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Gray matter substrates of depressive and anxiety symptoms in idiopathic REM sleep behavior disorder

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ABSTRACT

Introduction: Idiopathic rapid eye movement sleep behavior disorder (iRBD) is a prodromal stage of Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Depressive and anxiety symptoms are frequent features of PD, DLB and iRBD, and some studies suggest that depressive symptoms are a marker for neurodegeneration in iRBD. However, the pathophysiology of depressive and anxiety symptoms in iRBD is still unclear. This study aimed to investigate cortical and subcortical gray matter (GM) volume substrates of depressive and anxiety symptoms in iRBD patients.

Methods: Forty-six polysomnography-confirmed iRBD patients and 31 healthy controls (HC) without cognitive or mood impairment were recruited. All participants underwent 3-T magnetic resonance imaging and completed the Beck Depression Inventory Second Edition (BDI-II) and Beck Anxiety Inventory (BAI) questionnaires. Voxel-based morphometry analysis was performed to assess GM volume in cortical and subcortical structures. Between-group comparisons and regressions were performed.

Results: iRBD patients with depressive symptoms (BDI-II score > 13 or the use of antidepressants to treat depression) showed reduced GM volume in the caudate nucleus compared to HC and iRBD patients without depressive symptoms. Moreover, iRBD patients with anxiety symptoms (BAI score > 9 or the use of anxiolytics to treat anxiety) showed reduced GM volume in the left amygdala extending to the hippocampus compared to HC and iRBD patients without anxiety symptoms. In iRBD patients, higher BDI-II and BAI total scores were associated with lower GM volumes in these regions respectively.

Conclusion: Depressive and anxiety symptoms in iRBD patients are related to patterns of cortical and subcortical GM volume loss.

1. Introduction

Idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) is a parasomnia characterized by abnormal motor manifestations during REM sleep [1]. iRBD is recognized as a prodromal stage for synucleinopathies, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) [2]. Several prodromal signs of synucleinopathies have been identified in iRBD [3]. Depression and anxiety are frequent nonmotor features in PD, DLB and MSA [4–7], and depression can precede their clinical diagnostic by years [5,8]. Psychiatric symptoms are frequent in iRBD, and patients report more depressive and anxiety symptoms than healthy subjects [9–11]. Although depressive symptoms have been related to subsequent conversion and early signs of neurodegeneration in iRBD [9,12–14], it remains debatable whether depressive or anxiety symptoms in iRBD are risk factors for the development of synucleinopathies or whether they

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are associated features of RBD [3,15]. To our knowledge, the gray matter (GM) substrates of depressive and anxiety symptoms have never been studied in this population. A better understanding of the pathophysiology of these symptoms in prodromal stages of synucleinopathies would provide potential new biomarkers for evaluating the effectiveness of management interventions in this population (e.g. psychotherapy, drugs, and neuroprotection).

Major depressive disorder (MDD) and late-life depression are characterized by GM volume loss in the frontal, striatal, and limbic regions [16–18]. Otherwise, GM volume loss in patients with anxiety disorders has been reported in the frontal lobes, and in the anterior cingulate cortex, amygdala, and hippocampus [19,20]. In PD patients, using voxel-based morphometry (VBM), GM volume loss has been related to depressive and anxiety symptoms. Depression-related atrophies in PD were reported in the orbitofrontal and rectal gyrus, frontal and temporal lobes, caudate nucleus, hippocampus, amygdala, precuneus, and cerebellum [21–24]. In addition, GM volume loss in the left amygdala, precuneus, and anterior cingulate gyrus were reported to correlate with anxiety symptoms in PD [25,26]. To our knowledge, no study using VBM has investigated GM abnormalities related to depressive and anxiety symptoms in PD with RBD, DLB, MSA or iRBD patients.

Using VBM, we investigated cortical and subcortical GM volume substrates of depressive and anxiety symptoms in iRBD patients using group comparisons and regressions. We hypothesized that the severity of depressive and anxiety symptoms in iRBD patients would be associated with the patterns of cortical and subcortical GM volume previously reported in PD with depressive and anxiety symptoms and populations with depression and anxiety disorders.

2. Material and methods

2.1. Subjects

One hundred participants were recruited from the Center for Advanced Research in Sleep Medicine of the *CIUSSS-NÎM – Hôpital du Sacré Coeur de Montréal* (Montreal, Canada) as part of our ongoing study on neuroimaging in RBD [27,28]. Fifty-nine individuals were diagnosed with iRBD based on clinical and polysomnographic (PSG) criteria according to the International Classification of Sleep Disorders Third Edition and nocturnal video-PSG recording (JM) [1,3]. All iRBD patients underwent a neurological examination (RBP). The motor examination subscale of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was administered to all patients. Mild cognitive impairment (MCI) diagnosis was based on a complete neuropsychological assessment according to previously published criteria (JFG) [29]. Forty-one HC were recruited from the general population through newspaper advertisements and by word of mouth. They underwent cognitive assessment to rule out MCI (all HC included in the study were cognitively normal). Most HC (74%) underwent PSG to rule out the presence of RBD, and the remaining HC tested negative on the RBD questionnaire. HC and iRBD patients were excluded if they were diagnosed with dementia, schizophrenia, and bipolar disorders based on Diagnostic and Statistical Manual of Mental Disorders Fifth Edition criteria [30]. Participants with parkinsonism, other neurological disorder, or history of stroke, head trauma, chronic obstructive pulmonary disease, EEG abnormalities suggesting epilepsy, or encephalitis were also excluded. This study was approved by a university hospital ethical committee. All participants gave their written informed consent to participate in this study.

2.2. Depression and anxiety questionnaires

Participants completed the 21-item Beck Depression Inventory, Second Edition (BDI-II) to assess the severity of clinical depressive symptoms [31]. Each item was rated according to the past two weeks on a four-point Likert scale from 0 to 3. Total scores higher than 13 indicate clinically significant depressive symptoms, based on guidelines and previous studies in iRBD [9,31]. Participants also completed the 21-item Beck Anxiety Inventory (BAI) to assess anxiety symptom severity [32]. Items were rated according to the last month on a four-point Likert scale from 0 to 3. Total scores of 0–9 indicate normal anxiety, and scores higher than 9 indicate clinically significant anxiety symptoms, based on guidelines [32]. In the present study, we included all participants who completed at least one questionnaire.

