Investigating the Structural Integrity of Brain Tissue in Intermittent Explosive Disorder: A Turboprop-DTI and Voxel-Based Morphometry Study

H. Peng[1], K. Arfanakis[1], K. L. Phan[2], and E. L. Coccaro[2]

[1]Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, United States, [2]Department of Psychiatry, University of Chicago, Chicago, IL, United States

Introduction: Intermittent explosive disorder (IED), often referred to as “road-rage disease”, is characterized by episodic, impulsive aggression. There is very limited information regarding the structural brain correlates of IED. Reduced frontal grey matter has been reported in IED patients compared to healthy controls [1]. Also, reduced fractional anisotropy (FA) has been measured in the fornix, forceps minor, and posterior cingulate gyrus of IED patients using diffusion tensor imaging (DTI) [2]. Therefore, the purpose of this investigation was to use voxel-based morphometry (VBM) and Turboprop-DTI [3] in order to test the hypothesis that patients with IED are characterized by significantly lower brain volume in the frontal lobe, and significantly reduced FA in white matter, when compared to normal controls. The use of Turboprop-DTI as opposed to echo-planar-based DTI was particularly crucial, since Turboprop-DTI is relatively immune to image artifacts caused by magnetic field inhomogeneities, which are prominent in brain regions of interest to the present investigation, such as the frontal, temporal lobes and brainstem.

Methods: Fifty-five healthy controls and forty-nine IED patients participated in this study. IED diagnoses were verified using the Structured Clinical Interviews for DSM-IV (SCID), for DSM-IV personality (SIDP), and with the intermittent explosive disorder interview (IED-M) [4,5]. High-resolution T_1-weighted MP-RAGE, and Turboprop-DTI images were acquired for all subjects on a 3T GE MRI scanner (Waukesha, WI). The parameters for MP-RAGE were: TE=3.2ms, TR=8ms, preparation time=725ms, flip angle 6°, field of view 24cm x 24cm, 120 sagittal slices, 1.5mm slice thickness, 192x256 image matrix reconstructed to 256x256. The parameters for Turboprop-DTI were: TR=5000ms, 8 spin-echoes per blade, 5 k-space lines acquired per spin-echo, FOV=24cm x 24cm, 128 samples per line, 256x256 final image matrix, 36 axial slices, slice thickness=3mm, 12 diffusion directions, and b-value=900sec/mm^2. The T_1-weighted and Turboprop-DTI data from a healthy subject were selected and used as a template for the data analysis (the selection was based on criteria that are beyond the focus of this work). The segmentation tool of SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) was used on the T_1-weighted volumes to produce grey and white matter maps (in native space) for all subjects. The grey and white matter maps of each subject were then normalized to the corresponding maps of the template. All normalized grey and white matter volumes were smoothed using a Gaussian kernel with full width at half maximum (FWHM) equal to 12mm. Group comparisons of grey and white matter between the 55 control subjects and the 49 patients with IED, were performed using the general linear model. A factor for the subjects’ age was included in the model. Only differences with p-value < 0.001 and clusters with volume larger than 120 mm^3 were considered significant. FA maps were produced for all subjects using in-house software. The Brain Extraction Tool of the software package FSL (Oxford Center for fMRI of the Brain, Oxford, UK) was applied on all b=0sec/mm^2 volumes to remove the skull and noise outside of the brain. The binary brain masks were then applied on the FA volumes. The FA maps from all subjects were smoothed using Gaussian kernels with FWHM of 5mm, and 9mm, separately, and normalized to the FA template using affine and non-linear regularization. Group comparisons of FA values between the normal controls and IED patients, were performed using the general linear model. Age was also included in the model. Only differences with p-value < 0.05, corrected for multiple comparisons using “false discovery rate” correction, and clusters with volume larger than 20 mm^3, were considered significant.

