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Early cortical atrophy is related to depression in patients with neuropathologically confirmed Parkinson's disease

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ABSTRACT

Objective: Depression is a common comorbidity in Parkinson's disease (PD) and other synucleinopathies. In non-PD geriatric patients, cortical atrophy has previously been connected to depression. Here, we investigated cortical atrophy and vascular white matter hyperintensities (WMHs) in autopsy-confirmed parkinsonism patients with the focus on clinical depression.

Methods: The sample consisted of 50 patients with a postmortem confirmed neuropathological diagnosis (30 Parkinson's disease [PD], 10 progressive supranuclear palsy [PSP] and 10 multiple system atrophy [MSA]). Each patient had been scanned with brain computerized tomography (CT) antemortem (median motor symptom duration at scanning = 3.0 years), and 19 patients were scanned again after a mean interval of 2.7 years. Medial temporal atrophy (MTA), global cortical atrophy (GCA) and WMHs were evaluated computationally from CT scans using an image quantification tool based on convolutional neural networks. Depression and other clinical parameters were recorded from patient files.

Results: Depression was associated with increased MTA after controlling for diagnosis, age, symptom duration, and cognition ($p = 0.006$). A similar finding was observed with GCA ($p = 0.017$) but not with WMH ($p = 0.47$). In PD patients alone, the result was confirmed for MTA ($p = 0.021$) with the same covariates. In the longitudinal analysis, GCA change per year was more severe in depressed patients than in nondepressed patients ($p = 0.029$).

Conclusions: Early medial temporal and global cortical atrophy, as detected with automated analysis of CT-images using convolutional neural networks, is associated with clinical depression in parkinsonism patients. Global cortical atrophy seems to progress faster in depressed patients.

1. Introduction

Depression is a common comorbidity in patients with neurodegenerative movement disorders, including Parkinson's disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) [1–5]. These conditions are characterized by a progressive loss of midbrain and cortical neurons, which affects various brain regions involved in motor, cognitive, and emotional processing. Up to 50% [1,2] of patients with PD experience depression, and together with the prominent loss of substantia nigra pars compacta neurons, PD has been linked to structural and functional changes in brain regions responsible for emotion processing and mood regulation, such as the prefrontal cortex (PFC), amygdala, and hippocampus [6,7]. Structural alterations in these areas are often observed in individuals with comorbid depression and PD. [8,9] However, it remains unclear whether depression in PD patients is a reflection of reactive secondary depression, dopamine depletion, the loss of other neurotransmitters, or structural changes in cortical or subcortical regions. Depression is a frequent nonmotor symptom also in patients with MSA and PSP, with reported prevalence rates ranging from 15% to 80% [3–5], depending on the employed

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diagnostic criteria for depression.

Only limited data exist on how regional atrophy contributes to depression in patients with neuropathologically confirmed parkinsonian disorders. The findings of earlier MRI studies have indicated that medial temporal lobe atrophy (MTA) is an important associated factor in geriatric depression [10,11], and hippocampal volume loss has been connected to depression duration in individuals with recurrent major depression [12]. It is important to note, however, that these studies, together with the majority of other structural brain imaging studies of cortical atrophy, have been performed with 1.5–3.0 T brain MR-imaging. MRI is clearly superior to computerized tomography (CT) in soft tissue imaging and resolution, particularly with higher field strenghts, but the benefits of CT are its speed, cost and availability. Therefore, brain CT remains a valid option for neurodegenerative disorder patients in many clinical situations, particularly in acute imaging.

In the current study, we aimed to investigate the usefulness of CT to explore MTA, global cortical atrophy (GCA), and white matter hyperintensities (WMHs) in patients with neuropathologically confirmed cases of PD, PSP and MSA, with a particular focus on clinical depression. Given the previously reported connection between depression and substantia nigra dopaminergic neuron density [13], we also examined the interrelationships of nigral neurons, cortical atrophy and depressive symptoms.

