Neuroscience Letters 583 (2014) 114–119

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Enlargement of visual processing regions in social anxiety disorder is related to symptom severity

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HIGHLIGHTS

- Reports of structural alterations in SAD have been few and mixed.
- We found increased gray matter volume in visual areas in social anxiety disorder.
- Social anxiety severity was positively related to regional gray matter volume.
- Increased gray matter volume could underlie abnormal emotional processing in SAD.

ARTICLE INFO

Article history:
Received 27 August 2014
Received in revised form
10 September 2014
Accepted 15 September 2014
Available online 26 September 2014

Keywords:
Social phobia
Gray matter
VBM
Voxel based morphometry
Anxiety

ABSTRACT

Social anxiety disorder (SAD) is associated with altered brain function and structure, but most structural studies include small samples and findings are mixed. This study compared regional gray matter volume between 48 SAD patients and 29 healthy controls (HC) as well as the relationship between volume and symptom severity. Structural magnetic resonance images from SAD patients and HC were evaluated using standard voxel-based morphometry (VBM) processing in the SPM8 software package. Social anxiety symptom severity was rated in SAD patients by a clinician using the Liebowitz Social Anxiety Scale (LSAS). SAD patients had greater regional gray matter volume in the lingual gyrus and lateral occipital cortex than the controls, and within the SAD group a positive correlation was found between symptom severity and regional gray matter volume in the lingual gyrus and the retrosplenial cortex. These findings replicate and extend earlier reports of enlarged visual processing areas in SAD. Increased gray matter volume in regions involved in visual processing and self-consciousness could underlie, or be the result of, abnormal emotional information processing and self-focused attention previously demonstrated in patients with SAD.

Social anxiety disorder (SAD), characterized by negative self-focused attention and excessive fear of scrutiny by others [1], is a common, disabling psychiatric condition with life-time prevalence numbers estimated at 10–15% [2,3]. An increasing number of studies have reported on brain correlates of the disorder [4,5]. Functional neuroimaging studies have quite consistently reported altered neural reactivity and connectivity during emotional and disorder-relevant tasks in fear network regions including the amygdala, insula, hippocampus, and anterior cingulate cortex [4,6–10]. Recent reports have extended these findings to include altered reactivity in other brain areas, e.g. visual processing regions during exposure to emotional faces [11–13], as well as the striatum during cognitive [14] and emotional tasks [15].

Studies of brain structural changes in SAD, on the other hand, have been more inconclusive [5]. The first structural neuroimaging study of SAD was published in 1994 [16] and did not report anatomical deviations in SAD patients as compared to healthy controls. The relatively few follow-up studies that have been published have

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http://dx.doi.org/10.1016/j.neulet.2014.09.033
0304-3940/

Table 1
Demographics in patients with social anxiety disorder (SAD) and healthy controls (HC).

	SAD ($n = 48$)	HC ($n = 29$)	Statistic	p-Value
Age, mean (SD)	33.8 (9.3)	23.7 (2.0)	$t = 5.851$	<0.0001
Sex, men, women	24 M, 24 W	13 M, 16 W	$\chi^2 = 0.042$	0.838
Education, (SD)			$\chi^2 = 0.628$	0.731
≤9 years	1	0		
10–12 years	22	14		
≥12 years	25	15		
Handedness	45 right, 3 left	23 right, 6 left	$\chi^2 = 2.387$	0.122
Generalized SAD	30 (62.5%)	N/A		
LSAS, mean (SD)	72.1 (24.0)	10.1 (8.7)	$t = 16.260$	<0.0001
Comorbidity				
GAD	10	0		
Specific phobia	7	0		
Depressive episodes	3	0		
Panic disorder	2	0		
OCD	1	0		
Earlier psychological treatment	4	0		
Earlier psychotropic medication				
SSRI	4	0		
Unknown antidepressants	2	0		
Perfenazin	1	0		

GAD, generalized anxiety disorder; LSAS, Liebowitz social anxiety scale; M, mean; N/A, not applicable; OCD, obsessive compulsive disorder; SSRI, selective serotonin reuptake inhibitor; W, women.

had small samples and reported inconsistent results, with both increased and decreased volume or cortical thickness, as well as null findings [17–24]. Functional alterations in fear network regions consistently appear in SAD, with increased reactivity to emotional and disorder-relevant stimuli, e.g. emotional face processing [4,6], while structural alterations are inconsistent [5]. Similar inconsistencies between brain activation and structural studies have been reported in cortical regions [18–23], including visual areas [18–20,23].

