REVIEW ARTICLE

Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies

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Depression, anxiety and apathy are common mood disturbances in Parkinson's disease (PD) but their pathophysiology is unclear. Advanced neuroimaging has been increasingly used to unravel neural substrates linked to these disturbances. A systematic review is provided of neuroimaging findings in depression, anxiety and apathy in PD. A PubMed, MEDLINE and EMBASE search of peer-reviewed original research articles on these mood disturbances in PD identified 38 studies on depression, eight on anxiety and 14 on apathy in PD. Most of the imaging studies used either position emission tomography or single-photon emission computed tomography techniques. These studies generally suggest increased neural activity in the prefrontal regions and decreased functional connectivity between the prefrontal–limbic networks in depressed patients. Functional imaging studies revealed an inverse correlation between dopaminergic density in the caudate and putamen with the severity of anxiety in PD. There was no consistent correlation between dopaminergic density of thalamus and anxiety. Studies demonstrated both positive and inverse correlations between apathy and metabolism or activity in the striatum, amygdalar, prefrontal, temporal and parietal regions. The clinical variability of study subjects and differences in image pre-processing and analytical strategies may contribute to discrepant findings in these studies. Both nigrostriatal and extra-nigrostriatal pathways (in particular the frontal region and its connecting areas) are affected in mood disorders in PD. Identifying the relative contributions of these neural pathways in PD patients with overlapping motor and mood symptoms could provide new pathophysiological clues for the development of better therapeutic targets for affected patients.

Introduction

Parkinson's disease (PD) involves the degeneration of dopaminergic neurons in the substantia nigra pars compacta that leads to clinical manifestations of resting tremor, bradykinesia, postural instability and rigidity. There is increasing evidence to suggest that PD is not simply a pure motor disorder but rather a systemic disease with variegated non-motor symptoms, such as mood disturbances [1]. Depression is a prevalent mood disturbance in PD, occurring in around 2.7%–90% of patients [2], and affects quality of life [3].

Anxiety and apathy are also frequent symptoms in patients with PD [4,5]. In fact, studies have shown that depression often coexists with anxiety [6] and apathy [7]. The clinical presentations of depression share some similarities with anxiety and apathy, such as fatigue, agitation, psychomotor retardation, lack of facial expression and difficulties concentrating [8]. It has been suggested that depression and anxiety may be two related but separable entities since they are

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associated with different demographic and clinical features in PD [9,10]. Likewise, a recent meta-analysis study showed that half of PD patients with apathy did not suffer from concomitant depression, thereby implying that apathy may be a separate clinical entity [7]. Clinical observations and behavioural studies seem to suggest distinct aetiologies involving considerable overlap between these mood disturbances. However, the exact mechanism of these three mood disturbances in PD remains to be elucidated.

Advanced neuroimaging techniques have been increasingly employed to explore the neural substrates of mood disturbances in PD. However, the exact neuropathology of these three common mood disturbances in PD remains to be elucidated. To address current gaps in knowledge, a concise summary is provided of neuroimaging studies on mood disturbances in PD, highlighting new insights from these studies and drawing attention to the potential limitations and future research prospects.

Methods

MEDLINE, PubMed (alone or via MeSH) and EMBASE searches for peer-reviewed original research on humans with search terms 'depression', 'anxiety', 'apathy', 'mood symptoms', 'Parkinson's disease', 'Parkinson disease', 'neuroimaging', 'magnetic resonance imaging (MRI)', 'functional MRI', 'diffusion tensor imaging (DTI)', 'resting state functional MRI', 'single-photon emission computed tomography (SPECT)', 'positron emission tomography (PET)' and 'transcranial sonography (TCS)' identified 38 studies on depression, 8 on anxiety and 14 on apathy in PD (Fig. 1). Suitable references included in these studies were also extracted. The inclusion criteria were studies involving PD patients who did not have any other neurological conditions (e.g. stroke and dementia), using at least one of the aforementioned neuroimaging modalities, measuring at least one of the mood symptoms, and reporting the neural substrates of at least one of the mood symptoms in PD. Studies focusing on the pre-to-post intervention changes of mood symptoms but providing no information about the neural substrates of mood symptoms using one of the neuroimaging modalities were not included in our review.

Neuroimaging of depression in PD

Of the 38 studies on depression, 33 reported findings from one single imaging modality: 19 used either PET [11–13,15–19] or SPECT [20–30] techniques, four used T1-weighted imaging [31–33], three used DTI [34–36],

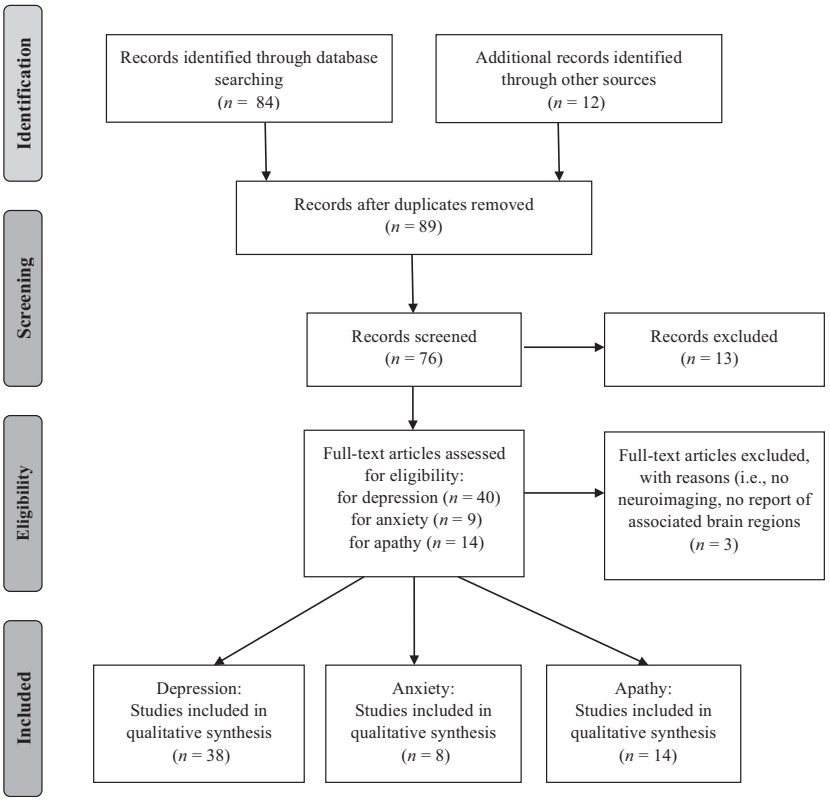

Figure 1 Flow diagram of study selection.

six used resting state functional MRI (RS-FMRI) [37–42] and two used TCS methods [43, 44]. The remaining four of the 38 studies reported findings from structural T1-weighted imaging plus another imaging method, including PET [14], DTI [45], task FMRI [46] and RS-FMRI [47], respectively. One study performed both TCS and T2-weighted MRI [48]. Whilst most studies excluded participants with cognitive impairment (e.g. dementia), one study [12] included PD patients with dementia and two studies did not specify whether their participants had cognitive decline [29,30]. Approximately half of these studies scanned PD patients in the 'on-medication' state, whilst the other half of the studies acquired imaging data in the 'off-medication' state and four studies did not specify the state of PD patients during imaging acquisition. As for the use of antidepressants, some studies requested patients to discontinue antidepressants before MRI scanning whilst other studies involved both on- and off-medication patients. In addition, some studies did not indicate the patients' severity or types of depression. For studies that reported depression types or severity, heterogeneous depression features of patients were noted, such that two studies only recruited patients with minor depression [24,39], another three studies only included patients with major depression [17,25,38] and four studies excluded patients with depression [18,19,26,28], whilst most studies had patients with various severities of depression (e.g. [13,20,23]). See Table 1 and Table S1 for the details of these studies.

