RESEARCH ARTICLE

A dimensional approach to determine common and specific neurofunctional markers for depression and social anxiety during emotional face processing

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Abstract

Major depression disorder (MDD) and anxiety disorder are both prevalent and debilitating. High rates of comorbidity between MDD and social anxiety disorder (SAD) suggest common pathological pathways, including aberrant neural processing of interpersonal signals. In patient populations, the determination of common and distinct neurofunctional markers of MDD and SAD is often hampered by confounding factors, such as generally elevated anxiety levels and disorder-specific brain structural alterations. This study employed a dimensional disorder approach to map neurofunctional markers associated with levels of depression and social anxiety symptoms in a cohort of 91 healthy subjects using an emotional face processing paradigm. Examining linear associations between levels of depression and social anxiety, while controlling for trait anxiety revealed that both were associated with exaggerated dorsal striatal reactivity to fearful and sad expression faces respectively. Exploratory analysis revealed that depression scores were positively correlated with dorsal striatal functional connectivity during processing of fearful faces, whereas those of social anxiety showed a negative association during processing of sad faces. No linear relationships between levels of depression and social anxiety were observed during a facial-identity matching task or with brain structure. Together, the present findings indicate that dorsal striatal neurofunctional alterations might underlie aberrant interpersonal processing associated with both increased levels of depression and social anxiety.

KEYWORDS

biomarker, depression, face emotion, putamen, social anxiety, trait

1 | INTRODUCTION

Major depression disorder (MDD) and anxiety disorders have high estimated lifetime prevalence rates of 16.6% and 12.1% respectively, and are a major cause of distress both for patients and their families (Adams, Balbuena, Meng, & Asmundson, 2016; Kessler et al., 2003, 2005). Epidemiological data indicates high rates of comorbidity

between MDD and anxiety disorders (Adams et al., 2016; Kessler, Stang, Wittchen, Stein, & Walters, 1999), particularly social anxiety disorder (SAD) (Adams et al., 2016; Chavira, Stein, Bailey, & Stein, 2004; Ohayon and Schatzberg, 2010). Such comorbidities suggest that they share common vulnerabilities and pathways (Langer and Rodebaugh, 2014), including genetic influences (Kendler et al., 2011), personality traits (Bienvenu, Hettema, Neale, Prescott, & Kendler, 2007), and affective-cognitive symptoms, that is, biased emotional processing and poor social functioning (Ladouceur et al., 2005; Wells and Carter, 2002).

On the symptomatic level, both MDD and SAD are characterized by impaired decoding of interpersonal affective-cognitive signals, which

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has been associated with poor social functioning, and might constitute an etiological factor contributing to the development and maintenance of both disorders (Demenescu, Kortekaas, den Boer, & Aleman, 2010). Across both disorders, aberrant, often negatively biased, processing of facial expressions has been consistently reported (Bourke, Douglas, & Porter, 2010; Gilboa-Schechtman, Foa, Vaknin, Marom, & Hermesh, 2008; Gilboa-Schechtman, Foa, & Amir, 1999; Pishyar, Harris, & Menzies, 2004).

Notably, previous findings on emotional face processing in MDD and SAD suggest an emotion-specific negative processing bias in both disorders. Whereas both are characterized by increased interpersonal sensitivity for, and a response bias toward, angry facial expressions, MDD has been associated with an enhanced vigilance and selective attention for sad facial expressions (Bourke et al., 2010; Stuhmann, Suslow, & Dannlowski, 2011). However, the few studies that directly compared facial emotion processing in MDD and SAD patients suggest a more complex picture, with MDD patients displaying a higher sensitivity for sad expressions and a higher identification bias for both angry and happy expressions, while SAD patients display a stronger response bias for sad faces (Gilboa-Schechtman et al., 2008; Joormann and Gotlib, 2006).

In accordance with the common and distinct facial emotion processing alterations on the behavioral level, recent meta-analyses of functional imaging studies on altered neural emotional face processing comparing separate samples of MDD and SAD with healthy controls have revealed both overlapping and disorder-specific networks. Meta-analytic data in SAD has revealed increased neural activity in the amygdala, globus pallidus, hippocampal and temporal regions, and the prefrontal and anterior cingulate cortex (Binelli et al., 2014; Gentili et al., 2016; Hattingh et al., 2013). Similar analyses in MDD have most consistently reported increased activity in striatal, including globus pallidus, and limbic, particularly amygdala and hippocampal, regions and decreased frontal and anterior cingulate activity (Delvecchio et al., 2012; Fitzgerald, Laird, Maller, & Daskalakis, 2008; Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013; Lai, 2014; Palmer, Crewther, & Carey, 2015). Together, the available neuroimaging data suggest common alterations in striatal and limbic regions as well as distinct, disorder-specific, alterations in prefrontal regions during emotional processing. Notably, emotional valence including face emotions has been shown to play an important role in modulating these neural abnormalities in both disorders (Groenewold et al., 2013; Hattingh et al., 2013).

Some initial studies have directly compared SAD and MDD patients to determine common and disorder-specific neural markers. Given the high comorbidity between the disorders, a common methodological approach in this context is the comparison of patients with either MDD or SAD with a comorbid group exhibiting both disorders. For example, one study employing this approach reported that MDD plus SAD patients could be specifically characterized by alterations in the middle cingulate cortex and precentral gyrus (less activity in MDD alone and more in SAD alone) and the posterior cingulate cortex (more activity in MDD alone and less in SAD alone) (Vaughn, Hamilton, Chen, Joormann, & Gotlib, 2012).