2. Methods

Using records of the Department of Pathology at Turku University Hospital, Finland, from 2002 to 2021, we identified patients who had received a neuropathological diagnosis of PD, PSP, or MSA. The hospital records of these patients were examined to identify patients who had underwent CT scanning over their disease course. From this search, 50 patients with antemortem CT imaging and neuropathologically confirmed diagnoses of PD, PSP, or MSA were found (30 patients with PD, 10 patients with PSP and 10 with MSA) (Table 1), with a median motor symptom duration of 3.0 years at the first CT scan. In addition, longitudinal CT imaging data were available for 19 patients (PD $n = 10$, PSP $n = 5$, and MSA $n = 4$; two CT scans per patient, median imaging interval = 2.7 years [range 0.6–8.7 years]). The study was approved by the local ethical committee and was conducted according to the principles of the Declaration of Helsinki.

Postmortem tissue sampling and neuropathological evaluations were performed using conventional methods to detect neurodegenerative disorders, with minor modifications [14]. A clinical PD diagnosis was neuropathologically confirmed when Lewy body disease of Braak stages 3–6 was present in combination with a loss of pigmented neurons in the substantia nigra [15]. The diagnosis of MSA was made when glial cytoplasmic inclusions positive for alpha-synuclein in immunohistochemical analyses were present, according to the MSA criteria proposed by the Neuropathology Working group on MSA [16]. For the diagnosis of PSP, phospho-tau positive neurofibrillary tangles and tufted astrocytes were required in characteristic locations according to the Rainwater Charitable Foundation criteria [17].

MTA, GCA and WMHs were evaluated computationally from CT scans using an image quantification tool based on convolutional neural networks (CNNs), as described previously [18,19]. Briefly, CT scans were skullstripped and registered to a common template space. Two CNNs were trained using a separate training set of 214 CT scans to segment cerebrospinal fluid (CSF) and WMHs. MTA and GCA were computed based on the CSF volume in the medial temporal lobe and cortex, respectively. WMHs were quantified using the Fazekas score measuring the WMH volume in the deep white matter.

The clinical histories of the patients were examined from hospital records systematically. Checklists were used when collecting the data. A patient was classified as depressed if a code for an ICD-10 depression diagnosis (F32) was present in their record, the treating physician had recorded depression at clinical visits and/or the patient had been prescribed antidepressive medications for a mood disorder. The following additional clinical data were collected and categorized as available (last documented value): levodopa equivalent daily dose of dopaminergic medications (LEDD, mg), Mini-Mental State Examination (MMSE) total score, body measurements (height and weight) and Hoehn and Yahr (HY) stage [20]. In addition, information about various clinical symptoms that had arisen during the course of the disease was recorded (present/not present), including constipation, urinary incontinence, urinary retention, swallowing difficulties, voice problems, sleep disorders, hyposmia, orthostatism and hallucinations. Descriptive data related to rigidity, bradykinesia, resting tremor, and cognitive problems were also collected. Clinical symptoms were considered present if they were documented in the patient's records by a physician, and considered absent if there was no mention of the symptom or if the patient had not reported any symptoms. Therefore, underreporting of certain symptoms and signs is possible, such as hyposmia in the case of PD.

Table 1
Main demographic and clinical characteristics of PD, PSP and MSA patients.

	PD	PSP	MSA	*p*-value
n	30	10	10	–
Age at motor symptom onset (years)	70.4 [14.1]	68.0 [14.8]	62.0 [29.0]	0.37
Age at imaging (years)	76.2 (7.3)	71.3 (7.6)	66.9 (14.9)	0.024*
Age at death (years)	80.1 (6.7)	73.2 (6.8)	68.7 (14.5)	0.002**
Sex (m/f)	25/5	7/3	6/4	0.29
LEDD (mg)	500 [440]	100 [540]	496 [1089]	0.029*
Disease duration at imaging (years)	3.2 [5.5]	2.8 [5.1]	1.0 [5.5]	0.31
Total disease duration (years)	9.3 (4.6)	5.1 (3.5)	4.8 (3.3)	0.006**
Clinical phenotype	TD ($n = 18$) PIGD ($n = 9$) Unknown ($n = 3$)	PSP-RS ($n = 7$) PSP-PGF ($n = 1$) PSP-P ($n = 1$) PSP-F ($n = 1$)	MSA-P ($n = 7$) MSA-C ($n = 3$)	–
Global cortical atrophy (GCA)	1.52 (1.16)	1.78 (1.01)	1.06 (1.17)	0.36
Medial temporal cortex atrophy (MTA)	1.28 (1.14)	1.45 (1.36)	0.97 (1.26)	0.67
WMHs (Fazekas)	1.79 [0.87]	1.04 [1.42]	1.34 [1.94]	0.051
Depression (y/n)	5/25	4/6	4/6	0.18
Dementia (y/n)	12/18	2/8	0/10	0.042