The PET or SPECT studies of depression in PD examined neural metabolic activity in the resting state using various radiotracers. The majority reported reduced neural metabolic activity in PD patients with depression (dPDs) in comparison with patients with PD alone or healthy controls (HCs) or found inverse correlations between depression and neural metabolism. The abnormal regions were predominantly in the frontal lobe and striatum as well as the subcortical or limbic regions including thalamus, amygdala, hippocampus, anterior cingulate cortex and insula. A few studies reported an increase of neural metabolism in the prefrontal and subcortical regions (i.e. caudate and putamen, and amygdala), compared to HCs or PD patients without depression. Some found positive correlations between depression and neural metabolic activity in these regions [13,14,17,19,20]. One study with a large sample size of early PD patients did not find any correlation between depression severity and neural metabolism of the raphe nucleus [30].

Of the seven studies using T1-weighted imaging, only one reported bilaterally increased thalamic grey matter (GM) volume in dPD patients compared to PD patients without depression [47], and three did not find any GM volumetric differences between HCs and dPDs [14,31,48], whereas three studies showed that dPD patients had decreased GM volumes in the prefrontal, parietal and insular regions as well as the limbic system (anterior cingulate cortices and amygdala) [31,32,46] compared to HCs or non-depressed PD patients and further demonstrated inverse correlations between depression and brain volumes in the prefrontal and limbic regions [32,33].

A study using TCS and T2-weighted imaging showed decreased echogenicity but increased hyperintensity in the mesencephalic midline structure in depressed PD patients, thereby suggesting an alteration in the basal limbic system in dPD [44]. The other two studies applying TCS demonstrated hypoechogenicity in the brainstem raphe in dPD patients as opposed to HCs and non-depressed PD patients [43,48]. Using DTI techniques, three out of four studies reported compromised white matter connectivity indexed by decreased fractional anisotropy (FA) in various tracts, including the bilateral anterior cingulate cortex and thalamus and multiple tracts connecting to the left frontal and deep temporal lobes [34–36]. However, one study reported a non-significant group difference in the FA of the corpus callosum and uncinate fasciculus, a tract that interconnects the amygdala, hippocampus, temporal pole and the orbitofrontal cortex [45].

Compared to DTI findings, RS-FMRI studies of depression in PD revealed both increased and decreased resting state neural activities in dPD patients, compared to non-depressed PD patients and HCs. In dPD patients, increased functional connectivity between spatially discrete regions in the resting state was observed in the subcortical areas, such as the connectivity of the left amygdala with the bilateral mediodorsal thalamus [37], whilst decreased connectivity was seen in the connection between cortico-limbic [37] or cortico-cortico networks [38]. In addition, depression was inversely correlated with functional connectivity between the amygdala and prefrontal and posterior cingulate cortices [38,47], whilst it was positively correlated with regional neural activities in the left amygdala, right cingulate and thalamus, and bilateral cerebellum prefrontal cortices [40–42,47]. With regard to regional neural functional activity during the resting state, dPD patients showed regionally increased activity mainly in the prefrontal and limbic regions [39,41,42,47], but also in the temporal and parietal regions [41]. In essence, these studies generally suggest that there is a regionally increased neural activity in the prefrontal regions and decreased functional connectivity between the prefrontal–limbic

Table 1 Neuroimaging studies in depression in Parkinson's disease (PD)

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Ballanger *et al.* (2012) [11]	4 dPDs 8 PDs 7 HCs	4/0 6/2 5/2	No data	4.5 ± 3.3 7.0 ± 3.0	27.3 ± 11.6 25.9 ± 4.5	[^{18}F]MPPF PET	WB	DSM-IV/BDI, MADRS	HCs > dPDs: [^{18}F]MPPF uptake in left dorsal anterior cingulate and orbitofrontal cortices, and right hippocampus and temporal cortex HCs > PDs: Bi. inferior frontal cortex and right ventral striatum and insula PDs > dPDs: Left hippocampus and superior temporal and orbitofrontal cortices and right insula
Bohnen *et al.* (2007) [12]	12 PDs 6 PD-Ds 10 HCs	12/0 6/0 10/0	No data	5.7 ± 4.1 3.8 ± 2.3	No data	[^{11}C]PMP PET	ROI	CSDD	Inverse correlation between cortical cholinergic activity and depressive symptoms
Boileau *et al.* (2008) [13]	7 dPDs 7 HCs	4/3 4/3	1.71 ± 0.49	4 ± 2.9	21.1 ± 0.34	[^{11}C]DASB PET	ROI	DSM-IV/ HAM-D, IDS	dPDs > HCs: [^{11}C]DASB binding in dorsolateral and prefrontal cortices Positive correlation between [^{11}C]DASB binding in the orbitofrontal cortex and depression
Ceravolo *et al.* (2013) [20]	44 PDs	No data	No data	1.14 ± 0.98	17.9 ± 7.7	[^{123}I]FP-CIT SPECT	ROI	DSM-IV-TR/ HAM-D, HAM-A, BDI	More depressed PDs > less depressed PDs: DAT binding in bi. caudate and putamen Positive correlation between depression and DAT binding bi. caudate and putamen
Felicio *et al.* (2010) [21]	10 PDs 10 dPDs	5/5 6/4	2.5 ± 0.4 2.2 ± 0.5	4.7 ± 2.2 4.0 ± 2.4	29.5 ± 10.6 26.3 ± 10.0	^{99m}Tc-TRODAT-1 SPECT	ROI	BDI	dPDs > PDs: DAT density in left caudate and right putamen
Guttman *et al.* (2007) [19]	9 PDs 13 HCs	7/2 5/8	2.56 ± 0.53	12.22 ± 3.73	No data	[^{11}C]DASB PET	ROI	HAM-D, IDS	Inverse correlations between depression scores and [^{11}C]DASB binding in putamen and insular and occipital cortices
Hesse *et al.* (2009) [22]	110 PDs 20 dPDs 18 HCs	59/51 13/17 8/10	1.6 ± 1.6 2.3 ± 0.9	3.1 ± 4.9 4.4 ± 4.5	28.6 ± 13.1 31.4 ± 13.7	[^{123}I]FP-CIT SPECT	ROI	DSM-IV/BDI	PDs > dPDs: [^{123}I]FP-CIT binding in striatum, thalamus, midbrain/brainstem HCs > dPDs without SSRI treatment: [^{123}I]FP-CIT binding in thalamus and midbrain
Huang *et al.* (2013) [14]	26 PDs 12 HCs	16/10 7/5	1–2.5	5.5 ± 0.7	No data	[^{18}F]FDG-PET, T1-weighted	ROI (PET) WB (T1)	BDI, BAI, AES	Positive correlation between depression and metabolic elevations bi. amygdala No volumetric difference between HCs and PDs

(continued)