However, the identification of common and distinct neurofunctional markers for the two disorders is often hampered by serious confounding factors inherent in patient-based studies such as medication, complex interactions between co-morbid disorders, and disorder-specific brain structural alterations (van Tol et al., 2010). These issues have led researchers to argue that traditional patient-based research strategies alone might not reveal valid biomarkers and encouraged the development of dimensional disorder conceptualizations such as the Research Domain Criteria (RDoC) framework (Cuthbert, 2014; Insel et al., 2010; Sanislow et al., 2010; Wakschlag et al., 2015).

Against this background, the present study employed a dimensional approach assessing individual variations in the levels of depression and social anxiety in healthy subjects to determine common and specific functional MRI-based neural markers for MDD and SAD while controlling for a range of important confounders inherent in patient studies, such as medication. To this end, associations between levels of depression and social anxiety with fMRI-based neural activity and connectivity were investigated during explicit emotional face processing in a large sample ($n = 91$) of healthy subjects. To facilitate the determination of distinct neurofunctional markers, trait anxiety was controlled for as it represents a stable general anxiety marker across different domains with a strong involvement in both depression and social anxiety (Anagnostou et al., 2012). Moreover, recent studies even found that depression biomarkers overlapped with those for generalized anxiety disorder (Drysdale et al., 2017; Wager and Woo, 2017). To further control for potential confounding effects of associations between levels of depression or social anxiety with simple face recognition, participants additionally underwent a face and house matching fMRI paradigm. Finally, to account for potential associations between the disorder-relevant dimensions and brain structure a voxel-based morphometry (VBM) analysis was conducted. Based on previous meta-analytic findings in MDD and SAD patients, we expected that higher levels of depression and social anxiety would be associated with emotion processing-related increases of neural reactivity in limbic and striatal regions and differential alterations in prefrontal responses.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 92 healthy, young right-handed Chinese (Han) students (47 males; age range = 18–27 years; $M \pm SD = 21.68 \pm 2.22$ years) participated in the study after providing written informed consent. All volunteers reported no history of medical, neurological, or psychiatric disorders, and no history of head injury as well as frequent drug, cigarette or alcohol use and were free of MRI contraindications. This study was approved by the local Ethics Committee at the University of Electronic Science and Technology of China (UESTC), and conformed to the latest revision of the Declaration of Helsinki.

TABLE 1 Group characteristics of subject age and questionnaire scores in this study ($N = 91$) and from the lab database for structural data analysis ($N = 234$)

Variables	$N = 91$		$N = 234$	
	Mean	SD	Mean	SD
Age (years)	21.69	2.24	21.65	2.13
State-Trait Anxiety Inventory (STAI)				
Trait	40.76	7.86	39.93	7.54
State	38.87	8.46	\	\
Liebowitz Social Anxiety Scale (LSAS)	45.25	20.52	51.18	23.53
Fear/anxiety	24.03	11.15	26.97	12.58
Avoidance	21.22	10.95	24.28	12.13
Beck Depression Inventory (BDI-II)	7.03	6.43	6.36	5.42

Note. SD, standard deviation.

2.2 | Measurements

To test associations between brain structure, neural activity and pathology relevant symptom dimensions, levels of depression, social anxiety, and trait anxiety were assessed using validated Chinese versions of the Beck Depression Inventory, BDI-II (Beck, Steer, Ball, & Ranieri, 1996; Wang et al., 2011) which assess the level of depressive symptoms during the last two weeks; Liebowitz Social Anxiety Scale, LSAS (He and Zhang, 2004; Liebowitz, 1987), and the State-Trait Anxiety Inventory, STAI (Li and Qian, 1995; Spielberger,

Gorsuch, Lushene, Vagg, & Jacobs, 1983) (see Table 1 for details). The covariance matrix and correlation coefficients of the scales used in the regression models are presented in Supporting Information, Table S1 (BDI, LSAS, STAI-Trait, for completeness also STAI-State is presented). Given that collinear regressors in fMRI models might lead to unreliable estimations (Andrade, Paradis, Rouquette, & Poline, 1999; Mumford, Poline, & Poldrack, 2015) collinearity between the regressors was initially assessed using the variance inflation factor (VIF) (for a similar approach see also (Chau et al., 2017; Ohashi et al., 2017)). A VIF >5 is typically considered to indicate problematic collinearity (Mumford et al., 2015; O'Brien, 2007). VIFs in this study were <1.6 (Supporting Information, Table S2), arguing against problematic collinearity.

2.3 | Stimuli

For the *emotional face processing task*, a total of 150 faces were selected from two standardized Asian facial expression databases: Chinese Facial Affective Picture System (Gong, Huang, Wang, & Luo, 2011) and Taiwanese Facial Expression Image Database (TFEID) (Chen and Yen, 2007), including happy, angry, fearful, sad, and neutral faces each from 30 different individual actors (15 males). Faces were rescaled and covered with an oval frame to mask individual characteristics (e.g., hair) (Figure 1a).

For the *face-matching task*, a total of 60 neutral faces (30 pairs, 15 male pairs) and 60 houses (30 pairs) were selected from our own database (faces were previously used in (Gao et al., 2016)) (Figure 1b).

