Relationship Between Structure and Function of the Auditory System is Altered in 16p11.2 Deletion and Duplication

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Introduction: Deletion and duplication of the BP4-BP5 segment of chromosome 16 at location p11.2 has been associated with developmental disorders such as dysfunctions in language, mild to moderate intellectual disability, and autism spectrum disorders (ASD). By pursuing a "genetics first" approach to our study design, we can more directly examine the underlying mechanisms influencing neurobehavioral phenotypes in a more etiologically-homogeneous population [1]. We are motivated to examine the structure and function of the auditory system in children with 16p11.2 copy number variations given prior electrophysiological and microstructural findings in individuals with ASD. Diffusion MR is sensitive to white matter architecture and has been used to detect white matter abnormalities associated with ASD in the superior temporal gyrus [2]. Magnetoencephalography (MEG) has shown delayed latency of the auditory evoked field in ASD and in children with 16p11.2 deletions [3].

This multimodal study hypothesizes that the relationship between white matter integrity and the timing of the auditory evoked response is altered in children with 16p11.2 deletions and duplications. We use diffusion tensor imaging (DTI) and high angular resolution diffusion imaging (HARDI) to quantify the microstructure of the auditory radiation. MEG is used to measure the M100 evoked potential, which is generated by neurons in the superior temporal gyrus in response to an auditory stimulus. The latency of the M100 provides a measure of transmission speed through white matter and synapses.

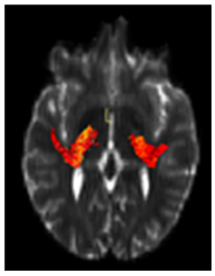

Fig 1: HARDI fiber tracking of auditory radiation.

Methods: This work included children imaged at two institutions participating in a multisite study. MR imaging was performed on a 3T Siemens Trio scanner with a 32 channel head coil. Diffusion MR and MEG data was acquired from 39 controls (mean age 13.2yrs, range 7.3-17.2yrs), 30 deletion carriers (mean age 11.2yrs, 8.0-16.3yrs), and 9 duplication carriers (mean age 11.3yrs, 7.4-16.9yrs). DTI included 30 gradient directions at b=1000s/mm^2 and 2mm isotropic resolution. HARDI included 64 gradient directions at b=3000s/mm^2 and 2mm isotropic resolution. The auditory radiation was defined with probabilistic HARDI tractography and tract-specific measures from the DTI (b=1000s/mm^2) acquisition [4].

MEG was performed with a whole head system (CTF). Tones at 200, 300, 500, and 1000Hz of 300ms duration were presented with 130 trials each. The M100 response for each frequency and hemisphere was source localized to the superior temporal gyri and the time between stimulus and M100 peak was measured. M100 varies by hemisphere and stimulus frequency; however, a single M100 per subject was established with a linear mixed model with fixed effects of hemisphere, condition, group category and data acquisition site; numeric covariates of age and DTI metric values; random effects of subject with random slopes of condition and hemisphere. The model was used to obtain fitted values from the model and predicted left and right M100 latencies for subjects with missing observations. Then correlations between the M100 and diffusion metrics for each hemisphere were determined.

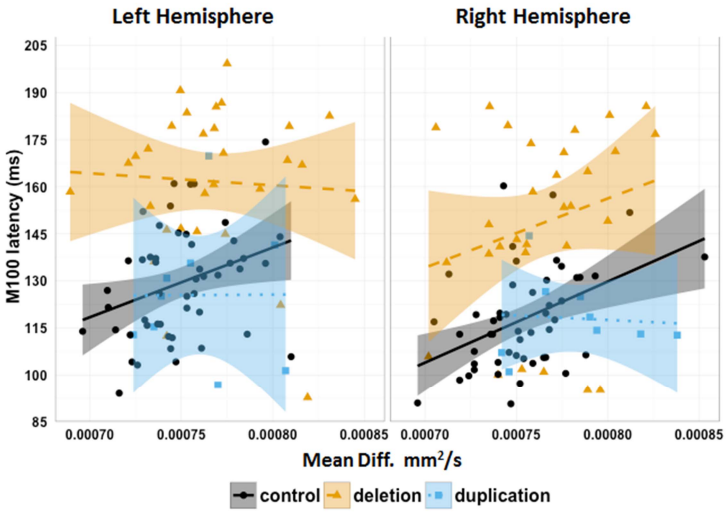

Figure 2: Mean diffusivity vs. M100 for left and right Auditory Radiations.

Results: In the controls, low (fast) M100 was significantly correlated with low mean diffusivity for both the left and right hemispheres and with radial diffusivity in the right hemisphere ($p<0.05$, each). In the deletion and duplication populations, no significant correlation between DTI metrics and M100 was observed (Figure 2). As previously reported, the M100 of the deletion population was significantly ($p<0.05$) increased and the mean diffusivity significantly increased ($p<0.05$) compared to controls (figure 3).

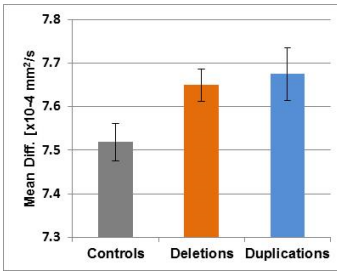

Fig 3: Marginal means of Mean Diff.±standard error.

Discussion: The relationship between white matter integrity and the timing of the auditory evoked response is altered in children with 16p11.2 deletions and duplications. The alterations to structure and function caused by 16p11.2 copy number variation may underlie the biological basis for developmental disorders such as ASD. In controls, degree of white matter myelination, axonal density and integrity as measured with DTI were observed to modulate the speed of the M100 response. In both the deletion and duplication groups, mean diffusivity was elevated and DTI metrics were not good predictors of M100 latency. However, the M100 was delayed only in the deletion group, indicating a mechanistic difference driven by genetics and not revealed with DTI. In addition to the microstructural changes observed, other factors such as neurotransmitters and cortical organization must be considered, which elongate M100 in the deletion population and break the relationship between M100 and DTI measures in both deletion and duplication groups. This multimodal study indicates varying gene doses may similarly have an abnormal structure-function relationship, but exhibit divergent electrophysiology.

References: [1] The Simons VIP Consortium, Neuron 2012. [2] Nagae et. al, AJNR 2012. [3] Roberts, TP, et. al., Autism Res. 2010. [4] Berman et. al, AJNR 2013.