

Research paper

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



Bianca Besteher^{a,*}, Christian Gaser^{a,b}, Kerstin Langbein^a, Maren Dietzek^a, Heinrich Sauer^a, Igor Nenadic^{a,c}

^a Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany

^b Department of Neurology, Jena University Hospital, Jena, Germany

^c Department of Psychiatry and Psychotherapy, Philipps-University Marburg/Marburg University Hospital - UKGM, Marburg, Germany

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-subcales 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-

* Corresponding author.

E-mail address: bianca.besteh@med.uni-jena.de (B. Besteher).

<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

0165-0327/ © 2017 Elsevier B.V. All rights reserved.

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

Table 1
Overview of VBM-results correlated to SCL-90-R subscales for depression, anxiety and somatization.

Co-ordinates of maximum voxel	Anatomical region	k (number of voxels)	T	p at peak-level (FDR-corr.)
Depression – positive correlation				
–57; –8; 12	Left Rolandic Operculum, postcentral gyrus, superior temporal cortex	397	<u>5.22</u>	0.011
–22; –76; 26	Left middle and sup. occipital gyrus	74	<u>4.38</u>	0.020
–52; –30; 50	Left postcentral and inf. parietal gyrus	38	<u>4.37</u>	0.020
–12; –64; 54	Left precuneus and sup. Parietal gyrus	11	<u>4.06</u>	0.032
–39; 20; 33	Left middle and inf. frontal gyrus	2	<u>3.96</u>	0.038
–58; –22; 30	Left postcentral gyrus	14	<u>3.96</u>	0.039
57; 14; 2	Right Rolandic operculum and inf. frontal gyrus	6	<u>3.90</u>	0.043
Anxiety – positive correlation				
2; –42; 56	Left and right precuneus, left and right middle cingulate gyrus	842	<u>4.59</u>	0.031
–42; –66; 12	Left middle temporal (and middle occipital) gyrus	95	<u>4.59</u>	0.031
42; –27; 51	Right pre- and postcentral gyrus	628	<u>4.44</u>	0.031
12; –52; 57	Right precuneus	99	<u>4.21</u>	0.031
–40; –50; 45	Left inferior parietal gyrus	99	<u>4.17</u>	0.031
32; –69; 27	Right middle and sup. occipital gyrus	55	<u>4.16</u>	0.031
–57; –8; 14	Left Rolandic operculum, postcentral and superior temporal gyrus	187	<u>4.14</u>	0.031
45; –2; 42	Right precentral gyrus	8	<u>3.93</u>	0.031
–39; 20; 33	Left inferior frontal gyrus	8	<u>3.92</u>	0.031
–32; –40; 45	Left inferior parietal gyrus	3	<u>3.85</u>	0.031
51; 14; 33	Right inferior frontal gyrus	26	<u>3.84</u>	0.031
–26; –78; 26	Left middle and sup. occipital gyrus	92	<u>3.80</u>	0.032
6; 28; 60	Right superior frontal gyrus	8	<u>3.68</u>	0.036
–51; 18; 6	Left inferior frontal gyrus	9	<u>3.52</u>	0.044
Somatization – positive correlation				
–46; 20; 10	Left inferior frontal cortex	203	<u>4.03</u>	p < 0.001, uncorrected
Somatization- negative correlation				
3; –76; –14	Vermis cerebelli	25	<u>3.42</u>	p < 0.001, uncorrected
–2; –16; 70	Left lobulus paracentralis/Right SMA	63	<u>3.42</u>	

subclinical psychopathology and brain structure, we chose to test both positive and negative correlations.

As for the above mentioned correlation between age and the anxiety subscale we also performed the analyses with age as a nuisance variable.

Based on our anatomical hypotheses, we additionally performed an analysis with small volume correction for dACC and insula in both hemispheres applying a mask to the brain wide analysis created using the SPM Neuromorphometrics atlas.

3. Results

We found several clusters with a significant positive correlation of gray matter volume with the depression and anxiety scale values of SCL-90-R, while the somatization showed both positive and negative correlations only at lower uncorrected thresholds (for overview see Table 1).

For the depression subscale we found significant ($p < 0.05$, FDR-corrected) positive correlations in left Rolandic operculum, postcentral gyrus, superior temporal and middle and superior occipital gyrus and several very small clusters all over the cortex (Fig. 1). Correction for age removed some of the effects on cortical volume. Only the largest cluster (coordinates of peak voxel: –57; –8; 12) remained significant after FDR-correction ($p < 0.05$). All other clusters remained significant at an uncorrected level ($p < 0.01$).

For the anxiety subscale we found significant ($p < 0.05$, FDR-corrected) positive correlations with gray matter in left middle and superior temporal and inferior parietal gyrus, paracentral lobule and Rolandic operculum as well as right pre- and postcentral gyrus. In both hemispheres, volume in middle cingulate gyrus, precuneus, and superior and middle occipital gyrus correlated positively with the anxiety score. Again, there were no negative correlations (Fig. 2).