FIGURE 1 The procedure for (a) the emotional face processing task and (b) the face matching task

Given that subjects had to match a previously shown stimulus with two simultaneously presented stimuli from the same condition (house or face) we assessed the similarity between stimulus pairs in a pre-study. An independent sample ($n = 20$, 10 males) rated the similarity between each pair of faces or houses on a 9-point Likert scale (1 = not similar at all, 9 = very similar). No significant differences between the face and house stimuli set were found ($M_{\text{face}} \pm SD = 4.25 \pm 1.19$; $M_{\text{house}} \pm SD = 4.27 \pm 1.28$; $p = .903$), indicating that differences in cognitive load between conditions were controlled for.

2.4 | fMRI paradigms

The *emotional face processing* paradigm used an event-related design. Trials were distributed over 3 subsequent runs of 50 trials each, and balanced for face emotion and gender (duration = 570 s per run). For each trial, a face was shown for 7000 ms, with the first 1500 ms for passive viewing, and then 2500 ms for subjects to identify the emotion shown (select from the five alternatives *neutral, sad, happy, angry, fearful* presented below the facial picture) and finally 3000 ms to rate the emotional intensity of the emotion displayed (1 = very weak to 9 = very strong). After each trial a jittered fixation-cross was presented for 3600–4400 ms (mean ITI = 4000 ms, see Figure 1a) that served as low-level baseline.

The *face-matching task* used an ABBA-block design incorporating 10 blocks (5 for faces) in a single run of 460 s duration. There were 6 trials in each block. In each trial, a fixation was shown first for 1500 ms, and then a face or house was presented for 1500 ms, followed by the paired faces or houses for 2500 ms during which subjects had to choose which face or house had been presented previously. Blocks were separated by a low-level baseline (fixation cross) presented for 12 s. The order of blocks was balanced across the gender of the participants, with half of the males and half of the females starting with a facial stimuli block (Figure 1b).

Stimuli were presented using E-Prime 2.0 software (Psychological Software Tools, Pittsburgh, Pennsylvania), and presented with a cloned projection display in the scanner gantry.

2.5 | Image acquisitions

MRI data were obtained on a 3 T GE Discovery MR750 system (General Electric, Milwaukee, WI, USA) located in the neuroimaging center of the UESTC. High-resolution whole-brain T1-weighted images were acquired using a spoiled gradient echo pulse sequence (TR = 6 ms; TE = 1.964 ms; flip angle = 9° ; number of slices = 156; slice thickness, 1 mm; FOV = $256 \times 256 \text{ mm}^2$; matrix = 256×256). A total of 230 volumes of T2*-weighted echo planar images were acquired during the face matching task and 285 volumes per run of the emotional face processing task with the following acquisition parameters: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; number of slices = 39; slice orientation = axial; slice thickness = 3.4 mm; spacing = 0.6 mm; field of view (FOV) = $240 \times 240 \text{ mm}^2$; matrix = 64×64 ; flip angle = 90° .

2.6 | Data analysis

2.6.1 | MRI data preprocessing

Structural MRI data processing was performed in Matlab (R2014b, MathWorks, Inc., USA) using the Computational Anatomy Toolbox (CAT12; <http://dbm.neuro.uni-jena.de/cat>) based on the Statistical Parametric Mapping (SPM12; <http://www.fil.ion.ucl.ac.uk/spm>) software. During preprocessing, default settings were used as described in the toolbox manual (<http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>). The SPM12 tissue probability maps (TPMs) were used for the initial spatial registration and segmentation. The images were segmented into three tissue types: gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). A group-specific template based on all participants was created using the DARTEL algorithm. Next, participants' scans were warped onto it through a flow field which stored the deformation information. Finally, gray matter images were affine spatially normalized to Montreal Neurological Institute (MNI) space and smoothed with an 8 mm FWHM Gaussian kernel. Data quality was assessed and total intracranial volume (TIV) was estimated to be used as covariate on the second level.

Functional MRI data were preprocessed using SPM12. For each functional time series, the first five volumes were discarded to allow for MR equilibration, and the remaining functional images were initially realigned to the first image. The T1 images of each subject were segmented into GM, WM, and CSF and a skull-stripped bias corrected brain image was created using the *ImCalc* function. Next, the functional images and the structural images were coregistered. Finally, the images were normalized to the standard MNI template, resampled at $3 \times 3 \times 3 \text{ mm}^3$ voxel size, and spatially smoothed using an 8 mm FWHM Gaussian kernel.

After preprocessing, the first-level design matrix was built for each paradigm including the six movement parameters as covariates. The face emotion task included separate regressors for the five face viewing phases (happy, angry, fearful, sad, and neutral) as contrasts of interest, as well as separate regressors for the responses for emotional identity and emotional intensity (across all conditions) as regressors of no interest. The face matching task incorporated separate regressors for face and house matching, generating face > house and house > face as contrasts of interest.

2.6.2 | Statistical analysis

Statistical analyses of the behavioral indices (accuracy and emotional intensity for the emotional face processing task; accuracy for the face matching task) were conducted using SPSS Statistics 22 (Armonk, NY: IBM Corp.).