In a recent study from our lab we observed increased cortical thickness in visual processing areas including the fusiform gyrus and lingual gyrus [23] in SAD patients, possibly related to abnormal evaluation of emotional stimuli. However, the sample consisted only of men and was rather small with 14 SAD patients and 12 healthy controls (HC). Since few of the structural findings in SAD have been replicated and studies typically have included relatively few subjects, reducing statistical power and generalizability, the aim of the present study was to investigate brain structure in a new larger sample of 48 SAD patients and 29 HC participants, including both men and women. Because the cortical thickness measures used in our previous study [23], cannot detect putative subcortical structural alterations, we chose a volume-based approach for the current study. In addition to case–control differences, we also sought to investigate the relationship between regional gray matter volume and social anxiety symptom severity.

1. Methods

1.1. Participants

Forty-eight SAD patients and 29 HC participants were included in the study (see Table 1). SAD patients were recruited through newspaper advertisement and volunteered to participate by signing up and completing online screening questionnaires at a dedicated website. Initial screening included the Social Phobia Screening Questionnaire (SPSQ) [2] and exclusion criteria, i.e. ongoing or within 2 months discontinued psychological treatment or treatment with psychotropic medication, current drug or alcohol abuse/dependency, any other serious psychiatric or neurologic disorder that may have a major influence on the results, menopause, or magnetic resonance imaging safety criteria. Patients passing initial screening were interviewed using the Mini International Neuropsychiatric Interview (MINI) [25] and the diagnostic questions from the SCID-I [26] to ascertain that they fulfilled the DSM-IV criteria for SAD [1]. A psychiatrist conducted a medical examination and assessed the severity of social anxiety symptoms using the clinician administered Liebowitz Social Anxiety Scale (LSAS) [27]. All patients had a primary SAD diagnosis (see Table 1 for comorbidity). HC participants were recruited from public billboards at Uppsala University. None of the HCs fulfilled the screening criteria for SAD, and none of them reported any other current or previous psychiatric disorders according to the screening interview. The exclusion criteria were the same for the HC subjects as for the SAD patients.

1.2. Ethics statement

The study was conducted in accordance with the Helsinki Declaration and approved by the Regional Ethics Committee. All participants provided informed written consent.

1.3. Behavior and demographic analyses

All demographic and behavior data were analyzed with between group t-tests or chi-square/Fisher's exact test with R 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

1.4. Image acquisition

Structural T1-weighted MR images were acquired using an inversion recovery turbo spin echo sequence with 60 contiguous axial slices (echo time = 15 ms; repetition time = 5700 ms; inversion time = 400 ms; field of view = 230 mm × 230 mm; voxel size = 0.8 mm × 1.0 mm × 2.0 mm). All images were acquired with a Philips Achieva 3.0T whole body MR-scanner (Philips Medical Systems, Best, The Netherlands).

1.5. Image analyses

The T1-weighted images were processed using the standard voxel-based morphometry (VBM) pipeline in the Statistical parametric mapping software package (SPM8; www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2012a (The Mathworks Inc., Natick, MA, USA) software package. Each participant's image was segmented into gray matter, white matter, and cerebrospinal fluid by New segment in SPM8. Diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) was then used to create a study-specific template for the 77 participants. The template was subsequently affine registered to the Montreal Neurological Institute (MNI) space and the individual gray matter images were warped to this template and resliced to 1.5 mm isotropic voxels. The warped gray matter images were scaled by the Jacobian determinants to preserve volumetric information and smoothed with an 8 mm isotropic Gaussian kernel. The smoothed, modulated, spatially normalized gray matter images represent regional gray matter volume and were used in the following statistical analyses.

SAD patients were compared to HC participants on voxel-wise regional gray matter volume using a two-sample t-test within SPM8, and associations between social anxiety symptom severity and regional gray matter volume within the SAD group were analyzed using voxel-wise multiple regression analyses with total