Table 1 *(Continued)*

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Imamura *et al.* (2011) [23]	22 PDs 16 minor dPDs 14 major dPDs 9 HCs	10/12 7/9 12/24/5	2.98 ± 0.85 3.53 ± 0.96 3.32 ± 0.87	6.33 ± 4.81 6.77 ± 5.87 4.3 ± 3.4	22.3 ± 17.4 33.4 ± 18.5 26.7 ± 13.5	^{123}I-IMP SPECT	ROI	DSM-IV/BDI	HCs > dPDs: rCBF in bi. PCC, hippocampus, cuneus, superior parietal and primary visual areas
Matsui *et al.* (2006) [24]	18 PDs 22 dPDs	5/17 2/20	3.2 ± 0.4 3.3 ± 0.5	8.8 ± 5.8 10.5 ± 6.8	28.9 ± 15.7 38.4 ± 15.3	^{123}I-IMP SPECT	ROI	DSM-IV/ HAM-D	PDs > dPDs: Perfusion in left superior and inferior frontal gyri
Mayberg *et al.* (1990) [15]	4 PDs 5 dPDs 6 HCs	4/0 3/2 4/2	≤3	8.5 ± 4 7.2 ± 2	No data	[^{18}F]FDG-PET	ROI	DSM-III/ HAM-D	HCs and PDs > dPDs: Metabolic activity in caudate and orbital-inferior frontal area Inverse correlation between metabolism in orbital-inferior frontal area and depression scores
Mentis *et al.* (2002) [16]	15 PDs 14 HCs	No data	3.3 ± 0.9	No data	No data	[^{18}F]FDG-PET	WB	BDI	In PDs, inverse correlation between depression and metabolism in lateral/medial frontal, ACC, orbitofrontal cortex Positive correlation between depression and metabolism in cerebellum
Pålhagen *et al.* (2009) [25]	11 dPDs 14 PDs 12 MDs	6/5 8/6 7/5	2.2 ± 0.4 1.8 ± 0.4	9.7 ± 4.7 6.9 ± 2.4	24.9 ± 10.8 22.6 ± 10.1	HMPAO SPECT	ROI	DSM-III–IV/ HAM-D, MADRS	dPDs vs. MDs: ↑ rCBF in right frontal and left frontoparietal regions; ↓ rCBF in right preoccipital region dPDs + PDs vs. MDs: ↓ rCBF in bi. preoccipital regions and occipital lobe dPDs vs. PDs: ↑ rCBF in bi. frontoparietal areas, right dorsolateral and left anterior frontal areas dPDs + MDs vs. PDs: ↑ rCBF in right dorsolateral frontal area
Politis *et al.* (2010) [18]	10 dPDs 24 PDs 10 HCs	6/4 20/4 8/2	3.1 ± 0.6 2.5 ± 0.8	10.3 ± 9.1 8.6 ± 4.5	81.9 ± 16.3 61.2 ± 18.5	[^{11}C]DASB PET	ROI	DSM-IV/ HAM-D, BDI	dPDs and HCs > PDs: Serotonergic binding in amygdala, hypothalamus, caudal raphe nuclei and PCC HCs > dPDs: Serotonergic binding in ACC, caudate nucleus, insula, prefrontal cortex, putamen, rostral raphe nuclei, thalamus and ventral striatum
Rektorova *et al.* (2008) [26]	20 PDs	10/10	No data	5.6 ± 3.5	20.9 ± 10.8	[^{123}I]FP-CIT SPECT	ROI	MADRS	Inverse correlation between depression scores and DAT availability in bi. striatum and putamen, left striatum and putamen → depression

(continued)

Table 1 *(Continued)*

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Remy *et al.* (2005) [17]	8 dPDs 12 PDs 7 HCs	5/3 9/3	1–3.5 1–3.5	3.1 ± 1.8 4.9 ± 2.6	24.3 ± 11.2 23.3 ± 6.7	[^{11}C]RTI-32 PET	ROI	BDI, AES, STAS	HCs > PDs + dPDs: Binding value in bi. caudate, putamen, ventral striatum and substantia nigra HCs > dPDs: Binding value in ACC, thalamus PDs > dPDs: Binding value in bi. thalamus and locus coeruleus ACC, right amygdala and left ventral striatum Inverse correlation between depression and binding value in left ventral striatum
Vriend *et al.* (2014) [27]	100 PDs	61/39	2.08 ± 0.64	3.5 ± 4.4	23.6 ± 11.5	[^{123}I]FP-CIT SPECT	ROI	BDI	Inverse correlation between depression and DAT binding
Weintraub *et al.* (2005) [28]	76 PDs 46 HCs	57/19 24/22	No data	7.5 ± 5.5	No data	^{99m}Tc-TRODAT-1 SPECT	ROI	POMS, STAS	Inverse correlation between depression and DAT availability in left anterior putamen
Wu *et al.* (2011) [29]	17 PDs 13 MDs 10 HCs	9/8 7/6 5/5	No data	1.17 ± 0.5	No data	^{99m}Tc-TRODAT-1 SPECT	ROI	CCMD-3, DSM-IV/ HAM-D	HCs and MDs > PDs: Dopaminergic availability in bi. striatum
Qamhawi *et al.* (2015) [30]	345 PDs 56 SWEDDs 185 HCs	231/114 40/16 126/59	1.5 ± 0.5 1.4 ± 0.5	0.53 ± 0.5	19.6 ± 8.9 12.5 ± 6.8	[^{123}I]FP-CIT SPECT	ROI	GDS	No significant relationship between depression and raphe specific binding ratio
Becker *et al.* (1997) [43]	30 HCs 13 dPDs 17 PDs	24/6 11/2 14/3	2–4 (PDs + dPDs)	9.7 ± 5.8 (PDs + dPDs)	27.7 ± 13.1	TCS	ROI	CGI HAM-D	HCs + PDs > dPDs: Raphe echogenicity Inverse correlation between raphe echogenicity and depression severity
Berg *et al.* (1999) [48]	31 patients (20dPDs 11 PDs)	16/15	2.58 ± 0.76	6.6 (1–17)	No UPDRS, but CURS = 35.1 (16–50)	TCS T2-weighted	ROI	DSM-IV/ HAM-D, BDI	dPDs > PDs: More hyperintense in mesencephalic midline Higher T2 values in pontine midline, but lower in mesencephalic midline Decreased echogenicity in mesencephalic midline
Walter *et al.* (2007) [44]	55 HCs 55 MDs 45 PDs 45 dPDs	27/28 11/44 23/22 23/22	No data	 7.4 ± 6.4 8.1 ± 6.4	32.4 ± 20.7 34.1 ± 18.5	TCS	ROI	DSM-IV/BDI, HAM-D	HCs + PDs > MDs + dPDs: Echogenicity in brainstem dPDs: Hyperechogenicity in substantia nigra, hypoechogenicity in brainstem raphe

(continued)

