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Research paper

Distinct grey matter volume alterations in adult patients with panic disorder and social anxiety disorder: A systematic review and voxel-based morphometry meta-analysis

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ABSTRACT

Background: The paradox of similar diagnostic criteria but potentially different neuropathologies in panic disorder (PD) and social anxiety disorder (SAD) needs to be clarified.
Methods: We performed a qualitative systematic review and a quantitative whole-brain voxel-based morphometry (VBM) meta-analysis with an anisotropic effect-size version of seed-based D mapping (AES-SDM) to explore whether the alterations of grey matter volume (GMV) in PD are similar to or different from those in SAD, together with potential confounding factors.
Results: A total of thirty-one studies were eligible for inclusion, eighteen of which were included in the meta-analysis. Compared to the respective healthy controls (HC), qualitative and quantitative analyses revealed smaller cortical-subcortical GMVs in PD patients in brain areas including the prefrontal and temporal-parietal cortices, striatum, thalamus and brainstem, predominantly right-lateralized regions, and larger GMVs in the prefrontal and temporal-parietal-occipital cortices, and smaller striatum and thalamus in SAD patients. Quantitatively, the right inferior frontal gyrus (IFG) deficit was specifically implicated in PD patients, whereas left striatum-thalamus deficits were specific to SAD patients, without shared GMV alterations in both disorders. Sex, the severity of clinical symptoms, psychiatric comorbidity, and concomitant medication use were negatively correlated with smaller regional GMV alterations in PD patients.
Conclusion: PD and SAD may represent different anxiety sub-entities at the neuroanatomical phenotypes level, with different specific neurostructural deficits in the right IFG of PD patients, and the left striatum and thalamus of SAD patients. This combination of differences and specificities can potentially be used to guide the development of diagnostic biomarkers for these disorders.

1. Introduction

Panic disorder (PD) and social anxiety disorder (SAD), formerly referred to as "acute anxiety attack" and "social phobia", respectively, are among the common forms of anxiety disorders. In addition to common manifestations of threat-relevant responses, overlapping symptoms such as similar manifestations of panic attacks, and shared dysfunction in the systems for social processes (Fonzo et al., 2015), the clinical features of PD and SAD are different to some extent. For example, PD and SAD differ in the object and breadth of the recognized threat (Craske et al., 2009). Specifically, PD involves intrusive worries about diverse circumstances, while SAD involves fear/avoidance of social situations. Moreover, there is a key difference between the panic attacks of PD and those of SAD; that is, whether they are unexpected or expected in nature (Barlow et al., 1994; Craske et al., 2010; Rachman et al., 1987). Unexpected panic attacks, or attacks without any obvious trigger or cue, are an essential element of PD and are theorized to contribute to the high levels of overall anxious apprehension in PD

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(Barlow, 1988; Craske, 1991; Craske et al., 1995). Expected panic attacks with an obvious trigger or cue reliably occur in response to phobic stimuli (e.g., public speaking for the person with SAD) (Brown et al., 2016). Panic attacks in PD are characterized by more symptoms and greater symptom severity than those in SAD (Brown et al., 2016; Rapee et al., 1992). Therefore, it is of significance to explore whether the neuropathological substrates in PD are similar or different to those in SAD and to further provide individual interventions for both disorders.

In this field, increasing neuroimaging studies have investigated the disorder-related structural changes of grey matter volume/density (GMV/GMD) in PD and SAD patients relative to healthy controls (HC) and have reported heterogeneous findings, with larger, smaller, and no GMV alterations in some cortical and subcortical regions. For investigations of PD using a whole-brain voxel-based morphometry (VBM) approach, studies have reported that compared to HC, patients with PD exhibited smaller GMVs in the prefrontal and temporal-parietal-occipital cortices, insula, limbic regions and cerebellum (Lai and Hsu, 2011; Lai and Wu, 2013; Picado et al., 2015), together with larger GMVs in the left inferior frontal gyrus (IFG) and cuneus (Picado et al., 2015). Also patients with PD showed significantly smaller GMVs in the bilateral orbitofrontal cortex (OFC) (Atmaca et al., 2012; Roppongi et al., 2010) and temporal lobes (Vythilingam et al., 2000) relative to HC, together with a larger hippocampus volume (Garakani et al., 2007) or no volume differences of the bilateral amygdala, hippocampus or hypothalamus (Terlevic et al., 2013; Vythilingam et al., 2000; Yoon et al., 2016) by a region of interest (ROI) approach. Previous reviews of structural brain imaging revealed relatively substantial heterogeneity among significant study findings, which makes it difficult to relate specific regions of aberrant GMV changes to PD (Del Casale et al., 2013; Sobanski and Wagner, 2017). Two meta-analyses of whole-brain VBM studies reported smaller cortical GMVs in the bilateral dorsomedial prefrontal cortex (DMPFC), left dorsolateral prefrontal cortex (DLPFC), right OFC, superior temporal gyrus (STG), middle temporal gyrus (MTG) and insula using the activation likelihood estimation (ALE) approach (Wu et al., 2018), as well as lower subcortical GMVs in the right striatal-limbic areas using seed-based D mapping (SDM) (Lai, 2011), in PD patients relative to HC.

For investigations of SAD using a ROI approach, studies found larger GMVs of the bilateral OFC and left insula (Liu et al., 2020), or no significant GMV differences in cortical regions in SAD patients relative to HC (Syal et al., 2012). With respect to the volume alterations of subcortical regions such as the amygdala and hippocampus, ROI-based studies reported null findings (Liu et al., 2020; Potts et al., 1994; Syal et al., 2012) or larger bilateral amygdala volumes (Suor et al., 2020) in SAD patients relative to HC. A multiplex multigenerational neuroimaging study provided preliminary evidence that grey matter (GM) characteristics of multiple ROIs were candidate endophenotypes of SAD (Bas-Hoogendam et al., 2018). It was also found that GM structural brain changes were potential neuroimaging endophenotypes in SAD patients (Bas-Hoogendam et al., 2016), despite being heterogeneous (Bas-Hoogendam et al., 2018; Bruhl et al., 2014a). A meta-analysis of whole-brain VBM studies using an anisotropic effect-size version of seed-based D mapping (AES-SDM) revealed that, relative to HC, SAD patients exhibited larger GMVs in the left precuneus, right supplementary motor area (SMA) and middle occipital gyrus (MOG), and a smaller left putamen (Wang et al., 2018), but further research is needed to improve the understanding of the SAD-related structural brain alterations (Bas-Hoogendam, 2019).

In addition, there is considerable heterogeneity across studies in terms of sample sizes, demographic and clinical characteristics of the subjects, image acquisition and analysis protocols used. These factors may partially account for the inconsistent findings reported in structural neuroimaging studies of anxiety disorders (Jayakar et al., 2020; Montag et al., 2013; Shang et al., 2014; Wang et al., 2018). Small sample sizes may, in particular, result in false-positive or false-negative findings. To our knowledge, only one study directly compared the GMV differences between PD and SAD patients and found different cortical and subcortical GMV alterations; this study was included in our meta-analysis (Talati et al., 2013).

Taken together, in light of the above inconsistencies in the locations and levels of regional GMV alterations in PD or SAD patients relative to HC, as well as the scarcity of research directly comparing GMV alterations between both disorders, it is necessary to further investigate the potential general and specific GMV alterations between PD and SAD by an explorative comparison strategy. Thus, in addition to investigating GMV differences between PD or SAD patients and HC, the current study aimed to clarify common and specific neuroanatomical profiles of PD and SAD and the potential effect of demographic and clinical information of patients by conducting a combined qualitative systematic review and quantitative meta-analysis.

2. Methods

2.1. Literature search

A systematic literature search was performed using PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (https://apps.webofknowledge.com/), Embase (http://ovidsp.dc2.ovid.com/) and ScienceDirect (https://www.sciencedirect.com/) databases up to January 2020. The search keywords were "panic disorder OR panic attacks OR acute anxiety attack OR social anxiety OR social anxiety disorder OR social phobia (including public speaking phobia)" AND "magnetic resonance imaging OR MRI OR morphometry OR voxel-based OR voxel-wise OR voxel-based morphometry OR VBM". Additionally, the reference lists of the included original articles and relevant papers were manually reviewed for studies that might have been be missed during the database searches.

2.2. Selection criteria

The studies were included if they (1) compared GMV/GMD differences among PD and SAD patients and HC, (2) included adult subjects (age $\geq$ 18 years), (3) included pretreatment baseline data, and (4) allowed patients with psychiatric comorbidities in the case that patient's main diagnosis included PD or SAD. A combined summary result was preferentially included if a study investigated several subgroup comparisons. Eligible studies reporting no between-group differences were included and estimated conservatively to have a null effect size in SDM. Studies were excluded if they (1) focused on subjects under 18 years of age and (2) were theoretical papers, reviews including meta-analyses, and case reports. Each study included was independently extracted by two authors (Wang X.L and Cheng B.C.) to minimize data extraction errors. Any inconsistencies were discussed, and a consensus was reached about the appropriateness of the study for the present study.

The studies for the meta-analysis had to meet the following additional criteria: (1) used a whole-brain VBM approach and (2) reported the effect coordinates of significant clusters in Montreal Neurological Institute (MNI) or Talairach space. A study was excluded if (1) it was a VBM study with small volume correction (SVC), (2) it did not perform statistical comparisons between patients and HC, or (3) the peak coordinates of effects were unavailable even after the author(s) were contacted via e-mail.

2.3. Quality assessment and data extraction

The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Knobloch et al., 2011; Moher et al., 2009). A 12-point checklist was used to estimate the quality of each enrolled study, which focused on both the demographic and clinical aspects of individual study samples and the imaging methodology. Each point was scored as 0, 0.5 or 1 if the criteria were unfulfilled, partially met or fully

met, respectively, and any study scoring > 8.0 points was included in the current study. Although not specifically designed as an assessment tool, this checklist provided an objective indication of the rigor of each study to warrant inclusion in this analysis (Table S1) and was used in previous meta-analytic studies (Sanderson et al., 2007; Shepherd et al., 2012).

Data were extracted from the review of each included article in the following manner. First, we recorded demographic and clinical information, basic methodological information, MRI scanning parameters, and main findings. Second, we recorded the data for SDM calculations, including the coordinates of significant findings and values related to effect size (e.g., *t*/z statistics and *P* value).

2.4. Data analyses

2.4.1. Descriptive summarizing

We described the information regarding the sample size, age, sex ratio of subjects, age at onset, duration of illness, symptom severity, psychiatric comorbidity, medication state, magnetic field strength, smoothing level, data analysis approach, the statistical threshold and the method used to correct results, and the main findings of each study included. In the qualitative systematic review, data summaries were categorized into results examining GMVs among PD and SAD patients and HC.