2.3. MRI

2.3.1. MRI data acquisition

High-resolution, 3D volumetric T1-weighted brain images were acquired on a 3 T Siemens TrioTIM MR scanner (Siemens, Erlangen, Germany) equipped with a 12-channel head matrix coil at the *Unité de Neuroimagerie Fonctionnelle* of the *Institut universitaire de gériatrie de Montréal* (www.unf-montreal.ca). We used magnetization-prepared rapid acquisition with gradient-echo sequence, with the following parameters: 2.91 ms echo time, 2.3 s repetition time, 900 ms inversion time, 9° flip angle, 160 slices, 256 × 240 acquisition matrix, 256 × 240 mm field view (voxel size: 1 × 1 × 1 mm^3), and 238 Hz/Px bandwidth, with an interleaved encoding scheme.

2.3.2. Voxel-based morphometry analysis

Neuroimaging data were analyzed using Statistical Parametric Mapping 12 software (Wellcome Trust Center for Neuroimaging, London, UK) running on MATLAB 8.5 (MathWorks, Natick, MA, USA). First, MRI scans were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) using the Unified Segmentation algorithm. A GM template was then constructed using DARTEL, based on the GM and WM of all participants (iRBD patients and HC). The GM template was then affine-registered to the MNI standard space, which, coupled with the warping parameters, allowed normalizing GM, WM, and CSF to the MNI space. Finally, normalized GM images were modulated to preserve the total signal power for each region, and smoothing was applied using an 8-mm full width at half maximum kernel. Image quality was assessed visually at all processing steps.

2.4. Statistical analysis

Demographic and clinical analyses were performed using IBM SPSS Statistics 23.0 (IBM Corporation, Armonk, NY, USA). iRBD patients were divided into two subgroups: iRBD patients with depressive symptoms (iRBD-DEP; BDI-II total scores > 13 or the use of antidepressants to treat depression) and iRBD patients without depressive symptoms (iRBD-nDEP; BDI-II total scores 0–13). iRBD patients were also divided into two subgroups: iRBD patients with anxiety symptoms (iRBD-ANX; BAI total scores > 9 or the use of anxiolytics to treat anxiety) and iRBD patients without anxiety symptoms (iRBD-nANX; BAI total scores 0–9). Medication and reasons for treatment were noted during a clinical interview with the participant conducted by a psychiatrist (JM) or neurologist (RPB) and from medical records. Patients taking antidepressants or anxiolytics for reasons other than to treat depressive or anxiety symptoms (e.g., pain, insomnia, or RBD symptoms) and without clinically significant depressive or anxiety symptoms on the questionnaires were included in the RBD-nDEP and RBD-nANX groups. We performed one-way analyses of variance followed by Bonferroni post hoc comparisons for normally distributed variables, and Kruskal–Wallis tests and Mann–Whitney *U* tests for non-normally distributed variables. Pearson chi-square tests were performed for categorical variables. We applied a multiple regression analysis based on completed BDI-II and BAI scores to replace missing data for BDI-II and BAI items. We also examined the variance inflation factor (VIF) to detect any collinearity issue between the BDI-II and BAI total scores.

2.4.1. Voxel-based morphometry analysis

Using SPM12, two general linear models were constructed to assess GM volume differences between iRBD patients associated with depressive (group factor: iRBD-DEP, iRBD-nDEP, HC) or anxiety symptoms (group factor: iRBD-ANX, iRBD-nANX, HC), controlled for age, gender, total intracranial volume (TIV), and education. To control for the effect of MCI in iRBD patients, two additional models including MCI status, TIV, age, gender, and education were constructed to compare GM volume between iRBD patients with and without depressive or anxiety symptoms. In addition, two multiple regression analyses were conducted on the whole brain in all iRBD patients, with BDI-II and BAI total scores as independent variables. These regressions were also controlled for age, gender, TIV, education, and MCI status. In a second step, we conducted additional analysis adding respectively the BDI-II or BAI total scores as covariates to identify specific regions independently related to depressive and anxiety symptoms. Two voxel-wise correction thresholds were applied. First, results were considered significant at $P < 0.05$ corrected for family-wise error (FWE). Then, we applied a threshold of $P < 0.001$ uncorrected for multiple comparisons with a cluster threshold of 100 voxels. This second threshold was used to avoid type II errors in this exploratory research, since we had a small sample size, expected a small to medium effect size, and included several covariates in our models.

3. Results

3.1. Demographic and clinical features

Of the 59 iRBD patients and 41 HC from the initial sample, 23 were excluded for clinical signs of parkinsonism or dementia (six patients), abnormal scan (three patients), or both questionnaires (BDI and BAI) uncompleted (four patients and 10 HC). Thus, 46 iRBD patients and 31 HC were included in the study. Seventeen iRBD patients were included in the iRBD-DEP group (11 had clinically significant depressive symptoms on the BDI-II including 6 patients taking antidepressants, and 6 other patients taking antidepressants but without clinically significant depressive symptoms on the BDI-II). The patients included on the basis of the use of antidepressants only had a recent history of major depressive disorder and were close to the threshold of the BDI-II (range 7–12). Sixteen iRBD patients were included in the iRBD-ANX group (all had clinically significant anxiety symptoms on the BAI, including 2 patients taking anxiolytics). Thirteen iRBD patients were taking anxiolytics for other clinical symptoms (ie. RBD symptoms) and were included in the iRBD-nANX group. There was some overlap between iRBD patients with anxiety and depressive symptoms. Nine iRBD patients only had depressive symptoms or were taking antidepressants, eight iRBD patients only had anxiety symptoms, eight iRBD patients showed both symptoms, and 21 iRBD patients did not report clinically significant psychiatric symptoms. All participants completed the BAI, but two patients without psychiatric symptoms did not complete the BDI. Unfortunately, the small sample size of each subgroup did not allow between-group comparisons.

The demographic and clinical features for the iRBD-DEP, iRBD-nDEP, iRBD-ANX, iRBD-nANX, and HC groups are presented in Table 1 iRBD-ANX patients had a higher proportion of MCI and reported higher BDI-II total scores than iRBD-nANX patients. iRBD-DEP patients had higher BAI total scores than iRBD-nDEP patients but the difference was not significant ($p = 0.079$). The proportion of MCI was higher in all patient groups compared to HC. iRBD patients, BDI-II total scores correlated negatively with the education's number of years ($r = -0.39$, $p < 0.05$) and positively with BAI total scores ($r = 0.53$, $p < 0.05$). BDI-II and BAI total scores did not correlate with any other demographic or clinical features. The VIF between the BDI-II and BAI total scores was under 2, which means that there was no collinearity issue. Therefore, these two variables could be included in the same statistical models for additional analysis.

