White matter alterations in social anxiety disorder

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ABSTRACT

White matter architecture in patients with social anxiety disorder (SAD) has rarely been investigated, but may yield insights with respect to altered structural brain connectivity. Initial evidence points to alterations in the uncinate fasciculus (UF). We applied diffusion tensor imaging in 25 patients with SAD and 25 matched healthy subjects. Whole-brain fractional anisotropy (FA) maps were used for group comparison and voxel-wise correlation with psychometric and clinical measures. Additionally, a region-of-interest analysis of the UF was performed. Patients with SAD had reduced FA compared to healthy subjects in or near the left UF and the left superior longitudinal fasciculus. There were no regions with increased FA in SAD. In the region-of-interest analysis, a negative correlation between FA and trait anxiety was identified in the left and right UF in patients, but not in healthy subjects. No correlations with social anxiety scores were observed. The present study partially confirms previous results pointing to frontal WM alterations in or near the UF in patients with SAD. SAD-specific dimensional associations of FA with trait anxiety might reflect general pathological and/or compensatory mechanisms as a function of symptom severity in patients. Future studies should disentangle in which way the identified WM alterations match functional alterations.

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1. Introduction

Social anxiety disorder (SAD) is a common anxiety disorder (Jefferys, 1997) with a life-time prevalence of about 10% (Kessler et al., 1994). It is characterized by exaggerated fear during the anticipation of or confrontation with evaluation by others. Since genetic factors are known to play a role in SAD (Mosing et al., 2009; Stein and Stein, 2008) and based on the commonly early age of onset (Stein and Stein, 2008), manifestations in the brain's structural architecture can be expected.

Examination of white matter (WM) may yield insights into structural connectivity and complement functional neuroimaging studies. Until now, little is known about WM architecture in SAD. First evidence points to alterations in the uncinate fasciculus (UF) (Phan et al., 2009), a fiber bundle connecting inferior frontal cortices including orbitofrontal cortex with the anterior temporal lobe and the amygdala (Ebeling and von Cramon, 1992; Ghashghaei et al., 2007; Petrides and Pandya, 2007). Since the amygdala mediates emotional arousal states (Davis and Whalen, 2001) and the orbitofrontal cortex is implicated in cognitive control of emotions (Ochsner and Gross, 2005), the UF may play a key role in the emergence or regulation of fear. Therefore, the UF represents a WM structure of interest for diffusion tensor imaging (DTI) studies related to fear and anxiety. Theories of SAD point to biases at different stages of cognitive-attentional processing (Hirsch and Clark, 2004), probably not mediated by the UF alone. Therefore, it can be expected that WM alterations are present in further brain areas mediating interpretative or associative processes.

DTI is a magnetic resonance based technique allowing the examination of WM structural properties, such as microstructural anisotropic diffusion reflected by fractional anisotropy (FA) (Basser and Pierpaoli, 1996). In the present study, we assessed FA throughout the whole-brain in patients with SAD and in healthy control subjects. Additionally, we concentrated on FA within the UF in a region-of-interest approach. Given the results of related previous studies (Kim and Whalen, 2009; Phan et al., 2009), which for the first time investigated associations between FA and anxiety, we expected that reduced rather than increased FA would be a characteristic of abnormal WM architecture in anxious individuals. First, we aimed at identifying altered WM structures in

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patients with SAD compared to healthy subjects. Specifically, we hypothesized reduced FA in the UF. Further, we sought to determine the dimensional impact of trait anxiety, social anxiety and SAD duration on FA.

2. Materials and methods

2.1. Subjects

Twenty-seven outpatients with current diagnosis of generalized SAD participated in this study. They were recruited from the outpatient clinic at the Department of Psychiatry and Psychotherapy of the University Hospital Zurich. Control subjects were recruited via direct address and email-advertisement. Due to severe artifacts in DTI images related to technical problems during data acquisition, two patients with SAD had to be excluded from further analyses. The remaining 25 patients with SAD were matched with 25 healthy subjects in terms of age and gender (see Table 1). All subjects were right-handed according to a handedness questionnaire (Annett, 1970). Diagnosis of generalized SAD and comorbid Axis-I diagnoses were established using the Mini-International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998) (German version by Ackenheil et al., 1999). One patient met life-time criteria for a depressive episode, but was not currently depressed; three patients met criteria for a current depressive episode in the course of a major depressive disorder, however, SAD was the primary diagnosis. One patient met criteria for prior alcohol dependency, currently remitted. There were no further psychiatric comorbidities. Altogether, nine patients were taking antidepressant medication due to depressive symptoms (selective serotonin reuptake inhibitors in five subjects, selective serotonin/norepinephrine reuptake inhibitors in two subjects, mirtazapine in one subject, and clomipramine/zolpidem in one subject). Two of the mentioned subjects were additionally taking lithium, one quetiapin. In all subjects, the dose of drugs had been stable for more than one month when participating in the study. Healthy control subjects were free of current or past psychiatric disorders (semi-structured diagnostic interview) and of medication (except oral contraceptives). Exclusion criteria in all subjects were neurological disorders, head trauma, pregnancy, excessive consummation of alcohol, cigarettes and caffeine, and contraindications against magnetic resonance imaging. All subjects provided written informed consent and were compensated for their participation. The study was approved by the local ethics committee.

