Using Volumetric Measures of Neuroanatomy to Cluster Multiple Mouse Models of Autism.

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Background - Autism Spectrum Disorders (ASDs) are complex and still poorly understood. They are highly heritable, yet no single gene discovered to date accounts for more than 1-2% of known cases (1). Currently 250+ genes have been associated with Autism in the human population (2), and while ASD is associated with communication and social deficits, as well as repetitive behaviours, individual clinical presentations are highly heterogeneous (3).

Objectives - The purpose of this work is to take an expansive approach in order to identify the similarities and differences in neuroanatomy across the autistic spectrum. To this end, we examined 20+ mouse models of ASD candidate genes using high resolution structural MRI.

Methods – Mouse models of Autism were acquired either from the Jackson Laboratory (jax.org) or through collaboration with other research labs. Ten mice minimum were included for each individual genotype and each model had a corresponding wild type control.

MRI Acquisition - For the 20+ mouse models of autism, 400+ individual scans were acquired using previously detailed high-throughput techniques (4), which allow 16 mouse brains to be scanned at a time. A 7.0 Tesla MRI (Varian Inc., Palo Alto, CA) was used to acquire ex-vivo anatomical images of brains within skulls. A T2-weighted, 3D fast spin-echo sequence was used, with a TR of 2000 ms, and TE_{eff} of 42 ms over 6 echoes, two averages, field-of-view of 14 × 14 × 25 mm^3 and matrix size = 250 x 250 x 450 giving an image with 0.056 mm isotropic voxels. Total imaging time was ~12 h.

Individual Data and Cluster Analysis – We used image registration to align the brains from each individual model, which allowed us to calculate the volumes on a regional (62 different regions) (5) or a voxelwise basis (voxel - 3D pixel). Group differences were calculated as effect sizes for each model. Using hierarchical clustering methods, the models were then grouped together based on their similarities and differences.

Results – Across all models the most affected regions were the corpus callosum and the cerebellum, with mean absolute effect sizes >1 (Figure 1). The clustering segregated the models into 4 distinct groupings, 1) the models in which the differences in the autism model were larger compared to the wild type, 2) where they were smaller, 3) where they were unchanged, and 4) where there was some mixture of larger and smaller differences. The $Mecp2^{308}$ Rett syndrome model was found to be quite similar to the Neuroligin3 R451C knockin model as well as the Intergrinβ3 knockout (Figure 2). Unexpectedly, despite the well-known connection between the Neuorligins and Neurexins in the brain, the Neurexin1α knockout did not overlap with the Neuroligin3 R451C knockin (Figure 2).

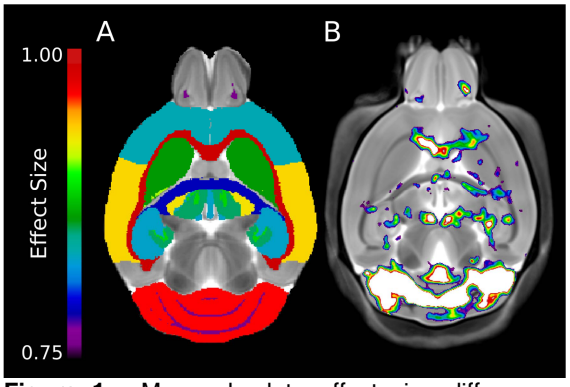

Figure 1 - Mean absolute effect size differences between all mouse models of autism and their corresponding wild-type. Shown in either a regional (A) or voxelwise basis (B)

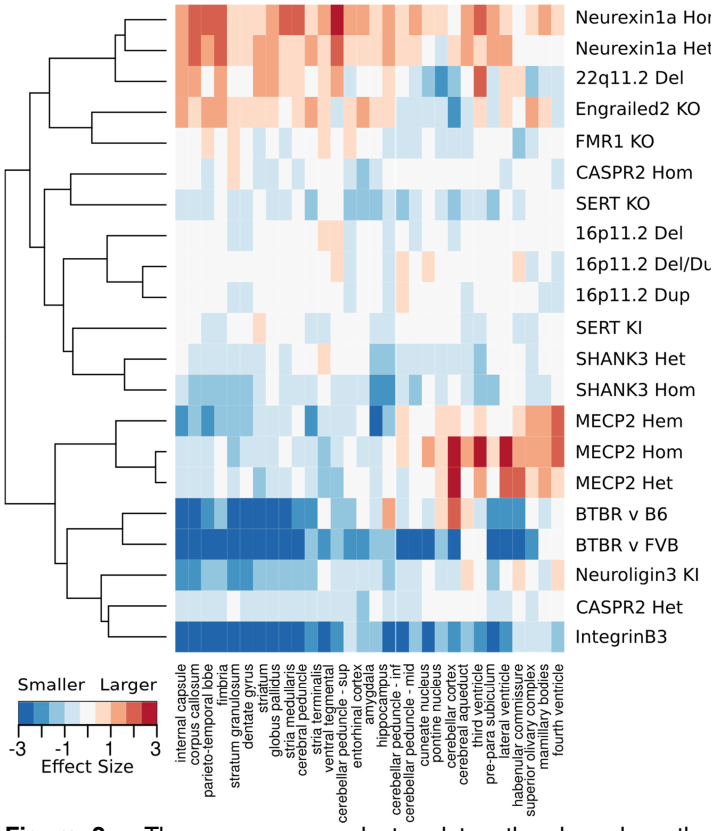

Figure 2 – The groups were clustered together based on the correlation of the effect size differences across all 62 regions examined in the study. Note – in the interest of saving space this figure is an abridged version and does not show all 62 regions

Conclusions – Here we group autism models together based solely on their neuroanatomical differences. These findings help to explain some of the variability seen in human autism as well as highlight regions of interest, such as the corpus callosum and the cerebellum, that are commonly found in ASD. Importantly, the whole brain analyses performed allow us to group disparate autism mouse models by their phenotypic similarities.

References – 1) Abrahams and Geschwind, Arch. Neurol. 2010;67(4):395-9. 2) Banerjee-Basu and Packer, Dis Model Mech. 2010;3(3-4):133-5. 3) Reiss, J Child Psychol. Psychiatry. 2009;50(1-2):87-98. 4) Lerch et al. Methods Mol Bio. 2011; 711:349-61. 5) Dorr et al. Neuroimage. 2008; 42(1):60-9.