An Investigation of the Microstructure of Brain Tissue in Social Anxiety Disorder: A Turboprop-DTI Study

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Introduction: Social anxiety disorder (SAD), also known as social phobia, is characterized by long-lasting anxiety or fear, leading to relatively extreme distress and impaired ability to function [1]. Recent fMRI and PET studies have shown increased amygdala activity in response to anxiety-provoking stimuli [2]. This response seems to be exaggerated in patients with social phobia [3]. Even though the amygdala is believed to be regulated by areas of the orbitofrontal and pre-frontal cortex (PFC) [4], there have been only few investigations of the structure of white matter pathways between the amygdala and these regions in social phobia, and no investigations utilizing diffusion tensor imaging (DTI). The purpose of this study was to investigate the microstructure of brain tissue that mediates contact between the amygdala and frontal cortex, in patients with social phobia, by means of Turboprop-DTI [5]. We hypothesized that patients with social phobia have significantly reduced fractional anisotropy (FA) in white matter pathways that connect the amygdala and frontal cortex/PFC, compared to normal controls.

Methods: Twenty-three healthy controls and twenty-five patients with social phobia were included in this study. Patients were diagnosed with SAD – generalized subtype based on Diagnostic and Statistical Manual (DSM-IV) criteria (7 of 12 social fears) using the Structured Clinical Interview for DSM-IV [1]. Diagnosis was further verified with additional probes from the Social Phobia Interview [6] and the Liebowitz Social Anxiety Scale [7]. High-resolution Turboprop-DTI data were acquired on all subjects using a 3T GE MRI scanner (Waukesha, WI). The parameters for the scans were TR=5000ms, 8 spin-echoes per blade, 5 k-space lines per spin-echo, FOV=24cm x 24cm, and 128 samples per line, resulting in a 256x256 final image matrix with 36 axial slices, slice thickness=3mm, 12 diffusion directions, and b-value=900sec/mm^2. The Brain Extraction Tool of the FSL software package (Oxford Center for fMRI of the Brain, Oxford, UK) was applied to all b=0sec/mm^2 volumes to create binary brain masks for all subjects. These masks were applied to FA maps to generate roughly deskulled volumes, with additional fine deskulling performed manually when necessary. A single deskulled FA volume from a normal subject was selected to be the template. The FA maps from all subjects were smoothed with a Gaussian kernel with full width at half maximum (FWHM) of 9mm, and normalized to the FA template using affine and non-linear registration (SPM5, Wellcome Department of Imaging and Neuroscience, London, UK). Voxel-based statistical analysis of FA values in patients with social phobia and healthy controls were preformed using the general linear model, with age included as a covariate. Only differences with p-value < 0.01 and clusters with volume larger than 100mm^3 were considered significant.

Results and Discussion: Regions that showed significant differences in FA between patients and controls were overlaid on top of averaged FA maps. FA was significantly reduced in the left thalamus of patients with social phobia (T-score=3.11) (Fig. 1A), in fibers of the right uncinate fasciculus (T-score=2.85) (Fig. 1B), and in association fibers adjacent to the left superior longitudinal fasciculus (T-score=2.93) (Fig. 1C), compared to normal controls. Reduced FA values suggest microstructural abnormalities in brain tissue of patients with social phobia. Our finding of reduced FA in the left thalamus in patients with social phobia is significant, since, animal, lesion and neuroimaging studies indicate that incoming sensory signals of fear travel from the thalamus to the amygdala [8], which is hyperactive in threatening situations in social phobia. Furthermore, of particular interest is our finding of reduced FA in the uncinate fasciculus, since this is a pathway that connects the amygdala to the orbitofrontal cortex, which is believed to regulate the reactivity of the amygdala to anxiety-causing stimuli [4]. This finding suggests that microstructural abnormalities exist in the connection between the regulatory orbitofrontal cortex and amygdala in patients with social phobia, which may be responsible for the exaggerated, dysregulated responses in amygdala associated with enhanced anxiety to threatening situations. To our knowledge this is the first study utilizing DTI to probe the microstructure of brain tissue in patients with social phobia. The size of the two cohorts investigated, as well as the use of an advanced DTI acquisition technique that provides DTI data free of image artifacts, enhance the significance of this study.

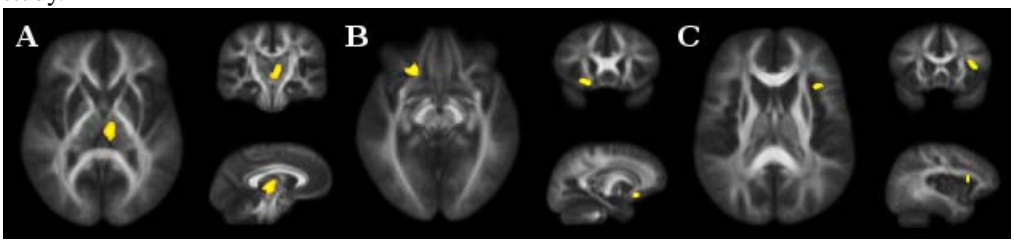

Figure 1. Regions of significantly reduced FA in patients with social phobia compared to healthy controls. Underlying gray-scale maps were produced by averaging the FA maps from all subjects. In the axial and coronal images, viewer left corresponds to image right.

References: [1] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders – DSM-IV*. Washington, DC: APA, 1994. [2] Stein, M. B. *et al*, *Arch Gen Psychiatry* 2002; 59:1027-1034. [3] Phan, K. L. *et al*, *Biol Psychiatry* 2006; 59:424-429. [4] Banks, S. J. *et al*, *Social Cognitive and Affective Neuroscience Advanced Access* Jul 2007. [5] Pipe, J.G. *et al*, *Magn Reson Med* 2006; 55:380-385. [6] Stein, M. B. *et al*, *Am J Psychiatry* 1998; 155:90-97 [7] Heimberg, R. G. *et al*, *Psychological Medicine* 1999; 29:199-212. [8] Das, P. *et al*, *Neuroimage* 2005; 26:242-248.