3.2. Depressive symptoms

3.2.1. iRBD-DEP vs. iRBD-nDEP vs. HC

Using a $P < 0.05$ corrected for FWE, we found that iRBD-DEP patients had lower GM volume in the right caudate nucleus (19 voxels, $Z = 4.56$, peak voxel: 10, 10, 10) and the right cuneus (5 voxels, $Z = 4.55$, peak voxel: 8, −78, 42) compared to HC. Using a $P < 0.001$ uncorrected, we found lower GM volume in the right caudate nucleus, the calcarine gyrus bilaterally extending to the left cuneus, the postcentral gyrus bilaterally, the right supramarginal gyrus, the right cuneus, and the left inferior frontal gyrus in iRBD-DEP compared to iRBD-nDEP patients (Table 2 and Fig. 1A). Moreover, compared to HC, iRBD-DEP patients showed lower GM volume in both caudate nuclei, the left pallidum extending to the putamen, insula and amygdala, the right insula extending to the putamen and amygdala, the medial superior frontal gyrus in both hemispheres, the right frontal pole, the left inferior temporal gyrus and the parieto-occipital regions including the right cuneus, the right lateral occipital gyrus, the right lingual gyrus extending to the calcarine gyrus, the left paracentral gyrus, and the left calcarine gyrus extending to the cuneus (Table 2 and Fig. 1B). iRBD-nDEP patients showed lower GM volume in the right inferior temporal gyrus only compared to HC (Fig. 1C). No significantly higher GM volumes were found between both patient group and HC. When the BAI was added as additional covariate, we found similar results, except for GM volume loss in the right supramarginal gyrus (iRBD-DEP vs. iRBD-nDEP patients) and GM volume loss in the medial frontal and occipital regions (iRBD-DEP vs. HC).

3.2.2. Regressions

Using $P < 0.05$ corrected for FWE, we found no significant correlations between GM volume and BDI-II total scores. Using $P < 0.001$ uncorrected, we found that higher BDI-II total scores in iRBD patients were associated with GM volume loss in both caudate nuclei, the right superior parietal gyrus, bilateral postcentral gyrus, and the left calcarine gyrus (Table 2 and Fig. 1D). No positive correlations were found between GM volume and BDI-II total scores in iRBD patients. When the BAI was added as additional covariate, we also found that higher BDI-II total scores were associated with GM volume loss in the insula, inferior and middle frontal, inferior temporal, and fusiform gyrus.

3.3. Anxiety symptoms

3.3.1. RBD-ANX vs. RBD-nANX vs. HC

Using $P < 0.05$ corrected for FWE, no significant GM volume differences were found between the groups. Using $P < 0.001$ uncorrected, we found lower GM volume in the left amygdala extending to the hippocampus and parahippocampal regions in iRBD-ANX patients compared to iRBD-nANX patients (Table 2 and Fig. 2A). Moreover, compared to HC, iRBD-ANX patients showed lower GM volume in the left amygdala (Fig. 2B). Compared to HC, iRBD-nANX patients showed lower GM volume in the left putamen (Fig. 2C). No significantly higher GM volumes were found between both patient group and HC. When the BDI-II was added as additional covariate, no between-group difference was found.

3.3.2. Regressions

Using $P < 0.05$ corrected for FWE, we found no significant correlations between GM volume and BAI total scores. Using $P < 0.001$ uncorrected, we found that, higher BAI total scores in iRBD patients were associated with GM volume loss in the left amygdala extending to the hippocampus (Table 2 and Fig. 2D). No positive correlations were found between GM volume and BAI total scores in iRBD patients. When the BDI-II was added as additional covariate, no correlation was found.

Table 1
Demographic and clinical characteristics of participants.

Variables	iRBD-DEP (n = 17)	iRBD-nDEP (n = 27)	iRBD-ANX (n = 16)	iRBD-nANX (n = 30)	HC (n = 31)	p value[h]
Age, yrs	67.35 ± 5.32	65.85 ± 6.25	65.65 ± 6.61	66.48 ± 6.34	63.28 ± 8.35	ns
Men, n (%)	12 (71)	22 (81)	12 (75)	24 (80)	21 (68)	ns[g]
Education, yrs	12.65 ± 3.18	13.78 ± 4.22	12.50 ± 3.10	13.67 ± 4.15	14.84 ± 4.05	ns
Handedness (% right-handed)	100	96	100	97	97	ns[g]
RBD duration (PSG)	2.20 ± 3.05	0.75 ± 1.41	1.15 ± 2.00	1.28 ± 2.27	–	ns[g]
RBD duration (subjective)	15.98 ± 14.53	10.54 ± 10.82	13.85 ± 13.48	11.95 ± 12.12	–	ns[g]
UPDRS-III	5.14 ± 5.11	4.11 ± 3.22	5.75 ± 5.08	3.67 ± 2.55	–	ns[g]
MoCA (/30)	25.27 ± 3.44	26.06 ± 2.70	25.27 ± 3.24	26.23 ± 2.60	–	ns[g]
TIV	1.45 (0.16)	1.44 (0.12)	1.41 (0.10)	1.46 (0.15)	1.41 (0.16)	ns
BDI-II	15.64 ± 7.05	5.26 ± 4.06	13.06 ± 6.88	7.10 ± 6.88	3.06 ± 2.97	< 0.001[a,b,d,e,g]
BAI	11.06 ± 7.39	5.92 ± 6.13	15.81 ± 4.58	3.60 ± 3.07	2.47 ± 4.30	< 0.001[b,d,e,g]
MCI, n (%)	6 (35)	11 (41)	10 (63)	8 (27)	0 (0)	< 0.001[b,c,d,e,f,g]

iRBD = idiopathic rapid eye movement sleep behavior disorder; iRBD-DEP = iRBD with depression; iRBD-nDEP = RBD without depression; iRBD-ANX = iRBD with anxiety; iRBD-nANX = iRBD without anxiety; HC = healthy controls; ns = not significant; PSG = polysomnography; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III; MoCA = Montreal Cognitive Assessment; BDI-II = Beck Depression Inventory, Second Edition; BAI = Beck Anxiety Inventory; MCI = mild cognitive impairment; TIV = total intracranial volume.

[a] iRBD-DEP > iRBD-nDEP.
[b] iRBD-DEP > HC.
[c] iRBD-nDEP > HC.
[d] iRBD-ANX > iRBD-nANX.
[e] iRBD-ANX > HC.
[f] iRBD-nANX > HC.
[g] Nonparametric tests.
[h] iRBD-DEP vs. iRBD-nDEP vs. HC or iRBD-ANX vs. iRBD-nANX vs. HC.