For the meta-analysis, we combined studies on the GMV differences between PD or SAD patients and HC, and calculated the following variables in PD patients for further meta-regression analysis: the mean ages, the percentages of female patients, and the proportions of PD patients with psychiatric comorbidity and currently taking medication in the included studies. Because fewer than 9 studies were included that investigated SAD (Radua and Mataix-Cols, 2009), we could not perform a meta-regression analysis and did not calculate the above variables for SAD.

2.4.2. Voxel-based meta-analysis

AES-SDM software version 5.15 (http://www.sdmproject.com/) (Radua et al., 2014b) was used to identify brain regions that potentially show consistent significant GMV differences among PD patients, SAD patients, and HC. The steps of the method are summarized as follows.

2.4.2.1. Pooled meta-analyses. SDM entailed voxel-wise random-effects meta-analysis that provided a mean map, combining the data of each included study and representing both negative and positive differences in the same map (Radua and Mataix-Cols, 2009). The default 20 mm for the full-width at half-maximum (FWHM) was set to provide the optimum balance between sensitivity and specificity (Radua et al., 2012). Then, reported peak coordinates and effect sizes (derived, for example, from *t* values) of GMV differences were used to recreate, for each study, an effect-size map of the GMV differences between patients with PD or SAD and HC. This recreation of the brain maps used anisotropic kernels to estimate the effect size of those voxels close to a peak based on the correlation between each voxel and the peak voxel, with these brain maps randomly permuted 50 times. Thresholds were set at $P < 0.005$ (voxel level), with peak $Z > 1$ (peak height) and a cluster extent greater than or equal to 10 voxels (Radua and Mataix-Cols, 2012), and the results are shown in MNI coordinates.

2.4.2.2. Analyses of reliability, heterogeneity and publication bias. First, to test the replicability of the results, a systematic whole-brain jack-knife sensitivity analysis was applied to investigate the effect of an individual study on the estimated pooled effect size by repeating the pooled meta-analysis n times (n = the number of datasets included) after discarding one different individual dataset in successive iterations. If clusters remained significant in at least 75% of the combinations of studies, the findings were considered highly replicable. Next, the statistical heterogeneity (between-studies) of individual clusters was examined using a random-effects model with Q/Q_H statistics (χ^2 distribution converted to *z* values) and tested with a permutation approach ($P < 0.005$, uncorrected for FDR; peak height z = 1), in which any result presenting a voxel threshold of $P < 0.005$, uncorrected for FDR, and with a peak height of $Z > 1$ was considered to show significantly elevated heterogeneity. Then, publication bias was evaluated with Egger's tests to assess the asymmetry of funnel plots for each significant cluster of between-group comparisons, in which any result showing $P < 0.05$ was significant for publication bias (Radua et al., 2014a).

2.4.2.3. Meta-regression analysis. The potential effects of mean age, the proportions of sex, handedness, psychiatric comorbidity and medication use in PD patients were evaluated by meta-regression using a linear random-effects model with a threshold of $P < 0.0005$ to minimize the detection of spurious relationships (Radua and Mataix-Cols, 2009). We discarded any results that were not significant in the pooled meta-analysis (Radua and Mataix-Cols, 2009).

2.4.2.4. Conjunction analysis between meta-analysis groups. An AES-SDM allows conjunction analyses to be performed to compare the results obtained between different meta-analytic groups (for example, PD vs SAD patients relative to HC). In particular, a linear modal tool is employed in meta-analytic group comparisons to investigate whether computed effect sizes differ significantly between groups (Radua et al., 2010). Thus, effect size comparisons could be made between PD and SAD patients using a less conservative threshold of $P < 0.001$. The multimodal analysis function of an AES-SDM also made it possible to identify brain regions where a single meta-analysis of PD and SAD groups relative to respective HC showed robust common GMV abnormalities, while taking into account error in the estimation of *P* values within the individual meta-analyses (Radua et al., 2013; Wise et al., 2016). The statistical significance of each voxel was determined using randomization tests with a threshold of $P < 0.005$ to protect against false positives, without the correction described by Radua and others (Radua et al., 2013; Wise et al., 2016).

3. Results

3.1. Characteristics of included studies

A total of 31 studies with 408 PD patients and 430 HC as well as 536 SAD patients and 574 HC were included in this systematic review (Figure 1), one of these studies compared the regional GMV differences among patients with PD, patients with SAD and HC (Talati et al., 2013), and the other 18 and 12 studies only recruited patients with PD and patients with SAD, respectively. The detailed information from each included study is presented in Table 1. The quality assessment score of each study included is presented in Table S2. The range of scores was 9-12, with an average score of 12.5 and 10.9 points for the PD and SAD studies, respectively.

Of the 31 studies, 18 whole-brain VBM studies were included in the meta-analysis to quantitatively explore regional GMV alterations among PD and SAD patients and HC. These 18 studies comprised 11 PD studies with 243 patients and 252 HC and 8 SAD studies with 384 patients and 445 HC, with one study (Talati et al., 2013) recruiting individuals for both PD and SAD groups. Table 2 shows the demographic and clinical information of the studies included in the pooled meta-analyses for patients with PD and SAD.

3.2. Qualitative GMV findings

In the included studies, 7 and 31 studies reported the total GMV and regional GMV alterations, respectively, among patients with PD, patients with SAD and HC. Some studies have explored the effect of demographic and clinical variables on regional GMV measures.

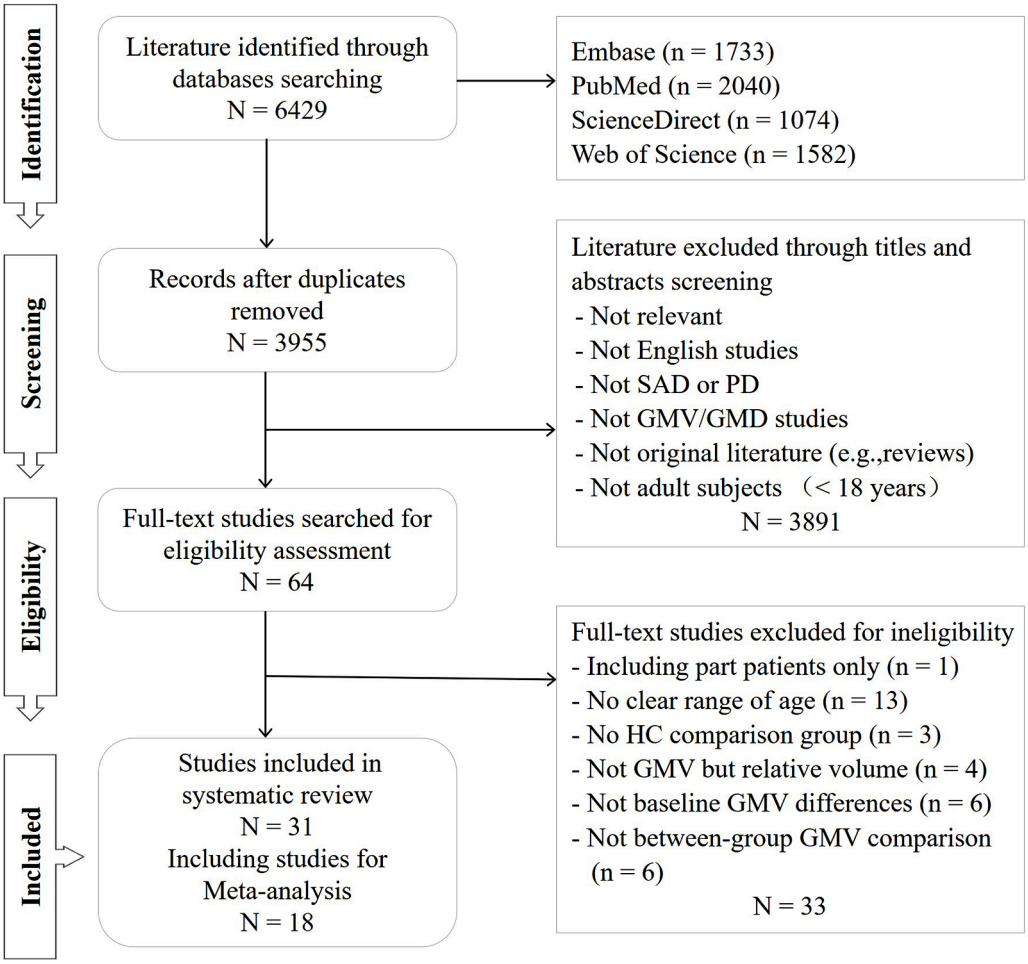

Figure 1. Flow chart of the literature search.

3.2.1. *Total GMV findings*

Regarding the global GMV measures, studies reported the absence of significant differences between patients with PD (Massana et al., 2003b; Uchida et al., 2008) or patients with SAD (Kawaguchi et al., 2016; Machado-de-Sousa et al., 2014; Meng et al., 2013; Talati et al., 2013; Tukel et al., 2015) and corresponding HC.

3.2.2. *Regional GMV findings*

Regarding regional GMV alterations, the findings showed differences in the directions (smaller vs larger) and locations (cortical vs subcortical) and of GMV alterations in patients with PD or SAD relative to the respective HC, which was reviewed separately as follows.

PD patients versus HC. Using the whole-brain and ROI approaches, studies mainly reported smaller GMV alterations in the multiple prefrontal and temporal-parietal cortices (mainly in the prefrontal cortex (PFC)) and subcortical bilateral amygdala, striatum, thalamus and brainstem, together with inconsistent insula volume in PD patients compared to HC. Specifically, three of the studies included reported larger GMVs of the bilateral insula, precuneus, cuneus and lingual gyri, left transverse temporal gyrus, STG and hippocampus, right MTG and occipital cortices, midbrain and brainstem in PD patients relative to HC (Protopopescu et al., 2006; Talati et al., 2013; Uchida et al., 2008). Meanwhile, an overwhelming number of studies identified smaller GMV alterations in the bilateral superior frontal gyrus (SFG), IFG, DMPFC, OFC, middle cingulate, precentral and rectus gyri, insula, temporal lobe, right middle frontal gyrus (MFG), ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), postcentral gyrus and SMA, and cerebellum in patients with PD relative to HC (Asami et al., 2008; Asami et al., 2009; Lai, 2014; Lai et al., 2010; Lai and Wu, 2012, 2015; Protopopescu et al., 2006; Sobanski et al., 2010; Talati et al., 2013; Uchida et al., 2008; Uchida et al., 2003; Yoo et al., 2005). Similarly, PD patients also exhibited smaller subcortical volumes of the bilateral amygdala, striatum/putamen and thalamus, and right parahippocampal gyrus (PHG) than HC (Asami et al., 2018a; Asami et al., 2009; Asami et al., 2018c; Hayano et al., 2009; Lai, 2014; Lai et al., 2010; Massana et al., 2003b; Protopopescu et al., 2006; Talati et al., 2013; Yoo et al., 2005). In contrast, other authors reported no significant differences in regional GMVs (Maggioni et al., 2019; Na et al., 2013), including in the bilateral temporal lobes, hippocampus (Hayano et al., 2009; Lai, 2014; Massana et al., 2003b), or amygdala (Lai, 2014), between PD patients and HC.