LEDD = levodopa equivalent daily dose, TD = tremor dominant, PIGD = postural instability gait disorder, PSP-RS = Richardson syndrome subtype, PSP-PGF = progressive gait freezing subtype, PSP-P = parkinsonism subtype, PSP-F = frontal subtype, MSA-P = parkinsonism subtype, MSA-C = cerebellar subtype. Values are median [IQR], mean (SD) or n. *p* values are from the Kruskall–Wallis test, one-way ANOVA or the chi-square test.

The normality of the data was evaluated using histograms and Kolmogorov–Smirnov tests. Group differences were tested with one-way ANOVA, Kruskall–Wallis test or the chi-square test as appropriate, together with post hoc comparisons using Bonferroni corrections. The normality of residuals of the linear model was checked and the normality assumption was met. ANCOVA was used to investigate changes in CT-based GCA, MTA (mean and separately left and right) and WMHs using age, symptom duration and group as covariates. The p values < 0.05 were considered statistically significant.

3. Results

The main demographic and clinical characteristics of the studied PD, PSP and MSA patients are presented in Table 1. Main characteristics

between depressed and non-depressed patients are presented in Table 2. There were no sex-differences in MTA, GCA, or vascular lesion load ($p > 0.83$).

3.1. Medial temporal cortex atrophy (MTA)

MTA was more severe in depressed patients than in nondepressed patients after controlling for the effects of age at scanning, motor symptom duration at scanning and group (estimated marginal mean MTA depressed = 2.30 [95% CI 1.56–3.03] vs. nondepressed = 1.01 [0.55–1.48]; $F(1,39) = 8.62$, $p = 0.006$) (Table 1, Figs. 1 and 2). The effect was significant for both right ($F(1,39) = 8.03$, $p = 0.007$) and left ($F(1,39) = 8.13$, $p = 0.007$) MTA. The covariate age at scanning, was significantly positively related to MTA (more severe atrophy with increasing age; $F(1,39) = 9.85$, $p = 0.003$), but not to symptom duration ($F(1,39) = 0.03$, $p = 0.86$) or group ($F(2,39) = 0.64$, $p = 0.53$). The relationship between MTA and depression remained significant when PSP and MSA patients were excluded from the analysis (depressed PD mean = 2.42 [1.37–3.48] vs. nondepressed 1.06 [0.62–1.50]; $F(1,23) = 6.13$, $p = 0.021$). Increased MTA was associated with the use of antidepressive medications ($F(1,39) = 5.52$, $p = 0.024$), but it was not significantly associated with documented dementia ($F(1,39) = 0.02$, $p = 0.90$), the last recorded MMSE score ($F(1,16) = 2.31$, $p = 0.15$), psychotic episodes ($F(1,39) = 0.82$, $p = 0.37$), the use of antipsychotic medications ($F(1,39) = 0.53$, $p = 0.47$), or the substantia nigra TH-positive neuron density at death ($F(1,39) = 0.29$, $p = 0.59$).

