Voxel-based morphometry multi-center mega-analysis of brain structure in social anxiety disorder

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ABSTRACT
Social anxiety disorder (SAD) is a prevalent and disabling mental disorder, associated with significant psychiatric co-morbidity. Previous research on structural brain alterations associated with SAD has yielded inconsistent results concerning the direction of the changes in gray matter (GM) in various brain regions, as well as on the relationship between brain structure and SAD-symptomatology. These heterogeneous findings are possibly due to limited sample sizes. Multi-site imaging offers new opportunities to investigate SAD-related alterations in brain structure in larger samples.

An international multi-center mega-analysis on the largest database of SAD structural T1-weighted 3T MRI scans to date was performed to compare GM volume of SAD-patients (n = 174) and healthy control (HC)-participants (n = 213) using voxel-based morphometry. A hypothesis-driven region of interest (ROI) approach was used, focusing on the basal ganglia, the amygdala-hippocampal complex, the prefrontal cortex, and the parietal cortex. SAD-patients had larger GM volume in the dorsal striatum when compared to HC-participants. This increase correlated positively with the severity of self-reported social anxiety symptoms. No SAD-related differences in GM volume were present in the other ROIs. Thereby, the results of this mega-analysis suggest a role for the dorsal striatum in SAD, but previously reported SAD-related changes in GM in the amygdala, hippocampus, precuneus, prefrontal cortex and parietal regions were not replicated. Our findings

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1. Introduction

Social anxiety disorder (SAD) is one of the most common anxiety disorders (Stein and Stein, 2008), with an estimated lifetime prevalence between 6 and 13 percent (Kessler et al., 2012; Stein et al., 2010). Patients with SAD are characterized by intense fear of, distress in, and avoidance of situations in which they may be scrutinized (American Psychiatric Association, 2013). The disorder is highly disabling, as impairments in social life and work situations are frequently reported (Mack et al., 2015). In addition, the disorder is associated with significant psychiatric co-morbidity, such as depressive disorders and substance abuse (Stein and Stein, 2008). These findings stress the need for improvements in the treatment of SAD. Understanding the neurobiological mechanisms that underlie this disorder has the potential to advance treatment.

Previous magnetic resonance imaging (MRI) studies on brain anatomy differences in SAD have reported heterogeneous findings, implicating regions such as the frontal cortex, the parietal cortex, occipital cortex, temporal regions and subcortical limbic areas, as reviewed by Brühl et al. (2014a); see also Goodkind et al. (2015) reporting on a transdiagnostic meta-analysis of structural neuroimaging studies. Several of these changes were correlated with clinical characteristics, such as the severity of social anxiety symptoms (Brühl et al., 2014b; Frick et al., 2014a; Irle et al., 2014, 2010; Liao et al., 2011; Syal et al., 2012; Talati et al., 2013; Tükel et al., 2015) or disease duration (Meng et al., 2013). In addition, recent treatment studies in SAD-patients have identified structural changes in bilateral caudate and putamen, right thalamus and cerebellum after 8-weeks of paroxetine treatment (Talati et al., 2015) and alterations in parieto-occipital and prefrontal GM volumes after cognitive behavioral group therapy (Steiger et al., 2016), while a classification study using multi-voxel pattern analysis was able to discriminate SAD-patients from healthy control participants based on the pattern of regional gray matter (GM) volume over the whole brain (Frick et al., 2014b). Together, these studies provide evidence for the idea that certain brain regions are clinically associated with SAD.