SAD patients versus HC. Using whole-brain and ROI approaches, the included studies mainly reported larger GMVs in the prefrontal and temporal-parietal-occipital cortices and smaller GVMs in the local prefrontal-temporal regions and thalamus, together with inconsistent GMV alterations in the bilateral insula, limbic structures and striatum. Studies revealed that relative to HC, patients with SAD exhibited greater GMVs in the bilateral SFG, IFG, SMA, MTG, fusiform gyrus, angular and supramarginal gyri, left superior parietal areas, precuneus, MOG and PHG, right inferior temporal gyrus (ITG), and cerebellum (Irle et al., 2014; Mansson et al., 2016; Talati et al., 2013; Tukel et al., 2015), as well as greater subcortical volumes in the bilateral amygdala, hippocampus (Koc et al., 2018; Machado-de-Sousa et al., 2014), and right putamen/caudate (Bas-Hoogendam et al., 2017). Meanwhile, studies also reported smaller GMVs of the bilateral OFC, insula and STG, left ACC and IFG, right postcentral gyrus, precuneus and superior occipital

Table 1
Demographic and clinical information and main findings for studies of PD and SAD included in the systematic review

Study	Subjects Number (female)/ Age at study, years	Age of onset/ Illness duration (years)	Score of symptom severity (scale type)	Number of combined Comorbidity	Number of current medication users	Method Field strength (Tesla)/ Smoothing (mm)	Software/ Method (Whole brain or ROI)	Regions of interest	Statistic of gray matter volume (correction)	Main findings Patients > HC	Patients < HC
PD vs. HC											
Asami et al., 2008[1]	PD: 26 (16)/37.7 ± 10.1 HC: 26 (16)/38.2 ± 9.7	NA/3.8 ± 3.3	8.7 ± 4.9 (PDSS)	4 past MDD, 11 past AG, 1 dysthymia, 3 AG at the time of the study	21 antidepressants, 19 receiving benzodiazepines	1.5/12	SPM/VBM and Manual tracing/ROI	ACC	$P < 0.05$ (FWE)	*ROI*: None	*ROI*: R ACC
Asami et al., 2009[2]	PD: 24 (15)/37.0 ± 10.0 HC: 24 (15)/37.0 ± 8.7	NA/4.0 ± 3.7	10.1 ± 5.0 For female 6.4 ± 4.1 For male (PDSS)	13 AG, 3 MDD, 1 dysthymia	19 antidepressants, 17 receiving benzodiazepines	1.5/12	SPM/VBM/ Whole brain	None	$P < 0.05$ (FDR)	*Whole brain*: None	*Whole brain*: B dorsomedial PFC, insula cortex, STG, occipital-temporal gyrus, R ventromedial PFC, ACC, amygdala, and L cerebellum.
Asami et al., 2018[3]	PD: 38 (25)/39.7 ± 9.9 HC: 38 (25)/39.0 ± 11.1	NA/4.7 ± 5.8	12.3 ± 5.5 (PDSS)	6 past MDD	38 currently taking antidepressant and/or benzodiazepine medications	1.5/NA	FreeSurfer/NA/ ROI	Amygdala and the amygdala sub-nuclei	$P < 0.05$ (NA)	*ROI*: None	*ROI*: R whole amygdala, lateral nucleus and basal nucleus of amygdala.
Asami et al., 2018[4]	PD: 25 (25)/39.7 ± 9.9 HC: 25 (25)/39.0 ± 11.1	NA/4.7 ± 5.8	12.3 ± 5.5 (PDSS)	6 past MDD	23 currently taking antidepressant and/or benzodiazepine medications	1.5/8	SPM/VBM/ROI	B thalamus	$P < 0.05$ (FWE)	*ROI*: None	*ROI*: B thalamus
Hayano et al., 2009[5]	PD: 27 (17)/38.2 ± 9.9 HC: 30 (21)/ 35.3 ± 10.5	NA/5.4 ± 6.4	8.8 ± 4.8 (PDSS)	3 past MDD, 11 AG at the time of the study	4 benzodiazepine alone, 3 SSRI alone, 1 SSRI and SNRI, 12 benzodiazepine and SSRI, 2 benzodiazepine and SNRI, 2 benzodiazepine and tricyclic antidepressant, or 1 benzodiazepine, SSRI and tetracyclic antidepressant	1.5/8	SPM/VBM/ROI	B amygdala and hippocampus	$P < 0.05$ (FWE)	*ROI*: None	*ROI*: R amygdala
Lai et al., 2010[6]	PD: 16 (11)/37.9 ± 8.8 HC: 15 (11)/ 34.3 ± 9.9	NA/NA	18.6 ±2.9 (PDSS)	16 MDD, 6 AG	None	3/7.5	FSL/VBM/ Whole brain	Non	$P < 0.005$ (FWE)	*Whole brain*: None	*Whole brain*: B medial frontal gyrus, rectus gyrus, subcallosal gyrus, STG, occipital lingual gyrus, amygdala, striatum, thalamus, R MFG, parahippocampal gyrus, and B cerebellum.
Lai et al., 2012[7]	PD: 30 (19)/47.0	NA/NA	21.6 ± 2.3 (PDSS)	None	None	3/7.5	FSL/VBM/ Whole brain	None	$P < 0.005$ (FWE)	*Whole brain*: None	

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Table 1 (*continued*)

Study	Subjects Number (female)/ Age at study, years	Age of onset/ Illness duration (years)	Score of symptom severity (scale type)	Number of combined Comorbidity	Number of current medication users	Method Field strength (Tesla)/ Smoothing (mm)	Software/ Method (Whole brain or ROI)	Regions of interest	Statistic of gray matter volume (correction)	Main findings Patients > HC	Patients < HC
	± 10.6 HC: 21 (11)/41.1 ± 11.8										*Whole brain*: L OFC, IFC, STG, and R insula.
Lai et al., 2014[8]	PD: 15 (11)/ 36.8 ± 7.9 HC: 15 (11)/ 34.3 ± 9.9	NA/NA	19.6 ± 2.8 (PDSS)	15 MDD	None	3/NA	FSL/Manual segmentation/ ROI	B amygdala, hippocampus, putamen, and thalamus	$P < 0.05$ (*U* test correction)	*ROI*: None	*ROI*: B putamen, thalamus, and L hippocampus.
Lai et al., 2015[9]	PD: 53 (28)/43.3 ± 10.1 HC: 54 (29)/40.4 ± 10.5	NA/0.5 ± 0.2	23.4 ± 2.7 (HARS)	None	None	3/7.5	FSL/VBM/ Whole brain	None	$P < 0.005$ (FWE)	*Whole brain*: None	*Whole brain*: R IFG and insula
Maggioni et al., 2019[10]	PD: 11 (6)/ 33.6 ± 9.5 HC: 21 (14)/ 36.0 ± 13.5	NA/NA	15.2 ± 6.2 (HARS)	3 personality disorders	8 receiving antidepressants	1.5/NA	FreeSurfer/NA/ ROI	SFG, OFC, MFG, ACC, posterior cingulate cortex, and precentral gyrus, postcentral, superior parietal, supramarginal and inferior parietal gyri, STG, MTG, ITG and fusiform gyri, lateral occipital gyrus, and insula	$P < 0.05$ (FDR)	*ROI*: None	*ROI*: None
Massana et al., 2003[11]	PD: 12 (6)/ 35.3 ± 5.6 HC: 12 (6)/ 35.0 ± 5.9	NA/NA	NA	10 AG;	None	1.5/NA	ANALYZE/ Manually tracing/ROI	B temporal lobe, amygdala, and hippocampus	$P < 0.05$ (Bonferroni correction)	*ROI*: None	*ROI*: B amygdala
Massana et al., 2003[12]	PD: 18 (11)/ 36.8 ± 11.3 HC: 18 (10)/ 36.7 ± 8.8	NA/NA	NA	15 AG	NA	3/12	SPM/VBM/ Whole brain	None	$P < 0.05$ (Correction)	*Whole brain*: None	*Whole brain*: L parahippocampal gyrus
Na et al., 2013[13]	PD: 22 (9)/ 40.2 ± 10.6 HC: 22 (11)/ 40.2 ± 12.4	NA/NA	NA	12 AG	NA	3/8	SPM/VBM/ Whole brain	None	$P < 0.05$ (FWE)	*Whole brain*: None	*Whole brain*: None
	PD: 10 (6)/	NA/NA	NA	2 AG, 1 past alcohol abuse,	1 medicated	3/12	SPM/VBM/ Whole brain	None	$P < 0.05$ (Correction)	*Whole brain*: Midbrain and pons,	*Whole brain*: OFC, R SFG, R MFG,

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Table 1 (*continued*)

