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Depressive symptoms interact with CSF levels of p-tau in predicting cognitive performance in the early stages of Parkinson's disease

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A B S T R A C T

Amyloid-β deposition and tau pathology are suggested to play a role in the emergence of depressive symptoms and cognitive decline in Parkinson's disease (PD). Additionally, studies have reported an association between presence of the APOE4 allele and poorer cognition in PD. The present study aims to investigate whether amyloid-β, tau pathology and APOE4 carrier status interact with depressive symptoms in predicting global cognition in PD.

We analysed data from 348 persons with PD (PwPD) and 160 healthy controls (HCs). Linear mixed effects regression analyses were conducted to examine if CSF levels of Aβ42 and p-tau, and APOE4 carrier status did interact with depressive symptoms, as assessed by the Geriatric Depression Scale (GDS), in predicting cognition performance, as measured by Montreal Cognitive Assessment Test (MoCA) scores, over three years.

Results of a first linear regression model conducted considering both PwPD and HC indicated that MoCA scores were significantly predicted by GDS, as well as by the interaction between GDS and p-tau, Group and p-tau, and between Group, p-tau and GDS. Results of the models conducted in the two groups separately indicated that, while in HC MoCA scores were predicted by age and time only, a significant interaction between GDS and CSF levels of p-tau emerged as a predictor of MoCA scores in PwPD. Specifically, post hoc analysis revealed a negative association between CSF levels of p-tau and cognitive performance that was significant only in PwPD with the highest GDS scores.

Taken together, results of this study confirm that, in early stages of PD, depressive symptoms interact with CSF levels of p-tau in predicting cognitive performance. Findings highlight the importance of assessing and treating depression in PwPD as early as possible, as it might reduce the likelihood of future cognitive decline.

1. Introduction

The global aging of the world population, and the consequent increase of age-related neurodegenerative disorders such as Alzheimer's (AD) and Parkinson's diseases (PD), call for urgent action aimed at managing those disorders, and possibly preventing and/or delaying dementia. Depression is a modifiable risk factor for dementia (Livingston et al., 2020a,b), and in elderly individuals, depressive symptomatology is often associated with cognitive decline (Formánek et al., 2020). Moreover, longitudinal evidence suggests that early-life depression is associated with greater risk of developing cognitive decline in later life (Dafsari and Jessen, 2020; Livingston et al., 2020a,b; Zhu et al., 2016). A cohort study reported that depression increased the risk of dementia by 10–20 times in the first year after depression diagnosis, which then decreased but still persisted even 20 years or more after the diagnosis (Holmquist et al., 2020).

The neurobiological mechanisms underlying this relationship have been the object of recent investigations, with findings suggesting that neuroinflammation and microglia activation might be the potential contributing factors that may explain the relationship between dementia and depression (Santos et al., 2016). Activated microglia, whilst being linked to the mechanisms involved in depression (Yirmiya et al., 2015), have also been found to be associated with two biomarkers of AD dementia, namely amyloid deposition, and tau aggregation, in both individuals with mild cognitive impairment (MCI) and in individuals with a diagnosis of AD dementia (Dani et al., 2018; Ismail et al., 2020).

Studies investigating the association between depression, and amyloid and tau biomarkers using positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis have shown that amyloid plaques and/or tauopathy are associated with depressive symptomatology also in cognitively normal older adults (Babulal et al., 2020; Gatchel et al., 2017).

A meta-analysis reported that in 15 out of 19 cross-sectional studies, significant differences in amyloid-β levels were found between depressed and non-depressed older adults (Harrington et al., 2015). However, more recent PET papers have observed that tau, but not amyloid, is associated with depressive symptomatology in cognitively normal older adults (Babulal et al., 2020; Gatchel et al., 2017; Moriguchi

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et al., 2021).

Overall, these findings suggest that not only depression is a risk factor for dementia, but there is also a link between depressive symptomatology and biomarkers of AD, with new evidence still required to define if this is the case also for non-AD dementia. As previously mentioned, aging is a risk factor for other neurodegenerative diseases, such as PD. After AD, PD is the most common neurodegenerative disorder among the most frequently observed neurological disorders, and a leading cause of disability worldwide (Karikari et al., 2018).

Although PD has been, for a long time, considered a movement disorder, it is now recognised as a multisystem neuropathology, characterised by many non-motor symptoms such as cognitive decline and depression (Laux, 2022).