Table 1 *(Continued)*

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Cardoso *et al.* (2009) [46]	20 dPDs 16 PDs	20/0 16/0	2.5 ± 0.6 2.3 ± 0.3	11.2 ± 6.9 10.2 ± 4.3	36.7 ± 12.2 32.8 ± 8.74	T1-weighted task FMRI	ROI (T1) WB (FMRI)	DSM-IV/ HAM-D	Structural (volume): dPDs > PDs: Bi. mediodorsal thalamic nucleis Functional (activity): PDs > dPDs: Bi. dorsomedial prefrontal cortices and middle cingulate gyri; left mediodorsal thalamus
Feldmann *et al.* (2008) [31]	23 dPDs 27 PDs 16 HCs	dPDs + PDs: 30/20 9/7	2.7 ± 0.4 2.7 ± 0.4	9.9 ± 5.2 11.2 ± 5.9	35.1 ± 9.3 33.6 ± 8.8	T1-weighted	WB	MADRS	No difference between HCs and PDs and between HCs and dPDs PDs > dPDs: Left orbitofrontal inferior gyrus and rectus; right temporal superior pole and rectus Inverse relationship between depression scores and grey matter volumes in bi. orbitofrontal and right temporal and limbic regions in dPDs
Kostić *et al.* (2010) [32]	24 PDs 16 dPDs 26 HCs	13/11 8/8 14/12	2 (1–3) 2 (1–3)	5 (1–19) 6 (1–14)	19 (10–35) 23 (4–36)	T1-weighted	WB	HAM-D	HCs > PDs + dPDs: GM in right ACC and insula; left middle frontal and angular PDs > dPDs: WM in right ACC and inferior orbitofrontal region PDs + dPDs: inverse correlation between WM volume in right inferior orbitofrontal region and depression scores
van Mierlo *et al.* (2015) [33]	67 PDs	43/24	2.1 ± 0.6	2.95 ± 3.39	23.27 ± 10.56	T1-weighted	WB, followed by ROI	BDI	Inverse correlation between depression and bi. hippocampus and right amygdalar volume
Huang *et al.* (2014) [34]	15 dPDs 15 PDs	9/6 9/6	2.7 ± 0.8 2.5 ± 1	5.3 ± 4.8 4.2 ± 4.0	54.6 ± 23.7 45.3 ± 26.1	DTI	WB	HAM-D	PDs > dPDs: FA in left uncinate fasciculus, superior and inferior longitudinal fasciculi, anterior thalamic radiation and forceps minor dPDs: Inverse correlation between depression and FA in left deep temporal cortex No difference or correlation was found in mean diffusivity
Li *et al.* (2010) [35]	14 dPDs 18 PDs	4/10 10/8	1.96 ± 0.99 1.83 ± 0.75	6.29 ± 5.51 5.67 ± 2.57	39.04 ± 22.28 33.83 ± 15.09	DTI	ROI	DSM-IV/ HAM-D	PDs > dPDs: FA in bi. mediodorsal thalamic areas Inverse correlations between depression and FA in bi. mediodorsal thalamic areas
Matsui *et al.* (2007) [36]	14 dPDs 14 PDs	2/12 4/10	3.1 ± 0.4 3.1 ± 0.4	8.8 ± 5.2 7.4 ± 5.1	34.9 ± 14.7 27.4 ± 14.1	DTI	ROI	HAM-D	PDs > dPDs: FA in bi. ACC No difference or correlation was found in mean diffusivity

(continued)

Table 1 *(Continued)*

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Surdhar *et al.* (2012) [45]	6 dPDs6 PDs 6 HCs	5/1 5/1 5/1	No data	No data	16.67 ± 11.6 11.83 ± 2.5	T1-weighted DTI	ROI	GDS	No FA difference in corpus callosum and uncinate fasciculus HCs > dPDs: GM volume in bi. amygdala
Huang *et al.* (2015) [47]	19 dPDs 28 HCs	10/9 9/19	2.6 ± 0.7 2.3 ± 1.0	5.2 ± 4.8 4.6 ± 5.0	57.7 ± 22.4 50.8 ± 22.4	T1-weighted RS-FMRI	ROI	HAM-D	Structural (volume): No difference between groups in amygdala Functional (activity): dPDs > HCs and PDs: Left amygdala regional cerebral functional activity PDs + dPDs: Positive correlation between depression scores and left amygdala PDs > dPDs: Connectivity between right amygdala and frontoparietal areas dPDs: Inverse correlation between functional connectivity of right amygdala with right middle frontal gyrus and depression
Hu *et al.* (2015) [37]	20 dPDs 39 PDs 41 HCs	9/11 26/13 20/21	1.4 ± 0.6 1.72 ± 0.64	5.35 ± 2.82 6.5 ± 3.54	27.65 ± 13.17 28.21 ± 13.17	RS-FMRI	ROI	DSM-V/ HAM-D	dPDs > PDs: Connectivity between left amygdala and bi. mediodorsal thalamus and between right amygdala and left superior temporal and calcarine gyri dPDs vs. HCs: ↑ connectivity between left amygdala and bi. mediodorsal thalamus; ↓ connectivity between left amygdala and left putamen, inferior frontal gyrus and right cerebellum; ↓ connectivity between right amygdala and left rectus, inferior orbitofrontal gyrus and right putamen
Lou *et al.* (2015) [38]	17 dPDs 17 PDs 17 HCs	8/9 9/8 9/8	2.71 ± 0.25 2.62 ± 0.28	No data	44.06 ± 12.34 40.47 ± 9.19	RS-FMRI	WB	DSM-IV/ HAM-D	PDs > dPDs: Connectivity in left dorsolateral prefrontal cortex and right superior temporal gyrus dPDs > PDs: Connectivity in right PCC HCs > dPDs: Connectivity in bi. frontal, temporal and parietal regions and left insula Inverse correlation between depression and PCC
Luo *et al.* (2014) [42]	29 dPDs 30 PDs 30 HCs	14/15 15/15 15/15	1.79 ± 0.62 1.73 ± 0.58	1.98 ± 1.64 2.12 ± 1.30	28.34 ± 16.9 26.83 ± 12.44	RS-FMRI	WB followed by ROI	DSM-IV/ HAM-D	dPDs > PDs and HCs: Regional cerebral function in left orbitofrontal area PDs + dPDs: Positive correlation between depression and regional cerebral function in left orbitofrontal cortex HCs > PDs > dPDs: Connectivity in the prefrontal–limbic network

(continued)

Table 1 *(Continued)*

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Sheng *et al.* (2014) [39]	20 dPDs 21 PDs 25 HCs	13/8 13/7 16/9	2.1 ± 0.75 1.95 ± 0.63	3.4 ± 1.7 4.0 ± 2.4	39.4 ± 10.8 43.8 ± 8.2	RS-FMRI	WB followed by ROI	DSM-IV/ HAM-D	dPDs vs. PDs: Regional activity: ↑ in left middle frontal gyrus and right inferior frontal gyrus; ↓ in left amygdala and bi. lingual gyri dPDs vs. PDs: Connectivity: ↓ within prefrontal–limbic system and ↑ in prefrontal cortex and lingual gyrus
Skidmore *et al.* (2013) [40]	15 PDs	12/3	No data	No data	37 ± 13	RS-FMRI	WB	HAM-D, LARS	Positive correlation between depression and regional cerebral function in bi. cunei and cerebellums, right subgenual cingulate, lateral geniculate and mesial frontal gyrus Depression was predicted by functional activity signal in right subgenual cingulate
Wen *et al.* (2013) [41]	17 dPDs 16 PDs 21 HCs	7/10 8/8 13/8	2.1 ± 1.9 1.5 ± 1	6.4 ± 5.4 5.6 ± 7.4	42. ±46 33.8 ± 24.2	RS-FMRI	WB	DSM-IV/ HAM-D	dPDs vs. PDs: ↑ Regional cerebral function in bi. (mostly right) frontal areas, including ACC and dorsolateral prefrontal cortex and left temporal lobe; ↓ regional cerebral function in bi. cerebellum dPDs vs. HCs: ↑ Bi. temporal and parietal regions and left inferior frontal gyrus; ↓ bi. caudate and precuneus, right frontal, superior temporal and thalamic areas Positive correlation between depression and regional cerebral function in the dorsolateral prefrontal cortex