General anxiety was measured with the trait version of the Spielberger State-Trait Anxiety Inventory (STAI, Spielberger et al., 1970; German version by Laux et al., 1981) in all participants. The degree of social anxiety was assessed in patients with the self-rating version of the Liebowitz Social Anxiety Scale (LSAS, Liebowitz, 1987; German version by Stangier and Heidenreich, 2005). The LSAS self-rating version has been shown to have high reliability (retest-reliability $r = 0.82$, Cronbach's $\alpha = 0.95$) and validity (correlation with the clinician-administered version $r \geq 0.78$) (Baker et al., 2002). Degree of depression in patients with SAD was assessed with Beck's Depression Inventory (BDI, Beck et al., 1961; German version by Hautzinger et al., 1994). Further patient-specific characteristics were collected in addition to the diagnostic interview: The duration of symptoms of SAD was assessed by retrospectively asking for the onset of symptoms (available in 20 patients). A positive family history of psychiatric disorders was present in 88.9% of the patients (mostly SAD and depression, assessed in 18 patients).

2.2. DTI data acquisition

DTI scans were acquired on a 3.0 T whole-body scanner (GE Medical Systems, Milwaukee, USA) equipped with a standard 8-channel head coil. One diffusion-weighted spin-echo echo-planar imaging (EPI) scan was obtained from all participants. Slices were acquired sequentially in transversal orientation (matrix 256×256 pixels, 39 slices, slice thickness 3.2 mm, field of view (FOV) $= 240 \times 240$ mm). Further imaging parameters were: echo time (TE) $= 87.8$ ms, repetition time (TR) $= 12000$ ms. Diffusion sensitization was achieved with 2 balanced diffusion gradients centered on the $180°$ radio-frequency pulse. Diffusion was measured in 21 non-collinear directions with a b-value of $b = 1000$ s/mm^2. Five additional interleaved non-diffusion-weighted volumes ($b = 0$ s/mm^2) served as reference volumes. Scan time was about 6 min. In addition to DTI, T1- and T2-weighted images were consecutively acquired to exclude possible T1-/T2-sensitive tissue abnormalities.

2.3. Data preprocessing

We applied preprocessing procedures for DTI data as implemented in FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). Using FMRIB Diffusion Toolbox (FDT) (Behrens et al., 2003), FA maps as well as maps of primary (λ_1), secondary (λ_2) and tertiary (λ_3) eigenvalues were created. λ_1-maps were used for analysis of axial diffusivity. Radial diffusivity maps were calculated as $\lambda_{23} = (\lambda_2 + \lambda_3)/2$. Preprocessing comprised the following steps: 1) Eddy current and head movement correction were applied using FDT. 2) Individual binary brain masks were created on the non-diffusion weighted images using Brain Extraction Tool (Smith, 2002). 3) Tensors were fitted to the data using FDT. 4) Linear and non-linear normalization of the FA maps into a standard stereo-tactic space (Montreal Neurological Institute, MNI; represented by the FMRIB58 FA template) were done with scripts

Table 1
Demographic, psychometric and clinical characteristics of the sample.

	SAD [a]	Healthy subjects	Test	T	df	p
Age	32 ± 10.4 years (range: 19–53)	32 ± 10.1 years (range: 20–57)	t	0.24	48	0.82
Gender	18 m, 7 f	18 m, 7 f				1.00
STAI-X2[b]	[e]50 ± 11.2 (range: 31–76)	[f]33 ± 7.4 (range: 22–55)	t	6.38	41.6	< 0.001
LSAS[c]	66 ± 23.0 (range: 26–107)	–				
BDI[d]	15 ± 10.8 (range: 0–41)	–				
Age of onset of SAD	15 ± 5.9 years (range: 6–30)	–				
Duration of SAD	16 ± 10.6 years (range: 3–44)	–				

[a] SAD: patients with social anxiety disorder.
[b] STAI-X2: Spielberger State-Trait Anxiety Inventory, trait section.
[c] LSAS: Liebowitz Social Anxiety Scale.
[d] BDI: Beck's Depression Inventory.
[e] corresponds to increased values (Laux et al., 1981).
[f] corresponds to values within the normal range (Laux et al., 1981).