Study	Subjects Number (female)/ Age at study, years	Age of onset/ Illness duration (years)	Score of symptom severity (scale type)	Number of combined Comorbidity	Number of current medication users	Method Field strength (Tesla)/ Smoothing (mm)	Software/ Method (Whole brain or ROI)	Regions of interest	Statistic of gray matter volume (correction)	Main findings Patients > HC	Patients < HC
Protopopescu et al., 2006[14]	35.5 ± 9.7 HC: 23 (11)/ 28.7 ± 7.5			1 past alcohol dependence; Secondary diagnoses included SP, SAD, GAD, and MDD.						L hippocampal, R occipital, and R middle temporal gyrus.	and R precentral gyrus, L middle cingulate gyrus, L fusiform gyrus and R caudate.
Sobanski et al., 2010[15]	PD: 17 (9)/ 34.9 ± 6.7 HC: 17 (9)/ 33.1 ± 6.2	NA/7.9 ± 5.2	32.0 ± 6.2 (Observer-rated Panic and Agora-phobia Scale)	16 AG, 1 SAD, 1 GAD, 2 AD, 2 PPD	17 medicated	1.5/12	SPM/VBM/ Whole brain and ROI	B temporal lobe, AHC, and frontal lobe	$P < 0.05$ (FWE)	*Whole brain*: None *ROI*: None	*Whole brain*: R MTG, OFC. *ROI*: B temporal lobe, and R frontal lobe.
Talati et al., 2013[16]	PD: 16 (13)/ 31.8 ± 10.0 HC: 20 (9)/ 31.4 ± 7.8	18.4 ± 3.4/NA	NA	3 MDD, 2 GAD, 5 SP, 2 OCD, 4 DUD, 4 AUD	None	1.5/8	SPM/VBM/ Whole brain	None	$P < 0.05$ (Correction)	*Whole brain*: B Cuneus, precuneus and lingual, L insula, R SOG.	*Whole brain*: B Precentral, R postcentral, R middle cingulate, L inferior parietal gyrus, R SMA, L caudate, R thalamus.
Uchida et al., 2003[17]	PD: 11 (8)/ 36.9 ± 11.9 HC: 11 (6)/ 34.3 ± 10.2	28.4 ± 9.5/8.0 ± 6.7	NA	6 AG, 5 MDD, 1 dysthymia	8 medicated: 4 SSRIs (1 benzodiazepine), 3 clomipramine, 1 benzodiazepine alone.	1.5/NA	Image J/ Manually tracing/ROI	Temporal lobes, focusing on amygdala and hippocampus.	$P < 0.05$ (NA)	*ROI*: None	*ROI*: L temporal lobe
Uchida et al.,2008[18]	PD: 19 (16)/ 37.1 ± 9.8 HC: 20 (16)/ 36.5 ± 9.9	29.7 ± 9.8/8.3 ± 6.0	NA	14 AG, 3 MDD, 2 dysthymia	14 antidepressants, 4 receiving benzodiazepines	1.5/8	SPM/VBM/ Whole brain and ROI	None Amygdala, hippocampus, insula, ACC, thalamus, hypothalamus and midbrain.	$P < 0.001$ for Whole brain (Uncorrection) $P < 0.05$ for ROI (Small-volume correction)	*Whole brain*: L insula, STG, transverse temporal gyrus, midbrain and pons. *ROI*: L insula, midbrain and pons.	*Whole brain*: R ACC *ROI*: R ACC
Yoo et al.,2005[19]	PD: 18 (9)/ 33.3 ± 7.1 HC: 18 (7)/ 32.0 ± 5.8	NA/3.6 ± 2.2	8.3 ± 5.7 (PDSS)	None	None	3/8	SPM/VBM/ Whole brain	None	$P < 0.05$ (Correction)	*Whole brain*: None	*Whole brain*: B putamen
SAD vs. HC											
Ahmed-Leitao et al., 2019[20] without early childhood trauma	SAD: 22 (11)/ 35.6 ± 9.3 HC: 25 (11)/ 30.5 ± 7.3	NA/NA	NA	0	None	3/NA	FreeSurfer/NA/ ROI	Hippocampus and hippocampal subfields	$P < 0.05$ (FDR)	*ROI*: None	*ROI*: None
		NA/NA	NA	0	None	3/NA			$P < 0.05$ (FDR)		

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Table 1 (*continued*)

Study	Subjects Number (female)/ Age at study, years	Age of onset/ Illness duration (years)	Score of symptom severity (scale type)	Number of combined Comorbidity	Number of current medication users	Method Field strength (Tesla)/ Smoothing (mm)	Software/ Method (Whole brain or ROI)	Regions of interest	Statistic of gray matter volume (correction)	Main findings Patients > HC	Patients < HC
Ahmed-Leitao et al., 2019[20] with early childhood trauma	SAD: 26 (12)/ 33.0 ± 9.7 HC: 25 (11)/ 30.5 ± 7.3						FreeSurfer/NA/ ROI	Hippocampus and hippocampal subfields		*ROI*: None	*ROI*: None
Bas-Hoogendam et al., 2017[21]	SAD: 174 (102)/ 30.6 ± 10.0 HC: 213 (116)/ 32.4 ± 10.5	NA/NA	77.9 ± 17.9 (LSAS) From 148 patients	8 MDD, 2 MDD + PD, 10 GAD, 3 GAD + SP, 2 GAD + PD, 3 PD, 6 SP, 26 Unknown	17 SSRI, 2 Beta-blocker, 4 antidepressants, 1 unknown medication	3/7.5	FSL/VBM/ Whole brain and ROI	AHC, basal ganglia, PFC, and parietal areas.	$P < 0.05$ (FWE)	*Whole brain*: None *ROI*: Right putamen	*Whole brain*: None *ROI*: None
Brühl et al., 2014[22]	SAD: 46 (17)/ 33.1 ± 10.6 HC: 46 (17)/ 33.0 ± 8.9	NA/NA	66.2 ± 20.4 (LSAS)	1 MDD	19 taking antidepressants	3/NA	FreeSurfer/ Segmentation procedure/ROI	Amygdala and hippocampus	$P < 0.05$ (Uncorrection)	*ROI*: None	*ROI*: None
Irle et al., 2010[23]	SAD: 24 (12)/ 32.0 ± 10.0 HC: 24 (12)/ 31.0 ± 9.0	17.0 ± 5.0/15.0 ± 10.0	38.0 ± 9.0 (Anxiety of LSAS) 29.0 ± 9.0 (Avoidance of LSAS)	7 APD, 1 BN, 1 PD	None	3/NA	CURRY/ Manual tracing/ROI	Amygdala and hippocampus	$P < 0.05$ (Bonferroni correction)	*ROI*: None	*ROI*: B amygdala and hippocampus.
Irle et al., 2014[24]	SAD: 67 (35)/ 31.0 ± 10.0 HC: 64 (31)/ 32.0 ± 10.0	16.0 ± 6.0/15.0 ± 9.0	37 ± 11 (Anxiety of LSAS) 31.0 ± 10.0 (Avoidance of LSAS)	19 APD, 16 MDD, 5 Dysthymia, 7 Specific phobia, 5 PD, 2 AG, 1 GAD	6 taking antidepressants	3/8	SPM/VBM and manual segmentation/ Whole brain and ROI	Precuneu, postcentral gyrus, inferior parietal cortex (i.e., supramarginal and angular gyrus)	$P < 0.001$ (Uncorrection)	*Whole brain*: R premotor cortex (SFG) and SMA, parietal cortices (L precuneus and R angular gyrus). *ROI*: None	*Whole brain*: None ROI: R postcentral gyrus
Kawaguchi et al., 2016[25]	SAD: 13 (8)/ 36.2 ± 11.8 HC: 18 (12)/ 33.8 ± 9.6	13.0 ± 10.3/23.3 ± 14.4	81.6 ± 14.3 (LSAS)	Current comorbidity 4 MDD, 1 PD, 1 Bulimia nervosa, Past comorbidity 2 MDD, 1 PD, 1 Bulimia nervosa, 1 Adjustment disorder	NA	3/8	SPM/VBM/ Whole brain and ROI	Insula, amygdala and hippocampus	$P < 0.05$ (FWE)	*Whole brain*: None *ROI*: None	*Whole brain*: None *ROI*: L anterior, and R posterior insula
Koc et al., 2018[26]	SAD: 22 (NA)/25 ± 4.1	NA/NA	NA	Non	NA	1.5/NA	GE Medical Systems program/	B amygdala and hippocampus	$P < 0.05$ (NA)	*ROI*: B hippocampus	*ROI*: Non

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Table 1 (*continued*)

Study	Subjects Number (female)/ Age at study, years	Age of onset/ Illness duration (years)	Score of symptom severity (scale type)	Number of combined Comorbidity	Number of current medication users	Method Field strength (Tesla)/ Smoothing (mm)	Software/ Method (Whole brain or ROI)	Regions of interest	Statistic of gray matter volume (correction)	Main findings Patients > HC	Patients < HC
	HC: 20 (NA)/ 31.2 ± 4.6						Manual drawing/ ROI				
Machado-de-Sousa et al., 2014[27]	SAD: 12 (5)/ 20.2 ± 0.0 HC: 14 (3)/19.8 ± 0.0	NA/NA	NA	None	None	1.5/NA	ANALYZE AVW/Manual tracing/ROI	B amygdala and hippocampus.	$P < 0.001$ (NA)	*ROI*: B amygdala and L hippocampus.	*ROI*: None
Mansson et al., 2016[28]	SAD: 26 (22)/32.3 ± 9.7 HC: 26 (18)/32.2 ± 10.5	15.9 ± 6.0/NA	76.3 ± 18.7 (LSAS)	NA	8 concurrent psychotropic medication	3/8	SPM/VBM/ Whole brain and ROI	B ACC, insula, amygdala and hippocampus	$P < 0.001$ for Whole brain (Uncorrection) $P < 0.05$ for ROI (FWE)	*Whole brain*: B IFG, SFG, MTG, L SMA, R IFG. *ROI*: None	*Whole brain*: L calcarine *ROI*: None
Meng et al., 2013[29]	SAD: 20 (6)/21.8 ± 3.7 HC: 19 (6)/21.6 ± 3.7	NA/4.2 ± 3.8	52.7 ± 11.7 (LSAS)	None	None	3/12	SPM/VBM/ Whole brain	None	$P < 0.05$ (Correction)	*Whole brain*: None	*Whole brain*: B thalami, R amygdala,and precuneus.
Talati et al., 2013[16]	SAD: 33 (9)/31.5 HC: 37 (19)/31.4 ± 9.1	NA/NA	NA	11 MDD, 5 GAD, 4 SP, 1 OCD, 1 DUD, 2 AUD	None	1.5/8	SPM/VBM/ Whole brain and ROI	B amygdala, B insula and ACC	$P < 0.05$ for Whole brain (Correction) $P < 0.05$ for ROI (Small-volume correction)	*Whole brain*: *SAD > HC*: L cerebellum, parahippocampal and fusiform; B supramarginal and angular gyrus, L MOG. *ROI*: None	*Whole brain*: B STG, L OFC, R SOG. *1* *ROI*: B insula, L ACC, and R amygdala
Tükel et al., 2015[30]	SAD: 27 (15)/27.7 ± 6.7 HC: 27 (15)/27.7 ± 5.8	14.5 ± 4.1/13.8 ± 7.0	74.0 ± 26.5 (LSAS)	None	None	1.5/8	SPM/VBM/ Whole brain	None	$P < 0.05$ (FWE)	*Whole brain*: L superior parietal gyrus, precuneus, R MTG, ITG, and fusiform.	*Whole brain*: None.
Zhao et al., 2017[31]	SAD: 24 (9)/24.5 ± 4.0 HC: 41 (15)/27.1 ± 7.2	NA/7.6 ± 3.8	57.0 ± 25.5 (LSAS)	None	None	3/8	SPM/VBM/ Whole brain	None	$P < 0.001$ (FDR)	*Whole brain*: None.	*Whole brain*: B OFC, putamen, and thalamus.