ACC, anterior cingulated cortex; AES, Apathy Evaluation Scale; ALFF, amplitude of low frequency function; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; bi., bilateral; CCMD-3, Chinese Classification of Mental Disorders version 3; CGI, clinical global impression; CSDD, Cornell Scale for Depression in Dementia; CURS, Columbia University Rating Scale; DAT, dopamine transporter; dPDs, PD patients with depression; DSM-IV, -IV-TR, -III, and -V, Diagnostic and Statistical Manual of Mental Disorders, 4th, 4th-TR, 3rd, and 5th editions; DTI, diffusion tensor imaging; FA, fractional anisotropy; GDS, Geriatric Depression Scale; GM, grey matter; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; H and Y, Hoehn and Yahr scale; HCs, healthy controls; IDS, Inventory of Depressive Symptomatology; LARS, Lille Apathy Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; MD, patients with major depression; PCC, posterior cingulate cortex; PDs, patients with PD alone; PD-Ds, patients with PD and dementia; PET, positron emission tomography; POMS, Profile of Mood States; rCBF, regional cerebral blood flow; ROI, region of interest; RS-FMRI, resting state functional magnetic resonance imaging; SPECT, single-photon emission computed tomography; STAS, State–Trait Anxiety Scale; SWEDD, patients with scans without evident dopaminergic deficits; TCS, transcranial sonography; UPDRS-III, Unified Parkinson's Disease Rating Scale III; WB, whole brain; WM, white matter.

networks in dPD patients. These changes correlated with depression severity.

These studies using different neuroimaging modalities suggest a wide spectrum of neural involvement. The implication of an extra-nigrostriatal pathway in the prefrontal, temporal and limbic cortices implies that other neurotransmitters, such as serotonin and noradrenaline, are also implicated in depression in PD [49–51]. This view is supported by studies using PET or SPECT to show that cortical cholinergic activity inversely correlated with depression [12] and changes of serotonin or noradrenaline in PD patients with depression, compared to HCs or PD patients without depression [11,13,16–18], in addition to dopaminergic alterations [19–22,26,27]. Although it is challenging to identify a unifying model of neuropathology of depression in PD, these observations suggest that depression is unlikely to be the result of a single brain region or neurotransmitter system but involves the dysregulation of cortico-limbic networks in addition to that of the nigrostriatal pathway.

Challenges and limitations

Comparisons between studies are difficult since imaging modalities and/or techniques are not uniform. Most were focused on PET or SPECT, but more recent studies have used non-invasive modalities, such as RS-FMRI, to explore the alterations of neural functional activity; other non-invasive imaging techniques, such as DTI, are limited. The inclusion versus exclusion of patients in the on-medication state and different severities of depression may restrain cross-study comparisons. For studies using PET or SPECT, diverse radiotracers were used to explore the associations of various neurotransmitters, including serotonergic, cholinergic and dopaminergic transporters, and general glucose metabolism with depression. Although [^{123}I]FP-CIT was a widely used radiotracer for measuring dopaminergic dysfunction [20,22,26,27], it was also used for determining serotonin level [30] in depression in PD. Although findings from studies using different radiotracers to target different neurotransmitters suggest the involvement of multiple neurotransmitters and the extra-nigrostriatal pathway in depression in PD, divergent radiotracers may be related to controversial results [20].

The majority of studies adopted region of interest (ROI) strategies to study various regions and few examined the whole brain; this may add to selection bias of the brain regions. The methods to evaluate depression are not comparable. Half of the studies only used scales (mostly one scale) to determine the severity of depression, whilst others followed the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria for depression. The most common scale used for measuring depression severity was the Hamilton Depression Scale (HAM-D), but other scales (e.g. Beck Depression Inventory) were also used.

Different imaging modalities may provide different aspects of neural alterations associated with depression in PD, but studies using DTI and FMRI (both task and resting state based) are still scarce. Differences in analytical strategies (ROI versus voxel-wise whole brain) and in the varied inclusion and exclusion criteria (e.g. on or off antiparkinsonian or antidepressant medications, minor or major depression) may preclude cross-study comparisons.

Neuroimaging of anxiety in PD

Compared to depression, only eight neuroimaging studies of anxiety in PD were identified. Most studies on anxiety used either PET or SPECT techniques [14,17,20,28,51,52], and only three studies used T1-weighted imaging [14,53,54], whilst no study used any other imaging modalities. For studies using either PET or SPECT, five of them used dopamine radiotracers [17,20,28,51,52], one study examined general glucose metabolism [14], whilst one study additionally explored noradrenaline in addition to dopamine [17]. All eight studies adopted ROI approaches with the caudate and putamen being the main foci, except for one study that additionally examined structural changes in the whole brain that were associated with anxiety in PD [14]. Additional inclusion of the prefrontal areas, such as the orbitofrontal cortex and inferior frontal gyrus, as the ROIs was found in two studies [17,53]. The amygdala and hippocampus as ROIs were studied in three [17,53,54] and two [53,54] studies, respectively, and the thalamus in two studies [17,53]. Most of the PET/SPECT studies [14,17,28,51] showed an inverse correlation between dopaminergic density in the caudate and putamen with the severity of anxiety in PD, whilst the study using T1-weighted imaging showed no significant anxiety-associated structural changes in these two key regions in PD [53]. Two studies demonstrated an inverse correlation between anxiety symptoms and brain volume [54] and dopaminergic density [17] of the amygdala, although this was not replicated in another study [53]. T1-weighted imaging studies did not reveal a significant role of the hippocampal areas in anxiety in PD [53,54]. There was no consistent correlation of the thalamus with anxiety based on brain volume and dopaminergic density [17,53]. Table 2 gives details of the studies.

Table 2 Neuroimaging studies in anxiety in Parkinson's disease (PD)

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Ceravolo *et al.* (2013) [20]	44 PDs	No data	No data	1.14 ± 0.98	17.9 ± 7.7	[^{123}I]FP-CIT SPECT	ROI	DSM-IV-TR/ HAM-D, HAM-A, BDI	Positive correlation between anxiety and DAT binding bi. caudate and putamen
Erro *et al.* (2012) [51]	9 anxPDs 25 PDs	4/5 18/7	No data	14.9 ± 3.5 16.2 ± 3.1	15.5 ± 5.7 13.3 ± 6.1	[^{123}I]FP-CIT SPECT	ROI	HADS-A	PDs > anxPDs: DAT density in bi. caudate and left putamen Inverse correlation between anxiety and DAT density in right caudate
Huang *et al.* (2013) [14]	26 PDs 12 HCs	16/10 7/5	1–2.5	5.5 ± 0.7	No data	[^{18}F]FDG-PET, T1-weighted	ROI (PET) WB (T1)	BDI, BAI, AES	Inverse correlation between anxiety and metabolic elevations in bi. caudate No volumetric difference between HCs and PDs
Moriyama *et al.* (2011) [52]	12 sad-PDs 20 PDs	9/3 15/5	2.6 ± 0.9 2.6 ± 0.5	7.1 ± 3.8 9.0 ± 6.2	34.7 ± 16.1 31.7 ± 12.2	^{99m}Tc-TRODAT-1 SPECT	ROI	DSM-IV-TR/BSPS	DAT binding potential was positively correlated with anxiety for bi. putamen and left putamen
Remy *et al.* (2005) [17]	8 dPDs 12 PDs 7 HCs	5/3 9/3	1–3.5 1–3.5	3.1 ± 1.8 4.9 ± 2.6	24.3 ± 11.2 23.3 ± 6.7	[^{11}C]RTI-32 PET	ROI	BDI, AES, STAS	Inverse correlation between anxiety and binding value in left ventral striatum, caudate, locus coeruleus, inferior thalamic region and bi. amygdala and medial thalamus
Weintraub *et al.* (2005) [28]	76 PDs 46 HCs	57/19 24/22	No data	7.5 ± 5.5	No data	^{99m}Tc-TRODAT-1 SPECT	ROI	POMS, STAS	Inverse correlation between anxiety and DAT availability in left anterior putamen
Tinaz *et al.* (2011) [53]	15 PDs 15 HCs	No data	2.17 ± 0.3	6 ± 2.8	31.53 ± 5.84	T1-weighted	ROI	STAS	No significant correlation between anxiety and brain volumetric features
Vriend *et al.* (2015) [54]	110 PDs	66/44	2.08 ± 0.58	3.3 ± 3.6	24.9 ± 10.4	T1-weighted	ROI	BAI, BDI	Inverse correlation between affective symptoms of anxiety and volume of left amygdala