Before assessing associations between levels of depression and social anxiety with neural indices the normal distribution of all questionnaire scales was assessed. Given that the BDI (Shapiro-Wilk, $p < .05$) did not show a normal distribution in the present sample non-parametric tests were employed to determine associations between levels of depression and social anxiety with neural indices. To evaluate associations between depression and social anxiety with brain structure, we used simple regression analyses as implemented in the

Statistical nonParametric Mapping (SnPM13) toolbox (<http://warwick.ac.uk/snpm>), for BDI or LSAS with STAI-Trait, gender and TIV as covariates, and a voxel-wise significance threshold of $p < .05$ FDR-corrected. Only clusters of $k \geq 10$ contiguous voxels that survived the voxel-wise FDR-correction are reported. Concordant analyses were run for the two neural activity tasks (without including TIV as covariate). Brain regions were identified using MNI coordinates and the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) as implemented in the WFU PickAtlas (School of Medicine, Winston-Salem, NC). To further explore common and distinct brain regions associated with levels of depression and social anxiety, overlap maps between results from neural associations of both symptom dimensions were calculated. To this end, the thresholded activity maps for the significant associations with levels of depression or social anxiety ($p < .05$, FDR-corrected) were exported and the overlap was examined using SPM's Image Calculator (ImCalc) and the function `i1.*i2`.

To identify associations between the symptom dimensions and neural processing on the network level, an exploratory functional connectivity analysis was conducted using a seed-to-whole brain approach and a generalized form of context-dependent psychophysiological interactions (gPPI) (McLaren, Ries, Xu, & Johnson, 2012), with a threshold of $p < .001$ uncorrected and cluster extent $k \geq 10$. For this analysis seed regions were constructed by placing 6-mm-radius sphere centered at peak coordinates of each cluster within the common region using MarsBaR (Brett, Anton, Valabregue, & Poline, 2002).

3 | RESULTS

One participant with clinically relevant symptom loads (BDI = 41, STAI-Trait = 72) was excluded, leaving a total of 91 subjects (47 males; age range = 18–27 years; $M \pm SD = 21.69 \pm 2.24$ years) for the final analyses (Table 1). Four subjects had head motions > 2.5 mm within a run of the emotional face processing task (two for Run 1, one for Run 3, and one for Runs 2 and 3), consequently these runs were excluded from further analyses. The quality of the scales was checked through reliability analysis with all three scales yielding excellent internal consistencies (Supporting Information).

3.1 | Task and gender effects

During the face emotion recognition paradigm, subjects showed high recognition accuracy (happy, $M \pm SD = 97.87\% \pm 3.56\%$; angry, $91.12\% \pm 8.58\%$; fearful, $88.56\% \pm 9.87\%$; sad, $93.64\% \pm 6.45\%$; neutral, $91.07\% \pm 11.43\%$), confirming that they attended reliably to the facial stimuli. In addition, emotional intensity ratings given indicated that the emotional expression faces were, as expected, rated higher than the neutral ones (happy, $M \pm SD = 5.01 \pm 0.88$; angry, 5.19 ± 0.79 ; fearful, 5.21 ± 0.69 ; sad, 4.81 ± 0.82 ; neutral, 2.95 ± 1.77). Additional repeated measures ANOVAs for both, the emotional face processing task and the face-matching task yielded main effects of stimulus type; however, no main or interaction effects involving participants gender (details see Supporting Information). Together, the behavioral

findings confirmed first that subjects attentively processed the stimuli and second that there were no effects of subject gender.

3.2 | Associations between levels of depression and social anxiety with behavior

To match the analysis of the brain imaging data, associations between levels of social anxiety and depression with emotion recognition accuracy were explored using nonparametric correlation analyses with BDI and LSAS scores as separate predictors and emotion recognition accuracy as dependent variable (computed with the Permutation Analysis of Linear Models toolbox -PALM, version alpha 109, <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM> (Winkler, Ridgway, Webster, Smith, & Nichols, 2014); permutation test, number of permutations 10,000). The analyses revealed a significant negative association between BDI scores and emotion recognition accuracy for happy facial expressions ($r = -0.205$, $p = .046$; controlling for STAI-Trait and gender as covariates). However, the very high accuracy for happy facial expressions (mean recognition accuracy 97.87%, 58 of 91 subjects reached 100% accuracy for happy faces) suggests a ceiling effect thus inhibiting an interpretation of this finding. No significant associations were observed between the BDI and accuracy for the other face conditions or the LSAS and emotion recognition accuracy (all $p > .383$, controlling for STAI-Trait and gender as covariates).

3.3 | Voxel-based morphometry (VBM)

There were no significant linear relationships between levels of depression or social anxiety and brain structure at $p < .05$ (FDR-corrected). To further evaluate the lack of associations, we included participants from a larger database of brain structural data from our lab (total $n = 234$, age range = 17–27 years, $M \pm SD = 21.65 \pm 2.13$) (Table 1), again there were no significant linear relationships with brain structure. The analyses were additionally repeated using non-DARTEL based preprocessing and quality assessments as implemented in CAT12. Again, no significant linear relationships were observed.

3.4 | Face matching task: Neural activity

There were no significant linear relationships between depression or social anxiety with face recognition-related neural activity under both face and face $>$ house conditions at $p < .05$ FDR-corrected threshold, controlling for both gender and trait anxiety.