4. Discussion

In this study, we used VBM to investigate subcortical and cortical GM volume alterations associated with depressive and anxiety symptoms in iRBD patients. In iRBD patients with clinically significant depressive symptoms, we found GM volume loss in the caudate nuclei, left calcarine and right cuneus compared to iRBD patients without significant depressive symptoms and HC. We also found GM volume loss in the left amygdala extending to the hippocampus in iRBD patients with clinically significant anxiety symptoms compared to iRBD patients without significant anxiety symptoms and HC. Moreover, higher severity of anxiety and depressive symptoms were correlated with lower GM volume in these regions in iRBD patients. The results of the present study provide new evidence that allows us to better understand the pathophysiology underlying the psychiatric symptoms reported in this population at high risk of synucleinopathies.

Depressive symptoms are frequent features in iRBD [9,10,14]. Frauscher et al. [10] found that 29% of iRBD patients had a history of depression. Another study found that iRBD patients reported more depressive symptoms than HC, and were 7 times more likely to show mild signs of depression, as determined using the BDI-II (cut-off > 13) [9]. Depression was also more frequent in iRBD patients (44.4%) than controls (18.3%) [14]. Depressive symptoms are also common in synucleinopathies. Indeed, the prevalence of clinically relevant depression in PD is approximately 35%, and up to 60% of DLB and MSA patients [4,7,33]. Depression is also recognized as a prodromal symptom of PD and DLB [5,8,34]. In iRBD, depressive symptoms are associated with early signs of neurodegeneration, such as hyposmia [9]. Moreover, iRBD patients with comorbid MDD had lower ^{18}F-DOPA uptake in the putamen and caudate nucleus as well as impaired olfactory function, suggesting that they are at risk of developing a synucleinopathy [12]. However, depression in iRBD has been found to be insufficient to predict conversion to synucleinopathies [3,15], except for one single-center, small-sample study that found that the presence of depressive disorders in iRBD predicted increased risk of developing PD [13]. These inconsistencies could be related to the heterogeneity of patients recruited and to the different diagnostic constructs across studies (e.g., mood disorder diagnosis or questionnaires, lifetime history of depression versus current symptoms) and further longitudinal studies are needed to clarify this question.

In the present study, the most robust finding was the association between the GM volume loss in the caudate nucleus and depressive symptoms, reported in group comparisons (iRBD-DEP vs. iRBD-nDEP and iRBD-DEP vs. HC) and regression analysis. In PD, one study using VBM reported GM volume loss in the right caudate nucleus in patients with depressive symptoms compared to controls [23]. In MDD and late-life depression, GM volume loss in the caudate nucleus has been reported in several studies [17,18,35–37]. The association was particularly evident in men with lifetime MDD [38], which is interesting because RBD is a male predominant condition [1,2]. Increasing evidence suggests that the caudate nucleus plays a role in affective disorder, as part of the cortico-striato-pallido-thalamic and amygdalo-striato-pallido-thalamic loops [18,39,40]. These circuits form the core of the neural system implicated in mood disorders [39,40]. The striatum (caudate and putamen) interacts with the serotoninergic system [41], and dysfunction of this system has been associated to depression in PD [42]. In iRBD, one study using transcranial sonography found a higher proportion of patients with depression having brainstem raphe hypoechogenecity, suggesting that dysfunction of the serotoninergic dorsal raphe nucleus might be implicated in the pathophysiology of depression in iRBD [14]. Further studies are needed to better understand the role of the serotoninergic system and the caudate nucleus in the depressive symptoms reported in iRBD.

We also identified an association between GM volume loss in posterior (calcarine, cuneus) and frontal (postcentral) regions and depressive symptoms in our sample. These regions are not usually related to depression in PD, MDD and late-life depression. Moreover, we also found GM volume loss in the inferior temporal gyrus in iRBD without depressive symptoms compared to controls. In iRBD, GM abnormalities in postcentral, temporal, and occipital regions have been related to other markers of neurodegeneration, such as impaired motor, cognitive, color discrimination, and olfactory functions [27,28]. In line with these findings, one recent study performed in PD patients with probable RBD found more altered white matter pathways in patients with depressive symptoms compared to those without depression [43]. These results suggest that the presence of depression in iRBD and PD patients with RBD is related to a more severe pattern of structural brain alterations.

Furthermore, RBD patients report more anxiety symptoms than

Table 2
Voxel-based morphometry results for group comparisons and multiple regressions.

	Region	Z value	Cluster size	MNI coordinates		
				X	Y	Z
iRBD-nDEP > iRBD-DEP	L Calcarine	4.34	746	−14	84	6
	R Caudate nucleus	4.24	405	8	2	4
	L Postcentral	4.16	193	−51	−20	58
	R Cuneus	4.08	103	6	−80	42
	L Inferior frontal	4.00	236	−56	10	16
	R Calcarine	3.66	162	16	−68	10
	R Surpramarginal	3.48	138	48	−30	44
	L Calcarine	3.41	102	−20	−69	10
iRBD-nDEP < iRBD-DEP	–					
HC > iRBD-DEP	R Caudate nucleus	4.56	562	10	10	10
	R Cuneus	4.55	207	8	−78	42
	L Caudate nucleus	4.20	538	−9	9	8
	L Pallidum	4.05	1674	−18	0	−10
	L Calcarine	4.04	309	−9	−80	15
	R Insula	3.99	864	44	12	−4
	R Lingual	3.90	773	20	−50	2
	R Occipital lateral	3.87	138	27	−70	−12
	R Medial superior frontal	3.86	442	4	56	16
	L Inferior temporal	3.80	264	−45	−15	−42
	L Paracentral	3.73	246	−3	−28	62
	R Frontal pole	3.66	139	22	64	−14
	L Medial superior frontal	3.36	106	−8	52	10
HC < iRBD-DEP	–					
HC > iRBD-nDEP	R Inferior temporal	3.69	124	46	−39	−20
HC < iRBD-nDEP	–					
Negative correlations with the BDI-II total scores	R Caudate nucleus	4.09	231	8	2	4
	R Postcentral	3.94	223	54	−15	34
	R Superior parietal	3.85	524	33	−63	36
	L Calcarine	3.83	573	−14	−87	4
	L Postcentral	3.79	354	−46	−30	48
	L Caudate nucleus	3.46	247	−9	6	9
Positive correlations with the BDI-II total scores	–					
iRBD-nANX > iRBD-ANX	L Amygdala	3.57	139	−21	0	−28
iRBD-nANX < iRBD-ANX	–					
HC > iRBD-ANX	L Amygdala	3.65	316	−32	0	−20
HC < iRBD-ANX	–					
HC > iRBD-nANX	L Putamen	3.52	250	−22	2	−3
HC < iRBD-nANX	–					
Negative correlations with the BAI total scores	L Amygdala	3.58	326	−22	2	−27
Positive correlations with the BAI total scores	–					

