Diffusion tensor imaging analysis with tract-based spatial statistics of the white matter abnormalities in early-treated phenylketonuria

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Introduction: Phenylketonuria (PKU) is a genetic condition characterized by an impaired ability to metabolize the amino acid phenylalanine into tyrosine, a precursor of dopamine and other neurotransmitters [1]. Whereas early and continued dietary treatment significantly reduces the impact of PKU on a patient, individuals with early-treated PKU (ETPKU) continue to experience neurologic and cognitive disruptions [2]. The most widely-reported neurologic finding in ETPKU is that of white matter abnormality as visualized on T_2-weighted magnetic resonance imaging (MRI) scan [3]. More recent studies utilizing diffusion tensor imaging (DTI) methods have reported a decreased rate of water diffusion (as measured by apparent diffusion coefficient or mean diffusivity value) in the white matter of individuals with ETPKU as compared with individuals without PKU [4]. Importantly, the majority of these past studies have relied on region-of-interest (ROI) analyses, which rely on *a priori* hypotheses and are limited to selection of a few white matter tracts. Therefore, the aim of this study was to investigate white matter fiber tract-specific changes in individuals with ETPKU compared to healthy non-PKU individuals by means of tract-based spatial statistics (TBSS) approach (FSL, Oxford, UK). We hypothesized that white matter compromise in individuals with ETPKU would be distributed across many cortico-cortical as well as subcortico-cortical tracts.

Methods: A sample of 10 individuals with ETPKU and 12 healthy controls (mean age: ETPKU = 23.3 yrs; non-PKU = 23.5 yrs) participated in the study. Two runs of single-shot spin-echo echo-planar DTI (SE-EPI-DTI) were acquired on all subjects using a 3T Siemens Trio MRI scanner (Erlangen, Germany). Fractional anisotropy (FA) maps from all subjects were aligned into MNI152 space using the nonlinear registration. The mean FA image was then created and thinned to create a mean FA skeleton. Each subject's aligned FA data were then projected onto this skeleton, and the resulting 4D FA skeleton data was fed into voxelwise cross-subject statistics. A randomise procedure (FSL, Oxford, UK) was used to perform the group analysis (500 permutations). Using the same skeleton projection vectors derived from the FA images, axial, radial and mean diffusivity (AD, RD and MD) data from all subjects were equally projected onto the skeleton before voxelwise randomise statistical analysis across subjects. A restrictive statistical threshold was used (cluster-based threshold $p < .05$, corrected for multiple comparisons). Post hoc Pearson correlation analyses were performed to detect possible effects of age on DTI indices for white matter tracts.

Results and Discussion: AD, RD and MD were significantly reduced in numerous white matter tracts of patients with PKU compared to normal controls, including genu, body and splenium of corpus callosum (gcc, bcc, scc), bilateral external capsule (ec), superior longitudinal fasciculus (slf), inferior longitudinal fasciculus (ilf), inferior fronto-occipital fasciculus (ifo), forceps minor (fminor), forceps major (fmajor), anterior, superior and posterior corona radiate (acr, scr, pcr) (Figure 1). This finding suggests that microstructural abnormalities are pervasive throughout the white matter tracts in individuals with ETPKU. Although the precise mechanisms underlying these white matter disruptions remains unclear, prior research has suggested status spongiosis change within the white matter and/or abnormal myelin sheaths related to increased myelin turnover [5]. The accumulation of intracellular debris produced as a byproduct of inadequate Phe metabolism has also been suggested as a mechanism of restricted water diffusion [6]. Consistent with previous work suggesting that PKU-related white abnormalities may worsen with age [3], we also found a negative correlation within the ETPKU group between age and mean value of AD, MD and RD of the whole brain white matter skeleton (No such correlation was found for the non-PKU group). In the future, it will be important to replicate these findings with a larger participant sample. Additional research examining the relationship between these white matter abnormalities and the cognitive impairments experienced by individuals with ETPKU is also needed.

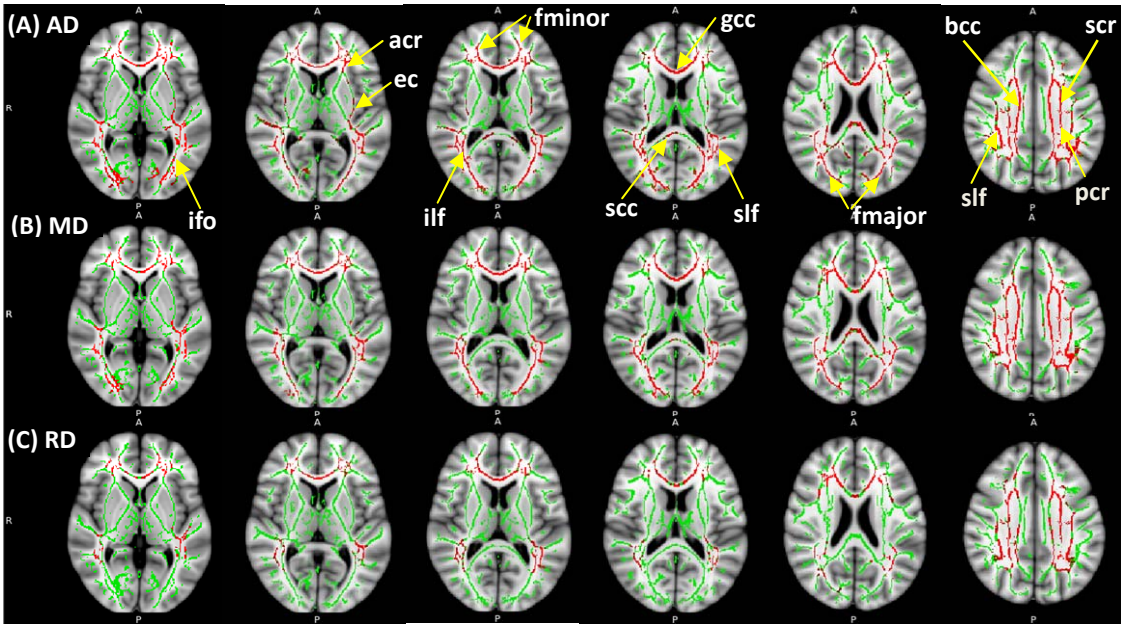

Figure 1. TBSS revealed regions of reduced AD (A), MD (B), and RD (C) in patients with ETPKU compared to the healthy controls. Red color represents significant voxels at $p < .05$ (corrected for multiple comparisons at cluster level). Mean FA skeleton of all subjects is overlaid in green on MNI152 T1-weighted brain image.

References: [1] Scriver CR *et al*, Hum Mutat. 2007; 28(9):831-45. [2] Christ SE *et al*, Mol Genet Metab. 2010; 99 Suppl. 1:S22-32. [3] Anderson PJ *et al*, Mol Genet Metab 2010; 99 Suppl. 1: S3-9. [4] White DA *et al*, Mol. Genet. Metab 2010; 99 Suppl. 1:S41-6. [5] Phillips MD *et al*, Am J Neuroradiol. 2001; 22(8):1583-6. [6] Leuzzi V *et al*, J Inherit Metab Dis. 2007; 30(2):209-16.