-axis) by centered age (x-axis) based on X-chromosome parent-of-origin. Linear mixed effects model represented by line. Shaded regions represent the 95% confidence interval of the intercept.
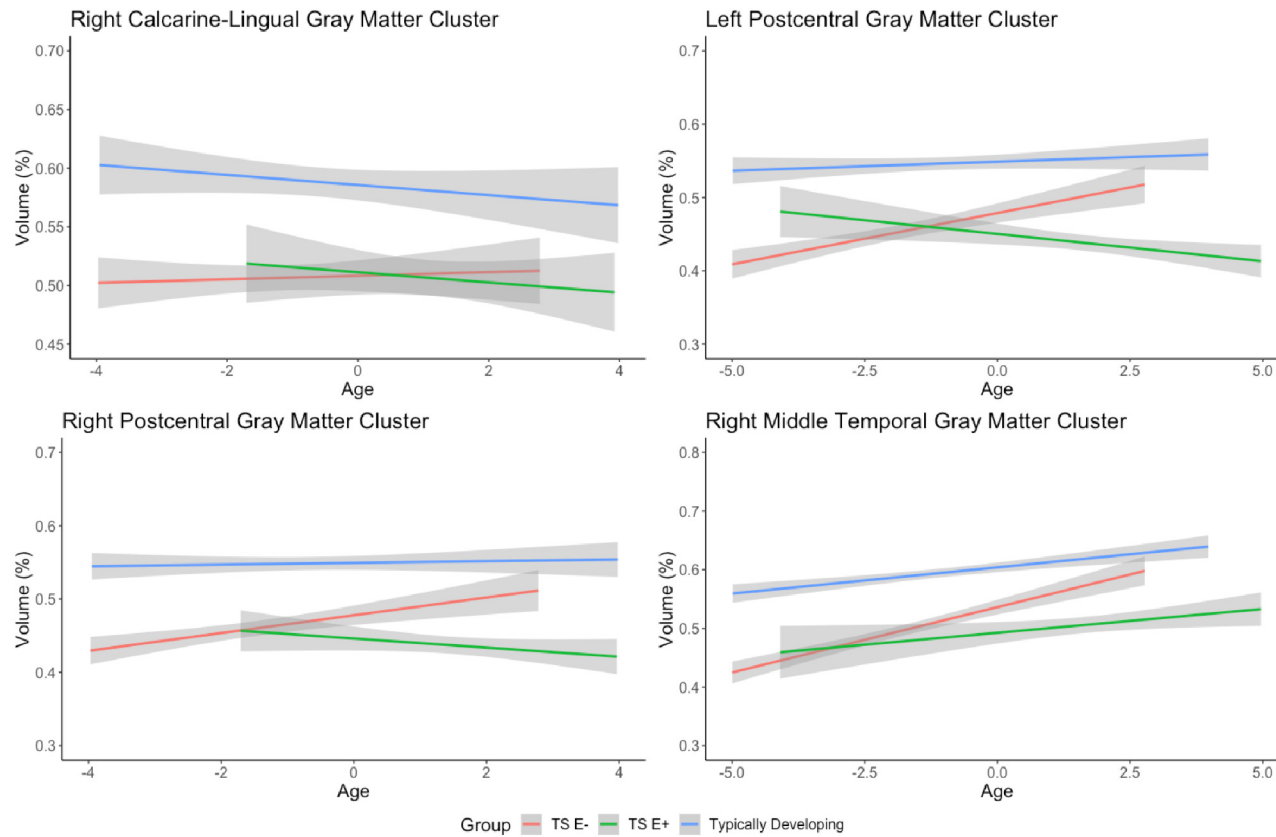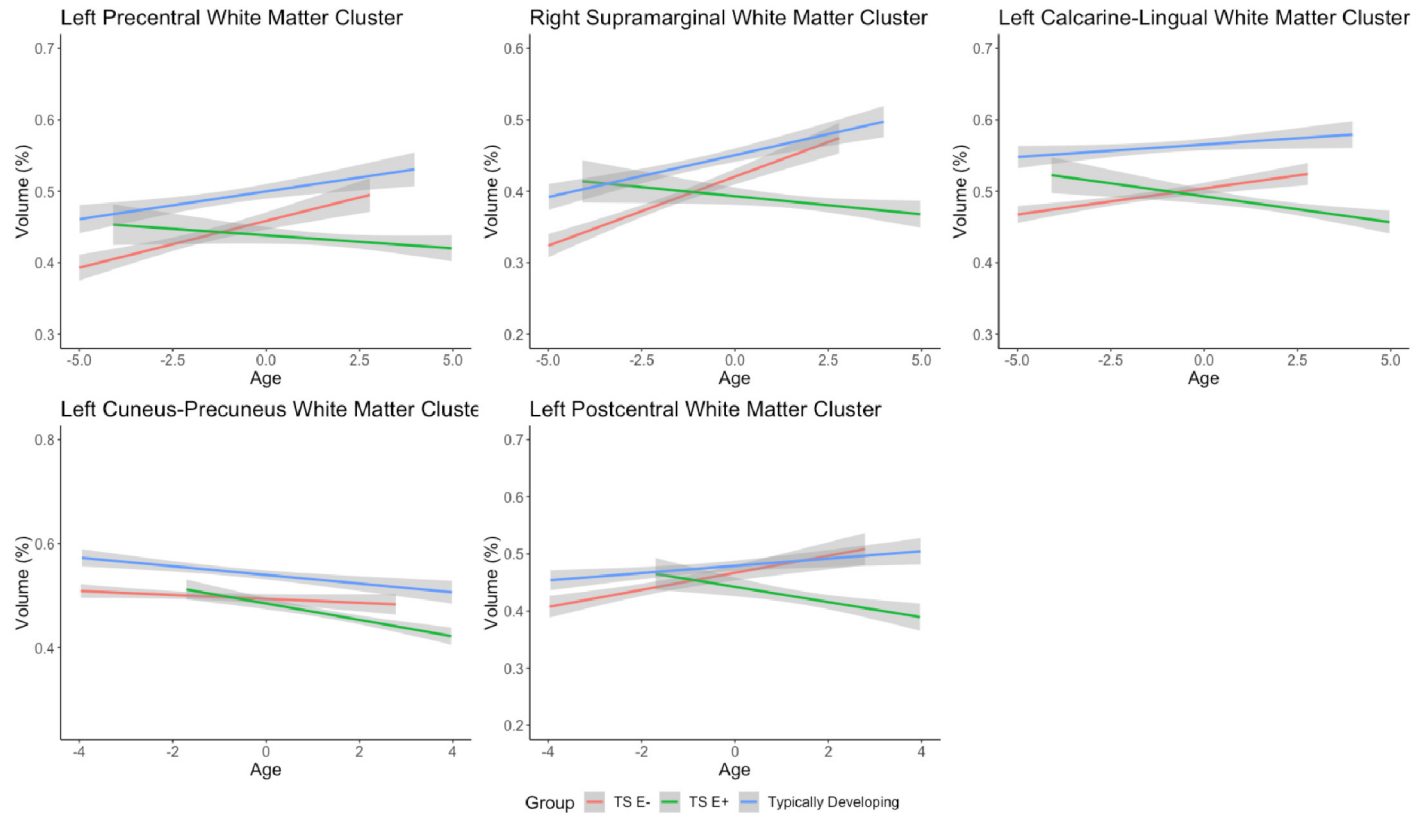
Supplementary Figure S2: Effect of estrogen on brain regions with slower gray matter growth in Turner Syndrome
Average trajectories depict local amount of gray matter in % volume (y-axis) by age (centered age x-axis) based on status of estrogen therapy. Linear mixed effects model represented by line. Shaded regions represent the 95% confidence interval of the intercept. Girls with TS E- show a more positive slope between ages 10 and 14 relative to TS E+ girls.

Supplementary Figure S3: Effect of estrogen on brain regions with increased gray matter growth in Turner Syndrome
Average trajectories depict local amount of gray matter in % volume (y-axis) by centered age (x-axis) based on status of estrogen therapy. Linear mixed effects model represented by line. Shaded regions represent the 95% confidence interval of the intercept. Girls with TS E- show a more positive slope between ages 10 and 14 relative to TS E+ girls.

Supplementary Figure S4: Effect of estrogen on slower white matter growth in Turner Syndrome
Average trajectories depict local amount of gray matter in % volume (y-axis) by centered age (x-axis) based on status of estrogen therapy. Linear mixed effects model represented by line. Shaded regions represent the 95% confidence interval of the intercept. Girls with TS E- show a more positive slope between ages 10 and 14 relative to TS E+ girls.