Relationship of Basal Cerebral Blood Flow, Thickness of Cortical Gray Matter and Fractional Anisotropy of Cerebral White Matter in Adolescents

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Introduction: Adolescence is a key developmental period during which a host of structural and functional brain circuits are rapidly developing. Notably, a reduction in global cerebral blood flow (CBF) and gray matter (GM) volume have been observed to be decreasing, while white matter (WM) has been shown to be significantly increasing among adolescents (1, 2). However, relative little is known regarding the interaction between these physiological and structural transformation in adolescents. In the current study, we sought to further investigate adolescent brain development through the simultaneous assessment of within-subject CBF measurements and structural changes using magnetic resonance imaging (MRI) techniques. Arterial spin labeling (ASL), high resolution T_1-weighted images, and fractional anisotropy (FA) were employed to determine CBF, GM thickness (GMT) and WM myelination, respectively, among a population-based sample of adolescents.

Material and Methods: Adolescents aged 12 to 16 years (from 11.7 to 15.8 years old; n = 267, 130 males and 137 females) were randomly recruited from the greater San Antonio area. All imaging data for this study were collected using a Siemens 3T Trio scanner. The ASL images were acquired with a pulsed ASL (PASL) sequence. Interleaved images with and without labeling were acquired with a field-of-view (FOV) =24 cm, in-plane matrix size= 64 x 64. Repetition time (TR) = 2440 ms, echo time (TE) = 19 ms, delay time (TI_1) = 700 ms, label time (TI_2) = 1000 ms and 13 slices. The equilibrium brain tissue magnetization (M_0) was measured using similar parameters as described above but $TR/TI_1/TI_2$ = 8000ms/5000ms/6000ms and repetition = 4. High-resolution (isotropic 0.8 mm), T_1-weighted images were acquired for regional measurement of GM thickness with TR/TE/TI/flip angle = 2100ms/3.04ms/785ms/11 degrees. Diffusion tensor imaging was performed using a single-shot, echo-planar, single refocusing spin-echo, T_2-weighted sequence with a spatial resolution of 1.7x1.7x3.0 mm. The sequence parameters were: TR/TE=8000ms/87ms, axial slice orientation with 50 slices and no gaps, 55 isotropically distributed diffusion weighted directions, two diffusion weighing values b=0 and 700 s/mm^2 and three b=0 images. *Data Analysis:* ASL images were processed to obtain quantitative basal global CBF values (3). T_1-weighted images and DTI images were used for extraction of cortical GMT and FA values, respectively. The pipeline of obtaining GMT was shown in Figure 1, which included skull stripping (A); spatial normalization, RF homogeneity correction and tissue segmentation (B); extraction of GM and WM pial surfaces (C, D); calculation of GM thickness (E, F) (4). The tract-based spatial statistics (TBSS) software was used for multi-subject analysis of FA images (5). The inter-subject variability in GMT, FA and CBF were then fitted using a general linear mixed effect (GLME) model (Eqs. [1-2]). $GMT\&FA \sim \beta_{age} Age + \beta_{sex} Sex + \beta_{agesex} Age\,Sex + \alpha$ [1];

$CBF \sim \beta_{age} Age + \beta_{sex} Sex + \beta_{agesex} Age\,Sex + GM + FA + \alpha$ [2]; Where βs are the covariate regression coefficients and α is a coefficient that accounts for random effects.

Results: Beta coefficients and their significance of the inter-subject variability determined are shown in Table 1. GMT and FA were significantly correlated with age, but not with gender or age*gender interaction. On the other hand, CBF showed negative beta coefficients with age, gender and GM but had no statistical significance with the three parameters, while showed positive coefficients beta with FA and was significantly correlated with FA. The normalized GMT, FA and CBF values across age were further demonstrated in Figure 2: GMT and FA reduced, while FA increased, with age.

