Journal of Affective Disorders 215 (2017) 111–117

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Effects of subclinical depression, anxiety and somatization on brain structure in healthy subjects

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ARTICLE INFO

Keywords:
Anxiety
Depression
Prefrontal cortex (PFC)
Somatization
Superior temporal gyrus
Voxel-based morphometry

ABSTRACT

Background: Dimensional approaches in highly prevalent psychiatric disorders like depression or anxiety could lead to a better understanding of pathogenesis and advantages in early detection and prevention. In an effort to better understand associations of brain structural variation across the depression/anxiety spectra, we investigated minor subclinical symptoms in a non-clinical healthy population.

Methods: We studied 177 healthy subjects from the community, who underwent high-resolution T1-weighted 3T MRI and completed the symptom-checklist-90 (SCL-90-R). Using voxel-based morphometry (VBM) analysis with CAT12 software, we correlated SCL-90-R-subscales for depression, anxiety, and somatization with gray matter across the brain.

Results: Significant positive gray matter correlations emerged across all three scales in different areas: the depression subscale correlated positively with gray matter in the Rolandic operculum, superior temporal gyrus (left) and postcentral gyrus (bilateral), the anxiety subscale correlated positively with middle temporal gyrus, Rolandic operculum, middle cingular gyrus and precuneus bilaterally, and the somatization subscale with left inferior prefrontal cortex. Somatization also showed negative correlations with cerebellar vermis and right supplementary motor area.

Limitations: Our study is limited to VBM and does not include surface-based measures. It also only contains subjects with very small psychological distress by partly overlapping symptoms.

Conclusion: Our findings are consistent with a non-linear relationship between symptom severity and cortical volume in several brain areas involved in both emotion regulation as well as altered in clinically manifest depressive/anxiety disorders.

1. Introduction

Categories of psychiatric disorders separating patients from healthy or non-affected subjects have dominated biological research in psychiatry, yet they neglect the dimensional aspect of psychopathology. Such dimensional approaches hypothesize a spectrum ranging from minimal psychopathology in healthy subjects, to those with a higher symptom burden, to people with subclinical phenotypes or prodromal stages, and finally manifest disorders. Thus, dimensional approaches have become equally important for early detection, intervention, and prevention of mental disorders. Current concepts, including those of endophenotypes, generally consider such spectra, yet there is little biological research in subclinical populations (Gottesman and Gould, 2003; Woody and Gibb, 2015).

Affective disorders in particular might show a continuum of severity spanning mild and/or transient sadness or anhedonia towards more severe combinations of symptoms (Benvenuti et al., 2015). So far, it remains unclear whether this clinical continuum is also reflected in a biological continuum (Kircanski et al., 2016). Testing putative biomarkers for their ability to reflect this range of psychopathology might therefore strengthen their use for early symptom detection and biological assessment of validity. Prominent examples for such common subthreshold clinical symptoms are depressive and anxiety-related behaviors, which are highly prevalent in non-clinical populations (Judd et al., 2002). Establishing neuroanatomical markers for early detection could also add to psychiatric diagnosing in general and lead to development of better early intervention or prevention.

So far, only a few studies have specifically investigated the correla-

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http://dx.doi.org/10.1016/j.jad.2017.03.039
Received 1 November 2016; Received in revised form 9 March 2017; Accepted 10 March 2017
Available online 16 March 2017

tion between subclinical symptoms and brain structure, and most of them have focused on a single psychopathological domain. Best evidence still exists for subclinical depressive symptoms through a couple of recent VBM and DTI findings. Previous studies show structural gray and white matter changes (among others) in dorsal anterior cingulate cortex (dACC), insula and ventromedial prefrontal cortex (vmPFC) (Vulser et al., 2015).

Similarly, a study correlating individuals' scores on the Hamilton Anxiety Scale found a significant negative association with dACC gray matter in 121 healthy subjects (Donzuso et al., 2014). Alexithymia, which is a major clinical feature in affective as well as somatization disorder, was also found to correlate negatively with dACC gray matter in a study using the Toronto Alexithymia Scale in 1 685 healthy subjects (Grabe et al., 2014). Another study found increased gray matter volume in parahippocampal gyrus correlating with trait anxiety and somatic complaints in a large healthy sample, suggesting neurobiological similarities between these symptoms (Wei et al., 2015).

Interestingly, some of these brain areas are also affected in clinically manifest disorders, such as MDD, generalized anxiety disorder (GAD) or somatoform disorders (SOM). Most intriguing is the volume decrease in insula and dACC found in a meta-analysis across patients with depression and anxiety, but also in schizophrenia, bipolar, and obsessive-compulsive disorder, thus implicating a common neurobiological substrate of these diseases (Goodkind et al., 2015). A similar network, including dACC and insula, as well as amygdala and hippocampus has been implicated in somatoform disorders (Perez et al., 2015).