AES, Apathy Evaluation Scale; anxPDs, PD patients with anxiety; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; bi., bilateral; BSPS, Brief Social Phobia Scale; DAT, dopamine transporter; dPDs, PD patients with depression; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; HADS-A, Hospital Anxiety Depression Scale – Anxiety Subscale; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; HCs, healthy controls; PDs, patients with PD disease alone; PET, positron emission tomography; POMS, Profile of Mood States; ROI, region of interest; sad-PDs, PD patients with social anxiety disorder; SPECT, single-photon emission computed tomography; STAS, State–Trait Anxiety Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale III; WB, whole brain.

Amongst the aforementioned studies, none of them included patients with cognitive symptoms (e.g. dementia); one study [52] recruited PD patients with social anxiety disorder, one study mentioned that some of the patients had social anxiety or panic attacks [20], whilst the remaining studies did not specify the anxiety type(s) of patients; likewise, only one study excluded patients with depression, a common comorbidity of anxiety [51]. Two studies [28,54] included patients in the on-medication state (i.e. patients were on antiparkinsonian medication during MRI scanning), one study [53] did not clarify the medication state of their patients, whilst the remaining studies included patients in the off-medication state. Patients in three of the eight studies used either antidepressant or anxiolytic medication during the study period [20,53,54], and there were three studies that did not indicate whether patients used antidepressant or anxiolytic medication [14,17,52]. See Table S2 for the clinical characteristics of studies on anxiety in PD.

Challenges and limitations

Although anxiety is a common mood complaint in PD, it is apparent that there are insufficient neuroimaging studies examining the underlying neuropathology of anxiety in PD. Whilst limited studies hamper our understanding of the pathogenesis of anxiety in PD, some methodological issues in the existing studies may also contribute to the difficulty in drawing meaningful conclusions. Only two of the eight studies applied strict diagnostic criteria (e.g. DSM-IV-TR criteria) in addition to the employment of anxiety scales, whilst the remaining six studies used one single scale to evaluate anxiety symptoms. Interestingly, only the two studies using both diagnostic criteria and scales to improve diagnostic accuracy demonstrated a positive correlation between anxiety and dopaminergic density in caudate or putamen [20,52]. Therefore, varied measurements of anxiety may, at least in part, explain the conflicting findings. Also, only two studies [20,52] specified the anxiety types of their patients and one study [28] excluded patients with anxiety. Although all studies excluded patients with cognitive impairment, most studies did not control for depression and did not provide specific information about patients' anxiety symptoms/types. Although most studies included PD patients in the off-medication state, some studies either involved patients in the on-medication state or did not indicate the medication state of their patients. The wide variety in anxiety measurements, symptoms and severity, the use of antiparkinsonian, antidepressant or anxiolytic medications, and the confounding effects of depression add to the difficulty of drawing conclusions on the neuropathology of anxiety in PD.

Further, most studies included rather small samples, which may lack enough statistical power to truly detect the neural substrates of anxiety. With regard to neuroimaging methodologies, the application of ROI methods with focus on putamen and caudate cannot provide comprehensive examinations of the pathogenesis of anxiety. On the contrary, results from such an approach may be compounded by the involvement of these regions in the pathogenesis of motor dysfunction. For studies using PET or SPECT, other neurotransmitters associated with anxiety in PD, such as acetylcholine, norepinephrine and serotonin, were under-studied given that most of these studies adopted radiotracers to examine dopaminergic changes. To date, only PET/SPECT and T1 structural MRI have been used in anxiety in PD. The application of other imaging modalities, such as DTI and FMRI, which are able to provide information about the pathology at the level of neural networks rather than at the level of individual regions may provide further insights.

Neuroimaging of apathy in PD

There were 14 neuroimaging studies of apathy in PD (Table 3). Similar to the studies of depression and anxiety in PD, most imaging studies of apathy in PD utilized either PET or SPECT techniques [14,17,55–60,61] and focused on measuring cerebral glucose metabolism with the exception of two PET studies [17,60] and one SPECT study [61] examining dopaminergic changes associated with apathy. Of the 14 studies, five involved T1-weighted imaging [14,62–65], two used RS-FMRI [40,64] and one study performed DTI in addition to T1-weighted imaging [65]. Approximately half of the studies used ROI methods with caudate, putamen and limbic regions being the most common ROIs. All 14 studies excluded patients with cognitive symptoms (e.g. dementia) and seven of them included patients who remained on antiparkinsonian medication during MRI scanning. Additionally, three of the 14 studies recruited patients who were on mood stabilizers. Amongst the 14 studies, five studies clearly excluded patients with depression [55,57–59,61], whilst seven studies did not [14,17,60,62–65] and two did not indicate whether patients with depression were excluded from the studies [40,56].

Most studies demonstrated an inverse correlation between apathy and cerebral metabolism in the striatum, cerebellum, and prefrontal, temporal, parietal and limbic lobes [14,17,56,57,59,61]. However,

