The Limbic System in Asperger Syndrome: A preliminary Diffusion Tensor Imaging Tractography Study

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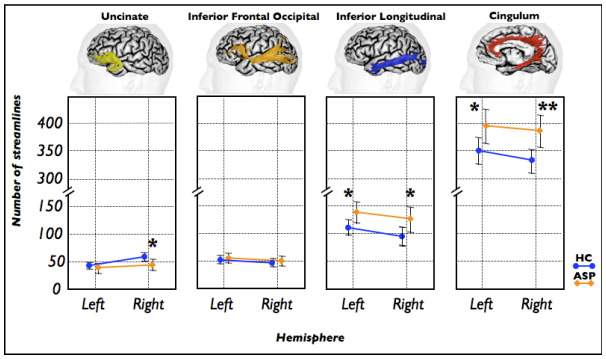
Objective: It has been suggested that people with Autistic Spectrum Disorder (ASD) have altered development (and connectivity) of limbic circuits[1,2]. However, direct evidence of anatomical differences specific to white matter pathways underlying social behavior and emotions in ASD, is lacking. We used Diffusion Tensor Imaging (DTI) tractography to compare, *in vivo*, tract-specific measurements along the principal limbic pathways between subjects with Asperger syndrome and healthy controls.

Methods: We recruited 66 male subjects: twenty-four males with Asperger Syndrome (mean age 23±12 years, age range: 9-54 years) and 42 age-matched male controls (mean age 25±10 years, age range: 9-54 years). DTI were acquired on a 1.5 T GE Signa NV/i LX (General Electric, Milwaukee, WI) and processed as described by Jones at al[3]. We quantified tract-specific diffusivity measurements as indirect indexes of tract volume (e.g. number of streamlines) and micro-structural organization and integrity (e.g. mean diffusivity, MD; fractional anisotropy, FA) of the main limbic tracts. These include the inferior longitudinal fasciculus (ILF), inferior frontal occipital fasciculus (IFOF), uncinate, cingulum and fornix.

Results: ***DTI measurements.*** *Streamline:* Subjects with Asperger syndrome had a statistically significant higher number of streamlines in the right (p=0.003) and left (p=0.03) cingulum and in the right (p=0.03) and left (p=0.04) inferior longitudinal fasciculus. In contrast people with Asperger syndrome had a significantly lower number of streamlines in the right uncinate (p=0.02) (**Figure 1)**. The number of streamlines for the right cingulum survived Bonferroni correction. *Mean Diffusivity*: The Asperger group showed significantly increase in the ILF bilaterally, right cingulum and in the right IFOF. *Fractional anisotropy*: individuals with Asperger syndrome had a significant decrease in FA within the IFOF in both hemispheres, and in the right uncinate fasciculus. ***Age-related differences.*** *Streamline:* There was a correlation between age and number of streamlines for the left and right cingulum in the healthy controls but not in Asperger syndrome. Only the correlation on the right cingulum survived Bonferroni correction (**Figure 2)**. Overall there were no differences between groups for the age-related correlation of the number of streamlines. However, when subjects were grouped according to age, young Asperger people (<18 years old) had a higher number of streamlines than controls in the right cingulum. These differences were not found for the older groups (**Figure 3).** *Mean diffusivity:* Within each group there were significant age correlations with mean diffusivity for the left ILF and for the cingulum and uncinate for both hemispheres in the control group and for the all tracts except the fornix in the Asperger group. However, there were statistically significant age-related differences between groups for the mean diffusivity of the left uncinate fasciculus (Z_{obs}=2.05) (p=0.02). *Fractional Anisotropy:*There were no within or between-groups differences in the age-related changes for the FA.

Discussion

In this first *in vivo* study of the limbic pathways differences were found between Asperger group and controls in the number of streamlines of the cingulum, ILF, and uncinate. The most robust difference was observed in the right cingulum, suggesting a greater involvement of those pathways connecting limbic regions involved in emotion processing and social cognition[4,5].



References:

1) Courchesne E,et al. *Curr. Opin. in Neurobiology*. 2005;15(2):225-230. **2)** Jones D. *Hum.Brain Mapp.* 2002;15(4):216-30 **3)** Wickelgren I. *Science*. 2005;308(5730):1856-8. **4)** Damasio AR. *Arch Neurol*. 1978;35(12):777-86. **5)** Mundy P. *J Child Psychol Psych*. 2003;44(6):793-809.

Figure 1
Differences between Asperger group (orange) and healthy controls (blue) in the number of streamlines for the four major limbic pathways of left and right hemispheres. Uncinate fasciculus (yellow), Inferior frontal occipital fasciculus (orange), inferior longitudinal faciculus (blue) and cingulum (red). * Differences are significant at p <0.05. **Differences are significant at p< 0.01.

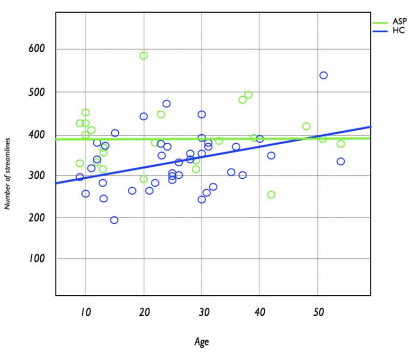


Figure 2
Correlation between age and number of streamlines in the right cingulum is statistically significant for the controls (blu) (r=.364 p<0.05) but not for the Asperger syndrome.

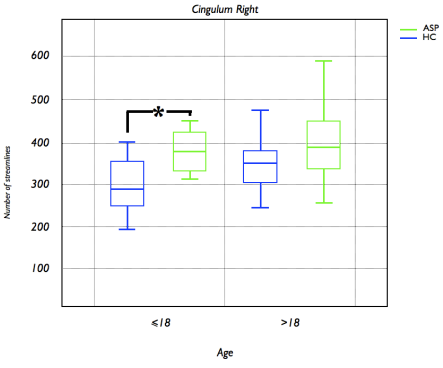


Figure 3
Between groups difference Differences in the number of streamlines of the right cingulum according to age.