

Diffusion Tensor MRI in Intermittent Explosive Disorder

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Introduction: Intermittent explosive disorder (IED), which is characterized by episodic, impulsive aggression, is an important social and clinical problem. Studies on structural cerebral changes using MRI [1] have shown a reduction of frontal neocortical grey matter in patients with IED. Diffusion tensor imaging (DTI) studies have detected white matter microstructural changes in the frontal lobe in patients with aggression [2]. However, traditional spin-echo echo-planar DTI suffers from severe susceptibility-related image distortions, which affect primarily the frontal and temporal lobes. The purpose of this investigation was to study the diffusion characteristics of the whole brain in patients with IED using a novel DTI data acquisition technique, named Turboprop-DTI [3], which is relatively immune to susceptibility-related artifacts. Fractional anisotropy (FA) values from the whole brain were compared between patients with IED and healthy controls using voxel-based analysis. A significant reduction of FA was detected in the fornix, forceps minor, and posterior cingulate gyrus of patients with IED compared to healthy controls.

Methods: Twenty-four healthy subjects and thirty-five patients with IED and personality disorder (PD) participated in this study. From the thirty-five patients, twenty were diagnosed with IED and PD, eleven with IED and borderline personality disorder (BPD), and four with IED, BPD and anti-social personality disorder (ASPD). 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]. All subjects were scanned with Turboprop-DTI on a 3T GE MRI scanner (Waukesha, WI). The parameters for the Turboprop-DTI acquisitions were: TR=5000ms, 8 spin-echoes per blade, 5 k-space lines acquired per spin-echo (therefore 40 lines per blade), FOV=24cm x 24cm, 192 samples per line, 256x256 final image matrix, 36 axial slices, slice thickness=3mm, minimum energy DTI encoding scheme with 12 diffusion directions [6], and b-value=900sec/mm². FA maps were produced for all subjects. The Brain Extraction Tool of the software package FSL (Oxford Center for fMRI of the Brain, Oxford, UK) was applied in all T₂-weighted volumes to remove the skull and noise outside of the brain. The binary brain masks were then applied on the FA volumes. The FA volume of one healthy control subject was used as a template. FA volumes from all other subjects were then normalized to the FA template using affine and non-linear regularization. All FA volumes were smoothed before normalization [7]. Smoothing was performed using Gaussian kernels with full width at half maximum (FWHM) of 5mm, 7mm, and 9mm, separately. Group comparisons of FA values between the 24 control subjects and 20 patients with IED and PD, were performed using the general linear model. Changes of FA due to age were controlled by including age as an additional factor in the model. Similar comparisons were performed between the 24 control subjects and all thirty-five patients with IED. Only differences with p-value < 0.001 and clusters with volume larger than 120 mm³ were considered significant.

Results: Regions that showed significant differences in FA values between the patients and normal controls for some but not all levels of smoothing were excluded. Significant differences that were present for all levels of smoothing were overlaid on the average T₂-weighted and FA maps from all subjects (Fig. 1, 2). In patients with IED and PD, significant reduction of FA was detected in the left fornix (t-score=4.12, Fig.1A1, A2), right forceps minor (t-score=4.15, Fig. 1B1, B2), and right posterior cingulate gyrus (t-score=3.79, Fig.1C1, C2). When comparing all patients with IED to normal controls, significant reduction of FA was seen in the left and right fornix (t-score=4.37, t-score=4.04, Fig. 2A1, A2), anterior commissure and right anterior limb of the internal capsule (t-score=4.05, Fig. 2A1, A2), right forceps minor (t-score=4.16, Fig.2B1, B2), left arcuate fasciculus (t-score=3.7, Fig. 2B1, B2), and right posterior cingulate gyrus (t-score=4.32, Fig.2C1, C2) of the patients. (All t-scores were estimated from comparisons between FA maps that were smoothed with FWHM of 9mm).

Discussion: The finding of decreased FA 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. The fornix is an important pathway of the limbic system, which is involved in emotional expression. The reduction of FA in the fornix of patients with IED may be related to the behavioral changes in patients with the disorder. Also, the reduction of FA in the posterior cingulate gyrus is in agreement with previous reports that implicate posterior regions of the cingulate cortex in aggressive disorders [8]. The findings of the comparisons between the normal controls and the patients with IED and PD were similar to those from the comparisons between the normal controls and all the IED patients. Small variations may be partly due to differences in statistical power. Further comparisons will be performed between the different subgroups of IED patients as soon as more patients are included in each subgroup.

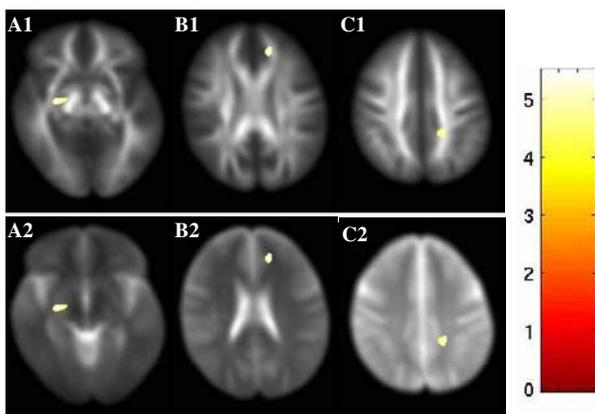


Figure 1. Regions with significant reduction of FA values in patients with IED and PD compared to normal controls, overlaid on average FA (top) and T₂-weighted (bottom) images. In this image, the statistical maps were produced from data smoothed with FWHM of 9mm and the grey-scale maps were produced from data smoothed with FWHM of 5mm.

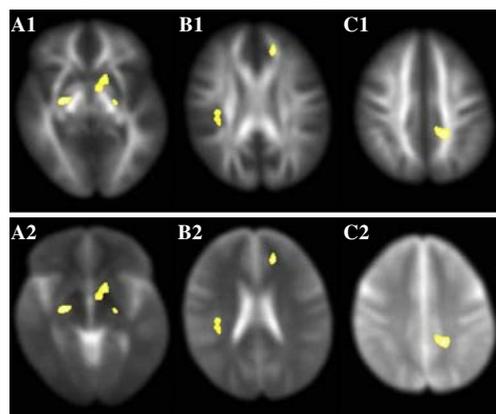


Figure 2. Regions with significant reduction of FA values in all patients with IED compared to normal controls, overlaid on average FA (top) and T₂-weighted (bottom) images. In this image, the statistical maps were produced from data smoothed with FWHM of 9mm and the grey-scale maps were produced from data smoothed with FWHM of 5mm.

References: [1] Woermann FG, et al, *J Neurol Neurosurg Psychiatry* 2000;68:162-169. [2] Hoptman MJ, et al., *Biol Psychiatry* 2002;52:9-14. [3] Pipe JG, *ISMRM* 2002;p.435. [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. [6] Hasan KM, et al., *J Magn Reson Imag* 2001;13:769-780. [7] Friston KJ, et al., *Hum Brain Mapp* 1995;2:189-210. [8] Goyer PF, et al., *Neuropsychopharmacology* 1994;10:21-8.