Regarding cognition, evidence shows that persons with PD (PwPD) show faster cognitive decline than non-PD elderly individuals, particularly affecting executive function, attention, visuospatial skills, and memory (Aarsland et al., 2021). While some PwPD remain cognitively unimpaired, others develop mild cognitive impairment (PD-MCI), which can then worsen to Parkinson's disease dementia (PDD), within approximately 10 years after PD onset (Johar et al., 2017). Prevalence of PDD has been reported to be up to 55 % (Severiano E Sousa et al., 2022), yet these rates vary depending on the study, participants' age, and the number of years since PD onset (Aarsland et al., 2021).

Importantly, evidence indicated that cognitive decline and dementia in PD are associated with the same AD dementia biomarkers, like amyloid plaque and tau pathology, as well as apolipoprotein E ε4 allele (*APOE*4) (Bäckström et al., 2022; Irwin et al., 2013; Mata et al., 2014).

As for depression, evidence also indicates that PwPD tend to be twice as likely of being diagnosed with depression than non-PD individuals (Ahmad et al., 2023). While in the general population the lifetime risk of depression is approximately 15–18 % (Cong et al., 2022), in PD, the estimated prevalence of depression ranges from 20 % to 50 % (Goodarzi et al., 2016) and is one of the most frequent non-motor symptoms of the disease (Jellinger, 2022). Given that depression has frequently been reported prior to PD clinical onset, as a prodromal PD symptom (Laux, 2022), it is suggested that depressive manifestations might not exclusively appear as a result of experiencing motor symptoms (Cong et al., 2022; Kazmi et al., 2021). Beyond the emotional disturbance that depression causes, it can also negatively impact prognosis, quality of life, other psychological disorders, everyday functions, motor abilities, and cognitive performance in people with PD (Jellinger, 2022; Kazmi et al., 2021; McKinlay et al., 2008) even when at a subthreshold level (Weintraub et al., 2004).

However, because of overlapping symptoms associated with PD or medication side effects, depression often goes unnoticed and undertreated (Jellinger, 2022; Laux, 2022; Weintraub et al., 2004).

A recent meta-analysis reported that depression is associated with cognitive decline in PD (Cong et al., 2022), while another study identified depression as a risk factor for developing cognitive impairment or dementia in PD (Marinus et al., 2018). Moreover, both depression and cognitive decline have been linked with higher levels of inflammatory markers also in PwPD (Lindqvist et al., 2013).

This would suggest that the previously mentioned dementia biomarkers, i.e., tau and amyloid, and APOE4, might be underlying the relationship between depression and dementia in PD as well. However, to the best of our knowledge, this hypothesis has not been investigated yet.

Therefore, the present study aims to fill this gap of knowledge, by testing the hypothesis of an involvement of amyloid-β and tau CSF biomarkers, and *APOE*4, in the association between depressive symptomatology and cognition in PD. Specifically, our hypothesis was that CSF Aβ42 and CSF phosphorylated tau (p-tau), or *APOE*4, would interact with depressive symptoms when predicting global cognition in PD. To test this hypothesis, we analysed longitudinal data over a four-year's time window, collected in PwPD at the early stages and in neurologically healthy control (HC) participants, measuring depressive symptoms, cognition, and CSF levels of Aβ42 and p-tau, and *APOE*4 carrier status. We predicted a negative association between depressive symptoms and cognitive performance in PwPD, and a significant moderation of this relationship by CSF levels of either Aβ42 or p-tau, *APOE*4, or both.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the Parkinson Progressive Marker Initiative (PPMI) database (Marek et al., 2011, 2018), that is, an ongoing observational, international, multicentre study aiming to investigate PD progression with longitudinal follow-ups in a large patient's cohort. PPMI enrolled individuals with early and untreated (de novo) PD, as well as healthy controls (HC) of similar age.

The PPMI study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines after approval of the local ethics committees of the participating sites, and participants provided informed consent (Marek et al., 2018).

This study initially considered data from 423 PwPD and 196 HC. From these groups, we excluded participants who, at either the 12- or 24-months follow-up, changed diagnosis and/or developed other neurological disorders. The final sample consisted therefore in 348 PwPD and 160 HC at baseline (T0). Attrition rates at 12 (T1), 24 months (T2) and 36 months (T3) are reported in Fig. 1.