In this study, we tested the hypothesis that minor psychopathology in healthy subjects is associated with brain structural variation, thus aiming to extend previous findings to include an analysis across multiple domains of psychopathology. Based on the previous studies cited above, we focused on depression and anxiety as highly prevalent symptoms, as well as somatization (because of the putative anatomical overlap in dACC and its specificity). For this purpose we used a single, commonly applied questionnaire for self-assessment of such symptoms (SCL-90-R). Specifically, we hypothesized that gray matter alterations would be correlated with depressive symptoms in dACC, insula and vmPFC, given their importance for emotion regulation. Furthermore we expected changes in these areas for anxiety and somatoform symptoms, and beyond that in parahippocampal gyrus.

2. Methods

2.1. Subjects

We included 177 subjects (94 female, 83 male; mean age 29.8 yrs, SD 8.9), who were recruited from the community as healthy controls for several ongoing case-control-studies of psychiatric disorders. All participants gave written informed consent to a study protocol approved by the local Ethics Committee of Jena University Medical School.

All subjects were screened for absence of current or previous psychiatric disorders (including substance abuse or dependence), psychiatric or psychotherapeutic treatment, or a first-degree family history of psychotic disorders using a semi-structured interview. For this purpose, subjects first received a telephone screening, followed up by an interview based on the inclusion and exclusion criteria. Further exclusion criteria for the study were: neurological CNS conditions (screening in particular for history of seizures/epilepsy, multiple sclerosis, and degenerative disorders), major internal medical conditions (e.g. uncontrolled hypertension or diabetes), a history of traumatic brain injury/loss of consciousness, and intellectual disability/learning impairment (defined as an IQ lower than 80). IQ was estimated using the MWT-B, a German language inventory similar to the NART, which showed a mean IQ (SD) across subjects of 106.2 (11.5) (Antretter et al., 2013). Subjects also completed the Edinburgh Handedness Inventory (Oldfield, 1971) showing a mean value of 80.4 (SD 20.6).

To assess subclinical occurrence of depressive, anxious, and somatoform symptoms, subjects completed SCL-90-R around the time of scanning, a well established self-rating instrument to assess a broad range of psychopathological symptoms (Derogatis et al., 1976). The SCL-90-R consists of 90 items, to be rated on a 0–4 Likert-type scale, which can then be analysed syndrome-wise with nine different scales. From these, we selected scale 4 depression symptoms within 13 items and scale 5 anxiety symptoms within 10 items, as well as scale 1 summarizing somatization symptoms within 12 items. Dividing the cumulating value of each scale by the number of items we calculated the scale value. Mean values were as follows: depression subscale mean 0.36 (SD 0.436, range 0–3, kurtosis 9.119, skewness 2.585); anxiety subscale: mean 0.21 (SD 0.292, range 0–2, kurtosis 16.247, skewness 3.173), and somatization: mean 0.28 (SD 0.26, range 0–1, kurtosis 4.449, skewness 1.885). Considering the clinical overlap of these symptoms (both at clinical and sub-clinical levels) we checked for inter-correlation of the scales via SPSS 23 software and found them to be significantly correlated ($p < 0.01$, two-tailed Pearson-correlation, $r=0.705$ between depression and anxiety subscale, $r=0.469$ between depression and somatization subscale and $r=0.439$ between anxiety and somatization subscale).

There were no significant correlations of gender with the subscales. Age correlated significantly only with the anxiety subscale ($p < 0.05$, $r=0.172$, two-tailed Pearson-correlation).

2.2. Magnetic resonance imaging (MRI) and voxel-based morphometry (VBM)

All subjects underwent high–resolution T1–weighted MRI on a 3 T Siemens Tim Trio scanner (Siemens, Erlangen, Germany) using a standard quadrature head coil and a MPRAGE sequence (TR 2300 ms, TE 3.03 ms, flip angle 9°, 192 contiguous sagittal slices, in-plane field of view 256 mm, voxel resolution 1×1×1 mm; acquisition time 5:21 min).

For voxel-based morphometry (VBM) analysis, we used the CAT12 toolbox (C. Gaser, Structural Brain Mapping group, Jena University Hospital, Jena, Germany) implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK). All T1-weighted images were corrected for bias – field inhomogeneities, then spatially normalized using the DARTEL algorithm (Ashburner, 2007) and segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) (Ashburner and Friston, 2005). The segmentation process was further extended by accounting for partial volume effects (Tohka et al., 2004), applying adaptive maximum *a posteriori* estimations (Rajapakse et al., 1997) and using a hidden Markov Random Field model (Cuadra et al., 2005). For exclusion of artefacts on the gray–white-matter border (i.e. incorrect voxel classification), we applied an internal gray matter threshold of 0.2. After pre-processing (and in addition to visual checks for artefacts) all scans passed through an automated quality check protocol. Finally, the scans were smoothed with a smoothing kernel of 8 mm (FWHM).

2.3. Statistics

For statistical comparison, we applied the general linear model (GLM) approach implemented in SPM12. We performed three analyses, using separate GLMs for each of the three SCL-90-R scales (depression, anxiety, and somatization) and included total intracranial volume (TIV) as a nuisance variable in each of the three GLMs in order to remove the related variance. We performed whole-brain analyses at a threshold of $p < 0.05$, correcting for multiple comparisons with the false discovery rate – method (FDR) investigating both positive and negative correlation between scale value and gray matter volume. Since both positive and negative correlations have been reported in studies of