Correction for age also removed some of the effects on cortical volume. All clusters only remained significant at an uncorrected level ($p < 0.01$).

For the somatization subscale derived from SCL-90-R we found not

significant correlations at $p < 0.05$ FDR-corrected, but some correlations at an uncorrected $p < 0.001$ threshold: a positive correlation of gray matter in a left-hemispheric inferior frontal cluster and negative correlations in cerebellar, left paracentral and right supplementary motor areas (Figs. 3 and 4). Under correction for age as a nuisance variable, no significant clusters survived.

Small volume correction for dACC and insula in both hemispheres did not show significant correlations with any of the three SCL-90-R scales.

Finally, based on the non-linear distribution of the depression, anxiety and somatization scales (Kolmogorov-Smirnov-Test for distribution $p < 0.05$ for all three scales, thus indicating deviance from a normal distribution), we performed additional analyses for all main clusters (clusters larger than the expected cluster size) of the three analysis sets; for these clusters, we extracted the mean gray matter values and performed a non-parametric Spearman correlation in SPSS. In all cases, the correlations were again significant ($p < 0.01$ for each cluster).

4. Discussion

Our study shows a distributed pattern of gray matter alterations in several brain areas in subclinical depressive, anxious and somatoform symptoms, mostly in left-hemispheric pre- and postcentral areas, as well as superior temporal clusters overlapping across the three symptom dimensions.

4.1. Gray matter increase correlated with mild depressive symptoms

In contrast to some previous studies we did not find negative correlations with gray matter volume (GMV) in dACC, but a positive association between gray matter in pre- and postcentral gyri and left superior temporal cortex with higher scale values for depressive symptoms in healthy subjects. In the existing studies on smaller samples of subclinically depressed individuals, only one showed volume reduction in superior temporal cortex – among other areas

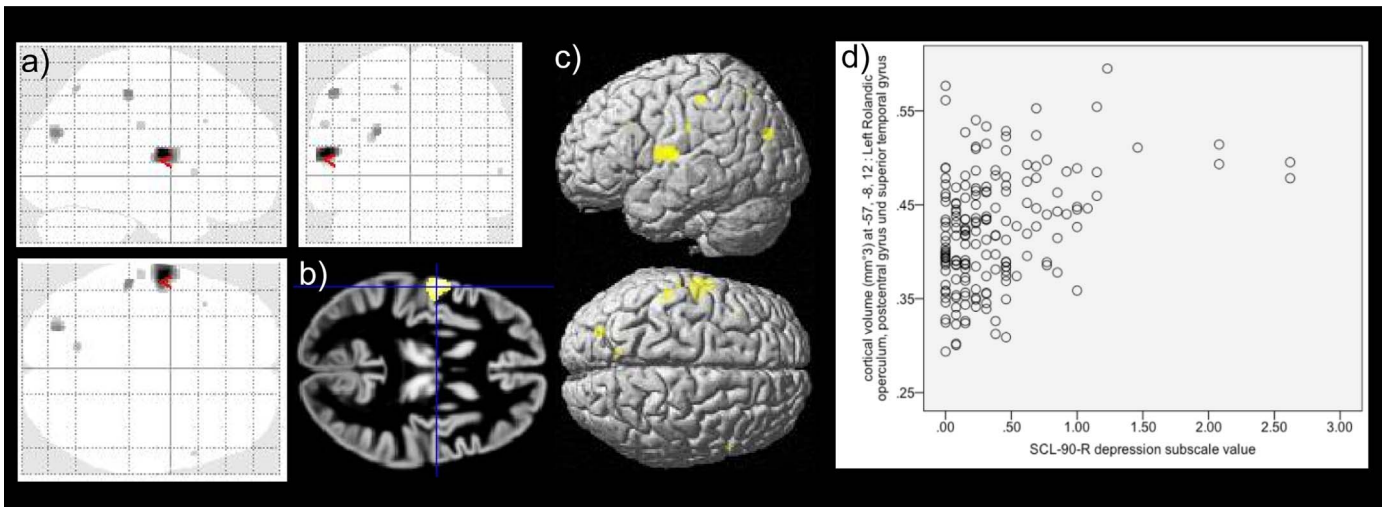


Fig. 1. Clusters of positive correlation of SCL-90-subscale for depressive symptoms with cortical volume ($p < 0.05$, FDR-corrected), presented as a) maximum intensity projection (MIP) – gray areas indicating a significant positive correlation, b) sections overlay on the sample's average image (yellow area indicating biggest cluster of significant positive correlation) and c) render overlay on a canonical surface (yellow areas indicating significant positive correlations); d) Scatter plot showing correlation between mean cortical volume of the biggest significant cluster and the depression subscale values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