PD vs. SAD Study	Number (female)/Age at study, years	Age of onset/ Illness duration (years)	Score of symptom severity (scale type)	Number of combined Comorbidity	Number of current medication users	Field strength (Tesla)/ Smoothing (mm)	Software/ Method (Whole brain or ROI)	Regions of interest	Statistic of gray matter volume (correction)	PD > SAD	PD < SAD
						1.5/8		None			

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Table 1 (*continued*)

PD vs. SAD Study	Number (female)/Age at study, years	Age of onset/ Illness duration (years)	Score of symptom severity (scale type)	Number of combined Comorbidity	Number of current medication users	Field strength (Tesla)/ Smoothing (mm)	Software/ Method (Whole brain or ROI)	Regions of interest	Statistic of gray matter volume (correction)	PD > SAD	PD < SAD
Talati et al., 2013[16]	SAD:16 (13)/ 34.1 ± 7.1 PD:16 (13)/ 31.8 ± 10.0	11.0 ± 0.0/ NA 18.4 ± 3.4/ NA	NA NA	5 MDD, 2 GAD, 4 SP, 1 OCD, 1 DUD, 0 AUD 3 MDD, 2 GAD, 5 SP, 2 OCD, 4 DUD, 4 AUD	None None		SPM5/VBM/ Whole brain		$P < 0.05$ (Correction)	*Whole brain*: B lingual gyrus, L cuneus, MFG, and R SOG.	*Whole brain*: B MFG, fusiform gyrus, parahippocampal gyrus, R IFG, ACC, and cerebellum.

Note. ACC, anterior cingulate cortex; AD, adjustment disorder with mixed disturbance of emotions and conduct; AG, agoraphobia; AHC, Amygdala–hippocampus complex; APD, avoidant personality disorder; AUD, alcohol use disorder (abuse or dependence); B, bilateral; BN, bulimia nervosa; DUD, drug use disorder (abuse or dependence); F, female; FDR, false discovery rate; FWE, family wise error; GAD, generalized anxiety disorder; HARS, Hamilton rating scales for anxiety; HC, healthy controls; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; L, left; LSAS, Liebowitz social anxiety scale; M, male; MDD, major depressive disorder; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; NA, not available; OCD, obsessive compulsive disorder; OFC, Orbitofrontal cortex; PD, panic disorder; PDSS, panic disorder severity scale; PFC, prefrontal cortex; PPD, paranoid personality disorder; R, right; ROI, region of interest; SAD, social anxiety disorders; SFG, superior frontal gyrus; SMA, supplementary motor area; SNRI, serotonin and norepinephrine reuptake inhibitors; SOG, superior occipital gyrus; SP, specific phobia; SPM, Statistical Parametric Mapping; SSRI, selective serotonin reuptake inhibitor; STG, superior temporal gyrus; VBM, voxel-based morphometry.

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Table 2
Demographic and clinical information for studies of PD and SAD included in the pooled meta-analyses (mean ± SD)

Study	Patients									Controls				Method	
	N	Age	Female, %	R handedness, %	Age of onset	Illness duration, y	Symptom score[#]	Comorbidity, n (%)	Medications, n (%)	N	Age	Female, %	R handedness, %	Strength (Tesla)/ Smoothing (mm)	Statistic of GMV (correction)
PD															
Asami 2009[1]	24	37.0 ± 10.0	62.5	100.0	NA	3.9 ± 3.4	NA	17 (70.8)	24 (100.0)	24	37.0 ± 8.7	62.5	100.0	1.5/12	$P < 0.05$ (FDR)
Lai 2010[2]	16	37.9 ± 8.8	68.8	100.0	NA	NA	18.6 ± 2.9	16 (100.0)	0 (0.0)	15	34.3 ± 9.9	73.3	100.0	3/7.5	$P < 0.005$ (FWE)
Lai 2012[3]	30	47.0 ± 10.6	63.3	100.0	NA	NA	21.6 ± 2.3	0 (0.0)	0 (0.0)	21	41.1 ± 11.8	52.4	100.0	3/7.5	$P < 0.005$ (FWE)
Lai 2015[4]	53	43.3 ± 10.1	52.8	98.1	NA	0.5 ± 0.2	NA	0 (0.0)	0 (0.0)	54	40.4 ± 10.5	53.7	96.3	3/7.5	$P < 0.005$ (FWE)
Massana 2003[5]	18	36.8 ± 11.3	61.1	100.0	NA	NA	NA	15 (83.3)	NA	18	36.7 ± 8.8	55.6	100.0	1.5/12	$P < 0.05$ (Corrected)
Na 2013[6]	22	40.2 ± 10.6	40.9	100.0	NA	NA	NA	12 (54.6)	NA	22	40.2 ± 12.4	50.0	100.0	3/8	$P < 0.05$ (FWE)
Protopopescu 2006[7]	10	35.5 ± 9.7	60.0	100.0	NA	NA	NA	NA	1 (10.0)	23	28.7 ± 7.5	47.8	100.0	3/12	$P < 0.05$ (Corrected)
Sobanski 2010[8]	17	34.9 ± 6.7	52.9	100.0	NA	7.9 ± 5.2	NA	17 (100.0)	17 (100.0)	17	33.1 ± 6.2	52.9	100.0	1.5/12	$P < 0.05$ (FWE)
Talati 2013[9]	16	31.8 ± 10.0	81.3	NA	18.4 ± 3.4	NA	NA	16 (100.0)	0 (0.0)	20	31.4 ± 7.8	45.0	NA	1.5/8	$P < 0.05$ (Corrected)
Uchida 2008[10]	19	37.1 ± 9.8	84.2	94.7	29.7 ± 9.8	8.3 ± 6.0	NA	19 (100.0)	18 (94.7)	20	36.5 ± 9.9	80.0	100.0	1.5/8	$P < 0.001$ (Uncorrected)
Yoo 2005[11]	18	33.3 ± 7.1	50.0	100.0	NA	3.6 ± 2.2	8.3 ± 5.7	0 (0.0)	0 (0.0)	18	32.0 ± 5.8	38.9	88.9	3/8	$P < 0.05$ (Corrected)
SAD															
BasHoogen 2017[12]	174	30.6 ± 10.0	58.6	98.9	NA	NA	NA	NA	NA	213	32.4 ± 10.5	54.5	96.7	3/7.5	$P < 0.05$ (FWE)
Irle 2014[13]	67	31.0 ± 10.0	52.2	92.5	16.0 ± 6.0	15.0 ± 9.0	NA	55 (82.1)	6 (9.0)	64	32.0 ± 10.0	48.4	90.3	3/8	$P < 0.001$ (Uncorrected)
Kawaguchi 2016[14]	13	36.2 ± 11.8	61.5	100.0	13.0 ± 10.3	23.3 ± 14.4	81.6 ± 14.3	11 (84.6)	NA	18	33.8 ± 9.6	66.7	100.0	3/8	$P < 0.05$ (FWE)
Mansson 2016[15]	26	32.3 ± 9.7	84.6	100.0	15.9 ± 6.0	NA	76.3 ± 18.7	NA	8 (30.8)	26	32.2 ± 10.5	69.2	100.0	3/8	$P < 0.001$ (Uncorrected)
Meng 2013[16]	20	21.8 ± 3.7	30.0	100.0	NA	4.2 ± 3.8	52.7 ± 11.7	0 (0.0)	0 (0.0)	19	21.6 ± 3.7	31.6	100.0	3/12	$P < 0.05$ (Corrected)
Talati 2013[9]	33	31.5 ± 0.0	27.3	NA	NA	NA	NA	24 (72.7)	0 (0.0)	37	31.4 ± 9.1	51.4	NA	1.5/8	$P < 0.05$ (Corrected)
Tukel 2015[17]	27	27.7 ± 6.7	55.6	100.0	14.5 ± 4.1	13.8 ± 7.0	74.0 ± 26.5	0 (0.0)	0 (0.0)	27	27.7 ± 5.8	55.6	100.0	1.5/8	$P < 0.05$ (FWE)
Zhao 2017[18]	24	24.5 ± 4.0	37.5	100.0	NA	7.6 ± 3.8	57.0 ± 25.5	0 (0.0)	0 (0.0)	41	27.1 ± 7.2	36.6	100.0	3/8	$P < 0.001$ (FDR)

Note. F, female; FDR, false discovery rate; FWE, family wise error; LSAS, Liebowitz Social Anxiety Scale; M, male; NA, not available; PD, panic disorder; PDSS, Panic Disorder Severity Scale; SAD, social anxiety disorder.
[#] LSAS for SAD patients, PDSS for PD patients.References

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gyrus (SOG) (Irle et al., 2014; Kawaguchi et al., 2016; Meng et al., 2013; Talati et al., 2013; Zhao et al., 2017), as well as smaller subcortical bilateral amygdala, hippocampus, putamen and thalamus volumes (Irle et al., 2010; Meng et al., 2013; Talati et al., 2013; Zhao et al., 2017) in patients with SAD relative to those in HC. In contrast, other authors found no significant differences in the whole-brain regional GMVs (Bas-Hoogendam et al., 2017; Kawaguchi et al., 2016), including in ROIs of the bilateral ACC and insula (Mansson et al., 2016), as well as in the subcortical bilateral amygdala and hippocampus (Ahmed-Leitao et al., 2019; Bas-Hoogendam et al., 2017; Bruhl et al., 2014b; Kawaguchi et al., 2016; Mansson et al., 2016), between SAD patients and HC.

PD versus SAD patients. Research investigating the neuropathological distinction between PD and SAD patients is scarce. Only one study using a whole-brain approach reported GMV differences in the prefrontal and temporal-parietal-occipital cortices, limbic regions and cerebellum between PD patients and SAD patients (Talati et al., 2013).

3.2.3. *Effects of demographic and clinical variables*

PD patients. Sixteen of 19 included studies reported the effects of demographic and clinical variables, such as the severity of anxiety-related symptoms and psychotropic medication use, on regional GMV alterations in patients with PD; of these 16 studies, 2 reported positive correlations of age of onset (Uchida et al., 2003) and the severity of social anxiety symptoms (Lai et al., 2010) with regional GMVs in PD patients, and 8 reported no such correlations (Asami et al., 2008; Asami et al., 2018a; Asami et al., 2009; Asami et al., 2018c; Maggioni et al., 2019; Massana et al., 2003b; Na et al., 2013; Uchida et al., 2008). There was neither a correlation between age (Asami et al., 2008; Massana et al., 2003b) and sex (Massana et al., 2003b) of PD patients and regional GMVs nor any effect of age on sex-affected regional GMV changes (Asami et al., 2009). Smaller female-specific volumes were observed in the bilateral DLPFC and ventrolateral prefrontal cortex (VLPFC), parietal cortex, thalamus and right cerebellum in PD patients compared to female controls, but no significant male-specific volume changes (Asami et al., 2009). Concerning clinical variables, patients with PD exhibited significant negative correlations between age at onset and the GMV of the OFC (Sobanski et al., 2010) and between illness duration and the left putamen volume (Yoo et al., 2005) or no such correlation (Asami et al., 2008; Asami et al., 2009; Uchida et al., 2008). Regarding clinical symptoms, some studies reported that the severity of anxiety-related symptoms in PD patients, such as the scores of the Panic Disorder Severity Scale (PDSS), Hamilton Anxiety Rating Scale (HARS), State-Trait Anxiety Inventory (STAI) State-Anxiety (S-Anxiety) Scale and Zung Self-rating Anxiety Scale (Z-SAS), was significantly negatively correlated with regional GMVs of the left SFG and fusiform gyrus, right insula and IFG, and subcortical bilateral putamen and thalamus, left amygdala and hippocampus (Hayano et al., 2009; Lai, 2014; Lai and Wu, 2012, 2015; Maggioni et al., 2019; Yoo et al., 2005). Others reported no correlation between the severity of anxiety-related symptoms and GMV alterations of the cortical and subcortical regions in PD groups (Asami et al., 2008; Asami et al., 2018a; Asami et al., 2009; Asami et al., 2018c; Massana et al., 2003b; Na et al., 2013). The clusters of significant GMV alterations in PD patients relative to HC remained present when excluding the patients who also met the criteria for current depressive disorders (Uchida et al., 2008). Regarding medication use, there were no significant differences in the bilateral putamen volumes between PD patients with and without a prior history of antipanic medication (Yoo et al., 2005), and other studies reported no significant effect of the total dose of antidepressants/benzodiazepines (Asami et al., 2008; Asami et al., 2009) or the duration of antidepressant drug therapy (Uchida et al., 2008) on regional GMV alterations in PD patients.