iRBD = idiopathic rapid eye movement sleep behavior disorder; iRBD-ANX = iRBD with anxiety; iRBD-DEP = iRBD with depression; iRBD-nANX = iRBD without anxiety; iRBD-nDEP = iRBD without depression; HC = healthy controls; L = left; R = right; BDI-II = Beck Depression Inventory, Second Edition; BAI = Beck Anxiety Inventory.
Results are significant at $p < 0.001$ (uncorrected) with a cluster threshold of 100 voxels, with age, gender, TIV, education, and MCI status as covariates.

healthy individuals [9–11]. Anxiety symptoms are also frequent in PD, DLB and MSA [6,7]. Indeed, 30% of PD patients have at least one anxiety disorder, and 65–70% of DLB and MSA patients show significant anxiety symptoms [6,7,44]. Anxiety disorder often precedes PD diagnosis by years [45]. In iRBD, preliminary results found a trend ($p = 0.12$) that anxiety symptom severity predicts conversion to synucleinopathies [3]. To our knowledge, this is the first study to investigate the neuroanatomical substrates of anxiety symptoms in iRBD. We found in group comparisons and regressions an association between anxiety symptoms and reduced GM volume in an area including the amygdala extending to the hippocampus. In early PD, reduced GM volumes in the left amygdala and hippocampus were associated with higher anxiety symptom [26]. In anxiety disorders, reduced GM volumes in the amygdala and hippocampus have also been frequently reported [20]. However, the causal relationship between GM volume loss in the amygdala of iRBD and PD patients remains unclear. Amygdala shrinkage has been proposed to be responsible for anxiety in PD and is supported by degeneration observed in the amygdala of PD in post-mortem studies [26,46]. Similar mechanisms might explain the anxiety-related GM volume loss in our RBD population. It is also important to note that anxiety and depression frequently overlap in these populations. In PD, 41% of patients reported both anxiety and depressive symptoms [47]. In the present study, 18% of iRBD patients reported both symptoms. Moreover, when controlling for the severity of depressive symptoms, the reduced GM volume found in the amygdala was not significant anymore. Similar results have been reported in PD [26]. These results suggest that the amygdala atrophy is not specific to anxiety symptoms, but may also be related to the severity of depressive symptoms.

This study has some limitations. First, the BDI-II and BAI measure only the current severity of depressive and anxiety symptoms, they do not allow a definitive psychiatric diagnosis. Second, confounding variables such as cognitive impairment, motor symptoms, RBD duration, and antidepressant use might have contributed to our results. We found no correlations between UPDRS motor score, RBD duration, and GM volume loss. To limit for the impact of cognitive impairment, we added MCI status as covariate in the analysis. However, all HC subjects were cognitively intact, while MCI was present in a significant

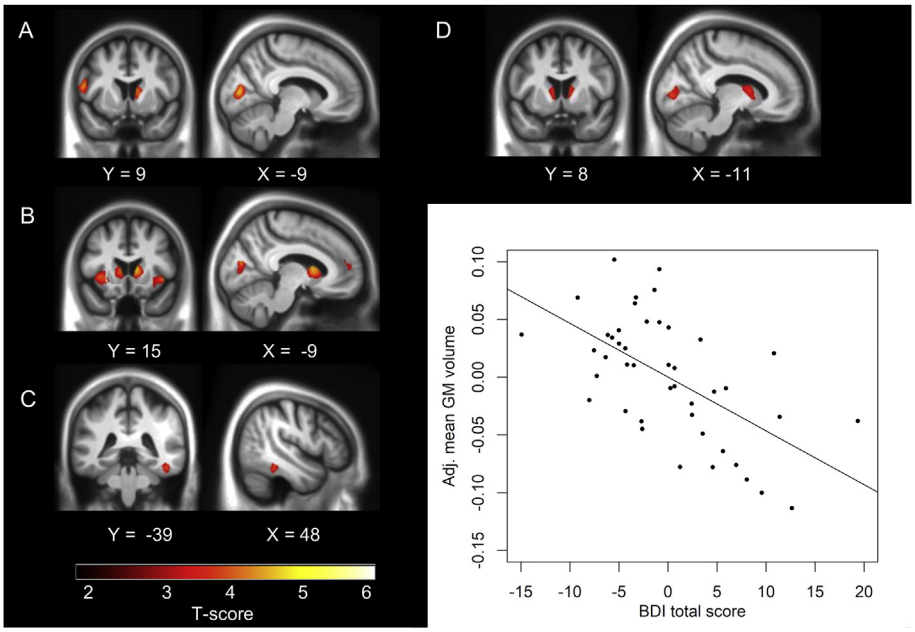

Fig. 1. Comparison of gray matter (GM) volume between participants. A) HC > iRBD-DEP; B) iRBD-nDEP > iRBD-DEP; C) HC > iRBD-nDEP. D) Upper side: regions showing significant negative correlations between BDI-II total scores and GM volumes in iRBD patients. Low side: plot of the negative partial correlations between the mean GM volume in the bilateral caudate nuclei and the BDI-II total score. Coordinates (x,y,z) are reported as MNI152 space coordinates. Results are significant at $p < 0.001$ (uncorrected) with a cluster threshold of 100 voxels, with age, gender, TIV, education, and MCI status as covariates.

proportion of iRBD patients, which limits the interpretation of our findings in regard to the HC group. Third, because iRBD-ANX patients were more depressed than iRBD-nANX patients and iRBD-DEP patients were marginally more anxious than iRBD-nANX patients, these phenotypes were more ambiguous. However, our findings for depression-related atrophies remain when controlling for the severity of anxiety symptoms. An additional limitation was the small patient sample after the creation of subgroups and the inclusion of both patients taking medication and medication-naïve patients in the iRBD-DEP and iRBD-ANX groups. We cannot exclude that other brain regions might be related to mood symptoms in iRBD with more statistical power.

5. Conclusion

In summary, we found two patterns of GM volume loss in iRBD related to mood symptoms: a depression-related pattern in the caudate nucleus, and an anxiety-related pattern in the amygdala extending to the hippocampus. Further studies should investigate the progression of the GM changes found in the present study, and whether they are related to mood symptom changes or neurodegeneration in this population.