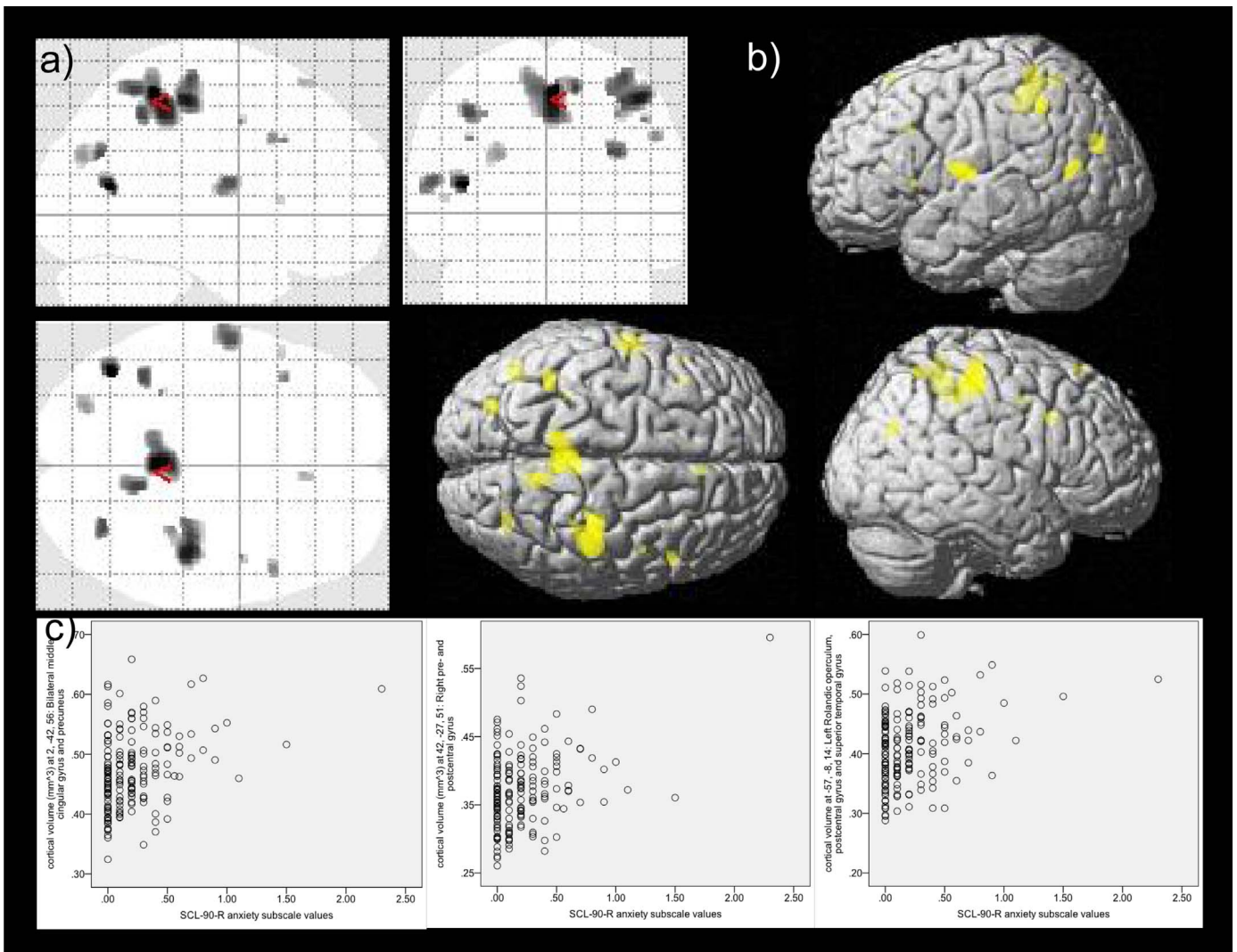


Fig. 2. Clusters of positive correlation of SCL-90-subscale for anxiety symptoms with cortical volume ($p < 0.05$, FDR-corrected), presented as a) maximum intensity projection (MIP) – gray areas indicating a significant positive correlation and b) render overlay on a canonical surface (yellow areas indicating significant positive correlations), c) Scatter plots showing correlation between mean cortical volume of the biggest significant clusters and the anxiety subscale values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

