Studying the influence of the seXY chromosomes on brain development: a mouse model.

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Introduction. Sex dimorphism and more general the role of sex chromosomes on brain development may provide crucial insight into neuropsychiatric disorders as nearly all of them have different ages of onset and gender bias in prevalence. A recent neuroimaging study in humans found local cortical morphology differences in Turner syndrome (XO) compared to normal (XX) female subjects. The nature of these neurodevelopmental differences caused by sex chromosomes remains largely unknown. The XO mouse model (JAX #314; 2) combined with whole brain high-resolution imaging offer a unique opportunity to investigate the role of sex chromosomes in brain development across various neurodevelopmental stages and genotypes. This study compares brain morphology in young adult mice of three genotypes: males (XY), females (XX), and Turner syndrome females (XO).

Methods. S*ubjects:* Thirty-three (10 XO, 12 XX, 11 XY) B6CBACa-$A^{w\text{-}J}$/A-Eda^{Ta}/O (JAX # 314) mice were used in this study. *Specimen Preparation:* At 80 days of age mice were anaesthetized and perfused. Following perfusion the heads were removed along with the skin, lower jaw, ears and the cartilaginous nose tip. The remaining skull structures containing the brain were placed in 4% PFA for 12 hours. After an incubation period of 5 days the skulls were transferred to PBS and 0.01% sodium azide and 2mM ProHance solution for at least 7 days. *MRI acquisition:* A multi channel 7.0 Tesla MRI scanner (Varian Inc., Palo Alto CA) with a 6cm inner bore diameter insert gradient was used to acquire anatomical images of the brains within the skulls. Three custom made coils were used to image three brains in parallel. The parameters used were optimized for grey/white matter contrast: a T2-weighted, 3D fast spin-echo sequence, with TR/TE=352/32 ms, four averages, field-of-view=14x14x25mm, matrix size=432x432x780 giving an image with 32 µm isotropic voxels. Total imaging time was 11.3h. *Data Analysis:* The MRI scans were non-linearly aligned to a three dimensional atlas of the mouse brain with 62 structures identified (3). The resulting deformation fields for each individual brain were used to calculate volumes.

Results. Significant structure volume differences between genotypes (FDR<0.05) are found in the bed nucleus of the stria terminalis, the periaqueductal grey and the anterior commissure. In all three cases the structure volumes per genotype are XO<XX<XY. Local cortical thickness is increased in XO mice compared to both other genotypes in visual and sensory-motor regions. Local cortical thickness is decreased in the parahippocampus.

Discussion and Conclusion. Similar to findings in humans, XO mice show cortical thickening in large areas spanning the sensory-motor and visual cortical areas. Local cortical thinning is found on the parahippocampus. In addition XO mice show a marked local structure decrease in known sexually dimorphic brain regions like the bed nucleus. High-resolution whole brain imaging in mice provides an ideal model to study the role of sex chromosomes on neurodevelopment. The differences found in XO mice point to the XO genotype as some kind of "extreme female" phenotype.

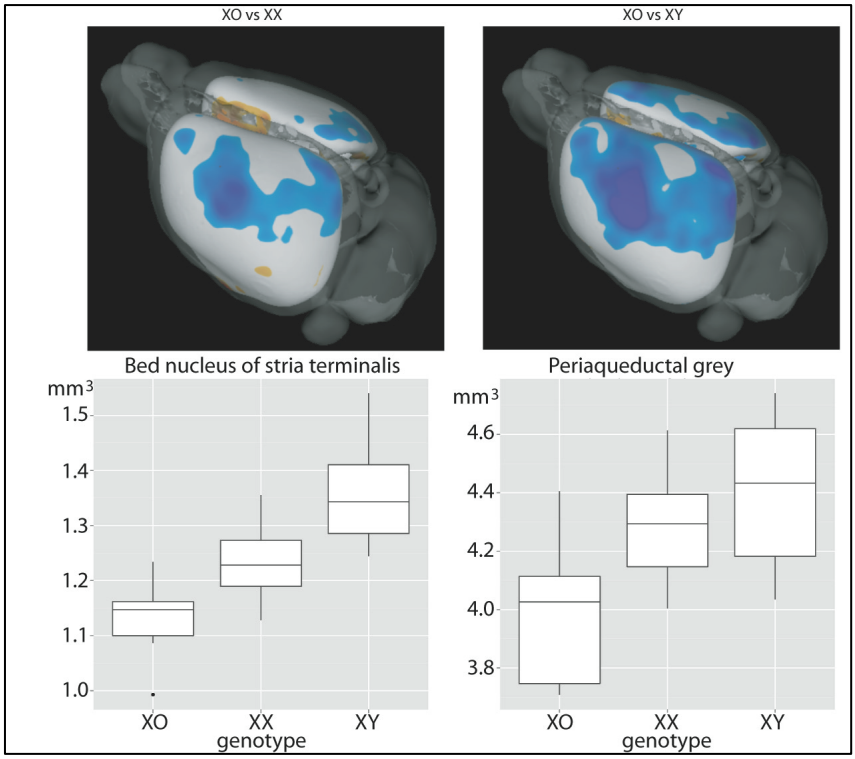

Fig.1:
Top panels illustrate significant (FDR<0.1, XY vs. XO) cortical thickness differences between genotypes (blue=thicker, yellow thinner). Bottom panels illustrate structure volume differences.

References. (1) Raznahan et al. NeuroImage (2010); (2) Probst et al. J. Hered. (2008); (3) Dorr et al. *Neuroimage* 42: 60-69 (2008)