3.5 | Emotional face processing task: Neural activity

Results from the regression analysis revealed an association between levels of depression and neural activity during processing fearful faces. The BDI scores, controlling for trait anxiety and gender as covariates, were positively correlated with activity during processing of fearful faces in the left caudate ($k = 443$, $t_{87} = 4.69$, $x/y/z: -18/23/-7$), right globus pallidus ($k = 168$, $t_{87} = 4.59$, $x/y/z: 15/5/2$), left inferior parietal lobule ($k = 260$, $t_{87} = 4.41$, $x/y/z: -33/-55/44$), bilateral anterior cingulate cortex (right, $k = 13$, $t_{87} = 3.08$, $x/y/z: 15/38/-1$; left, $k = 68$,

TABLE 2 Simple regression for BDI and LSAS, with gender and STAI-Trait as nuisance covariates, using SnPM on whole-brain level and showing positive effects in response to fearful and sad faces

Regions	Cluster k	Coordinates			t
		x	y	z	
BDI: fearful faces					
Positive correlation					
Calcarine sulcus, R	373	24	−91	−1	4.99
Inferior occipital gyrus, R		33	−82	−4	4.16
Cerebellum, R		9	−76	−16	4.01
Caudate, L	443	−18	23	−7	4.69
Putamen, L		−21	−10	11	4.55
Midbrain		9	−28	−22	3.98
Triangular inferior frontal gyrus, R	22	54	29	5	4.60
Globus pallidus, R	168	15	5	2	4.59
Globus pallidus, R		12	−4	−7	3.67
Caudate, R		9	8	14	3.60
Inferior parietal lobule, L	260	−33	−55	44	4.41
Inferior parietal lobule, L		−36	−52	35	4.04
Middle occipital gyrus, L		−30	−64	29	3.97
Middle temporal gyrus, R	28	39	−64	11	4.26
Posterior cingulate cortex, L	105	−6	−37	17	4.21
Precuneus, L		−9	−43	5	3.46
Lingual gyrus, L	169	−24	−91	−16	4.19
Inferior occipital gyrus, L		−27	−82	−4	4.13
Inferior occipital gyrus, L		−15	−94	−10	3.80
Anterior cingulate cortex, L	68	−9	35	5	4.19
Anterior cingulate cortex, L		−18	50	−1	3.19
Precentral gyrus, R	57	21	−19	59	4.17
Superior frontal gyrus, R		27	−13	65	3.02
Fusiform gyrus, R	58	39	−67	−16	4.14
Inferior temporal gyrus, R		48	−58	−13	4.13
Fusiform gyrus, R		27	−61	−16	3.14
Precentral gyrus, R	43	54	5	38	4.11
Cerebellum, R	124	12	−73	−40	4.03
Cerebellum, R		33	−58	−40	3.86
Cerebellum, R		3	−58	−43	3.76
Orbital inferior frontal gyrus, L	52	−45	38	−10	3.95
Triangular inferior frontal gyrus, L		−39	38	8	3.70
Postcentral gyrus, L	56	−51	−7	38	3.94
Medial prefrontal cortex, L	112	−3	35	50	3.78
Medial prefrontal cortex, L		−15	35	26	3.63
Medial prefrontal cortex, L		−6	32	35	3.60
Middle temporal gyrus, L	73	−63	−22	−10	3.68
Hippocampus, L		−42	−31	−7	3.41
Middle temporal gyrus, L		−54	−34	−7	3.33
Superior frontal gyrus, R	23	21	56	11	3.64
Middle frontal gyrus, L	22	−33	11	50	3.53
Superior frontal gyrus, R		27	−13	65	3.02
Hippocampus, R	20	33	−13	−16	3.52

(Continues)

TABLE 2 (Continued)

Regions	Cluster k	Coordinates			t
		x	y	z	
Medial prefrontal cortex, L	10	−12	65	8	3.42
Cerebellum, L	11	−33	−64	−43	3.38
Fusiform gyrus, L	10	−30	−58	−19	3.29
Precuneus, R	18	3	−64	35	3.22
Precuneus, L		−3	−55	41	3.04
Cerebellum, L	17	−12	−73	−40	3.20
Posterior cingulate cortex, R	14	6	−43	5	3.17
Parahippocampal gyrus, R		12	−37	2	2.95
Cerebellum, R	10	18	−37	−22	3.10
Anterior cingulate cortex, R	13	15	38	−1	3.08
Supplemental motor area, L	10	0	5	44	3.07
LSAS: Sad faces					
<i>Positive correlation</i>					
Globus pallidus, L	95	−21	−4	−7	5.93
Putamen, L		−18	8	−1	4.79
Superior temporal gyrus, L	11	−48	2	−4	4.90

The results are reported threshold at $p < .05$ FDR-corrected on the voxel level, only cluster with $k \geq 10$ on whole-brain level are reported. Coordinates of peak voxels (x/y/z) are given in Montreal Neurological Institute space. Abbreviations: LSAS = Liebowitz Social Anxiety Scale; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory.

$t_{87} = 4.19$, x/y/z: $-9/35/5$), bilateral posterior cingulate cortex (right, $k = 14$, $t_{87} = 3.17$, x/y/z: $6/-43/5$; left, $k = 105$, $t_{87} = 4.21$, x/y/z: $-6/37/17$), bilateral inferior frontal gyrus (right, $k = 22$, $t_{87} = 4.60$, x/y/z: $54/29/5$; left, $k = 52$, $t_{87} = 3.95$, x/y/z: $-45/38/-10$), left medial prefrontal cortex ($k = 112$, $t_{87} = 3.78$, x/y/z: $-3/35/50$), right hippocampus ($k = 20$, $t_{87} = 3.52$, x/y/z: $33/-13/-16$), bilateral fusiform gyrus (right, $k = 58$, $t_{87} = 4.14$, x/y/z: $39/-67/-16$; left, $k = 10$, $t_{87} = 3.29$, x/y/z: $-30/-58/-19$), and other regions including right precentral gyrus, left postcentral gyrus, right precuneus, bilateral middle temporal gyrus, left lingual gyrus, right superior frontal gyrus, left middle frontal gyrus, left supplemental motor area, and bilateral cerebellum (Table 2 and Figures 2a and 3). No significant negative linear relationship was observed, and none during processing of other emotional or neutral faces. Levels of social anxiety (LSAS scores) were positively associated with activity during processing of sad faces in the left globus pallidus ($k = 95$, $t_{87} = 5.93$, x/y/z: $-21/-4/-7$), and left superior temporal gyrus ($k = 11$, $t_{87} = 4.90$, x/y/z: $-48/2/-4$) (Figure 2b), controlling for trait anxiety and gender as covariates. Findings remained stable after additionally controlling for state anxiety levels as assessed by the state anxiety subscale of the STAI, as covariate. To further evaluate interaction effects of levels of depression and social anxiety on the observed associations, follow-up analyses specifically examined the interaction term for the BDI and LSAS using SnPM simple regression models. These analyses did not reveal significant interaction effects on processing of fearful or sad faces. No significant linear relationships were found for the other face emotion conditions. Finally, no significant