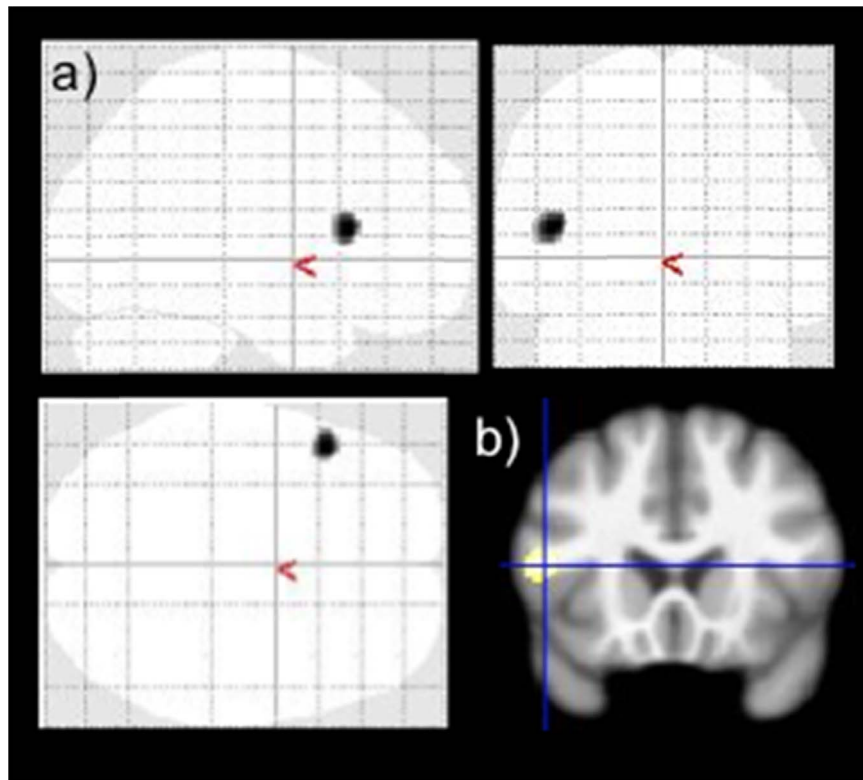


Fig. 3. Clusters of negative correlation of SCL-90-subscale for somatoform symptoms with cortical volume ($p < 0.001$ uncorr.), presented as a) maximum intensity projection (MIP) – black areas indicating a significant negative correlation and b) coronal overlay on the sample's average image (yellow area indicating significant negative correlation). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(orbitofrontal cortex, anterior cingulate, thalamus, temporal pole and superior frontal gyrus) (Webb et al., 2014), applying criteria for subthreshold depression and somewhat higher levels of psychopathology and distress than in our study. Other studies on subthreshold

depression revealed gray matter loss in subclinically depressed women in bilateral ACC and right rectal gyrus (Hayakawa et al., 2013) and decreased GMV in the right inferior parietal lobule, as well as increased GMV in the amygdala, posterior cingulate cortex, and precuneus (Li

