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Gray and white matter volume abnormalities in generalized anxiety disorder by categorical and dimensional characterization

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ABSTRACT

Increasing efforts have been made to investigate the underlying pathophysiology of generalized anxiety disorder (GAD), but only limited consistent information is available on gray (GM) and white matter (WM) volume changes in affected adults. Additionally, few studies employed dimensional approaches to GAD pathology. This study compares structural brain imaging data from $n=19$ GAD subjects and $n=24$ healthy comparison (HC) subjects, all medication-free and matched on age, sex and education. Separate categorical and dimensional models were employed using voxel-based morphometry for GM and WM. Significantly higher GM volumes were found in GAD subjects mainly in basal ganglia structures and less consistently in the superior temporal pole. For WM, GAD subjects showed significantly lower volumes in the dlPFC. Largely consistent findings in dimensional and categorical models point toward these structural alterations being reliable and of importance for GAD. While lower volume in the dlPFC could reflect impaired emotional processing and control over worry in GAD, basal ganglia alterations may be linked to disturbed gain and loss anticipation as implicated in previous functional GAD studies. As perturbations in anticipation processes are central to GAD, these areas may warrant greater attention in future studies.

1. Introduction

Generalized anxiety disorder (GAD) is a prevalent (Wittchen et al., 2011; Kessler et al., 2012) and impairing anxiety disorder (Andlin-Sobocki and Wittchen, 2005; Hoffman et al., 2008). Despite growing research on neurobiology (Hilbert et al., 2014), findings on the neuroanatomical correlates of GAD remain inconsistent, possibly due to cross-study differences in methodology. Additionally, limited information is available on dimensional approaches to core GAD symptoms as emphasized in recent clinical, diagnostic and research frameworks (American Psychiatric Association, 2013; Cuthbert, 2014). The current study provides data that complement results from functional investigations and inform theories of GAD etiopathogenesis.

The overall few available studies of the neuroanatomy in GAD did not generate consistent findings. Several studies relied on a region-of-interest (ROI) approach, with different studies targeting different ROIs, limiting the chance for consistent findings. Only four studies used whole-brain approaches to assess GM volume in GAD (Schienle et al., 2011; Liao et al., 2013; Strawn et al., 2013; Moon et al., 2014), with two of these studies investigating adolescents (Liao et al., 2013; Strawn et al., 2013). The remaining two studies in adults did not report comparable findings. To remedy the current lack of replicated findings concerning GM volumes in GAD, more whole brain data are needed. A similar lack of volumetric studies is apparent for white matter (WM). Here, no whole-brain data in adults are yet available. However, investigating these volume changes in WM might prove to be complementary to studies of other indices of WM such as fractional anisotropy.

Among the regions more frequently investigated for structural changes in GAD, only higher GM volumes in the amygdala (Etkin et al., 2009; Schienle et al., 2011) and lower GM volumes in the hippocampus (Abdallah et al., 2013; Moon et al., 2014) have been successfully replicated. However, several other areas have not been investigated sufficiently, although they were prominently included in functional studies on GAD. These include ventral areas of the anterior cingulate cortex (ACC) as well as parts of the dorsomedial

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and dorsolateral prefrontal cortex (PFC), all of which are related to emotion processing and emotion regulation deficits in GAD (Etkin et al., 2010; Paulesu et al., 2010; Etkin and Schatzberg, 2011; Ball et al., 2013), and the basal ganglia, for which especially the putamen has shown altered responses to gain and loss anticipation in GAD (Guyer et al., 2012).

Beyond comparisons of patients and healthy individuals on a categorical group level, increasing emphasis has been placed on a continuous or dimensional conceptualization of psychopathology in recent years. As a result, both the DSM-5 (American Psychiatric Association, 2013) and the Research Domain Criteria framework (e.g., Insel and Cuthbert, 2009; Cuthbert, 2014) feature dimensional approaches to mental disorders. However, research on neural correlates of GAD-related dimensions is limited, although a resting state study by Oathes et al. (2015) already provided information from dimensional approaches to supplement diagnostic group analyses.

Taken together, the aim of the present voxel-based morphometry study was to examine GM and WM tissue in GAD subjects and healthy comparison subjects, using both a dimensional approach, as reflected in ratings of worry severity, and a categorical approach, as reflected in dichotomous GAD diagnosis. Based on the existing literature on both structural and functional changes in GAD, higher GM volumes in the amygdala and putamen and lower GM volumes in the dorsomedial and dorsolateral PFC, hippocampus and ventral ACC were expected for GAD compared with healthy controls. For the dimensional approach, a positive relationship between putamen GM volume and habitual worry severity but a negative relationship between dorsomedial and dorsolateral PFC and ventral ACC GM volumes and habitual worry severity were expected.