Results: Regions that showed significant differences in FA values between the patients and normal controls for both levels of smoothing were overlaid on averaged FA maps. Significant reduction of FA was observed bilaterally in white matter adjacent to the amygdala of IED patients (right T-score=5.2, left T-score=4) (Fig.1A), in fibers of the superior longitudinal fasciculus bilaterally (right T-score=3.3, left T-score=3.6) (Fig.1B), in the brainstem (T-score=6.1) (Fig.1C), in bilateral posterior thalamic radiations (PTR) (right T-score=3.9, left T-score=3.7), and in right anterior thalamic radiations (ATR) (T-score=4.0) (Fig.1D), when compared to normal controls. FA was also significantly reduced in the forceps minor of IED patients, where ATR, U-fibers that connect the left and right frontal lobes, and corticopontine fibers are located (right T-score=4.4, left T-score=3.7) (Fig.1E). In addition, significantly reduced FA was detected in fibers of the right posterior cingulate gyrus of IED patients, which includes PTR, corticopontine fibers, and fibers of the corpus callosum that connect the left and right posterior cingulate gyri (T-score=4.3) (Fig.1F). VBM analysis revealed significantly reduced white matter volume in the right forceps minor of the IED cohort (T-score=4.5) (Fig.2).

Discussion: The limbic system controls emotional expression, including aggression, and contains brain structures such as the amygdala, hippocampus, parahippocampal gyrus, thalamus, and cingulate cortex. In this work, it was demonstrated that patients with IED were characterized by significantly reduced FA values in fibers connected to structures of the limbic system, such as the fibers in the posterior cingulate gyrus (cingulate cortex), the ATR and PTR (thalamus), and brainstem (amygdala, thalamus, cingulate cortex). Reduced FA values suggest abnormalities in the microstructural integrity of these white matter pathways. Current analysis can not reveal if the fibers adjacent to the amygdala and parahippocampal gyri, characterized by significantly reduced FA, are actually connected to these structures. Further research is required to clarify this point. Also, the finding of decreased FA and white matter volume in the forceps minor of IED patients compared to normal controls is in agreement with previous studies that suggest involvement of the frontal lobe in IED. To our knowledge, this is the first study to combine VBM and Turboprop-DTI in the investigation of the structural correlates of IED. The large size of the IED and healthy control cohorts, and the advanced DTI techniques used, enhance the validity of our results. The findings of this study may have a significant impact on the diagnosis, as well as the treatment of IED.

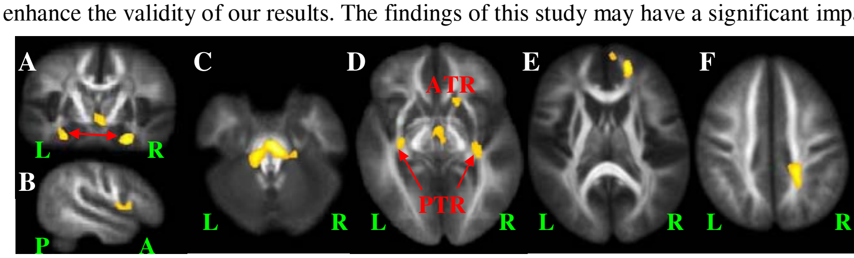
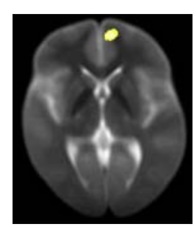


Figure 1. Regions with significantly reduced FA values in IED patients compared to normal controls (in yellow), overlaid on averaged FA maps. The statistical maps were produced from data smoothed with FWHM of 9mm. The grey-scale maps were produced by averaging the FA maps from all subjects.

Figure 2. Region with significantly reduced white matter volume in IED patients compared to normal controls (in yellow), overlaid on an averaged b=0sec/mm^2 image.



References: [1] Woermann FG, *et al., J Neurol Neurosurg Psychiatry* 2000;68:162-169. [2] Peng H, *et al., ISMRM 2006:p.3459.* [3] Pipe JG, *et al., Magn Reson Med* 2006;55:380-385. [4] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders - DSM-IV.* Washington, DC: APA, 1994. [5] Coccaro EF, *et al., Compr Psychiatry*. 1998;39:368-376.