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Gray matter abnormalities in patients with social anxiety disorder: A voxel-based morphometry study

Raşit Tükel [a,*], Kubilay Aydın [b], Çağrı Yüksel [c], Erhan Ertekin [a], Ahmet Koyuncu [d], Cumhur Taş [e,f]

[a] Department of Psychiatry, Istanbul University, Istanbul Faculty of Medicine, İstanbul, Turkey
[b] Department of Radiology, Neuroradiology Division, Istanbul University, Istanbul Faculty of Medicine, İstanbul, Turkey
[c] McLean Hospital, Harvard Medical School, MA, USA
[d] Private practice
[e] Department of Psychology, Uskudar University, İstanbul, Turkey
[f] Division of Cognitive Neuropsychiatry and Psychiatric Preventative Medicine, Ruhr University, Bochum, NRW, Germany

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ABSTRACT

The main objective of this study was to investigate the gray matter volume (GMV) differences between the patients with social anxiety disorder (SAD) and healthy controls, using VBM analysis. A total of 27 consecutive patients (15 women and 12 men) with SAD and 27 age and sex-matched healthy control subjects were included in this study. With magnetic resonance imaging, we examined GMV differences between SAD and healthy control groups. We found that GMV in the right middle and inferior temporal, left superior parietal, left precuneus and right fusiform areas were significantly greater in patients with SAD than in healthy controls. In addition, GMV in the right inferior and middle temporal regions were positively correlated with the social avoidance and total social anxiety scores of the participants in the SAD group. Lastly, greater GMV in the left superior parietal and precuneal regions were correlated with the higher disability in the social life of the patients with SAD. Our results suggest that the regions that showed significant GMV differences between the two groups play an important role in the pathophysiology of SAD and increased GMV in these regions might reflect a pathological process of neural abnormalities in this disorder.

1. Introduction

Social anxiety disorder (SAD) is a common illness characterized by marked and persistent fear of social or performance situations in which an individual is at risk of embarrassment, humiliation, or possible scrutiny of others (American Psychiatric Association, 1994). Ample studies have investigated the clinical and neuropsychological profile of patients with SAD and demonstrated a greater self-focused attention and an attention bias towards fear-inducing stimuli (Becker et al., 2001; Heinrichs and Hofmann, 2001; Spector et al., 2003; Andersson et al., 2006). In addition, genetic heritability in SAD has been evidenced by a substantial number of studies (Hettema et al., 2001). Today, there is an increasing trend towards investigating the functional and structural brain differences of patients with SAD, which would ultimately improve our insights into the development of the disorder.

Functional imaging studies have found significant evidence of hyperactivity in the limbic regions, especially the amygdala, hippocampus, and insula of patients with SAD, when viewing emotionally charged faces (Freitas-Ferrari et al., 2010), being in a situation of anticipation of public speaking (Tillfors et al., 2001; Lorberbaum et al., 2004) and also during eye contact (Schneier et al., 2011). Although the predominance of evidence implicates an important role of the amygdala in the pathophysiology of SAD (Freitas-Ferrari et al., 2010), investigations of other regions have also provided some corroboration of functional abnormalities. For instance, a recent study found an increased activation of the anterior cingulate cortex during the processing of facial expressions such as disgust (Amir et al., 2005). Another study demonstrated a reduced neural activation in the striatal and parietal regions, which was related to implicit learning (Sareen et al., 2007).

A resting-state connectivity study found evidence of an intra-amygdalar abnormality and engagement of a compensatory fronto-parietal executive control network in patients with generalized anxiety disorder (Etkin et al., 2009). Increased mutual influences between the medial orbitofrontal gyrus and amygdala and

* Corresponding author. Fax: +90 212 6351204.
E-mail addresses: rtukel@gmail.com (R. Tükel), dr.aydink@superonline.com (K. Aydın), cagriyuksel@hotmail.com (Ç. Yüksel), erhanert76@yahoo.com (E. Ertekin), ahmet_koyu@hotmail.com (A. Koyuncu), cumhur.tas@uskudar.edu.tr (C. Taş).

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decreased influences from the bilateral inferior temporal gyri to the bilateral amygdala have also been found in patients with SAD (Liao et al., 2010). In another study that was conducted on healthy adults, shyness scores were correlated with increased gray matter volume (GMV) and altered functional connectivity due to increased activity in the cortical and limbic regions involved in processing social stimuli, while no structural or functional connectivity measures correlated with social or trait anxiety (Yang et al., 2013). These studies highlighted the possible aberrant activations in the cortico-limbic pathways and also displayed possible compensatory activations in response to aberrant activities within the cortico-limbic network.