3.2. Global cortical atrophy (GCA)

GCA was more severe in depressed patients than in nondepressed patients after controlling for the effects of age at scanning, motor symptom duration at scanning and group (estimated marginal mean GCA depressed = 2.20 [95% CI 1.58–2.82) vs. nondepressed = 1.29 [0.90–1.68]; $F(1,39) = 6.07$, $p = 0.018$). The covariate age at scanning was significantly positively related to GCA ($F(1,39) = 20.5$, $p < 0.001$) but not to symptom duration ($F(1,39) = 0.17$, $p = 0.69$) or group ($F(2,39) = 2.04$, $p = 0.14$). GCA was not associated with the use of antidepressive medications ($F(1,39) = 0.82$, $p = 0.37$), dementia ($F(1,39) = 0.18$, $p = 0.67$), the last recorded MMSE score ($F(1,16) = 0.94$, $p = 0.35$), psychotic episodes ($F(1,39) = 0.18$, $p = 0.67$), the use of antipsychotic medications ($F(1,39) = 0.01$, $p = 0.91$), or the substantia nigra TH-positive neuron density at death ($F(1,39) = 0.35$, $p = 0.56$).

Table 2
Demographic and clinical characteristics of depressed and non-depressed patients.

	Depressed	Non-depressed	*p*-value
n	13	37	–
Disease duration (years)	8.0 (4.9) [11]	7.4 (4.6) [34]	0.38
Age at motor symptom onset (years)	57.0 [18.9] [11]	71.2 [14.0] [34]	0.003**
Age at death (years)	75.5 [17.3] [13]	79.8 [10.4] [37]	0.015*
Last MMSE score	17 (5.2) [6]	22 (5.5) [17]	0.70
Brain weight (g)	1403 (144) [13]	1408 (136) [36]	0.70
Sex (m/f)	9/4	29/8	0.51
Speech and voice problems (y/n)	9/4	14/23	0.051
Sleep disorders (y/n)	7/6	10/27	0.079
Hyposmia (y/n)	1/12	4/33	0.75
Orthostatism (y/n)	8/5	10/27	0.026*
Constipation (y/n)	5/8	9/36	0.33
Urinary problems (y/n)	10/3	20/17	0.15
Dysphagia (y/n)	7/6	11/26	0.12
Dementia (y/n)	5/8	9/28	0.33
Hallucinations (y/n)	3/10	14/23	0.33

Values are median [IQR] or mean (SD). *p* values are from Mann–Whitney U tests, independent sample *t*-tests or chi-square tests.

3.3. White Matter Hyperintensities (WMH)

There was no difference in vascular lesion load (WMHs) between depressed and nondepressed patients (age, symptom duration and group used as covariates; $F(1,39) = 0.45$, $p = 0.51$). The same was true when the analysis was limited to PD patients ($F(1,23) = 1.20$, $p = 0.29$). Likewise, vascular lesion load was not associated with the use of antidepressive medications ($F(1,39) = 0.10$, $p = 0.76$), dementia ($F(1,39) = 0.70$, $p = 0.41$), the last recorded MMSE score ($F(1,16) = 0.06$, $p = 0.80$), psychotic episodes ($F(1,39) = 1.86$, $p = 0.18$), the use of antipsychotic medications ($F(1,39) = 0.21$, $p = 0.65$), or the substantia nigra TH-positive neuron density at death ($F(1,39) = 0.001$, $p = 0.97$).

3.4. Clinical phenotype

PD patients with the tremor-dominant phenotype had less vascular lesion load than PD patients with the postural instability gait disorder (PIGD) phenotype (tremor-dominant PD estimated marginal mean = 1.34 [0.95–1.73] vs. PIGD mean = 2.10 [1.55–2.64]; $F(1,22) = 5.31$, $p = 0.031$, age and symptom duration used as covariates). The PD motor phenotype was not associated with MTA ($F(1,22) = 0.01$, $p = 0.91$) or GCA ($F(1,22) = 1.00$, $p = 0.33$). Comparisons between patients with MSA-P and patients with MSA-C and between patients with PSP-RS and patients with other forms of PSP (PSP-PGF, PSP-P, and PSP-F) were not performed due to the small sample sizes of these subsamples.