Table 3 Neuroimaging studies of apathy in PD

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Huang *et al.* (2013) [14]	26 PDs 12 HCs	16/10 7/5	1–2.5	5.5 ± 0.7	No data	[^{18}F]FDG-PET, T1-weighted	ROI (PET) WB (T1)	BDI, BAI, AES	Positive correlation between apathy and bi. ACC and orbitofrontal lobes Inverse correlation between apathy and right inferior parietal and left superior temporal gyri No volumetric difference between HCs and PDs
Lawrence *et al.* (2011) [55]	10 low aPDs 10 high aPDs	No data	2.35 ± 0.6 2.7 ± 0.8	No data	25.6 ± 11.0 28.2 ± 11.4	$H_2{}^{15}O$ PET FMRI	ROI	AS	↓ Activity in left amygdala and striatum, bi. vmPFC, and midbrain in high aPDs
Le Jeune *et al.* (2009) [56]*	12 PDs	8/4	1.6 ± 1.2 (off) 0.9 ± 1.0 (on)	No data	14.3 ± 0.9 (off) 5.5 ± 3.4 (on)	[^{18}F]FDG-PET	WB	AES, MADRS, AMDP-AT	Positive correlation between apathy and metabolism in right, frontal and parietal regions and left fusiform gyrus Inverse correlation between apathy and metabolism in bi. cingulate and left middle frontal gyri
Remy *et al.* (2005) [17]	8 dPDs 12 PDs 7 HCs	5/3 9/3	1–3.5 1–3.5	3.1 ± 1.8 4.9 ± 2.6	24.3 ± 11.2 23.3 ± 6.7	[^{11}C]RTI-32 PET	ROI	BDI, AES, STAS	Inverse correlation between apathy and binding value in bi. ventral striatum
Robert *et al.* (2012) [57]	45 PDs (no depression)	No data	No data	11.3 ± 4.1	8.4 ± 5.9 (ON) 29.9 ± 12.2 (OFF)	[^{18}F]FDG -PET	WB	AES, MADRS	Positive correlations between apathy and cerebral metabolism in right inferior frontal gyrus, middle frontal gyrus, cuneus and insula Inverse correlations between apathy and cerebellar metabolism in bi. posterior cerebellums
Robert *et al.* (2014) [58]	36 PDs (no depression)	No data	No data	No data	7.9 ± 5.4	[^{18}F]FDG -PET	WB	AES, MADRS	Positive correlation between apathy and increased metabolism in left PCC
Robert *et al.* (2014) [59]	44 PDs (no depression)	No data	No data	11.4 ± 4.1	7.5 ± 5.2 (ON)† 32.6 ± 12.8 (OFF)	[^{18}F]FDG -PET	ROI	AES, MADRS, AMDP-AT	Inverse correlation between metabolism in right ventral striatum and postoperative increased AES scores
Thobois *et al.* (2010) [60]	12 aPDs 13 PDs	6/6 10/3	No data	10.3 ± 2.2 10.5 ± 3.0	14.5 ± 9.9 10.3 ± 5.9	[^{11}C]-raclopride PET	WB, ROI	BDI, BAI, SAS	aPDs > PDs: Binding value in bi. orbitofrontal and temporal cortices, and PCC; left dorsolateral prefrontal cortex, striatum and thalamus; right amygdala
Santangelo *et al.* (2015) [61]	14 aPDs 14 PDs	4/10 4/10	No data	13.5 ± 6.1 12.8 ± 5.8	14.27 ± 7.4 14.1 ± 8.9	[^{123}I]-FP-CIT SPECT	ROI	AES	PDs > aPDs: dopamine in right caudate Inverse correlation between dopamine density in right caudate and apathy

(continued)

Table 3 *(Continued)*

Study	Subjects	Sex (M/F)	H and Y (Mean ± SD)	Duration of PD (years)	UPDRS-III	Imaging modality	Imaging analytical method	Diagnosis/ measurement	Key findings
Isella *et al.* (2002) [62]	33 PDs 25 HCs	18/15 12/13	No data	4.9 ± 3.86	31.9 ± 15.69	T1-weighted	ROI	AES, GDS	PDs: Apathy was positively correlated with bi. temporal atrophy but inversely correlated with thickness of the right mesial temporal lobe
Reijnders *et al.* (2010) [63]	60 PDs	No data	1.5–3	6.6 ± 4.3	17.3 ± 4.9	T1-weighted	WB	AES, LARS, HAM-D, NPI	Inverse correlation between apathy and grey matter density in bi. precentral gyri, inferior frontal and parietal gyri, and insula, right precuneus and PCC
Baggio *et al.* (2015) [64]	25 aPDs 37 PDs 31 HCs	20/5 17/20 15/16	1.84 ± 0.69 1.70 ± 0.57	7.24 ± 4.13 7.54 ± 5.52	15.56 ± 7.94 15.37 ± 8.48	RS-FMRI T1-weighted	ROI	AS, BDI	HCs and PDs > aPDs: Functional connectivity in left limbic striatal and frontal networks PDs + aPDs: Apathy was inversely correlated with connectivities between left limbic striatal and left frontal areas and between left frontal subdivisions No group differences or correlations with apathy or GM volume or subcortical volume/ shape
Skidmore *et al.* (2013) [40]	15 PDs	12/3	No data	No data	37 ± 13	RS-FMRI	WB	HAM-D, LARS	Apathy was positively correlated with regional cerebral functional signal in right middle orbital gyrus and bi. subgenual cingulate, but inversely correlated with left SMA, IPL, fusiform gyrus, and bi. cerebellums Apathy was predicted by regional cerebral functional signal in left SMA
Carriere *et al.* (2014) [65]	10 HCs 10 aPDs 10 PDs	4/6 6/4 6/4	No data	11.9 ± 6.5 11.9 ± 3.2	28.1 ± 10.8 11.9 ± 3.2	T1-weighted DTI	T1: ROI DTI: WB	LARS	PDs + HCs > aPDs: Left nucleus accumbens HCs > aPDs: Bi. nucleus accumbens PDs > aPDs: Dorsolateral part of left caudate Positive correlation between apathy and atrophy in left nucleus accumbens No difference in FA

ACC, anterior cingulated cortex; AES, Apathy Evaluation Scale; ALFF, amplitude of low frequency function; AMDP-AT, Association for Methodology and Documentation in Psychiatry – Anxiety; aPDs, PD patients with apathy; AS, Apathy Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; bi., bilateral; dPDs, PD patients with depression; DTI, diffusion tensor imaging; FA, fractional anisotropy; GDS, Geriatric Depression Scale; GM, grey matter; HAM-D, Hamilton Depression Scale; HCs, healthy controls; IPL, inferior parietal lobule; LARS, Lille Apathy Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; NPI, Neuropsychiatric Inventory; PCC, posterior cingulate cortex; PDs, patients with PD alone; PET, positron emission tomography; ROI, region of interest; RS-FMRI, resting state functional magnetic resonance imaging; SAS, Starkstein Apathy Scale; SMA, supplementary motor area; SPECT, single-photon emission computed tomography; STAS, State-Trait Anxiety Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale III; vmPFC, ventromedial prefrontal cortex; WB, whole brain.

*Only the postoperative AES scores are used here as apathy significantly increased after subthalamic nucleus deep brain stimulation;

†Only pre-operative UPDRS-III scores are shown here.

positive correlations between apathy and prefrontal, temporal, parietal and limbic areas were also noted in some studies [14,56–58]. Studies using T1-weighted imaging reported reduced GM thickness in the temporal lobes [62] or increased atrophy in the frontal and parietal lobes (e.g. bilateral precentral gyri, right precuneus and posterior cingulate cortex), insula [63] and left nucleus accumbens [65] to be correlated with apathy, although this was not replicated in other studies [14,64]. The only study using DTI to examine the neural substrates of apathy in PD did not observe any difference in white matter integrity between patients with apathy and those without apathy and HCs [65]. For spontaneous neural activity measured with RS-FMRI, the study by Baggio and colleagues showed that PD patients with apathy had decreased functional connectivity between the left striatal and frontal areas, and amongst PD patients apathy was inversely correlated with functional connectivity between the subdivisions of the left frontal lobe [64]. Meanwhile, another RS-FMRI work indicated that apathy was positively correlated with regional cerebral functional activity in the right orbital gyrus and bilateral cingulate areas, but inversely correlated with the left parietal lobe (supplementary motor area and inferior parietal lobule) and bilateral cerebellum [40].

Challenges and limitations

These studies highlighted frontal, limbic and striatal involvement in apathy in PD. However, inconsistent findings of an increased or a decreased cerebral metabolic/functional activity was found in various brain regions. Apathy either was associated with a GM decrease or had no relationship with GM changes. There are several explanations for the inconclusive results. First, there were differences in the analytical methods. Most studies used ROI methods, whilst few examined the whole brain. Amongst studies using ROI methods, the selection of ROIs was not necessarily identical; hence the results can be different. Secondly, unlike depression and anxiety, a well-accepted standardized diagnostic system for apathy has not been established. Different studies therefore adopted different scales to measure apathy severity and all studies but one [63] used only one scale, presenting a potential issue with measurement validity and reliability. Also, differences in the medication state during MRI scanning and clinical characteristics (e.g. symptom severity and whether other mood symptoms were controlled for) may contribute to inconclusive findings. Thirdly, most studies only had one single imaging modality, making it difficult to directly examine the associated structural and functional changes in the same samples. Finally, given the limited studies, there is a great need for more research, especially studies incorporating other imaging modalities, such as DTI, to improve our understanding of the neuropathology of PD-related apathy.

