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Maturational trajectories of subcortical grey matter microstructure: A longitudinal study

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Introduction

Brain maturation is a complex ongoing process during childhood and adolescence continuing into early adulthood. Conventional MRI studies show that the subcortical grey matter structures continue to develop during childhood and adolescence[1]. Cross-sectional diffusion tensor imaging (DTI) studies have reported age-related increases in fractional anisotropy (FA) and decreases in mean diffusivity (MD) in several subcortical grey matter structures[2,3]. Moreover, DTI studies have suggested that the microstructure of some white matter tracts develop earlier in females than males, and that in males the development may continue into adulthood[4]. It is unknown whether males and females also differ in their maturational trajectories of subcortical grey matter microstructure. Here we examined the maturational trajectories of FA and MD of subcortical structures in males and females using a longitudinal dataset with high temporal resolution.

Methods

Eighty-eight children and adolescents aged 7-19 years, who underwent MRI from two to 11 times (Fig. 1), were included.

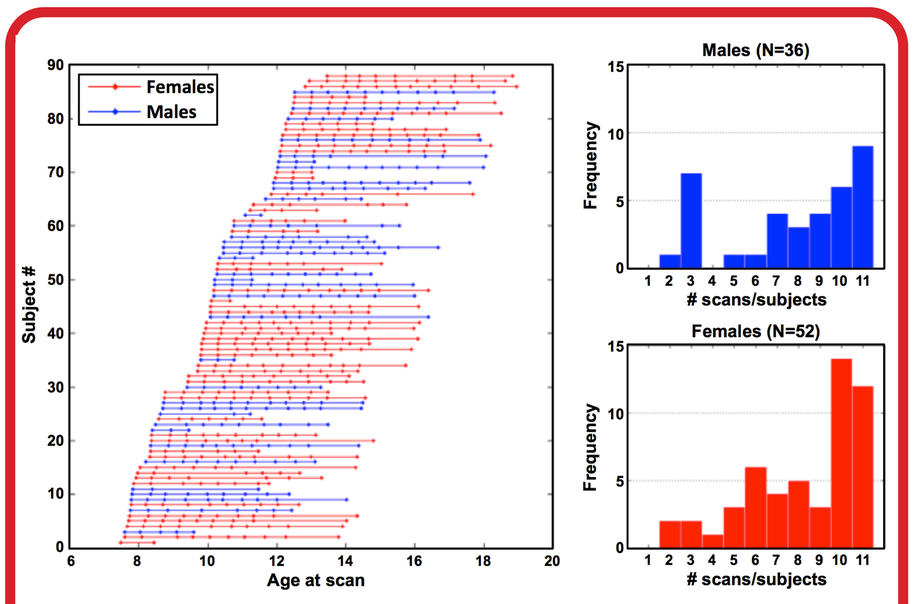

Figure 1. Left) Each line represents a participant (N=88) and the circles on the lines represent a MR-scan (N=713). The age of the participants is given on the x-axis. Right) The histograms show the frequency of the number of scans acquired in males (blue) and females (red).

T1-weighted and diffusion-weighted (61 directions, b=1200 s/mm^2, 10 b=0 images) images were acquired on a 3T MR-scanner.

High dimensional inter-subject warping (DARTEL, SPM8) was used to create an average inter-subject T1 template to delineate regions-of-interest (ROIs) in the amygdala, hippocampus, nucleus accumbens, caudate nucleus, putamen and thalamus.

DTI images were spatially normalized using high-dimensional warping of the tensors (DTI-TK[5]), and average intra- and inter-subject FA and MD templates were created. ROIs were eroded using a 1mm Gaussian kernel to minimize partial volume effects and projected into DTI space. The fit of the ROIs on intra-subject DTI templates was visually inspected, and data was excluded if the fit was poor (see tables). Mean ROI FA and MD values were then extracted.

Age-related changes over time in ROI MD or FA by sex were estimated using generalized additive mixed models (GAMMs) with smoothing splines in R.

Results

Significant age-related decreases in MD were observed for all ROIs in both females and males (Table 1, left). In females, the maturational trajectories of MD were non-linear and appeared to reach a plateau around the age of 12-13 years in all ROIs, except for the amygdala, in which maturation appeared more protracted (Fig. 2). In males, the maturational trajectories of MD were linear or almost linear, and MD continued to decrease throughout the studied age range (Fig. 2). For FA, significant age-related increases were observed in both males and females in the accumbens, amygdala and thalamus, while the increases were more modest in the caudate and hippocampus (Table 1, right). Significant age-related increase in putamen FA was observed in females, but not in males. The age-related increases in ROI FA tended to be linear or almost linear in both males and females, and were most pronounced in the accumbens and thalamus (Fig. 2).

Table 1. Results from the generalized additive mixed models of age-related changes in MD (left) or FA (right) by sex. Separate approximate significance levels (F and P statistics) of the smooth terms are given for boys and girls for each ROI.