Authors' contributions

PAB: Conception and design of the study, acquisition, analysis and interpretation of data, manuscript writing, and editing.

SR: Acquisition of data, critical revision of intellectual content.

MG: Analysis and interpretation of data, critical revision of intellectual content.

RBP: Conception and design of the study, acquisition of data, funding, and critical revision of intellectual content.

JM: Conception and design of the study, funding, and critical

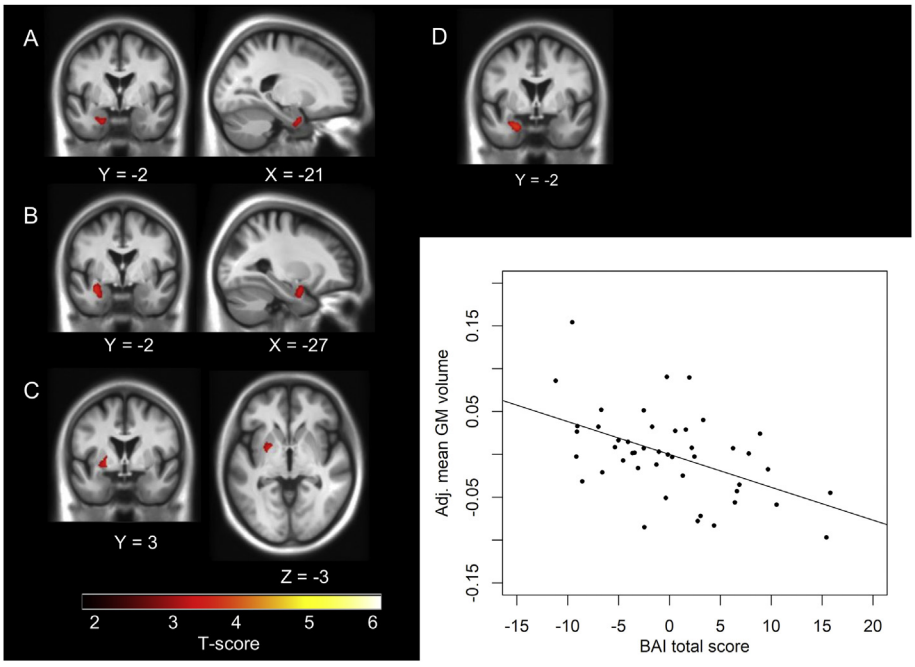

Fig. 2. Comparison of gray matter (GM) volume between participants. A) HC > iRBD-ANX; B) iRBD-nANX > iRBD-ANX; C) HC > iRBD-nANX. D) Upper side: regions showing significant negative correlations between BAI total scores and GM volumes in iRBD patients. Lower side: plot of the negative partial correlation between the mean GM volume in the left amygdala extending to the hippocampus and the BAI total score. Coordinates (x,y,z) are reported as MNI152 space coordinates. Results are significant at $p < 0.001$ (uncorrected) with a cluster threshold of 100 voxels, with age, gender, TIV, education, and MCI status as covariates.

revision of intellectual content.

JC: Conception and design of the study, acquisition of data, critical revision of intellectual content.

OM: Conception and design of the study, acquisition of data, critical revision of intellectual content.

AP: Acquisition of data and critical revision of intellectual content.

JFG: Conception and design of the study, acquisition and interpretation of data, critical revision of intellectual content, funding, supervision, and final approval of the version submitted.

Declarations of interest

None.