positive or negative linear relationships were observed between levels of trait anxiety (trait subscales of STAI) and neural activity with gender and BDI or LSAS as covariates.

Examining the overlap of the neural activity maps with significant associations for the symptom dimensions revealed that both were positively associated with increased reactivity in two clusters: the left globus pallidus ($k = 10$, $t_{87} = 4.26$, x/y/z: $-21/-7/-7$) and left putamen ($k = 27$, $t_{87} = 4.26$, x/y/z: $-18/8/-1$) (Figure 2c and 4a).

3.6 | Emotional face processing task: Functional connectivity

The exploratory analysis of associations between the symptom levels and functional connectivity revealed negative associations between BDI-scores and functional connectivity strengths between left putamen and right superior temporal gyrus ($k = 23$, $p = .0004$, $t_{87} = 3.49$, x/y/z: $60/-4/-10$), and right amygdala ($k = 32$, $t_{87} = 2.94$, $p = .0007$, x/y/z: $33/-1/-16$; including right insula, $t_{87} = 1.89$, $p = .0009$, x/y/z: $33/14/-16$) during processing of fearful faces (Figure 4b). On the other hand, positive associations were observed between LSAS scores and connectivity of the left putamen and right middle cingulate cortex ($k = 32$, $p = .0001$, $t_{87} = 5.07$, x/y/z: $12/-10/47$) during processing of sad faces (Table 3 and Figure 4c). No significant linear relationships were observed between the BDI or LSAS and functional connectivity of the left globus pallidus.

FIGURE 2 BOLD level analysis showed positive associations between (a) BDI and neural responses to fearful faces and (b) LSAS and neural responses to sad faces, with gender and trait anxiety as covariates. (c) Both BDI and LSAS scores were associated with responses in the left globus pallidus (GP, $-21/-7/-7$) and left putamen (PUT, $-18/8/-1$). All voxels are significant at $p < .05$ (FDR corrected) and cluster size $k \geq 10$ voxels. Coordinates (x/y/z) are given in standard Montreal Neurological Institute space. Abbreviations: LSAS = Liebowitz Social Anxiety Scale; BDI = Beck Depression Inventory; L = left; R = right [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This study employed a dimensional approach in healthy subjects to determine common and distinct neurofunctional markers of depression and social anxiety while controlling for confounders such as medication and generally increased levels of trait anxiety inherent in traditional patient-based studies. The implementation of this approach demonstrated that both symptom dimensions were positively associated with increased reactivity in left globus pallidus (GP) and putamen (PUT), although during processing of different negative emotional face stimuli. While higher levels of depression symptoms were associated with increased reactivity to fearful faces, higher levels of social anxiety symptoms were associated with increased reactivity to sad faces. Moreover, depressive symptom load was associated with increased reactivity to fearful faces in a network comprising core regions of the fear reactivity and emotion regulation network, including bilateral inferior frontal gyrus, anterior cingulate cortex, fusiform gyrus, right hippocampus, and left inferior parietal lobule and medial prefrontal cortex. Further exploring associations between levels of depression and social anxiety with functional connectivity of the globus pallidus and putamen revealed that higher levels of social anxiety were associated with

increased left putamen—right middle cingulate cortex interplay during processing of sad faces, while higher levels of depression were associated with decreased left putamen—right amygdala functional connectivity during processing of fearful faces. Analysis of linear relationships of the symptom dimensions with neural activity during a facial identity matching task and with grey matter volumes did not reveal significant linear relationships, arguing against strong confounding effects of individual variations in face perception or brain structure on the present findings.

Only few previous studies applied a dimensional approach to examine the associations between individual variations in levels of depression and social anxiety with neurofunctional markers. In line with the present observation of increased reactivity to threatening fearful faces and levels of depression, a previous study which also used a dimensional approach found that levels of depressive symptoms were positively associated with increased stress-reactivity during a public speaking task (Benson, Arck, Blois, Schedlowski, & Elsenbruch, 2011). Moreover, a study examining associations between anxiety, depression and fear learning, reported that high-anxiety participants demonstrated less discriminative skin conductance responses during acquisition of fear, whereas high-depression was associated with higher