Although such a mechanism may have a crucial role in the course of SAD, limited work in this area has been done to date. The region of interest-based approach and voxel-based morphometry (VBM), which is a systematic morphometric evaluation of the brain as a whole, are two widely-employed methods for the investigation of brain morphometry (Ashburner and Friston, 2001). Accordingly, VBM allows an objective and comprehensive assessment of volumes of gray matter (GM) and white matter (WM) throughout the brain and has been used in exploring the alterations of brain structures in patients with SAD in a few studies (Liao et al., 2011; Meng et al., 2013; Talati et al., 2013; Irle et al., 2014). Although no differences were demonstrated in total cerebral, caudate, putamen and thalamic volumes in an earlier study (Potts et al., 1994), reductions have recently been found in the amygdala and hippocampus volumes (Irle et al., 2010), in the right posterior inferior temporal gyrus, right parahippocampal/hippocampal gyrus (Liao et al., 2011), bilateral thalami, right amygdala, right precuneus (Meng et al., 2013), bilateral temporal poles and left lateral orbitofrontal cortex (Talati et al., 2013) GM volumes of patients with SAD compared with healthy controls. Furthermore, bilateral cortical thinning in the fusiform and post-central regions were also demonstrated (Syal et al., 2012). On the other hand, greater GM volumes have been found in the left parahippocampal, fusiform, middle occipital, bilateral supramarginal and angular cortices, and in the left cerebellum (Talati et al., 2013), and in the precuneus, postcentral gyrus and inferior parietal cortex, as well as in the premotor cortices including the supplementary motor cortex (Irle et al., 2014). In addition, increased cortical thickness has been reported in the left inferior temporal cortex (Frick et al., 2013), and in the left insula, right anterior cingulate, right temporal pole, right dorsolateral prefrontal cortex and right parietal cortex (Brühl et al., 2014) in patients with SAD relative to controls.

Given all of the above, the main objective of this study was to make a contribution to the literature and investigate the GMV differences between drug-free adult patients with SAD and age, sex, handedness and education-matched healthy control group using VBM analysis. As a secondary goal, we aimed to answer whether the severity of SAD and the concurrent levels of anxiety, depression, and disability are related with the observed morphologic brain differences. Specifically, we hypothesized that both a loss and an increase of GM, which may be related to the behavioral symptoms, would be present in patients with SAD.

2. Materials and methods

2.1. Subjects

A total of 27 consecutive patients (15 women and 12 men) with generalized subtype of SAD, who fulfilled Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) diagnostic criteria, and seen in the Outpatient Clinic of the Psychiatry Department of Istanbul Faculty of Medicine, between September 2011 and December 2012, were included in this study. Twenty-seven healthy control subjects who were screened for the absence of psychiatric disorders as well as any family history of psychiatric disorder were recruited on a voluntary basis and were matched to the patients for age and sex. All the patients and controls are right-handed.

Inclusion criteria were (1) SAD diagnosed using the Structured Clinical Interview for DSM-IV/Clinical Version (SCID-I/CV) (First et al., 1997); (2) aged between 18 and 50 years; (3) being medication-free for at least the previous 6 weeks. Exclusion criteria were (1) any current psychiatric disorder other than SAD diagnosed with the SCID-I/CV; (2) history of alcohol or drug abuse/dependence; (3) any serious concomitant general medical condition or neurologic disease; (4) history of medical disorders that may have a causal relationship with SAD; (5) pregnancy or lactation. Exclusion criteria for the patients and control subjects also included any contraindication for magnetic resonance (MR) imaging, alcohol or drug abuse; and any history of neurodegenerative disease, seizure, central nervous system infection, cerebrovascular disease, diabetes mellitus, and head trauma causing loss of consciousness that lasted more than 30 min or that required hospitalization.

Among our patients, 17 (63.0%) were drug-naïve (i.e. they have never used any psychotropic medication); whereas 10 patients were currently unmedicated (37.0%) but had taken different types of antidepressants, with different dosages, before the 6-week drug-free period. Interviews with the patients have revealed that antidepressants had been applied to treat social anxiety or depressive symptoms. Our patients had no lifetime comorbid Axis I disorder according to the SCID-I/CV interview.

The ethics committee of Istanbul University Istanbul Faculty of Medicine approved the study. Written informed consent was obtained from all participants after the procedures had been fully explained. This study adheres to the Declaration of Helsinki.

2.2. Clinical assessment

Diagnosis was made during the initial interview by trained psychiatrists. The Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987), a 24-item scale with 13 items on performance and 11 items on social interactions, the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967) and the Sheehan Disability Scale (SDS) (Sheehan, 1984), a scale consisting of “work”, “social life and leisure activities”, and “family life and home responsibilities” subscales, designed to determine the extent of disability in these respective areas, were administered to the patients during the second interview. A semi-structured interview form prepared by the authors was used to evaluate the demographic features of the subjects.

2.3. MRI data acquisition

Cranial MR imaging studies were performed on a 1.5T superconducting whole-body MR imaging system (Philips Medical Systems; Netherlands) with a standard head coil. High-resolution anatomic images of the whole brain were acquired from the patients and control subjects with a T1-weighted magnetization-prepared rapid acquisition of gradient echo sequence (TR = 11.08 ms, TE = 4 ms, TI = 300 ms, relaxation delay time = 500 ms, FA = 15°, FOV = 256 × 192 mm^2, matrix size = 256 × 192) yielding 128 sagittal sections with a defined voxel size of 1 × 1 × 1.3 mm^3. T2-weighted axial and coronal fluid attenuated inversion recovery (FLAIR) images were also acquired to exclude subjects with having any pathologic finding.