Aberrant Change of Arcuate Fasciculus Geometry in Children with Angelman Syndrome: Diffusion Tensor MRI study

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Introduction: Angelman syndrome (AS) is a genetic disorder characterized by mental retardation, speech impairment, and gait apraxia. Speech impairment is universal but severity differs, which can be characterized by myelination delay or a deficit of white matter associated with language production and conception, especially of arcuate fasciculus (AF) bridging Broca's and Wernicke's areas. We previously showed that the arcuate fasciculus is grossly underdeveloped in children with Angelman Syndrome [1]. The present study presents new DT-MRI methodology to identify aberrant shape of AF pathways and quantify abnormal tracts in terms of their geometry such as curvature and principal orientation. To our knowledge, the present study is the first study to quantify aberrant shape of AF fibers in AS patients.

Meterials and Methods: 7 AS patients (Age: 70 ± 25.8 months, 5 males) and 4 age matched normal controls (NC, Age: 79.8±17.3 months, 4 males) were recruited for this study. All AS patients were genetically proven to have a DNA deletion in chromosome 15 (q11-13). Axial-DTI ASSET data were acquired from all subjects on a 3 T GE Signa scanner (GE Healthcare, Milwaukee, WI) at TR = 1250 ms, TI = 88.7ms, field of view = 240 cm, 128x128 matrix, contiguous 3 mm thickness slices to cover whole brain using 55 isotropic gradient directions with b= 1000s/mm2, one b=0 acquisition, and number of excitations (NEX) =1 for a total acquisition time of 12min 8s. A 3-D FSPGR was also acquired from whole brain using TR/TE/TI of 9.12/3.66/400 ms, slice thickness of 1.2mm, and planar resolution of 0.94x0.94 mm^2 and used for anatomical reference. All DTI preprocessing including eddy currents corrections and realignment was conducted using FSL tools (www.fmrib.ox.ac.uk). Whole brain tractography was performed in each subject's native space using conventional stream line tractography (0.2 mm step size, FA>0.20, deflection<60^o). Since we are particularly interested in the quantification of AF tracts across the subjects, it is critical to define an identical seed ROI in each subject and also register resulting tracts properly in a common space. To achieve this, we employed tract normalization methodology recently deveopled by Singh et al. [2]. In our study, the seed ROIs were manually delineated on axial slices in MNI space to cover AF region [3] in left hemisphere and mapped to each subject space via the inverse of SPM deformation field (www.fil.ion.ucl.ac.uk/spm) which was obtained between each subject's fractional anisotropy (FA) image and MNI FA template beforehand. The resulting fibers were transferred back to the MNI space via correponding deformation field to be registered in the MNI space. To examine the consistency of registered AF fibers across the subjects of each group, a group consistency map was computed by summing up the number of fibers penetrating individual voxels of the MNI space. The voxels in which the arcuate fibers passed through in at least the half of the subjects of each group were assumed to represent "consistent pathway". The fibers inside these pathways were only considered to quantify their curvatures and principal orientiation. That is, for each fiber, Frenet equation was applied to measure its scale-free curvature, $k(s)$ [4] and for each group, the principal component analysis of whole fiber coordinates was performed to estimate the principal fiber oriententation, v.

Results and Discussion: Fig. 1 shows group consistency maps of AF fibers registered in the MNI space. Clearly, we can see highly coherent pathways in both groups (marked by white arrows) supporting the accuracy of the tract registration. Also, the profiles of the $k(s)$ and v of the consistent pathways of both groups are shown in Fig. 2. There exists a major peak in the curvature profiles of the AS subjects indicating steep change in their curve shapes as indicated by the yellow arrow in Fig. 1. By comparison, flat curvatures were observed in the NC group implying relatively less significant change in the shape. In addition, we observed about 66^o angular deviation between the v of both group as shown in the right panel of Fig. 2 where the v of the NC clearly points out the principal direction of posterior-inferior projections directly connected to Wericke's area. Fig. 3 shows central fibers passing through the "center of mass" of the group's consistent pathway volume. The arcuate fibers of AS group did not reach Wernicke' area but those of NC group reached as expected. The FA values along the NC-AF fibers were significantly lower in the AS patients implying poor myelination of the AF in the AS patients (see Fig. 4). This work presents a promising DTI geometric metric for evaluating language tracts in AS. Its correlation to specificd genetic mutations in AS will be further investigated in the future.

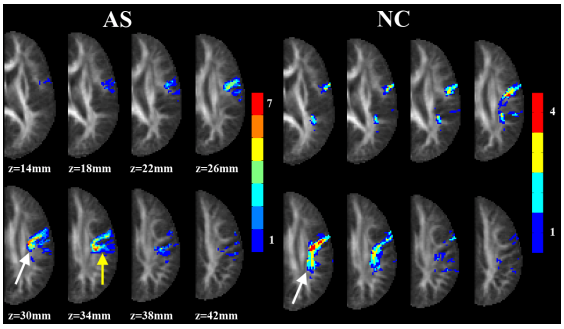

Fig.1 Group consistency map of the AF fibers. Color bar denotes the number of the subjects per voxel. Gray background shows the MNI FA templates obtained from the NC.

Reference: [1]B. Wilson et al, CNS meeting, 2009.[2]M. Singh et al., MRM 2009.[3] Catani et al., Cortex 2008, 44:953-961,.[4] P. Batcherlor et al., 2006, MRM, 55:894-903.

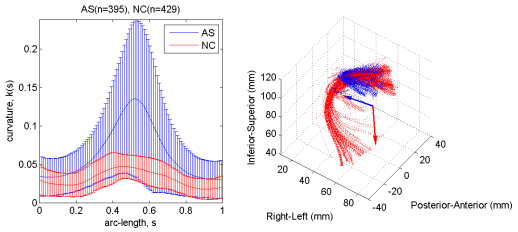

Fig.2. Geometrical features of the AF fibers (left) curvature profiles, k(s). Mean/standard deviation was plotted by solid line/vertical bar, respectively. n denotes the number of fibers. (right) principal orientation, v. Red/blue dots indicate fiber coordinates of the NC/AS.

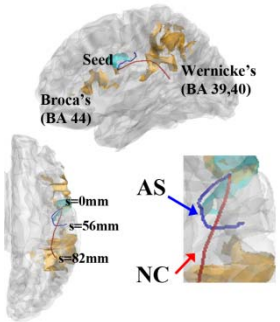

Fig.3. AF central fiber projecting from the seed region to Wernicke's area. s denotes an arc-length in mm.

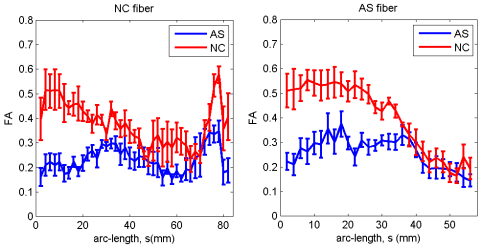

Fig.4. FA variation along the central fiber. Note a significant reduction of the FA value in AS patients after 40 mm of the NC fiber implying the possibility of notable demyelination to disrupt the AF fibers at those regions.