	Mean diffusivity (MD)						Fractional anisotropy (FA)					
	Boys			Girls			Boys			Girls		
Region-of-interest	edf*	F	p	edf*	F	p	edf*	F	p	edf*	F	p
Accumbens *(n=713)*	1.00	29.33	<.0001	4.83	23.08	<.0001	1.00	94.54	<.0001	2.41	33.74	<.0001
Amygdala *(n=702)*	1.95	112.5	<.0001	3.49	101.7	<.0001	1.00	15.99	<.0001	1.00	16.13	<.0001
Caudate *(n=703)*	1.00	26.40	<.0001	4.19	14.54	<.0001	1.00	5.64	.0178	1.00	4.22	.0403
Hippocampus *(n=705)*	1.00	26.25	<.0001	3.43	13.91	<.0001	1.00	10.40	.0013	2.40	2.87	.0481
Putamen *(n=713)*	2.38	44.27	<.0001	5.54	31.04	<.0001	1.00	1.28	.2580	1.00	17.76	<.0001
Thalamus *(n=712)*	1.00	108.6	<.0001	3.70	36.83	<.0001	1.00	165.8	<.0001	2.49	104.7	<.0001

** Effective degrees of freedom (edf), where 1 equals a linear fit, and higher values equals more curvature.*

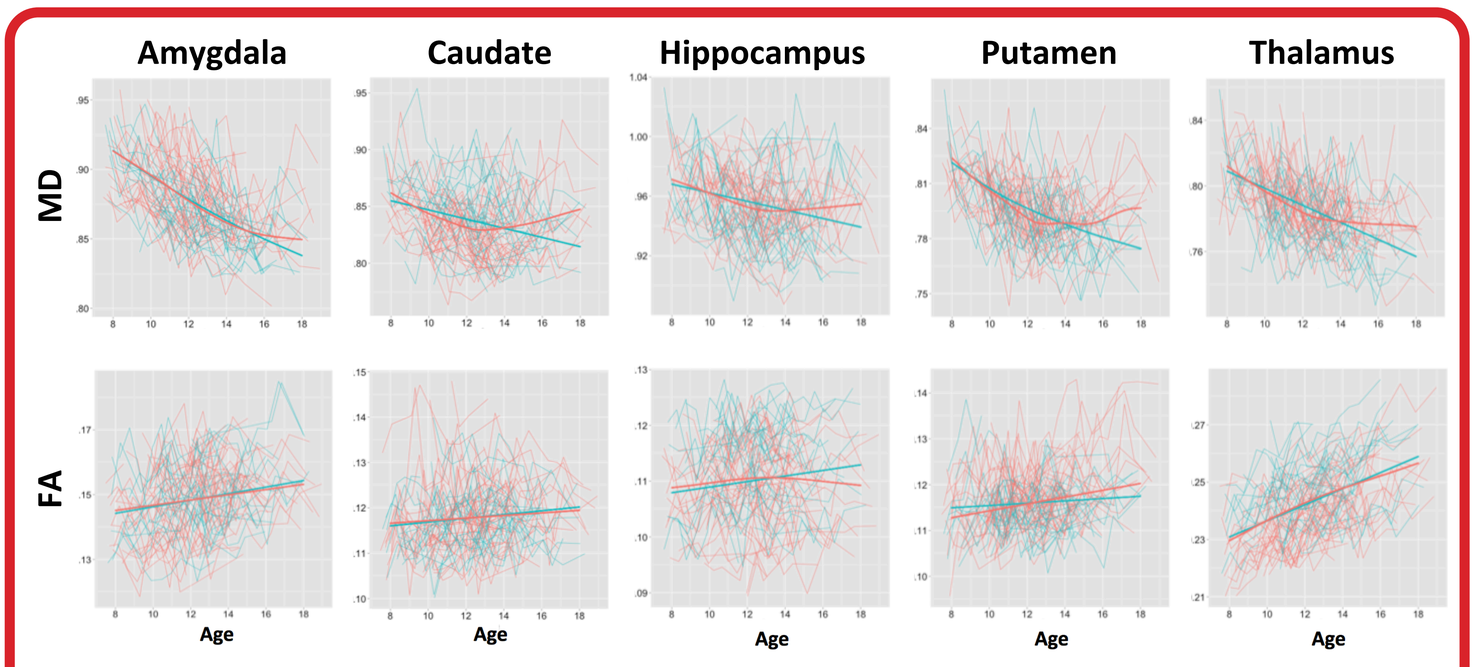

Figure 2. Spaghetti plots showing the maturational trajectories of mean diffusivity (MD) and fractional anisotropy (FA) in the subcortical ROIs across the age range 7-19 years. The thick lines represent the GAMM fitted maturational trajectories for males (blue) and females (red). MD significantly decreased with age in all ROIs, but appeared to reach a developmental plateau around the age of 12-13 years in females, except for the amygdala, whereas in males MD continued to develop throughout the studied age range. FA significantly increased with age in all ROIs, except in the putamen in males, though the increase in caudate and hippocampus FA was modest.

Conclusion

In a longitudinal cohort examined at high temporal resolution, we observed age-related decreases in MD and increases in FA in subcortical grey matter structures. The maturational trajectories of MD differed between males and females, in that females appeared to reach a developmental plateau in most ROIs around the age of 12-13 years, except for the amygdala. Interestingly, this is also the average age at which females reach sexual maturity. Males displayed a more protracted maturation of MD that continued to decrease throughout the studied age range of 7-19 years. It is unknown why the maturational trajectories in MD differ between males and females, but the differences may be mediated by differences in sex hormones and when the sexes enter puberty. Future studies should investigate how changes in sex hormones during puberty are related to sex differences in the maturational trajectories of the DTI parameters.

Acknowledgements

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