2. Methods

2.1. Subjects

The study included $n=19$ adults with GAD and $n=24$ healthy comparison subjects (HC). The following inclusion criteria were used: diagnosis of GAD according to DSM-IV-TR criteria, absence of any lifetime-diagnosis for the healthy comparison group. Exclusion criteria were: MRI-related exclusion, use of any psychotropic medication, a non-remitted diagnosis of substance dependence, or smoking of more than 10 cigarettes per day. All subjects were diagnosed using a standardized interview (Composite International Diagnostic Interview, CIDI; Wittchen and Pfister, 1997). Diagnoses were confirmed by clinical experts. Sixteen of the GAD subjects had at least one comorbid disorder. For detailed information about comorbidities, please refer to supplement A. Habitual worry severity was assessed using the Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990), which has been shown to possess good psychometric properties (Meyer et al., 1990; Brown et al., 1992) and sufficient sensitivity and specificity for discriminating between GAD and other anxiety disorders (Meyer et al., 1990; Fresco et al., 2003). Written informed consent was obtained from all subjects after the study procedures were explained. The study protocol was approved by the local ethics committee (EK13012009).

2.2. Analysis of demographic and clinical data

Demographic and clinical data were analyzed using chi-square tests and independent *t*-tests, respectively. SPSS 22 (IBM, New York, NY, USA) was used for all calculations, with the level of significance being set at $p<0.05$.

2.3. Structural MRI data acquisition and analysis

A 3-Tesla Trio-Tim MRI whole-body scanner (Siemens, Erlangen, Germany) with a 12-channel head coil was used to acquire the structural brain imaging data. Scans were obtained using a magnetization-prepared rapid gradient echo imaging sequence (MPRAGE; 176 sagittal slices, slice thickness=1 mm, echo time=2.26 ms, repetition time=1900 ms, flip angle=9°, field of view=256 × 256 mm, matrix=256 × 256). For preprocessing and analysis of the data, SPM8 (⟨http://www.fil.ion.ucl.ac.uk/spm/software/spm8/⟩) and the VBM8 toolbox (⟨http://dbm.neuro.uni-jena.de/vbm/download/⟩) were used. Anatomical data were segmented into GM, WM and cerebrospinal fluid (CSF), and normalized to Montreal Neurological Institute (MNI) space by the DARTEL algorithm (Ashburner, 2007) implemented in the VBM toolbox. In the process, the spatial resolution of the data was changed to $1.5 \times 1.5 \times 1.5\ mm^3$, and all images were modulated to account for differences in individual total tissue volume. Finally, the segmented, normalized and modulated images were smoothed with an 8 mm full-width half-maximum Gaussian kernel and checked for artifacts.

GM and WM data were analyzed separately, and an absolute image threshold of 0.15 was used for all analyses. Factorial models were used for the whole-brain analysis of group differences, and regression models for the dimensional analysis of habitual worry severity. Both approaches were completely independent from each other; diagnostic group membership was not included in the dimensional model, and PSWQ scores were not included in the categorical model. As there was considerable variance of age in the sample, age was included as a covariate in all analyses to make sure that results would not reflect age-related effects, particularly with regard to the regression analyses. To achieve an optimal balance between sensitivity and specificity and to ensure comparability to previous studies on GAD neuroanatomy, we used two different statistical thresholds for these analyses. Across the main analyses, a cluster-size based threshold for significance with 200 consecutive voxels at $p_{uncorr}<0.001$ as employed previously (e.g. Strawn et al., 2013; Wehry et al., 2015) was used. Additionally, a second analysis with a more conservative threshold using clusterwise FWE at $p_{cFWE}=0.05$ and a voxelwise cluster-forming threshold of $p_{uncorr}<0.001$ was conducted on all significant clusters from the first analysis. Across all calculations, a non-stationarity correction as implemented in SPM8 was applied. As worry and GAD are also closely connected to the concept of intolerance of uncertainty (Dugas et al., 1998), additional regression models were built based on scores of the intolerance of Uncertainty Scale, short version (IUS-12; Carleton et al., 2007).

3. Results

3.1. Demographic and clinical data

Table 1 shows demographic and clinical characteristics of both groups. GAD and HC subjects were well matched regarding all sociodemographic characteristics. As expected, GAD subjects showed elevated scores compared with HC subjects in all clinical characteristics. PSWQ, BDI and IUS scores were highly correlated (PSWQ-BDI: $r=0.778$, $p<0.001$; PSWQ-IUS: $r=0.809$, $p<0.001$; BDI-IUS: $r=0.786$, $p<0.001$). For the subsequent regression analyses, PSWQ and IUS scores were tested for normality using the Shapiro-Wilk test (Shapiro and Wilk, 1965). IUS scores were normally distributed across the whole sample ($p=0.538$), which was not the case for the PSWQ ($p=0.026$; see Fig. 1 for the distributions of these questionnaire scores within each group).

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