FIGURE 3 BOLD level analysis showed specific positive associations between BDI scores and neural responses to fearful faces in (a) left inferior parietal lobule (IPL, $-33/-55/44$), (b) bilateral anterior cingulate cortex (ACC; right, $15/38/-1$; left, $-9/35/5$), (c) bilateral inferior frontal gyrus (IFG; right, $54/29/5$; left, $-45/38/-10$), (d) left medial prefrontal cortex (mPFC, $-3/35/50$), (e) right hippocampus (HIPP, $33/-13/-16$), and (f) bilateral fusiform gyrus (FFG; right, $39/-67/-16$; left, $-30/-58/-19$). All voxels are significant at $p < .05$ (FDR corrected) and cluster size $k \geq 10$ voxels. Coordinates (x/y/z) are given in standard Montreal Neurological Institute space. Abbreviations: BDI = Beck Depression Inventory; L = left; R = right [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 (a) 6-mm-radius spheres centered at the peak MNI coordinates (putamen, PUT; globus pallidus, GP) involved in both depression and social anxiety symptoms were used to explore functional connectivity. (b) The functional connectivity of left PUT-right superior temporal gyrus ($60/-4/-10$) and left PUT-right amygdala ($33/-1/-16$) to fearful faces were negatively correlated with BDI, (c) whereas that of left PUT-right middle cingulate cortex ($12/-10/47$) to sad faces was positively associated with LSAS. All voxels are significant at $p < .001$ (uncorrected) and cluster size $k \geq 10$ voxels. Coordinates (x/y/z) are given in standard Montreal Neurological Institute space. Abbreviations: LSAS = Liebowitz Social Anxiety Scale; BDI = Beck Depression Inventory; L = left; R = right [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Significant associations between BDI and LSAS, with gender and STAI-Trait as nuisance covariates, and functional connectivity with the left putamen during processing negative faces

Regions	Cluster k	Coordinates			T
		x	y	z	
BDI: fearful faces					
Negative correlation					
Superior temporal gyrus, R	23	60	−4	−10	3.49
Amygdala, R	32	33	−1	−16	2.94
Insula, R		33	14	−16	1.89
LSAS: sad faces					
Positive correlation					
Middle cingulate cortex, R	32	12	−10	47	5.07

The results are reported threshold at $p < .001$ uncorrected on the voxel level, only cluster with $k \geq 10$ on whole-brain level are reported. Coordinates of peak voxels (x/y/z) are given in Montreal Neurological Institute space. Abbreviations: LSAS = Liebowitz Social Anxiety Scale; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory.

skin conductance reactivity during extinction of fear (Dibbets, van den Broek, & Evers, 2015). Together with the present data, the previous dimensional approach studies might indicate an association between levels of depression and increased reactivity to threatening stimuli, and additionally suggest that dimensional approaches might be an important complementary research strategy in addition to traditional patient-based research strategies.

In the present sample of healthy subjects, increased GP and PUT reactivity towards negative faces was found to be positively associated with both depression and social anxiety symptoms. This is consistent with previous meta-analyses on depression and social anxiety disorders showing increased reactivity in these regions during emotional face processing (Binelli et al., 2014; Delvecchio et al., 2012; Gee et al., 2013; Kanske and Kotz, 2011a,b; MacQueen, 2012; Wu et al., 2016). As core regions of the dorsal striatum and the basal ganglia, both GP and PUT, are not only involved in motor functions, but also play important roles in other domains, such as emotional regulation (Frank et al., 2014; Sztainberg, Kuperman, Justice, & Chen, 2011), salience processing (Gentili et al., 2016; Menon, 2015; Smith, Berridge, & Aldridge, 2011) and social-cognitive functions (MacQueen, 2012). Previous clinical studies demonstrated that both depression and social anxiety patients demonstrate marked impairments in emotion regulation (Jazaieri, Morrison, Goldin, & Gross, 2015; Joormann, 2010; Joormann and Stanton, 2016), aberrant salience processing (Hamilton et al., 2016; Pannekoek et al., 2013; Yuen et al., 2014), and deficient social cognition (Lavoie, Battaglia, & Achim, 2014; Weightman, Air, & Baune, 2014). Together with the present data from a dimensional approach, these findings suggest an important role of GP and PUT hyperresponsivity to negative social emotional stimuli as a core neuropathological feature in both depression and social anxiety disorders.

In addition, the associations between the two dimensions were found for neural reactivity during negative emotional face processing,

with levels of depression being associated with higher neural reactivity in regions involved in emotion regulation and emotion reactivity during processing of fearful faces. Interestingly, and in contrast with our initial hypothesis and a number of previous studies reporting decreased neural activity in frontal and anterior cingulate regions in depressive patients (Delvecchio et al., 2012; Fitzgerald et al., 2008; Groenewold et al., 2013; Lai, 2014; Palmer et al., 2015), the present dimensional approach revealed an association between higher reactivity to fearful faces in these regions, including the anterior cingulate and the inferior frontal cortex, and levels of depression. However, one study has reported increased left amygdala responses to masked fearful faces compared to other emotional faces in MDD patients, which were normalized with anti-depressant treatment (Sheline et al., 2001) and another has similarly reported increased medial prefrontal activity to fearful faces (Homan, Drevets, & Hasler, 2014). Furthermore, another study on individuals at risk of developing depression has reported increased amygdala and nucleus accumbens responses to fearful compared to happy faces (Monk et al., 2008). Inconsistent findings might be possibly explained in terms of frontal compensation for increased emotional reactivity in depression, as previously reported in a study comparing anxiety and depression patients (Etkin and Schatzberg, 2011).