SAD patients. Ten of 13 included studies reported mixed effects of clinical variables, such as the age of onset, illness duration, and anxiety-related symptom severity, on regional GMV alterations in SAD patients, 4 of which reported no such effect (Ahmed-Leitao et al., 2019; Bruhl et al., 2014b; Kawaguchi et al., 2016; Zhao et al., 2017). A study

Table 3
Clusters showing significant differences in GMV among patients with PD or SAD and controls in a meta-analysis of published studies that met the criteria for robustness.

Region	Peak MNI coordinates X	y	z	SDM Z value	*P* value	Voxel size	Cluster breakdown
PD patients vs. controls							
PD > controls							
None							
PD < controls							
Right insula, BA 48	38	-2	0	-2.987	0.000002	4859	Right insula, BA 48 Right lenticular nucleus, putamen, BA 48 Right superior temporal gyrus, BA 21,22,48 Right postcentral gyrus, BA 6,48 Right rolandic operculum, BA 48 Right inferior frontal gyrus, orbital part, BA 38 Right temporal pole, superior temporal gyrus, BA 38 Right inferior frontal gyrus, opercular part, BA 48
Right median cingulate/paracingulate gyri, BA 24	2	14	32	-1.847	0.001709	545	Right median cingulate/paracingulate gyri, BA 24
Right superior frontal gyrus, orbital part, BA 11	14	30	-14	-2.000	0.000735	159	Right superior frontal gyrus, orbital part, BA 11
SAD patients vs. controls							
SAD > controls							
Right superior frontal gyrus, dorsolateral, BA 6	12	-18	66	1.498	0.000101	551	Right superior frontal gyrus, dorsolateral, BA 6
Left precuneus, BA 7	-2	-56	52	1.274	0.000791	384	Left precuneus, BA 7; Bilateral precuneus
Right angular gyrus, BA 39	50	-62	24	1.148	0.001642	174	Right angular gyrus, BA 39; Right middle temporal gyrus, BA 39; Right middle occipital gyrus, BA 39
Right supplementary motor area, BA 8	14	20	56	1.225	0.001042	134	Right supplementary motor area, BA 6,8
SAD < controls							
Left lenticular nucleus, putamen, BA 48	-26	2	-6	-1.314	0.001187	453	Left lenticular nucleus, putamen, BA 48
Left thalamus	0	-16	6	-1.234	0.003028	42	Left thalamus
PD vs. SAD patients							
PD < SAD							
Right inferior frontal gyrus, opercular part, BA 48	56	8	4	1.810	0.000004	472	Right inferior frontal gyrus, opercular part, BA 48
SAD < PD							
Right lenticular nucleus, putamen, BA 48	32	-2	-14	-3.070	0.000002	951	Right lenticular nucleus, putamen, BA 48
Right thalamus	2	-24	8	-2.297	0.000196	139	Right thalamus; Left thalamus
Left lenticular nucleus, putamen, BA 48	-24	2	-8	-1.873	0.000915	13	Left lenticular nucleus, putamen, BA 48 Left striatum
Common alterations in PD and SAD							
None							

reported a significantly smaller right amygdala in older SAD patients and smaller bilateral amygdala in male but not female patients with SAD (Irle et al., 2010). Concerning clinical variables, patients with SAD exhibited significant positive correlations between age of onset and GMD of the right amygdala and thalamus, a negative correlation between illness duration and GMD of the right amygdala (Meng et al., 2013), or no effect of age of onset and illness duration (Irle et al., 2014; Zhao et al., 2017). Regarding the clinical symptoms of patients with SAD, there were positive correlations between greater severity of anxiety-related symptoms, such as the Liebowitz social anxiety scale

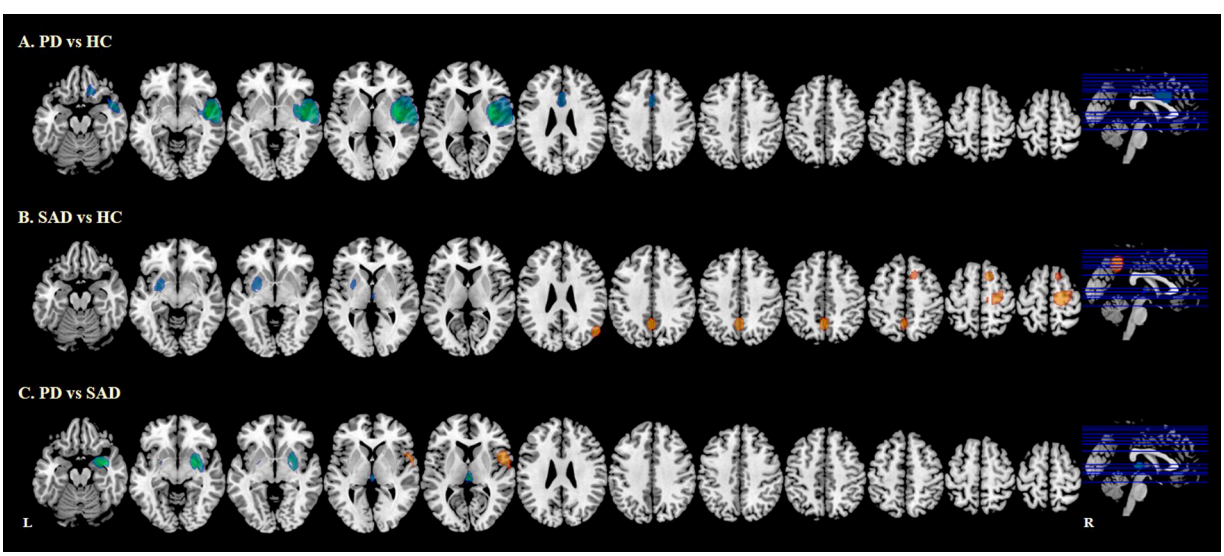

Figure 2. (**A**) Results of meta-analysis of brain grey matter volume (GMV) in patients with panic disorder (PD) relative to healthy controls (HC), (**B**) brain GMV results of patients with social anxiety disorder (SAD) relative to HC, and (**C**) brain regions showing significant differences in GMV between patients with PD and patients with SAD; the differences are more substantial in PD patients. Red-yellow and blue-green clusters represent larger and smaller GMVs, respectively, in patients relative to HC and in SAD patients compared to PD patients relative to HC.

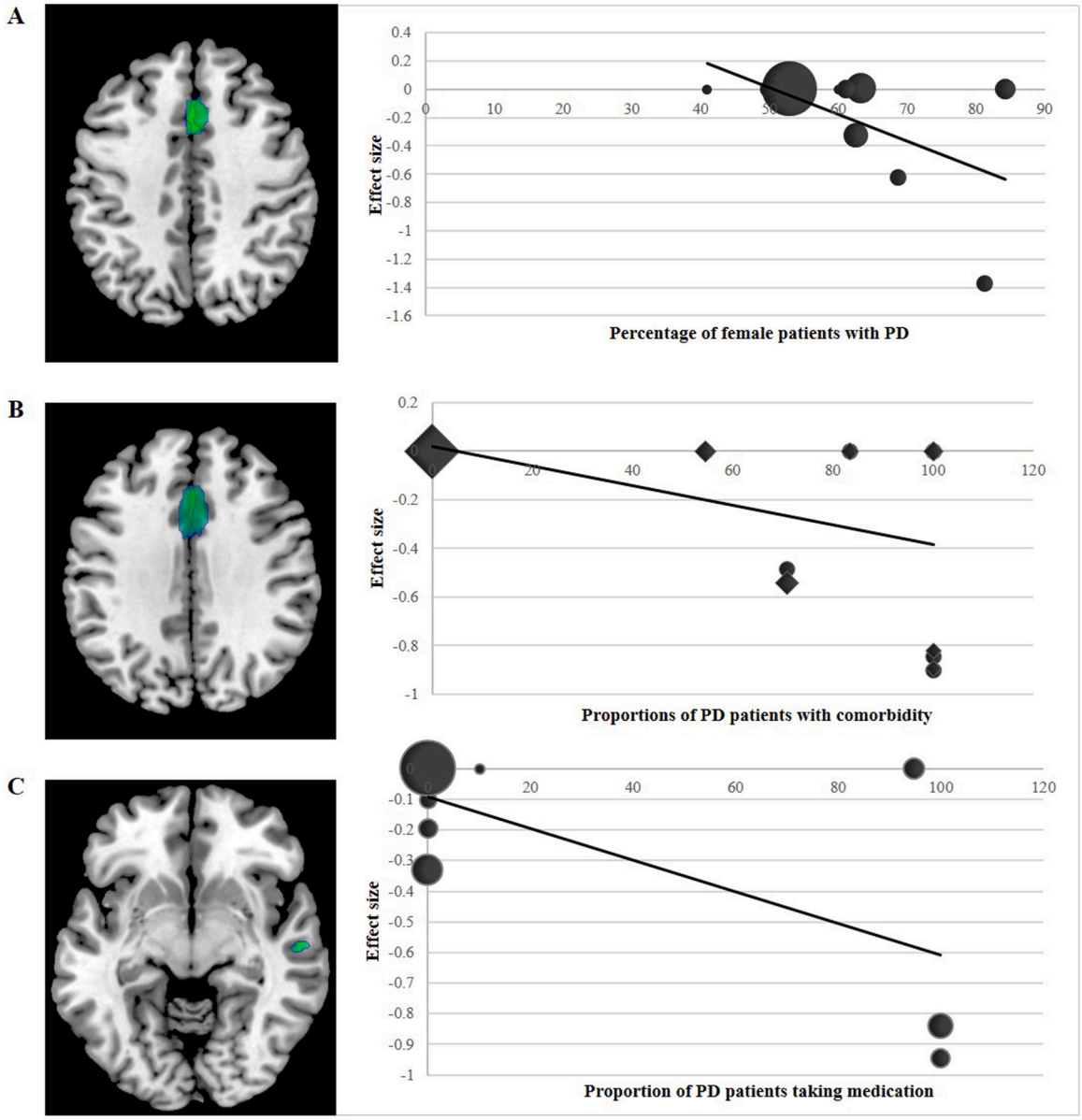

Figure 3. (**A**) Results of meta-regression analysis of the dependence of brain GMV on the percentage of female patients with PD, (**B**) results of meta-regression analysis of the dependence of brain GMV on the proportion of PD patients with psychiatric comorbidities (the circles and diamonds pointing to left and right median cingulate/paracingulate gyri, respectively), and (**C**) results of meta-regression analysis of the dependence of brain GMV on the proportion of PD patients currently taking medication.