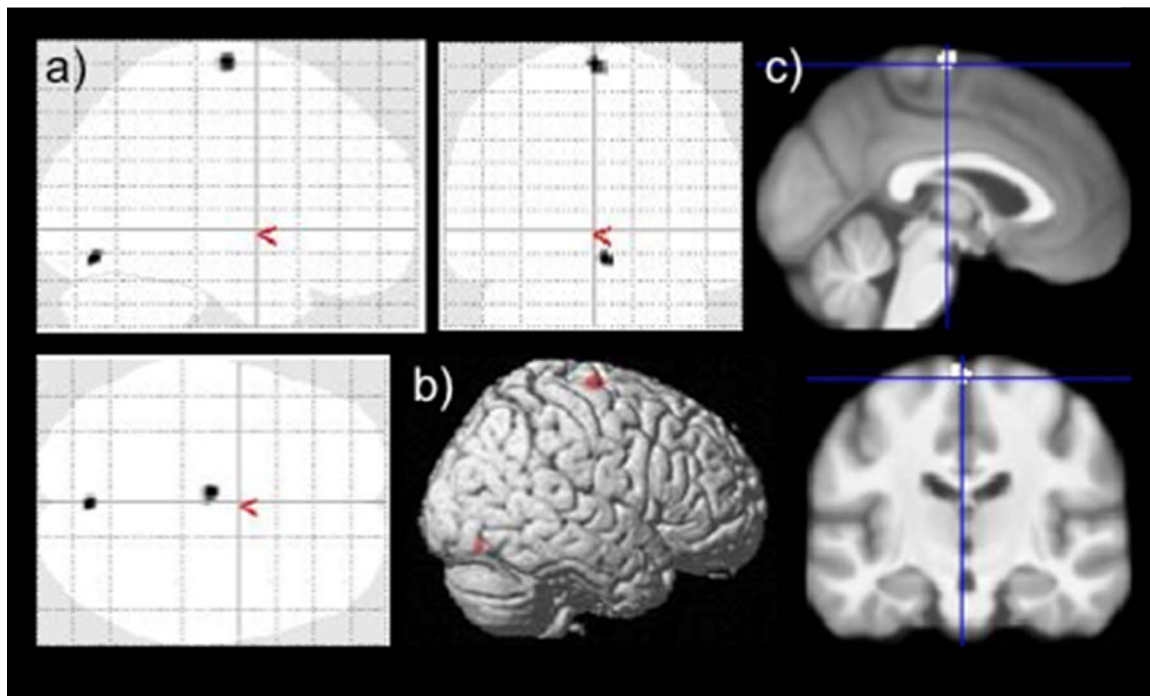


Fig. 4. Clusters of positive correlation of SCL-90-subscale for somatoform symptoms with cortical volume ($p < 0.001$ uncorr.), presented as a) maximum intensity projection (MIP) – black areas indicating a significant positive correlation, b) render overlay on a canonical surface (red areas indicating significant positive correlation) and c) sagittal and coronal overlay on the sample's average image (white areas marked by a blue crosshair indicating significant positive correlation). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

et al., 2015). However, patients with Huntington's disease and subthreshold depression had no differences in cortical volume compared to healthy controls (Sprenghelmeyer et al., 2014).

One study in 298 healthy subjects showed a positive correlation between gray matter volume of parahippocampal gyrus and negative automatic thoughts, which are an important psychopathological feature of major depressive disorder (MDD) (Du et al., 2015). Another analysis showed lower volumes of dorsal medial prefrontal cortex in subclinically depressed men (but not women), an area significantly associated with manifest MDD (Carlson et al., 2015). Recent studies appear inconsistent: while a study on healthy elderly found a positive association with posterior and trend-level association with anterior cingulate volumes (McLaren et al., 2016), a most recent study in a large cohort did not find dACC to be related to sub-threshold depressive symptoms (Allan et al., 2016).

Given the previous interest in the role of dACC and insula in major depression, one main finding of our study is the lack of significant effects in these regions, even when applying a small volume correction approach. Thus, our findings do not suggest that these areas are significant for low-level psychopathology in the absence of manifest disorder, at least in young to middle-aged healthy subjects.

Associations between minimal or subthreshold symptoms appear to overlap only partially with those seen in manifest depression. A meta-analysis on first-episode-depression showed GMV decrease in right SMA, middle temporal cortex and left insula. Several previous analyses were conducted on patients with a longer history of illness with different therapeutic procedures, suicide attempts etc., and regularly identify gray matter volume reduction in prefrontal cortex (PFC) (including the dorsolateral, medial and ventrolateral PFC and orbitofrontal cortex) as well as limbic areas (such as the hippocampus, amygdala and ACC) (Lener and Iosifescu, 2015). They therefore support the model of a disturbance in the frontotemporal network of emotion regulation in manifest depression. Our results, however, suggest other areas to be involved in subclinical depressive symptoms and related symptoms, given that both our and other studies show GMV to be positively correlated with symptom severity. Considering subclinical depressive symptoms risk symptoms for development of MDD as suggested by other groups through their epidemiological and functional findings (Akiskal et al., 1997; Davidson et al., 2015), there seems to be an underlying complex pathogenetic mechanism, which is poorly understood.

4.2. Gray matter increase in subjects with anxiety

Minimal subclinical anxiety symptoms in our healthy sample had an effect on several cortical areas, again solely positive correlations with GMV. In contrast to depressive symptoms, imaging studies on subclinical anxiety in healthy subjects are scarce. One study suggested a negative correlation of dACC gray matter with HARS score (Donzuso et al., 2014). Covering minor psychopathology in the anxiety spectrum in healthy individuals, there are two studies revealing positive correlations of GMV and simultaneously higher activity between a couple of regions (cerebellum, bilateral superior temporal gyri and parahippocampal gyri, right insula, frontal, precentral and inferior parietal gyri, precuneus) associated with higher shyness (Yang et al., 2013), as well as lower GMV in the posterior cingulate cortex/precuneus and higher GMV in the inferior temporal gyrus correlated with rejection sensitivity (Sun et al., 2014).

Categorical comparisons of anxiety disorder patients with healthy controls indeed show reductions in several of these cortical areas. Patients with generalized anxiety disorder (GAD) compared to healthy controls showed gray matter volume decrease in bilateral pre- and postcentral cortices (Makovac et al., 2016), while another study found decreased volume in left orbital and posterior cingulate gyrus and increased volume in right precuneus and precentral gyrus (Strawn et al., 2013). Other findings on social anxiety disorder (SAD) show

various gray matter alterations in patients including negative correlations of GMV in amygdala and insula (Kawaguchi et al., 2016), precuneus, postcentral gyrus and inferior parietal cortex, premotor cortices including the SMA (Irle et al., 2014), as well as positive correlations in occipital areas (Frick et al., 2014). A meta-analysis covering several anxiety disorders reports GMV increase in the right DLPFC, reduced volume in left middle temporal and right precentral gyri (Shang et al., 2014).

Taken together, studies in both subclinical and clinical anxiety do not suggest a linear continuum of brain structural changes, but rather differential correlations across multiple brain regions, diverging between healthy vs. clinical populations.