3.5. Global cortical atrophy (GCA) change/year

In patients with longitudinal data, the GCA change per one year was more severe in depressed patients than in nondepressed patients after controlling for the effects of motor symptom duration at scanning (estimated marginal mean GCA change/year depressed = 0.58 [95% CI 0.22–0.94] vs. nondepressed = 0.11 [−0.11–0.32]; $p = 0.029$; Table 3). No similar effects were observed with MTA or WMHs.

4. Discussion

The findings of this study showed that both MTA and GCA were associated with depression in patients with neurodegenerative movement disorders. This relationship was observed in the combined patient sample and separately in patients with PD. Depression was also linked to faster progression of cortical atrophy over a disease progression of 2.7 years.

The findings of previous MRI studies suggested that abnormal brain cortical atrophy and functional connectivity are associated with depression in PD [21–24]. However, the present study has two clear strenghts compared to earlier studies. First, all of our diagnoses were confirmed with postmortem neuropathological examinations. The diagnostic accuracy of PD and atypical parkinsonism syndromes is clinically suboptimal, particularly in the early stages of the diseases [25,26], which commonly induces noise in clinical data and compromises conclusions that are based on clinical diagnostic criteria. Therefore, despite the relatively small sample size (total $n = 50$, PD $n = 30$), the validity of the results is amplified by complete diagnostic certainty. We are not aware of previous imaging studies that have investigated depression in patients with parkinsonian disorders using autopsy-based diagnoses in association with imaging. Second, an automated approach to assess brain atrophy from CT scans was used and this method has been shown to be as precise as the technique used for evaluating brain atrophy from MRI scans [19]. The image analysis method used in this study demonstrates excellent reliability, effectively distinguishing cases with moderate to advanced structural changes from those with no or only minor findings, achieving an agreement rate of 84–90% when compared to MRI [18]. This is important because CT imaging is more widely available in health care facilities and more frequently used than MRI. CT remains a commonly used method, particularly when MRI is not

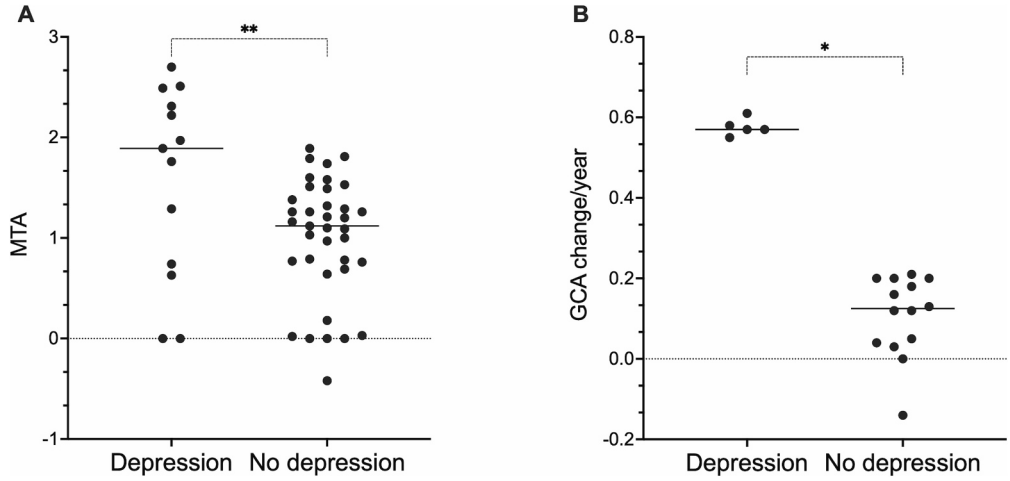

Fig. 1. Differences in cortical atrophy between patients with depression and patients without depression. A. Comparison of MTA in patients with and without depression ($p = 0.006$). B. Comparison of GCA yearly predicted progression in patients with and without depression ($p = 0.029$).