Functional MRI (fMRI) studies have also identified important candidate brain regions that may be related to structural changes associated with SAD-related psychopathology. These fMRI studies, typically examining brain activity in response to emotional stimuli or in response to cognitive tasks (Brühl et al., 2014a), most consistently point towards an increase of brain activation in SAD in the bilateral amygdala and hippocampus, prefrontal brain regions, bilateral insula, bilateral parietal cortex and bilateral precuneus, while findings on the direction of changes in the basal ganglia are mixed (Brühl et al., 2014a; Cremers and Roelofs, 2016). In addition, studies on functional connectivity, during rest as well as during cognitive tasks (Brühl et al., 2014a), revealed changes in connectivity of, among others, the putamen (Cremers et al., 2015) and the amygdala (Hahn et al., 2011; Pannekoek et al., 2013; Sladky et al., 2015), while recent positron emission tomography (PET) studies showed decreased serotonin receptor binding (Lanzenberger et al., 2007) and increased serotonin synthesis and transporter availability in the hippocampus, amygdala, anterior cingulate cortex (ACC) and striatal regions like the putamen and globus pallidus (Frick et al., 2015; Furnark et al., 2016). These results, together with the findings of a treatment study revealing a relationship between changes in amygdala structure and amygdala function in SAD (Månsson et al., 2016), suggest that the brain regions showing functional changes in SAD overlap to a large extent with the regions that have showed differences in brain structure.

However, the available evidence with respect to structural brain alterations in SAD is inconclusive, as both increases as well as decreases in GM volumes in various brain regions have been reported (Brühl et al., 2014a). Furthermore, findings concerning the relationship between brain structure and SAD-symptoms are inconsistent (Brühl et al., 2014b; Frick et al., 2014a; Irle et al., 2014; Tükel et al., 2015). These heterogeneous results are possibly due to differences in the employed methods, as well as the relatively small sample sizes employed in studies on SAD-related changes in brain structure (ranging from 12 to 67 SAD-patients), and variability in clinical parameters between the samples. Recent advances in multi-site imaging offer new opportunities to investigate the structural brain alterations associated with SAD.

In this international multi-center mega-analysis, which is part of the European and South African Research Network in Anxiety Disorders (EURSANAD) program initiated by the Anxiety Disorders Research Network (Baldwin and Stein, 2012), we investigated GM volume in a-priori defined regions of interest (ROIs) in a sample of 174 SAD-patients and 213 healthy control participants, using an optimized voxel-based morphometry (VBM) protocol (Ashburner and Friston, 2000; Lerch et al., 2017). VBM analyses have the advantage of using unbiased, standardized methods to investigate brain structure, and have been extensively used to investigate alterations in brain morphology across numerous major psychiatric conditions (Ashburner and Friston, 2000; Goodkind et al., 2015). The large sample of the present work provides the best statistical power to date to investigate GM alterations associated with SAD. Data were collected in multiple scan centers located in five countries (Germany, South Africa, Sweden, the Netherlands and the United States of America). Based on the available evidence reviewed above, our analysis focused on changes in GM volume in four a-priori defined ROIs that seem to be most prominently involved in SAD: the basal ganglia, the amygdala-hippocampal complex, the prefrontal cortex and the parietal cortex including the precuneus. Given the mixed findings on SAD-related increases versus decreases in GM in the previous structural MRI studies (Brühl et al., 2014a), we did not make specific predictions about the direction of the changes within these ROIs. Significant results within the ROIs were followed up by regression analyses to investigate the relationship between GM volumes and the severity of social anxiety symptoms within the patient group.

2. Material and methods

2.1. Participants

Structural T1-weighted 3T MRI scans were collected at research centers located in Europe, Africa and North-America, and brought together for quality control and initial analysis in Cape Town, South-Africa. Final analyses took place in Leiden, the Netherlands. The initial sample consisted of 251 SAD-patients and 230 healthy control (HC)-participants (Table 1), and results on these datasets have been published previously (Boehme et al., 2015; Boehme et al., 2014a, 2014b; Cremers et al., 2014; Geiger et al., 2016; Howells et al., 2015; Klump et al., 2016; Månsson et al., 2015; Månsson et al., 2013; Pannekoek et al., 2013; Phan et al., 2013; Syal et al., 2012; van Tol et al., 2010) – see online Supplementary Document 1 for more details on the in- and exclusion criteria and recruitment of participants for each sample. At each site, the local ethical committee approved data-collection and all participants provided written informed consent after the procedure had been fully explained.

Participants (18 years or older) were recruited through public announcements (online and within the community), consumer advocacy
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