4.3. Gray matter alterations in subjects with somatoform symptoms

Even fewer studies exist on brain imaging in somatization disorder or single somatoform symptoms in otherwise healthy subjects. Our results are therefore the first to establish a positive correlation of GMV with higher somatization subscale scores for left inferior frontal cortex and a negative correlation in the right SMA, left paracentral lobule and cerebellar vermis.

One study in healthy subjects found higher GMV in parahippocampal gyrus associated with more somatic complaints, but also positively correlated with trait-anxiety (Wei et al., 2015). Investigating somatization disorders caudate volume was increased in patients compared to healthy subjects (Hakala et al., 2004). There is also some support from functional imaging studies. Small samples of patients with somatoform disorders showed lower activation in fMRI in bilateral parahippocampal gyrus, left amygdala, left postcentral gyrus, left superior temporal gyrus, left posterior insula, and bilateral cerebellum performing empathy-based tasks (de Greck et al., 2012) and hypoperfusion in cerebellum, frontal, prefrontal, and temporoparietal areas (Garcia-Campayo et al., 2001). Additional larger samples are needed to investigate these phenomena in somatization disorders.

4.4. Limitations

A few limitations of our study need to be considered. While VBM is a well-established and widely used method, it does not assess particular surface-based measure relating to cortical folding or surface area. Yet, it is most comparable to the previous studies using a similar approach. Given that the mean values of the three SCL-90-R scales were low in our sample, our analysis focuses on the lower sector of the symptom severity spectrum, resulting in weaker effects despite considerable sample size. Also, scales are correlated with each other, which is expected given the biological and clinical overlap of these spectra (Benvenuti et al., 2015; Grillo, 2016; Kircanski et al., 2016; Langenecker et al., 2014). Our statistical approach in this study was to analyze these three major psychopathological domains in separate GLMs. It might be argued that an alternative approach incorporating all three subscales in our GLM and then performing correlations for each of the scales while removing variance related to the other two scales might be more specific. Given the high rates of co-occurrence of these symptoms both at clinical and sub-clinical levels, the latter approach might result in removal of variance essentially linked to core features of each subscale; this, however, might result in findings reflecting only a part of the phenotype and might thus introduce more limitations than advantages. Future studies might expand sample sizes even further, and contrast subgroups within the subclinical spectrum, and patients with higher distress and/or patients with manifest disorders. This might also allow the assessment of non-linear effects across a broader spectrum of severity of symptoms. As pointed out, our findings include many positive correlations, which points to the fact that the relation of symptoms to brain structure might not be linear across the entire spectrum. Also, it might be possible that factors related to compensation of liability might be important, but it is

unclear whether these might be stronger in the subclinical parts of the phenotype spectrum.

Our results clearly show that associations in brain structure are to be found in healthy individuals with subclinical depressive, anxious and somatoform symptoms, partly in areas critical for emotion regulation, which are also affected in manifest disorders. Further studies on this matter could therefore shed light on the (patho)genesis of these symptoms and the similarities to manifest diseases, possibly in order to predict an individuals state of risk.

Acknowledgments

This study was in part funded by a Junior Scientist Grant of the Friedrich-Schiller-University of Jena (to I.N.; grant 21007087). We are grateful to all our student research assistants for their help with this study.