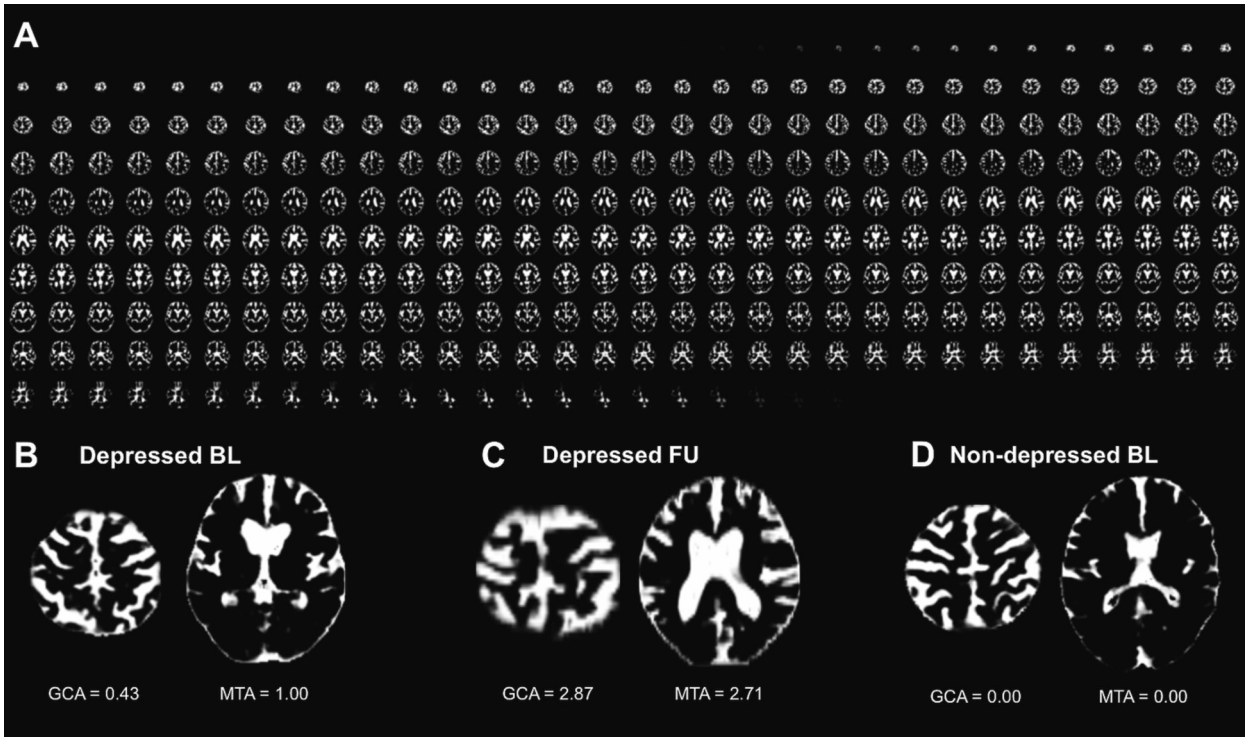

Fig. 2. Methodology of CSF segmentation and representative sections demonstrating atrophy in a depressed and a nondepressed patient. A. An example of CT-image segmentation results in a patient with neuropathologically confirmed PD with depression (age = 84.9 years at scanning, female). B. An image from a PD patient with depression (age = 80.4 years, female) scanned at an early disease stage showing mild MTA and CGA. C. An image from the same patient as in Panel B scanned 4.5 years later showing increased MTA and GCA. D. An image from a PD patient without depression (age = 72.4 years, male) scanned at an early disease stage showing mild MTA and GCA (BL = baseline, FU = follow-up).

available or contraindicated. Thus, an automated CT-based rating of atrophy could provide a broader means to differentiate parkinsonian individuals at risk of potential depressive symptoms by identifying atrophic processes in specific regions.

However, the retrospective nature of our study presents a limitation in establishing a definite causal relationship between atrophy and depression. The cross-sectional design does not allow us to determine whether atrophy precedes depression, or if depression leads to atrophy, or if there is a bidirectional relationship. Moreover, it is possible that a third underlying process may be influencing both atrophy and depression. Therefore, to gain deeper insights and clarify causal associations, future studies with longitudinal designs combined with comprehensive assessments of depression severity measure are warranted. The retrospective collection of clinical data from patient histories led to some unavailable and missing data, including depression scales, which should be taken into account for further studies. Additionally, the limited number of PSP and MSA cases in our study poses challenges in drawing definitive conclusions regarding these groups.