Summary

Although all of the three mood disturbances are common complications in PD, most neuroimaging works have focused on depression, suggesting that anxiety and apathy may be under-recognized mood complaints in PD. In early untreated PD, anxiety and apathy are common [66], implying that these two mood disturbances are also part of a spectrum of 'hypodopaminergy' in the same way as depression. Amongst the imaging studies of the three mood disturbances, the majority used one single imaging modality and ROI analytical strategies. For depression and anxiety, most studies adopted scales for evaluating the severity of mood symptoms, whilst few studies additionally applied standardized diagnostic criteria (e.g. DSM) to ensure the diagnoses. For apathy, the standardized diagnostic system has not been well established, leaving researchers to completely rely on scales to determine the severity. As some mood scales are based on participants' self-report, bias can be introduced to the study due to subjective perception. Other contributing factors to the discrepant findings across studies included variability in patients' demographics, medication conditions and symptomatology (e.g. comorbidities of different mood symptoms) as well as differences in image pre-processing and statistical analysis.

Involvement of the nigrostriatal pathway

The striatal areas, including putamen and caudate, were the most studied substrates in PD-related mood disturbances. The existing imaging works have underlined the involvement of these areas in depression, anxiety and apathy. Both increased and decreased neural activity of putamen and caudate have been identified in patients with depression, anxiety or apathy compared to non-depressed PD or HCs. Divergent positive and negative relationships between mood severity and the activity changes of the regions were reported. Compared to functional imaging studies, none of the existing structural imaging studies reported any significant macrostructural or microstructural changes associated with PD-related mood disturbances. Whether this implies greater sensitivity of neural functional changes or more susceptibility of neural functional activity as opposed to structural changes in the nigrostriatal pathway remains unclear, especially given that there is a lack of sufficient studies using either T1 MRI or DTI.

Involvement of the extra-nigrostriatal pathway

Whilst the striatum was the focus of most imaging studies in PD-related mood disturbances, it does not necessarily mean that the extra-nigrostriatal areas are not affected. In fact, our literature review identifies several areas that are beyond the nigrostriatal pathway. The reported extra-nigrostriatal areas are mainly in the frontal territory or its connecting areas, such as the orbitofrontal and ventromedial prefrontal cortices, cingulate cortex, amygdala and uncinate fasciculus. However, although the cause–effect relationship between mood severity and neural functional and structural features cannot be concluded, it should be clear that the frontal area and its connecting areas are implicated in PD-related mood disturbances.

Is the frontostriatal pathway a key component of a neural model for mood disturbances?

The aetiology of each of the mood disturbances is likely to be multifactorial [67–69]. The mechanisms of these mood disturbances are not fully elucidated, especially for anxiety and apathy. Nevertheless, existing studies suggest that the frontal and striatal areas are most robustly implicated in PD patients with symptoms of depression, anxiety or apathy. The frontostriatal pathway has been demonstrated to be the significant neural system affected by geriatric depression, anxiety and apathy [70–72]. Arguably this pathway (Fig. 2) may also be applicable to PD-related mood disturbances.

Conclusions

Published neuroimaging studies have predominantly focused on neuropathology of depression in PD, whilst little is known about the neural substrates of anxiety and apathy. Most imaging studies on mood disturbances in PD used ROI approaches with the striatum as the main study region. This approach may limit our understanding of the extra-nigrostriatal involvement in mood disturbances. Nonetheless, there is evidence suggesting that both nigrostriatal and extra-nigrostriatal pathways (in particular the frontal region and its connecting areas) are dysregulated. The frontostriatal pathway may be an attractive neural model for understanding mood disturbances in PD. Future studies using a multimodal imaging approach, unbiased whole-brain analytical methods, and taking into account the comorbidity effects when examining these mood symptoms will be required to elucidate the exact mechanisms. Identifying the relative contributions of these pathways in PD patients with overlapping motor and mood symptoms could provide

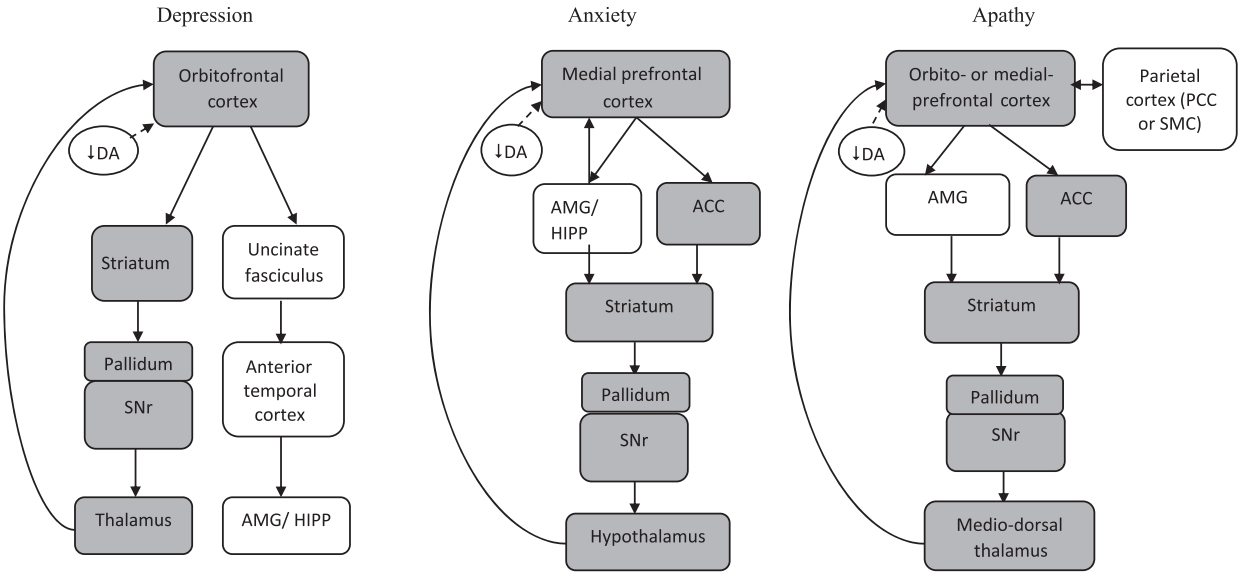

Figure 2 Simplified schemes of the depression, anxiety and apathy networks in PD. Generally, as PD pathology defined by dopaminergic deficiency progresses, the implicated neural areas that are associated with mood symptoms involve the prefrontal cortex including orbitofrontal cortex and medial prefrontal cortex and then extend to some regions in the anterior temporal and parietal lobes, and subcortical areas. Amongst the three mood symptoms, the shared brain regions are mainly within the frontostriatal pathway. Blocks in grey refer to the frontostriatal pathway; ACC, anterior cingulate cortex; AMG, amygdala; DA, dopamine; HIPP, hippocampus; PCC, posterior cingulate cortex; SMC, supplementary motor cortex; SNr, substantia nigra.

new pathophysiological clues for the development of better therapeutic targets for affected patients.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical characteristics of neuroimaging studies in depression in PD.
Table S2. Clinical characteristics of neuroimaging studies in anxiety in PD.
Table S3. Clinical characteristics of neuroimaging studies in apathy in PD.

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