References

- Akiskal, H.S., Judd, L.L., Gillin, J.C., Lemmi, H., 1997. Subthreshold depressions: clinical and polysomnographic validation of dysthymic, residual and masked forms. *J. Affect. Disord.* 45, 53–63.
- Allan, C.L., Sexton, C.E., Filippini, N., Topiwala, A., Mahmood, A., Zsoldos, E., Singh-Manoux, A., Shipley, M.J., Kivimaki, M., Mackay, C.E., Ebmeier, K.P., 2016. Sub-threshold depressive symptoms and brain structure: a magnetic resonance imaging study within the Whitehall II cohort. *J. Affect. Disord.* 204, 219–225.
- Antretter, E., Dunkel, D., Haring, C., 2013. The assessment of cognitive abilities in psychiatric patients: are widely used psychological tests still up-to-date*. *Psychiatr. Prax.* 40, 120–129.
- Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. *NeuroImage* 38, 95–113.
- Ashburner, J., Friston, K.J., 2005. Unified segmentation. *NeuroImage* 26, 839–851.
- Benvenuti, A., Miniati, M., Callari, A., Giorgi Mariani, M., Mauri, M., Dell'Osso, L., 2015. Mood spectrum model: evidence reconsidered in the light of DSM-5. *World J. Psychiatry* 5, 126–137.
- Carlson, J.M., Depetro, E., Maxwell, J., Harmon-Jones, E., Hajcak, G., 2015. Gender moderates the association between dorsal medial prefrontal cortex volume and depressive symptoms in a subclinical sample. *Psychiatry Res.* 233, 285–288.
- Cuadra, M.B., Cammoun, L., Butz, T., Cuisenaire, O., Thiran, J.P., 2005. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. *IEEE Trans. Med. Imaging* 24, 1548–1565.
- Davidson, S.K., Harris, M.G., Dowrick, C.F., Wachtler, C.A., Pirkis, J., Gunn, J.M., 2015. Mental health interventions and future major depression among primary care patients with subthreshold depression. *J. Affect. Disord.* 177, 65–73.
- Derogatis, L.R., Rickels, K., Rock, A.F., 1976. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br. J. Psychiatry* 128, 280–289.
- Donzuso, G., Cerasa, A., Gioia, M.C., Caracciolo, M., Quattrone, A., 2014. The neuroanatomical correlates of anxiety in a healthy population: differences between the state-trait Anxiety inventory and the Hamilton Anxiety Rating scale. *Brain Behav.* 4, 504–514.
- Du, X., Luo, W., Shen, Y., Wei, D., Xie, P., Zhang, J., Zhang, Q., Qiu, J., 2015. Brain structure associated with automatic thoughts predicted depression symptoms in healthy individuals. *Psychiatry Res.* 232, 257–263.
- Frick, A., Engman, J., Alaie, I., Bjorkstrand, J., Faria, V., Gingnell, M., Wallenquist, U., Agren, T., Wahlstedt, K., Larsson, E.M., Morell, A., Fredrikson, M., Furmark, T., 2014. Enlargement of visual processing regions in social anxiety disorder is related to symptom severity. *Neurosci. Lett.* 583, 114–119.
- Garcia-Campayo, J., Sanz-Carrillo, C., Baringo, T., Ceballos, C., 2001. SPECT scan in somatization disorder patients: an exploratory study of eleven cases. *Aust. N. Z. J. Psychiatry* 35, 359–363.
- Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., Grieve, S.M., Galatzer-Levy, I., Fox, P.T., Etkin, A., 2015. Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* 72, 305–315.
- Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* 160, 636–645.
- Grabe, H.J., Wittfeld, K., Hegenscheid, K., Hosten, N., Lotze, M., Janowitz, D., Volzke, H., John, U., Barnow, S., Freyberger, H.J., 2014. Alexithymia and brain gray matter volumes in a general population sample. *Hum. Brain Mapp.* 35, 5932–5945.
- de Greck, M., Scheidt, L., Bolter, A.F., Frommer, J., Ulrich, C., Stockum, E., Enzi, B., Tempelmann, C., Hoffmann, T., Han, S., Northoff, G., 2012. Altered brain activity during emotional empathy in somatoform disorder. *Hum. Brain Mapp.* 33, 2666–2685.
- Grillo, L., 2016. A possible role of anhedonia as common substrate for depression and anxiety. *Depress. Res. Treat.* 2016, 1598130.
- Hakala, M., Karlsson, H., Kurki, T., Aalto, S., Koponen, S., Vahlberg, T., Niemi, P.M., 2004. Volumes of the caudate nuclei in women with somatization disorder and healthy women. *Psychiatry Res.* 131, 71–78.
- Hayakawa, Y.K., Sasaki, H., Takao, H., Mori, H., Hayashi, N., Kunimatsu, A., Aoki, S., Ohtomo, K., 2013. Structural brain abnormalities in women with subclinical depression, as revealed by voxel-based morphometry and diffusion tensor imaging. *J. Affect. Disord.* 144, 263–268.
- Irle, E., Barke, A., Lange, C., Ruhlleder, M., 2014. Parietal abnormalities are related to avoidance in social anxiety disorder: a study using voxel-based morphometry and manual volumetry. *Psychiatry Res.* 224, 175–183.
- Judd, L.L., Schettler, P.J., Akiskal, H.S., 2002. The prevalence, clinical relevance, and public health significance of subthreshold depressions. *Psychiatr. Clin. N. Am.* 25, 685–698.