(LSAS) score and anticipatory speech anxiety, and the regional GMVs of the bilateral precuneus, MTG, ITG, left STG, superior parietal area, cuneus and supramarginal gyrus, right MFG, rectus and MOG, as well as the volume of the subcortical right putamen (Bas-Hoogendam et al., 2017; Irle et al., 2014; Mansson et al., 2016; Tukel et al., 2015). Meanwhile, SAD patients also exhibited significantly negative correlations between the severity of anxiety-related symptoms and GMVs of the bilateral precuneus, left intraparietal sulcus, right supramarginal gyrus, amygdala and hippocampus (Irle et al., 2014; Irle et al., 2010) or no such correlation with GMV changes in the brain regions (Kawaguchi et al., 2016; Meng et al., 2013; Zhao et al., 2017), including the amygdala and hippocampus (Bruhl et al., 2014b). SAD patients with comorbid avoidant personality disorder (APD) did not differ significantly from those without APD in any brain variable (Irle et al., 2014; Irle et al., 2010). There were no significant differences in any brain variables between SAD patients taking antidepressant drugs and those not taking antidepressant drugs (Irle et al., 2014).

3.3. *Quantitative meta-analysis of GMV differences*

3.3.1. *GMV differences between patients and HC*

PD patients versus HC. Relative to HC, patients with PD showed smaller GMVs in the right insula (extending to the right IFG, postcentral gyrus, STG, rolandic operculum and putamen), median cingulate/paracingulate gyri, and SFG, without larger regional GMVs (Table 3 and Figure 2A).

SAD patients versus HC. Relative to HC, patients with SAD showed larger GMVs in the left precuneus, right SFG, SMA, and angular gyrus (extending to the right MTG and MOG), together with smaller GMVs in the left putamen and thalamus (Table 3 and Figure 2B).

3.3.2. *GMV differences between PD and SAD patients*

The linear modal analysis showed smaller GMV in the right IFG and larger GMVs in the bilateral putamen and thalamus in patients with PD than in patients with SAD relative to HC (Table 3 and Figure 2C).

The multimodal analysis showed no shared GMV alterations between patients with PD and SAD.

3.3.3. Meta-regression analysis

PD patients. The percentage of female patients with PD in all 11 studies was negatively associated with smaller GMV in the right median cingulate/paracingulate gyri (peak MNI: x, y, z = 4, 18, 42; Z = -1.902; r = -0.564, P < 0.0001; 300 voxels; Figure 3A). The proportion of PD patients with psychiatric comorbidity in 10 studies was negatively associated with smaller GMV of the left (peak MNI: x, y, z = -4, 24, 34; Z = -1.686; r = -0.487, P < 0.0001; 166 voxels, the circles) and right (peak MNI: x, y, z = 6, 22, 32; Z = -1.678; r = -0.483, P < 0.0001; 140 voxels, the diamonds) median cingulate/paracingulate gyri (Figure 3B), respectively. The proportion of PD patients currently taking psychotropic drugs in 9 studies was negatively associated with a smaller GMV in the right STG (peak MNI: x, y, z = 56, -16, -8; Z = -2.235; r = -0.671, P < 0.001; 41 voxels; Figure 3C).

The mean age or handedness of PD patients was not significantly associated with regional GMV alterations. The following variables could not be studied because the data were available in fewer than nine studies: age of onset, illness duration and the severity of clinical symptoms.

SAD patients. Meta-regression analysis was not performed in the SAD group due to only eight studies being included.

3.3.4. Analyses of jack-knife, heterogeneity and publication bias

The results of the whole-brain jack-knife sensitivity analyses in PD and SAD patients are shown in Table S3 and Table S4, respectively. The heterogeneity analysis results for PD and SAD patients are shown in Table S5 and Table S6, respectively. Egger's test of funnel plot asymmetry revealed no significant publication bias of abnormal regions in PD patients vs HC (Figure S1 A1-A3), SAD vs HC (Figure S1 B1-A6), or between PD patients and SAD patients (Figure S2 C1-C4).

4. Discussion

Qualitatively and quantitatively, the current study revealed consistently smaller cortical-subcortical GMVs with a right-lateralized tendency involving the prefrontal and temporal-parietal cortices, subcortical striatum, thalamus and brainstem in PD patients relative to HC; the current study also revealed larger cortical GMVs of the prefrontal and temporal-parietal-occipital cortices, and smaller subcortical GMVs in the striatum and thalamus in SAD patients relative to HC. These findings indicate largely distinct neuropathological substrates underlying PD and SAD. Quantitatively, the right IFG structural deficit was specifically implicated in PD, and the left striatum-thalamus deficits were relatively specific to SAD, suggesting distinctly specific structural abnormalities in both disorders. Quantitatively, PD patients showed a smaller GMV in the PFC and larger GMVs in the subcortical striatum and thalamus than SAD patients, without shared GMV alterations in both disorders. Demographic and clinical variables such as the severity of anxiety-related symptoms, psychiatric comorbidity and concomitant medication use exhibited negative effects on regional GMV alterations in PD, while the effects were qualitatively inconclusive in SAD. These findings suggest that PD and SAD may present largely distinct neuropathological substrates, representing distinct anxiety sub-entities at the level of their neuroanatomical phenotypes.

4.1. GMV abnormalities in both disorders

4.1.1. Separate GMV alterations

Relative to their respective HC, patients with PD and those with SAD exhibited GMV changes of directionally inconsistent cortical and directionally consistent subcortical regions, as well as distributionally different cortical-subcortical regions. Qualitatively and quantitatively, our convergent evidence showed directionally consistent smaller GMVs in the cortical-subcortical regions in patients with PD compared to HC, in line with the findings from other studies, including meta-analyses (Atmaca et al., 2012; Del Casale et al., 2013; Lai, 2011; Lai and Hsu, 2011; Lai and Wu, 2013; Roppongi et al., 2010; Vythilingam et al., 2000; Wu et al., 2018). Similarly, lower cortical thicknesses of the prefrontal and temporal regions were also reported in PD patients compared with HC (Asami et al., 2018b; Kang et al., 2017). Distributionally smaller GMVs in PD patients compared to HC were located in the prefrontal and temporal-parietal cortices (mainly the PFC including the OFC) and subcortical bilateral striatum, thalamus and brainstem, especially the right-lateralized regions. Similarly, other studies, including reviews, also reported smaller GMVs of the prefrontal and temporal cortices, insula, ACC, and basal ganglia structures in PD patients relative to HC (Atmaca et al., 2012; Del Casale et al., 2013; Dresler et al., 2013; Lai and Wu, 2013; Picado et al., 2015; Roppongi et al., 2010; Vythilingam et al., 2000). It was speculated that emotional processing cannot be modulated through the deliberate and conscious application of top-down executive control over emotional stimulus processing and cannot inhibit the fear that occurs during periods of anxiety because of the atrophy of the PFC (Shang et al., 2014). Because lower GMV in PD mainly occurs in the cortical regions, especially the PFC, damage to the top-down control/regular system might be involved in the dysfunction of emotion processing and regulation in PD patients, which was also highlighted by recent reviews (Lai, 2019; Wu et al., 2018). In addition, quantitatively, patients with PD relative to HC exhibited right-lateralized GMV deficits in the prefrontal-temporal cortex, ACC and putamen, consistent with other studies that also found GMV deficits in the right STG, ITG and insula (Lai and Wu, 2013; Picado et al., 2015) in PD patients relative to HC, especially the asymmetric atrophy of the right temporal lobe (Dantendorfer et al., 1996; Fontaine et al., 1990; Ontiveros et al., 1989). The right-lateralized structural abnormalities are in line with models of disturbed, overactive and dysregulated ventral attentional networks in trait anxiety and anxiety disorders (Sylvester, et al. 2012), which are predominantly right-lateralized. These findings suggest that cortical-subcortical GMV deficits, especially right-lateralized structural deficits, may be the neuropathological basis underlying a damaged top-down control system in PD.

Directionally SAD patients generally exhibited larger cortical and smaller subcortical GMV alterations compared to HC qualitatively and quantitatively. Distributionally SAD patients exhibited larger GMVs in the prefrontal and temporal-parietal-occipital cortices and smaller GVMs in the subcortical striatum and thalamus compared to HC qualitatively and quantitatively. These findings were partially consistent with other studies, which reported larger cortical regional GMVs in the bilateral lingual gyrus and lateral occipital cortex, left fusiform gyrus and right MPFC (Frick et al., 2014; Liao et al., 2011); smaller subcortical GMVs in the left hippocampal gyrus and right PHG (Liao et al., 2011); or null findings (Cheng et al., 2015) in SAD patients compared to HC. Similarly, a conference abstract reported trend-level smaller left thalamus volume in SAD patients relative to controls (Groenewold et al., 2018). It was reported that after antidepressant treatment or psychotherapy, SAD patients also showed GMV changes in the prefrontal-parietal-occipital cortices, bilateral striatum, and right thalamus compared to baseline values (Steiger et al., 2017; Talati et al., 2015). These findings are consistent with evidence that the reward/avoidance basal ganglia circuitry plays a role in mediating SAD symptoms (Howells et al., 2015); this circuitry includes the caudate and putamen (collectively known as the striatum), thalamus, and cortical regions, such as the PFC (Caouette and Guyer, 2014). Thus, these findings provide evidence that structural cortical hypertrophy and subcortical atrophy may be involved in the neuropathology of SAD.

4.1.2. Disorder-specific GMV alterations

Our analysis quantitatively revealed significantly different GMV alterations in several areas between PD and SAD patients. In particular, a right IFG deficit was robustly and specifically implicated in PD, while

left striatum-thalamus deficits were relatively consistent and specific to SAD, suggesting the prominence of neural structural deficits may serve to distinguish PD from SAD.