The only region demonstrating positive associations with social anxiety symptoms was the superior temporal gyrus (STG). Increased reactivity of this region is in line with a recent meta-analysis in SAD reporting increased STG reactivity during face processing (Gentili et al., 2016), and original studies in patients with SAD (Binelli et al., 2014; Marazziti et al., 2014). Findings on increased STG activity in depression are less consistent with some meta-analyses reporting no consistent evidence for altered STG activity in MDD during emotion recognition (Dalili, Penton-Voak, Harmer, & Munafò, 2015) or emotional face processing (Delvecchio et al., 2012), whereas others have reported both decreased STG activity during positive (Groenewold et al., 2013) and negative stimuli (Fitzgerald et al., 2008), and hyperactivity in STG to negative versus neutral valence in depressive patients (Miller, Hamilton, Sacchet, & Gotlib, 2015).

An additional exploratory analysis examined differential connectivity patterns of the dorsal striatal regions showing overlapping increased neural reactivity in the context of both, increased levels of depression and social anxiety. This approach revealed that higher levels of depression were associated with reduced coupling of the left putamen with the contralateral STG, amygdala and insula whereas higher levels of social anxiety were specifically associated with increased coupling of the left putamen with the contralateral middle cingulate cortex. Given the exploratory nature of the present connectivity findings the corresponding results need to be interpreted cautiously. The negative associations between levels of depression and reduced putamen connectivity is in accordance with previous studies reporting decreased putamen-insula interaction during rest in MDD patients (Guo et al., 2015), and decreased functional coupling between the putamen, amygdala, insula, and STG in MDD patients before treatment, which normalized during the course of successful antidepressive treatment (Chen et al., 2008). Together with the putamen, the amygdala, insula and STG

are core nodes of the emotional face processing networks (Fusar-Poli et al., 2009), with successful encoding of emotional faces being dependent on the integration of information across nodes primarily involved in visual processing, including the STG (Stuhrmann et al., 2011), as well as limbic and striatal emotion processing regions, including the striatum and the amygdala (Haxby, Hoffman, & Gobbini, 2000). Overall, this suggests that the higher reactivity in emotional processing and emotion regulation nodes during presentation of fearful faces might interfere with the integrative processing of these faces on the network level. The specific importance of disruptions in the integrative fronto-striatal-limbic interplay in MDD is further emphasized by recent studies reporting that the intrinsic connectivity of this circuitry appears to reliably discriminate depression sub-types (Drysdale et al., 2017; Wager and Woo, 2017). With regard to social anxiety only the pathway between the putamen and middle cingulate cortex demonstrated increased connectivity. Both regions share functional connections (Hoffstaedter et al., 2012), thought to underlie the integration of emotion and motor-responses (Shackman et al., 2011), with stronger connectivity in this pathway during negative face possibly reflecting increased tendency to avoid or withdrawal negative social signals which constitutes a core feature of social anxiety disorders (Mkrtchian, Aylward, Dayan, Roiser, & Robinson, 2017).

In contrast to levels of depression where neural effects were associated with fearful faces those for social anxiety were associated with sad ones. Most previous patient-based studies showed an opposite pattern, suggesting that MDD patients are more sensitive to sad faces (Arnone et al., 2012; Surguladze et al., 2005) while SAD patients are more sensitive to fearful faces (Frick, Howner, Fischer, Kristiansson, & Furmark, 2013; Killgore and Yurgelun-Todd, 2005). However, as discussed above a number of studies on MDD patients or individuals at risk of MDD have also reported enhanced neural responses to fearful faces. Similarly, other studies have reported increased sensitivity to sad as well as fearful faces (Arrais et al., 2010) and hyperactivity to sad faces in prefrontal regions (Labuschagne et al., 2012) in SAD patients.

There are some limitations in this study. First, the BDI values were not normally distributed in our subject cohort, although nonparametric analyses were used to account for the non-normal distribution. Second, the implementation of the nonparametric approach limited the flexibility of the second level regression models leading to separate regression models for the BDI and LSAS as well as for each emotion, limiting the statistical strengths and the interpretation of emotion-specific associations. Similarly, the limitations did not allow direct implementation of a conjunction model to determine overlapping regions between the symptom scales while controlling for multiple comparisons on the voxel level. The computed overlap thus refers to a regional overlay of the activity clusters and needs to be interpreted with caution. Third, in line with previous studies in healthy subjects that examined associations between levels of depression with behavioral and neural indices (Benson et al., 2011; Dibbets et al., 2015; Levita et al., 2014), the current study employed the BDI-II to assess levels of depression. However, the BDI-II has been developed in a clinical context and might have a limited sensitivity to determine individual variations in a healthy sample. Fourth, participants in this study showed moderate levels of depression

and social anxiety symptoms, and thus the neural markers might additionally represent compensatory mechanisms that prevent the transition to a clinically relevant disorder.

5 | CONCLUSION

The current findings add to the growing literature on the neural reactivity toward emotional face processing associated with depression and social anxiety, and additionally suggest a key role of altered putamen reactivity as core pathological substrate across both disorders, whereas connectivity of this region might reflect specific alterations.

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CONFLICT OF INTEREST

The authors declare no financial interests or potential conflict of interest.

AUTHOR CONTRIBUTIONS

LL, BB, and KMK designed the experiments. LL and XZ prepared all the materials and programmed the procedures. LL, XZ, ZZ, XX, JK, and JD acquired the data. LL, BB, XZ, FZ, JW, and KMK analyzed the data. LL, BB, and KMK interpreted the data and drafted the manuscript. All the authors revised it critically for intellectual content, especially LL, BB, and KMK. All the authors gave final approval to the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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