Discussion: Consistent with the literature results, our data demonstrated reduction in CBF, GM pruning and WM myelination in adolescents in a within-subject, within-session manner (1, 2). We further demonstrated that the basal CBF during early adolescence is largely a function of white matter development indexed by FA. The negative beta coefficient between FA and CBF indicates that the myelination approaching-completion corresponds with decline in CBF during age 12-16 (6). Myelination is an energy-demanding process — myelin assembly needs increases in metabolism to support sorting and transporting lipids and proteins (7) — the slowing down of the process is thus expected followed by a decline of metabolism. Because basal CBF is known tightly coupled with basal cerebral metabolism (both with cerebral metabolic rate of glucose (CMR_{Glc}) and oxygen ($CMRO_2$); 8), the decline in CBF is suggested due to the reduced energy demand for the white matter myelination. In addition to the reduced rate of myelination, gray matter pruning also plays a key role in the decline of cerebral metabolism levels (9, 10). Glucose utilization in cortex has also been repeatedly found declined correspondingly during the pruning phase (during 4 until 16-18 of age) using ^{18}FDG PET methods (9). It is suggested, therefore, the decrease in CMR_{Glc} during adolescence is because of diminishing energy requirement. As a result, the decline in metabolism and thus CBF are also partially accounted for by the pruning of gray matter. In the present study, GMT was not found significantly correlated with CBF. Therefore, our data suggest that the age-related decline in CBF is predominantly accounted for by the slowing down of the myelination process, rather than the pruning of gray matter. In conclusion, we showed in a large group of healthy adolescents aged 12-16 years that gray matter pruning and white matter myelination occurred in parallel and the CBF reduction was mainly contributed by the reduced rate of myelination. It is expected that these findings will facilitate the understanding of the physiological (CBF) and structural (GMT and FA) interaction during a key developmental period for brain development.

Table 1.

	β_{age}±sd (t; p)	β_{sex}± sd(t;p)	$\beta_{age,sex}$ ± sd (t;p)	β_{GM}± sd (t;p)	β_{FA}± sd (t;p)
GMT	-0.02±0.01 (2.25. 0.02)*	-0.24±0.23 (1.0, 0.32)	-0.02±0.02 (1.2, 0.24)	-	-
FA	0.005±0.002 (3.74, 0.002)*	-0.02±0.03 (0.9, 0.4)	-0.003±0.002 (1.2, 0.23)	-	-
CBF	-0.2±0.6 (0.3; 0.77)	-3.0±11.9 (0.3; 0.80)	0.1±0.9 (0.1; 0.89)	-4.5±2.8 (1.6;0.11)	-62.8±21.9 (2.9; 0.005)*

Fig 1.

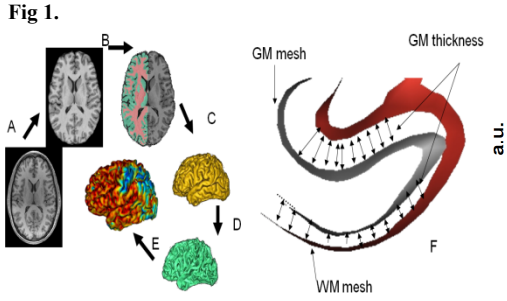
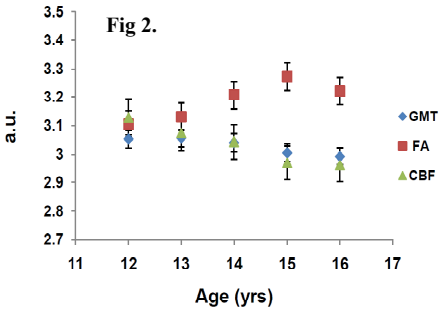


Fig 2.



References: (1) Rao et al., Pediatrics 2007, 120:e1245-54; (2) Sowell et al., Nat Neurosci 2003; 6:309-15; (3) Wang et al., MRM 2003, 49:796-802; (4) Kochunov et al., Neuroimage 2010, 53: 1135-46; (5) Smith et al., 2006 Neuroimage, 31:1487-1505; (6) Gao et al., 2009 AJNR Am. J. Neuroradiol. 30:290–6; (7) Chapter 4 in Basic Neurochemistry, 6th edition; (8) Raichle et al., PNAS 2001; 98:676-82; (9) Chugani et al., 1987 Ann Neurol, 22:487-97; (10) Chugani Prev. Med. 1998, 27:184-88.

Figure 1. T1-weighted image processing pipeline consists of skull stripping (A); spatial normalization, RF homogeneity correction and tissue segmentation (B); extraction of GM and WM pial surfaces (C,D); calculation of GM thickness (E, F); **Figure 2.** Normalized GMT, FA and CBF values across age in adolescents.