# Dissociation between Aging of Anterior and Posterior Corpus Callosum Microstructure Depends on Genotype

**K. M. Kennedy[1], K. M. Rodrigue[1], S. Land[2], and N. Raz[3]**

[1]Center for BrainHealth, School of Behavioral and Brain Science, University of Texas at Dallas, Dallas, TX, United States, [2]Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI, United States, [3]Institute of Gerontology and Dept of Psychology, Wayne State University, Detroit, MI, United States

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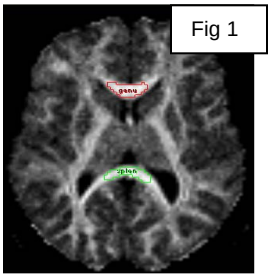
Kristen M. Kennedy, PhD [1], Karen M. Rodrigue, PhD[1], Susan Land, PhD[2], Naftali Raz PhD[3]

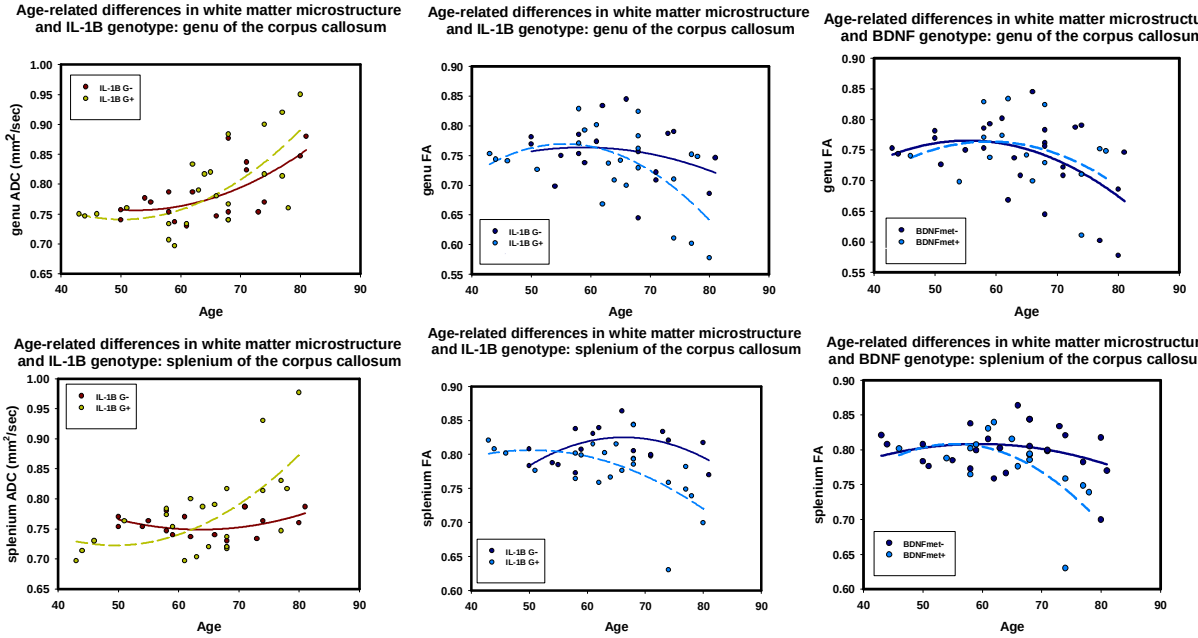
[1] Center for BrainHealth, School of Behavioral and Brain Science, University of TX at Dallas, Dallas, TX, United States; [2] Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan, United States; [3] Institute of Gerontology and Department of Psychology, Wayne State University, Detroit, Michigan, United States.

**INTRODUCTION:** Reduced white matter (WM) microstructural integrity is found in normal aging across the brain, but its mechanisms are poorly understood. The purpose of the current study was to investigate the influence of genetic factors on diffusion characteristics of WM. We examined the effects of two single nucleotide polymorphisms (SNP), a genetic marker of inflammation, interleukin-1 beta (IL-1β) A/G, and brain-derived neurotrophic factor (BDNF) val66met on fractional anisotropy (FA) and Apparent Diffusion Coefficient (ADC) in two regions of WM: genu and splenium of the corpus callosum. Availability of BDNF, a protein associated with neuron proliferation, differentiation and survival as well as synaptic plasticity, declines with age. Individuals with a genetic predisposition for decreased BDNF expression, therefore, may be especially vulnerable to age-related reduction in plasticity and repair mechanism. As risk for inflammation-related damage increases with age, genetic predisposition for release of pro-inflammatory cytokine conferred by IL-1β G allele, may have a synergistic negative effect on white matter. **MATERIALS AND METHODS:** Forty one healthy middle-aged and older adults (age range = 44-81 yrs; 64.2 ± 10; M/F = 16/25) were genotyped via standard buccal cell mouthwash protocol and imaged on a Siemens Sonata 1.5 T scanner. Single shot spin-echo planar DTI was acquired in six directions (resolution = 2x2x3mm; 33 axial slices; TR/TE = 5400/97 ms, and b values of 0 and 1000 sec/mm$^2$). Analyze DTI module (Mayo Clinic, Rochester, MN) was used to create FA and ADC maps from diffusion images. *ROI analysis:* The genu and splenium of the corpus callosum were manually drawn for each subject with high reliability: ICC(3) ≥ .91, as illustrated in Fig.1. Mean fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were computed for each ROI. Genotyping was conducted for BDNFval66met and IL1-β A/G polymorphisms.




**RESULTS:** Carriers of the high-activity pro-inflammatory cytokine allele IL-1β G displayed significantly higher ADC and lower FA in the splenium, but not the genu of the corpus callosum in comparison to A homozygotes (Figures 2a and 2b, respectively). BDNFmet carriers displayed lower FA in the splenium but not the genu (Figure 2c), whereas there were no differences in genu or splenium ADC. Furthermore, the BDNF met carriers exhibited an accelerated (quadratic) trajectory of estimated age change, while the BDNF val homozygotes evidenced a linear decline for the splenium. The trajectories for genu differed according to the presence of BDNF met allele: quadratic for val homozygotes, linear for met carriers. For the IL-1β G carriers there was an accelerated decline in FA in the genu and splenium, and in the IL-1β A homozygotes, there was linear decline in the genu, and accelerated (quadratic) decline in the splenium. Removal of one outlier attenuated the nonlinear trends in the splenium of BDNF Met and IL-1β G carriers, but the latter remained statistically significant.

**Figure 2** **(a)** **(b)** **(c)**




**CONCLUSIONS:** We observed dissociation between age differences in white matter regions and specific genetic factors. Normal aging is characterized by reduced integrity of the genu, regardless of the BDNF or IL-1B genotype, but deterioration of the splenium is observed only in carriers of genetic risk alleles. Thus, the findings suggest that in contrast to commonly observed anterior-posterior gradient of age-related declines, increase of posterior regional damage in age-related pathology (such as vascular disease), may be in part due to specific genetic factors.