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References

[1] American Academy of Sleep Medicine, International Classification of Sleep Disorders, third ed., American Academy of Sleep Medicine, Darien, 2014.
[2] M.J. Howell, C.H. Schenck, Rapid eyemovement sleep behavior disorder and neurodegenerative disease, JAMA Neurol 72 (2015) 707–712, https://doi.org/10.1001/jamaneurol.2014.4563.
[3] R.B. Postuma, J.F. Gagnon, J.A. Bertrand, D. Génier Marchand, J.Y. Montplaisir, Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials, Neurology 84 (2015) 1104–1113, https://doi.org/10.1212/WNL.0000000000001364.
[4] F. Fritze, U. Ehrt, H. Sønnesyn, M. Kurz, Depression in mild dementia: associations with diagnosis, APOE genotype and clinical features, Int. J. Geriatr. Psychiatr. 26 (2011) 1054–1061, https://doi.org/10.1002/gps.2643.
[5] H. Gustafsson, A. Nordström, P. Nordström, Depression and subsequent risk of Parkinson disease A nationwide cohort study, Neurology 84 (2015) 2422–2429, https://doi.org/10.1212/WNL.0000000000001684.
[6] M.P.G. Broen, N.E. Narayen, M.L. Kuijf, N.N.W. Dissanayaka, A.F.G. Leentjens, Prevalence of anxiety in Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 31 (2016) 1125–1133, https://doi.org/10.1002/mds.26643.
[7] L.-Y. Zhang, B. Cao, Y.-T. Zou, Q.-Q. Wei, R.-W. Ou, B. Zhao, Y. Wu, H.-F. Shang, Depression and anxiety in multiple system atrophy, Acta Neurol. Scand. 137 (2018) 33–37, https://doi.org/10.1111/ane.12804.
[8] D. Berg, R.B. Postuma, C.H. Adler, B.R. Bloem, P. Chan, B. Dubois, T. Gasser, C.G. Goetz, G. Halliday, L. Joseph, A.E. Lang, I. Liepelt-Scarfone, I. Litvan, K. Marek, J. Obeso, W. Oertel, C.W. Olanow, W. Poewe, M. Stern, G. Deuschl, MDS research criteria for prodromal Parkinson's disease, Mov. Disord. 30 (2015) 1600–1611, https://doi.org/10.1002/mds.26431.
[9] T.R. Barber, M. Lawton, M. Rolinski, S. Evetts, F. Baig, C. Ruffmann, A. Gornall, J.C. Klein, C. Lo, G. Dennis, O. Bandmann, T. Quinnell, Z. Zaiwalla, Y. Ben-Shlomo, M.T.M. Hu, Prodromal parkinsonism and neurodegenerative risk stratification in REM sleep behavior disorder, Sleep 40 (2017), https://doi.org/10.1093/sleep/zsx071.
[10] B. Frauscher, P. Jennum, Y.E.S. Ju, R.B. Postuma, I. Arnulf, V.C. De Cock, Y. Dauvilliers, M.L. Fantini, L. Ferini-Strambi, D. Gabelia, A. Iranzo, S. Leu-Semenescu, T. Mitterling, M. Miyamoto, T. Miyamoto, J.Y. Montplaisir, W. Oertel, A. Pelletier, P. Prunetti, M. Puligheddu, J. Santamaria, K. Sonka, M. Unger, C. Wolfson, M. Zucconi, M. Terzaghi, B. Högl, G. Mayer, R. Manni, Comorbidity and medication in REM sleep behavior disorder: a multicenter case-control study, Neurology 82 (2014) 1076–1079, https://doi.org/10.1212/WNL.0000000000000247.
[11] P. Mahlknecht, K. Seppi, B. Frauscher, S. Kiechl, J. Willeit, H. Stockner, A. Djamshidian, M. Nocker, V. Rastner, M. Defrancesco, G. Rungger, A. Gasperi, W. Poewe, B. Högl, Probable RBD and association with neurodegenerative disease markers: a population-based study, Mov. Disord. 30 (2015) 1417–1421, https://doi.org/10.1002/mds.26350.
[12] Y.K. Wing, S.P. Lam, J. Zhang, E. Leung, C.L. Ho, S. Chen, M.K. Cheung, S.X. Li, J.W.Y. Chan, V. Mok, J. Tsoh, A. Chan, C.K.W. Ho, Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression, Neurology 84 (2015) 516–522, https://doi.org/10.1212/WNL.0000000000001215.
[13] Y.K. Wing, S.X. Li, V. Mok, S.P. Lam, J. Tsoh, A. Chan, M.W.M. Yu, C.Y.K. Lau, J. Zhang, C.K.W. Ho, Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 83 (2012) 470–472, https://doi.org/10.1136/jnnp-2011-301232.
[14] D. Vilas, A. Iranzo, C. Pont-Sunyer, M. Serradell, C. Gaig, J. Santamaria, E. Tolosa, Brainstem raphe and substantia nigra echogenicity in idiopathic REM sleep behavior disorder with comorbid depression, J. Neurol. 262 (2015) 1665–1672, https://doi.org/10.1007/s00415-015-7745-0.
[15] S.M. Fereshtehnejad, J.Y. Montplaisir, A. Pelletier, J.F. Gagnon, D. Berg, R.B. Postuma, Validation of the MDS research criteria for prodromal Parkinson's disease: longitudinal assessment in a REM sleep behavior disorder (RBD) cohort, Mov. Disord. 32 (2017) 865–873, https://doi.org/10.1002/mds.26989.
[16] M. Du, J. Liu, Z. Chen, X. Huang, J. Li, W. Kuang, Y. Yang, W. Zhang, D. Zhou, F. Bi, K.M. Kendrick, Q. Gong, Brain grey matter volume alterations in late-life depression, J. Psychiatry Neurosci. 39 (2014) 397–406, https://doi.org/10.1503/jpn.130275.
[17] D. Arnone, A.M. McIntosh, K.P. Ebmeier, M.R. Munafò, I.M. Anderson, Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses, Eur. Neuropsychopharmacol. 22 (2012) 1–16, https://doi.org/10.1016/j.euroneuro.2011.05.003.
[18] M.D. Sacchet, E.E. Livermore, J.E. Iglesias, G.H. Glover, I.H. Gotlib, Subcortical volumes differentiate major depressive disorder, bipolar disorder, and remitted major depressive disorder, J. Psychiatr. Res. 68 (2015) 91–98, https://doi.org/10.1016/j.jpsychires.2015.06.002.
[19] J. Shang, Y. Fu, Z. Ren, T. Zhang, M. Du, Q. Gong, S. Lui, W. Zhang, The common traits of the ACC and PFC in anxiety disorders in the DSM-5: meta-analysis of voxel-based morphometry studies, PLoS One 9 (2014) e93432, https://doi.org/10.1371/journal.pone.0093432.
[20] E.R. Duval, A. Javanbakht, I. Liberzon, Neural circuits in anxiety and stress disorders: a focused review, Therapeut. Clin. Risk Manag. 11 (2015) 115–126, https://doi.org/10.2147/TCRM.S48528.
[21] T.J. van Mierlo, C. Chung, E.M. Foncke, H.W. Berendse, O.A. van den Heuvel, Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume, Mov. Disord. 30 (2015) 245–252, https://doi.org/10.1002/mds.26112.
[22] A. Feldmann, Z. Illes, P. Kosztolanyi, E. Illes, A. Mike, F. Kover, I. Balas, N. Kovacs, F. Nagy, Morphometric changes of gray matter in Parkinson's disease with depression: a voxel-based morphometry study, Mov. Disord. 23 (2008) 42–46, https://doi.org/10.1002/mds.21765.
[23] P. Liang, G. Deshpande, S. Zhao, J. Liu, X. Hu, K. Li, Altered directional connectivity between emotion network and motor network in Parkinson's disease with depression, Medicine 95 (2016) e4222, https://doi.org/10.1097/MD.0000000000004222.
[24] M. Goto, K. Kamagata, T. Hatano, N. Hattori, O. Abe, S. Aoki, M. Hori, T. Gomi, Depressive symptoms in Parkinson's disease are related to decreased left hippocampal volume: correlation with the 15-item shortened version of the Geriatric Depression Scale, Acta Radiol. 59 (2017) 341–345, https://doi.org/10.1177/0284185117719100.
[25] N. Wee, M.-C. Wen, N. Kandiah, R.J. Chander, A. Ng, W.L. Au, L.C.S. Tan, Neural correlates of anxiety symptoms in mild Parkinson's disease: a prospective longitudinal voxel-based morphometry study, J. Neurol. Sci. 371 (2016) 131–136, https://doi.org/10.1016/j.jns.2016.10.021.
[26] C. Vriend, P.S.W. Boedhoe, S. Rutten, H.W. Berendse, Y.D. Van Der Werf, O.A. Van Den Heuvel, A smaller amygdala is associated with anxiety in Parkinson's disease: a combined FreeSurfer - VBM study, J. Neurol. Neurosurg. Psychiatry 87 (2016) 493–500, https://doi.org/10.1136/jnnp-2015-310383.
[27] S. Rahayel, R.B. Postuma, J. Montplaisir, D. Génier Marchand, F. Escudier, M. Gaubert, P.-A. Bourgouin, J. Carrier, O. Monchi, S. Joubert, F. Blanc, J.-F. Gagnon, Cortical and subcortical gray matter bases of cognitive deficits in REM sleep behavior disorder, Neurology 90 (2018) e1759–e1770, https://doi.org/10.1212/WNL.0000000000005523.
[28] S. Rahayel, R.B. Postuma, J. Montplaisir, C. Bedetti, S. Brambati, J. Carrier, O. Monchi, P.A. Bourgouin, M. Gaubert, J.F. Gagnon, Abnormal gray matter shape, thickness, and volume in the motor cortico-subcortical loop in idiopathic rapid eye movement sleep behavior disorder: association with clinical and motor features, Cerebr. Cortex 28 (2018) 658–671, https://doi.org/10.1093/cercor/bhx137.
[29] D.G. Marchand, J. Montplaisir, R.B. Postuma, S. Rahayel, J.-F. Gagnon, Detecting the cognitive prodrome of dementia with Lewy bodies: a prospective study of REM sleep behavior disorder, Sleep 40 (2016), https://doi.org/10.1093/sleep/zsw014.
[30] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, fifth ed., American Psychiatric Publishing, Arlington, 2013.
[31] G.K. Beck, R.A. A.T., Steer, Brown, Manual for the Beck Depression Inventory-II, Psychological Corporation, San Antonio, 1996.
[32] A.T. Beck, N. Epstein, G. Brown, R.A. Steer, An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893–897, https://doi.org/10.1037/0022-006X.56.6.893.
[33] D. Aarsland, S. Påhlhagen, C.G. Ballard, U. Ehrt, P. Svenningsson, Depression in Parkinson disease - epidemiology, mechanisms and management, Nat. Rev. Neurol. 8 (2012) 35–47, https://doi.org/10.1038/nrneurol.2011.189.
[34] H. Fujishiro, S. Nakamura, K. Sato, E. Iseki, Prodromal dementia with Lewy bodies, Geriatr. Gerontol. Int. 15 (2015) 817–826, https://doi.org/10.1111/ggi.12466.
[35] T. Wise, J. Radua, E. Via, N. Cardoner, O. Abe, T.M. Adams, F. Amico, Y. Cheng, J.H. Cole, C. de Azevedo Marques Périco, D.P. Dickstein, T.F.D. Farrow, T. Frodl, G. Wagner, I.H. Gotlib, O. Gruber, B.J. Ham, D.E. Job, M.J. Kempton, M.J. Kim, P.C.M.P. Koolschijn, G.S. Malhi, D. Mataix-Cols, A.M. McIntosh, A.C. Nugent,