A smaller right IFG volume has been well documented in PD (Lai, 2011; Wu et al., 2018) but has been reported less often in SAD (Wang et al., 2018). The PFC, including the IFG, plays a critical role in emotional processing, especially that of anxiety and fear (Etkin et al., 2011). Similarly, the IFG may play an important role in suppressing a fear response by its "top-down governance" function (Kent et al., 2005; Schiller and Delgado, 2010). It was speculated that atrophy of the PFC was one of the main reasons for the occurrence of anxiety disorders and that emotional processing cannot be modulated through the deliberate and conscious application of top-down executive control over emotional stimulus processing and cannot inhibit fear occurring during periods of anxiety (Shang et al., 2014). GMV increases in the PFC after undergoing antidepressant treatment might represent enhanced inhibitory control over the panic symptoms of remitted PD patients (Liao et al., 2010). Additionally, a functional imaging study of healthy volunteers suggested the important role of the PFC in the pathogenesis of PD (Eser et al., 2009). These observations, coupled with the current results, may indicate the specific neuroanatomical basis of dysfunctional top-down suppression of the fear response in PD.

Smaller left putamen and thalamus volumes have been verified in SAD (Wang et al., 2018) but have been found less often in PD (Lai, 2011; Wu et al., 2018). In contrast to our finding, it was indicated that higher socially anxious tendencies were positively correlated with striatal volume in healthy individuals (Günther et al., 2018), suggesting a possible profile of the abnormal brain development trajectory in SAD (Liu et al., 2020). Previous research suggested a striatal circuitry functional profile shared by both a behaviourally inhibited temperament and SAD in adolescents (Guyer et al., 2012), the former of which predicted risk for later anxiety disorders, particularly SAD (Essex et al., 2010). As a part of the striatum, the putamen is implicated in cognitive control, social learning and reward processing (Delgado, 2007). The importance of structural changes in the striatum to the development of anxiety most likely lies in their contribution to related behaviours such as reward sensitivity, motivation, attention and emotional processing (Lago et al., 2017). Similarly, SAD patients with greater symptom severity tended to have smaller subcortical volumes relative to controls, with a trend for a smaller left thalamus volume (Groenewold et al., 2018). Lesions to this region have been linked to the development of phobias (Kazui et al., 2001). A previous study reported functional abnormalities of the thalamus during emotion processing in SAD patients (Bruhl et al., 2011). Moreover, the effect of habituation on social stimuli was found in the thalamus of SAD patients (Sladky et al., 2012). Thus, consistent with the evidence that the reward/avoidance basal ganglia circuitry plays a role in SAD (Howells et al., 2015), striatum-thalamus structural deficits may be implicated in the neuropathological basis of SAD.

4.1.3. Mixed or null findings in limbic structures

Notably, relative to HC, PD or SAD patients exhibited mixed volumetric variation in limbic structures such as the amygdala and hippocampus qualitatively or null findings quantitatively, which are parts of the fear circuit (Gorman et al., 2000). A review also pointed towards GMD alterations in subcortical regions, such as the amygdala and hippocampus, in SAD patients but often lacked consistency (Bas-Hoogendam et al., 2016). Similarly, other ROI studies revealed smaller right amygdala and bilateral hippocampus volumes (Liao et al., 2011; Mueller et al., 2013), or null findings in the bilateral amygdala and hippocampus (Syal et al., 2012; Vythilingam et al., 2000; Yoon et al., 2016) in SAD patients relative to HC. Two meta-analysis studies reported no anxiety-related volume variation in the amygdala and hippocampus in SAD (Bas-Hoogendam et al., 2017) or PD (Wu et al., 2018) using the VBM method. Some of the possible interpretations for this inconsistency could be the heterogeneity of the samples included and differences in the methods used, such as ROIs vs. the whole brain and manual segmentation vs. VBM (Uchida et al., 2008a). For instance, quantitative null findings may have been due to the insufficient sensitivity to detect variation in small limbic structures (e.g., the amygdala and hippocampus) (Bergouignan et al., 2009) or a Gaussian filter width that was inappropriate for the size of the brain structures studied (Uchida et al., 2008a) in the VBM procedure.

4.2. GMV alterations between both disorders

Quantitatively, our study indicated more substantial cortical deficits of the right IFG and subcortical structural alterations of the bilateral striatum and thalamus in PD than in SAD. The GMV increases in the prefrontal region might represent enhanced inhibitory control over the panic symptoms of remitted PD patients after undergoing antidepressant treatment (Lai and Wu, 2013). Psychotherapy may act in a similar way to increase the prefrontal control of subcortical structures (Brooks and Stein, 2015). As a part of the dorsal attention network, the right IFG is involved in regulating goal-directed top-down processes (Liao et al., 2010). It may also be that the cortical volume increases to compensate for dysfunctional frontal-striatal regions (Yoo et al., 2008). These findings may suggest a more damaged top-down control system in PD than in SAD, consistent with the clinical presentation that unexpected panic attacks in PD are associated with greater dysregulation than expected panic attacks in SAD (Brown et al., 2016). As a result, PD patients exhibited larger subcortical striatum and thalamus volumes than SAD patients. Previous studies have suggested that several adrenergic receptors and dopamine receptors exert an important influence on sympathetic regulation in the striatum (Flügge et al., 2003; Isovich et al., 2000). Therefore, structural alterations in the putamen might be associated with more somatic anxiety symptoms of PD than of SAD. It is assumed that as the thalamus belongs to the arousal system, it may cause anxiety patients to be more easily aroused by emotional stimuli. These findings may indicate a poor ability of compensatory hyperactivity of the cortical region to inhibit overactivity of larger subcortical regions in PD relative to SAD, suggesting worse inhibitory control over the panic responses in PD patients than in SAD patients.

Notably, quantitatively, no shared region of GMV alteration was found in patients with PD and those with SAD, inconsistent with other meta-analysis studies recruiting different anxiety disorders, including PD and SAD, which reported a common smaller GMV of the PFC/ACC in patients with anxiety disorders compared to HC (Radua et al., 2010; Shang et al., 2014). This inconsistency may be partly explained by the following. First, there are different sample characteristics of the included studies. In our study, we only recruited adult subjects with PD and/or SAD, while those two studies included subjects of different ages with different anxiety disorders, including PD and SAD. Second, different analysis methods were adopted. Our study performed a statistical multimodal analysis to explore the potentially common GMV alterations in PD and SAD patients relative to HC, while Shang et al conducted subgroup analyses and found "common" regional GMV alterations in the different anxiety subgroups, and Radua et al. performed an omnibus test (Q statistic) to determine if there were differences in GMV across the different anxiety disorders.

4.3. Effects of demographic and clinical variables

The current study found qualitatively and quantitatively negative effects of demographic and clinical variables, such as psychiatric comorbidity and concomitant medication use, on regional GMV alterations in PD patients, together with qualitatively mixed effects in SAD patients. The sex differences in cerebral volume were evenly distributed, with all four equally smaller lobes (Nopoulos et al., 2000) and a smaller cingulate cortex (Liao et al., 2014) being found in females compared to males, in line with our finding of the negative correlation between a higher percentage of female PD patients and a smaller right ACC volume quantitatively. Similarly, other studies also reported that PD patients

with more severe anxiety-related clinical symptoms tended to have more GMV deficits in the prefrontal and temporal-parietal cortices and subcortical regions (Lai, 2011; Lai and Hsu, 2011). Consistent with the negative effects of psychiatric comorbidity and current medication use on regional GMVs, other studies, including a meta-analysis, also indicated that psychiatric comorbidities like MDD and the use of medications like antidepressants, were potential confounders of GMV alterations in anxiety disorders including PD (Kim et al., 2013; Shang et al., 2014), despite the lack of a qualitative effect of prior history, total dose and duration of psychotropic medication use. These findings suggest the negative effects of sex, comorbid psychiatric disorders and medication use on abnormal brain structures in PD.

Similar to other studies (Frick et al., 2014; Liao et al., 2011), the current study indicated inconsistent effects of the severity of social anxiety-related symptoms on regional GMV alterations in SAD patients qualitatively, together with a null effect of psychiatric comorbidity or medication use. These findings may suggest the inconclusive effects of these clinical characteristics on brain structural abnormalities in SAD.

4.4. Limitations

This study has several limitations. First, the number of enrolled studies was relatively small, especially the number of studies included in the meta-analysis, which may result in insufficient statistical power. Second, the present research included some studies that might recruit some of the same patients with PD (Asami et al., 2008; Asami et al., 2018a; Asami et al., 2009; Asami et al., 2018c; Lai, 2014; Lai et al., 2010; Lai and Wu, 2012, 2015; Massana et al., 2003a; Massana et al., 2003b) and those with SAD (Irle et al., 2014; Irle et al., 2010), which may result in a partial overlap of included subjects. Third, the influence of comorbid disorders on the current results cannot be ruled out completely, considering that some patients of the PD groups in the PD studies had significant social anxiety and vice versa, especially comorbidities among anxiety disorders including PD and SAD (Kessler et al., 2005). Moreover, the present study performed a meta-analysis only utilizing the coordinates derived from the included studies rather than the original images, which may have limited the accuracy of these findings. Finally, we could not determine whether these structural alterations were part of the pathogenesis or a consequence of the disorders due to the cross-sectional nature of the included studies.

5. Conclusion

In conclusion, the current study revealed largely divergent brain GMV abnormalities in PD and SAD, indicating distinct neuropathological substrates in these disorders. The different specific neuroanatomical deficits were also revealed in the right IFG for PD, and the left striatum and thalamus for SAD, with PD patients tending to show more substantial structural alterations than SAD patients, suggesting that PD and SAD may present distinct anxiety sub-entities at the level of their respective neuroanatomical phenotypes. The demographic and clinical variables had potential negative effects on regional GMV alterations in PD, whereas the effects may be inconclusive in SAD. These findings will be useful in bridging the gap between the current symptom cluster-based classification of mental illness (as exemplified by the DSM-5) and a neurobiological dimension-based system. According to a recent report (Bas-Hoogendam et al., 2020), using a uniform analysis approach, future prospective and longitudinal studies with a larger sample of different anxiety subgroups and only one sex or a balanced sex proportion overcoming the above limitations are needed to clarify the progressive trajectory of the brain neuropathological changes in the pathophysiological processes across PD and SAD.

Author contributions

XW and BC contributed to the conception of the study. XW, BC, and SW contributed significantly to the analysis and manuscript preparation; XW, BC, SW, FL, YL, XL, and DK performed the data analyses and wrote the manuscript.

Author statement

The work was not submitted for publication or was not under consideration for publication elsewhere. All authors have approved the submission. All authors of this paper qualify for authorship, and the copyright will be transferred to the *Journal of Affective Disorders* if the paper is accepted.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.11.057.

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