Depressive symptoms and behaviors may be linked to reduced neuroplasticity and increased neuronal atrophy [27]. Although impaired neuroplasticity may be a contributing factor to depression, the mechanism by which brain atrophy leads to depression is still unclear. Since

Table 3
Longitudinal analyses.

	Depressed	Non-depressed	*p*-value
n	5	14	–
Motor symptom duration at last scan (years)	6.00 [1.58]	4.50 [7.94]	0.50
Median imaging interval (years)	2.75 [4.50]	3.08 [4.16]	0.82
MTA change/ year	0.33 [0.68]	0.10 [0.30]	0.22
GCA change/ year	0.40 [0.77]	0.07 [0.42]	0.044*
WMH change/ year	0.02 [0.66]	0.00 [0.56]	0.62
MTA predicted change/ year	0.38 (0.14)	0.18 (0.09)	0.26
GCA predicted change/ year	0.58 (0.17)	0.11 (0.10)	0.029*
WMH predicted change/ year	0.08 (0.32)	−0.18 (0.19)	0.50

Yearly changes in depressed (PD $n = 2$, PSP $n = 3$) and nondepressed (PD $n = 8$, MSA $n = 4$, PSP $n = 2$) patients. Values are median [IQR]. *P* values are from Mann–Whitney *U* tests. Predicted variables were compared with analysis of variance with motor symptom duration at last scan as a covariate. Values are mean (SE).

MTA and GCA are commonly associated with cognitive deficits in both PD and non-PD populations, it is important to consider whether the observed effect is driven by the link between brain atrophy and cognitive problems in PD patients. However, the findings of our analysis indicated that, unlike depression, cognitive capacity was not directly related to MTA, GCA or WMHs as studied 3 years after motor symptom onset. It is likely that the relationship between cognition and atrophic cortical processes becomes more evident in later stages of neurodegeneration when both atrophy and cognitive defects/dementia are more commonly observed [28]. Our results in relation to vascular lesion load further suggested that the nontremulous PIGD phenotype of PD is associated with a higher number of WMHs than tremor-dominant PD. This result is in line with previous studies using brain MRI [29–32]. It is possible that although vascular lesions are not associated with the pathophysiological process of the PIGD phenotype per se, they could modify and increase the severity of axial symptoms in PIGD patients.

The longitudinal part of our study demonstrated that patients with depression experienced a faster rate of brain atrophy than nondepressed patients. Depression is a common premotor symptom in PD and can occur years before motor symptoms [33]. The accelerated rate of brain atrophy in depressed patients could be explained by neuroinflammatory processes in the brain occurring before motor symptoms, since prior research findings suggests that neuroinflammation contributes to the development of depression [34]. Depressed patients have been found to have elevated levels of proinflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) in their serum and cerebrospinal fluid [34,35], as well as increased microglial activation in various brain regions [36,37]. However, it was beyond the scope of the present study to investigate the mechanisms underlying this association, and further studies focusing on neuroinflammation in patients with PD-related depression are warranted.

In conclusion, the present study demonstrates that early MTA and GCA are associated with clinical depression in PD, PSP and MSA patients even when cognitive capacity is taken into account. Furthermore, we found that the progression of GCA is linked with depression. These results, in line with findings in geriatric patients with non-PD -related depression and obtained after neuropathological confirmation, serve as another step toward a better understanding of the relationship between neurodegenerative diseases and mental health outcomes.

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Authors' roles

VK contributed to the conception and design of the study; EB, LS, RP, JK, MG, and VK contributed to the acquisition and analysis of data; EB and VK contributed to drafting the text and preparing the figs. LS, RP, JK and MG contributed to critical revision of the manuscript.

Declaration of Competing Interest

The authors declared no conflict of interest.

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