- Kawaguchi, A., Nemoto, K., Nakaaki, S., Kawaguchi, T., Kan, H., Arai, N., Shiraishi, N., Hashimoto, N., Akechi, T., 2016. Insular volume reduction in patients with social anxiety disorder. *Front. Psychiatry* 7, 3.
- Kircanski, K., LeMoult, J., Ordaz, S., Gotlib, I.H., 2016. Investigating the nature of co-occurring depression and anxiety: comparing diagnostic and dimensional research approaches. *J. Affect. Disord.*
- Langenecker, S.A., Jacobs, R.H., Passarotti, A.M., 2014. Current neural and behavioral dimensional constructs across mood disorders. *Curr. Behav. Neurosci. Rep.* 1, 144–153.
- Lener, M.S., Iosifescu, D.V., 2015. In pursuit of neuroimaging biomarkers to guide treatment selection in major depressive disorder: a review of the literature. *Ann. N. Y. Acad. Sci.* 1344, 50–65.
- Li, H., Wei, D., Sun, J., Chen, Q., Zhang, Q., Qiu, J., 2015. Brain structural alterations associated with young women with subthreshold depression. *Sci. Rep.* 5, 9707.
- Makovac, E., Meeten, F., Watson, D.R., Garfinkel, S.N., Critchley, H.D., Ottaviani, C., 2016. Neurostructural abnormalities associated with axes of emotion dysregulation in generalized anxiety. *NeuroImage Clin.* 10, 172–181.
- McLaren, M.E., Szymkowicz, S.M., O'Shea, A., Woods, A.J., Anton, S.D., Dotson, V.M., 2016. Dimensions of depressive symptoms and cingulate volumes in older adults. *Transl. Psychiatry* 6, e788.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Perez, D.L., Barsky, A.J., Vago, D.R., Baslet, G., Silbersweig, D.A., 2015. A neural circuit framework for somatosensory amplification in somatoform disorders. *J. Neuropsychiatry Clin. Neurosci.* 27, e40–e50.
- Rajapakse, J.C., Giedd, J.N., Rapoport, J.L., 1997. Statistical approach to segmentation of single-channel cerebral MR images. *IEEE Trans. Med. Imaging* 16, 176–186.
- Shang, J., Fu, Y., Ren, Z., Zhang, T., Du, M., Gong, Q., Lui, S., Zhang, W., 2014. The common traits of the ACC and PFC in anxiety disorders in the DSM-5: meta-analysis of voxel-based morphometry studies. *PLoS One* 9, e93432.
- Sprengelmeyer, R., Orth, M., Muller, H.P., Wolf, R.C., Gron, G., Depping, M.S., Kassubek, J., Justo, D., Rees, E.M., Haider, S., Cole, J.H., Hobbs, N.Z., Roos, R.A., Durr, A., Tabrizi, S.J., Sussmuth, S.D., Landwehrmeyer, G.B., 2014. The neuroanatomy of subthreshold depressive symptoms in Huntington's disease: a combined diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) study. *Psychol. Med.* 44, 1867–1878.
- Strawn, J.R., Wehry, A.M., Chu, W.J., Adler, C.M., Eliassen, J.C., Cerullo, M.A., Strakowski, S.M., Delbello, M.P., 2013. Neuroanatomic abnormalities in adolescents with generalized anxiety disorder: a voxel-based morphometry study. *Depress Anxiety* 30, 842–848.
- Sun, J., Li, H., Li, W., Wei, D., Hitchman, G., Zhang, Q., Qiu, J., 2014. Regional gray matter volume is associated with rejection sensitivity: a voxel-based morphometry study. *Cogn. Affect. Behav. Neurosci.* 14, 1077–1085.
- Tohka, J., Zijdenbos, A., Evans, A., 2004. Fast and robust parameter estimation for statistical partial volume models in brain MRI. *NeuroImage* 23, 84–97.
- Vulser, H., Lemaitre, H., Artiges, E., Miranda, R., Penttila, J., Struve, M., Fadaï, T., Kappel, V., Grimmer, Y., Goodman, R., Stringaris, A., Poustka, L., Conrod, P., Frouin, V., Banaschewski, T., Barker, G.J., Bokde, A.L., Bromberg, U., Buchel, C., Flor, H., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Lawrence, C., Loth, E., Mann, K., Nees, F., Paus, T., Pausova, Z., Rietschel, M., Robbins, T.W., Smolka, M.N., Schumann, G., Martinot, J.L., Paillere-Martinot, M.L., Consortium, I., com, I.Cwi-e., 2015. Subthreshold depression and regional brain volumes in young community adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* 54, 832–840.
- Webb, C.A., Weber, M., Mundy, E.A., Killgore, W.D., 2014. Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of mild depressive symptoms: a voxel-based morphometric analysis. *Psychol. Med.* 44, 2833–2843.
- Wei, D., Du, X., Li, W., Chen, Q., Li, H., Hao, X., Zhang, L., Hitchman, G., Zhang, Q., Qiu, J., 2015. Regional gray matter volume and anxiety-related traits interact to predict somatic complaints in a non-clinical sample. *Soc. Cogn. Affect. Neurosci.* 10, 122–128.
- Woody, M.L., Gibb, B.E., 2015. Integrating NIMH research domain criteria (RDoC) into depression research. *Curr. Opin. Psychol.* 4, 6–12.
- Yang, X., Kendrick, K.M., Wu, Q., Chen, T., Lama, S., Cheng, B., Li, S., Huang, X., Gong, Q., 2013. Structural and functional connectivity changes in the brain associated with shyness but not with social anxiety. *PLoS One* 8, e63151.