J.T. O'Brien, S. Pezzoli, M.L. Phillips, P.S. Sachdev, G. Salvadore, S. Selvaraj, A.C. Stanfield, A.J. Thomas, M.J. van Tol, N.J.A. van der Wee, D.J. Veltman, A.H. Young, C.H. Fu, A.J. Cleare, D. Arnone, Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis, Mol. Psychiatr. 22 (2016) 1455–1463, https://doi.org/10.1038/mp.2016.72.

[36] M.A. Butters, H.J. Aizenstein, K.M. Hayashi, C.C. Meltzer, J. Seaman, C.F. Reynolds, A.W. Toga, P.M. Thompson, J.T. Becker, Three-dimensional surface mapping of the caudate nucleus in late-life depression, Am. J. Geriatr. Psychiatry 17 (2009) 4–12, https://doi.org/10.1097/JGP.0b013e31816ff72b.

[37] P.C.M. Koolschijn, N.E. van Haren, G.J. Lensvelt-Mulders, H.E. Hulshoff Pol, R.S. Kahn, Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies, Hum. Brain Mapp. 30 (2009) 3719–3735, https://doi.org/10.1002/hbm.20801.

[38] M.L. Ancelin, I. Carrière, S. Artéro, J. Maller, C. Meslin, K. Ritchie, J. Ryan, I. Chasudieu, Lifetime major depression and grey-matter volume, J. Psychiatry Neurosci. 43 (2018), https://doi.org/10.1503/jpn.180026 e180026-e180026.

[39] J.L. Price, W.C. Drevets, Neural circuits underlying the pathophysiology of mood disorders, Trends Cognit. Sci. 16 (2012) 61–71, https://doi.org/10.1016/j.tics.2011.12.011.

[40] J.B. Savitz, W.C. Drevets, Imaging phenotypes of major depressive disorder: genetic correlates, Neuroscience 164 (2009) 300–330, https://doi.org/10.1016/j.neuroscience.2009.03.082.

[41] C. Miguelez, T. Morera-Herreras, M. Torrecilla, J.A. Ruiz-Ortega, L. Ugedo, Interaction between the 5-HT system and the basal ganglia: functional implication and therapeutic perspective in Parkinson's disease, Front. Neural Circ. 8 (2014) 21, https://doi.org/10.3389/fncir.2014.00021.

[42] S. Thobois, S. Prange, V. Sgambato-Faure, L. Tremblay, E. Broussolle, Imaging the etiology of apathy, anxiety, and depression in Parkinson's disease: implication for treatment, Curr. Neurol. Neurosci. Rep. 17 (2017) 76, https://doi.org/10.1007/s11910-017-0788-0.

[43] F. Ghazi Sherbaf, Y. Rostam Abadi, M. Mojtahed Zadeh, A. Ashraf-Ganjouei, H. Sanjari Moghaddam, M.H. Aarabi, Microstructural changes in patients with Parkinson's disease comorbid with REM sleep behaviour disorder and depressive symptoms, Front. Neurol. 9 (2018) 441, https://doi.org/10.3389/fneur.2018.00441.

[44] B. Borroni, C. Agosti, A. Padovani, Behavioral and psychological symptoms in dementia with Lewy-bodies (DLB): frequency and relationship with disease severity and motor impairment, Arch. Gerontol. Geriatr. 46 (2008) 101–106, https://doi.org/10.1016/j.archger.2007.03.003.

[45] E.L. Jacob, N.M. Gatto, A. Thompson, Y. Bordelon, B. Ritz, Occurrence of depression and anxiety prior to Parkinson's disease, Park. Relat. Disord. 16 (2010) 576–581, https://doi.org/10.1016/j.parkreldis.2010.06.014.

[46] A.J. Harding, E. Stimson, J.M. Henderson, G.M. Halliday, Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease, Brain 125 (2002) 2431–2445, https://doi.org/10.1093/brain/awf251.

[47] T. Yamanishi, H. Tachibana, M. Oguru, K. Matsui, K. Toda, B. Okuda, N. Oka, Anxiety and depression in patients with Parkinson's disease, Intern. Med. 52 (2013) 539–545, https://doi.org/10.2169/internalmedicine.52.8617.