Reasons for drop out were unfortunately unavailable; however, we did test the hypothesis that those who did not continue with the study were also the ones with more severe depression and cognitive decline. Results of this analysis did not show any significant difference in cognitive performance and depressive symptoms between participants who remained in the study and participants who dropped out; therefore, this hypothesis was not verified.

2.2. Selected clinical measures

Based on the current study's objectives, clinical measures were selected from the PPMI database (Marek et al., 2011, 2018). To measure the index of depressive symptomatology, the Geriatric Depression Scale (GDS-15) (Sheikh and Yesavage, 1986) was selected. As an index of global cognition, the Montreal Cognitive Assessment Test (MoCA) (Nasreddine et al., 2005) score was employed. For PwPD only, disease

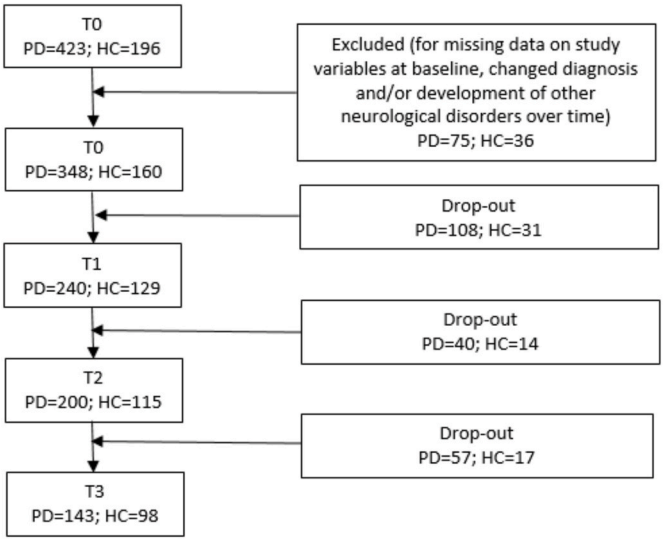

Fig. 1. Flow chart of attrition rates at baseline (T0), 12 months (T1), 24 months (T2) and 36 months (T3).

duration (months) and motor symptoms severity (MSD-UPDRS part III score; Goetz et al., 2008) were also considered.

2.3. Cerebrospinal fluid analyses

CSF samples were collected by lumbar puncture and analysed according to the PPMI Research Biomarkers Laboratory manual (http://ppmi-info.org) as previously reported (Kang, 2013; The Parkinson's Progression Marker Initiative et al., 2016).

Baseline and longitudinal measures of CSF Aβ1–42 and ptau181 were analysed using the multiplex Luminex xMAP platform (Luminex Corp: Austin, Texas, USA) with research-use-only Fujirebio-Innogenetics INNO-BIA AlzBio3 immunoassay kit-based reagents (Innogenetics Inc.: Harvard, MA, USA).

2.4. Genotyping

DNA was extracted from blood samples, which were collected at baseline. APOE genotypes were determined using allele-specific oligonucleotide probes labelled with fluorogenic reporter (TaqMan method), as reported elsewhere (The Parkinson's Progression Marker Initiative et al., 2016).

2.5. Statistical analysis

Differences between groups in age, gender, years of education, APOE4 carrier status, CSF levels of Aβ42 and p-tau, depressive symptoms (GDS score) and global cognition (MoCA score) at baseline, were assessed by carrying out Student's t-tests for continuous variables and Chi square tests for categorical variables. To reduce the chance of Type I error, Bonferroni correction for multiple comparisons was applied.

To assess the predictors of global cognition (MoCA scores) in the three-years' time window in PwPD and HCs, linear mixed effects regression analyses were conducted.

First, the full model, which comprised both PwPD and HC participants, included MoCA score as outcome, and the following predictors: fixed factors Group (PwPD vs. HC) and Time (3 dummy variables were computed, Time 1: Year 1 vs. Baseline; Time 2: Year 2 vs. Baseline; Time 3: Year 3 vs. Baseline); fixed effects covariates of age, gender and years of education; hypothesis-related fixed effects of interest, which were GDS scores (continuous), APOE4 carrier status, CSF Aβ42 and CSF p-tau; interactions between each variable and GDS (2-way interaction), each variable and Group (2-way interaction); each variable and GDS × Group (3-way interaction). In this model, each participant's identification number was entered as a random factor.

Interaction terms were removed from the full model by order of decreasing p-value within the above described 3-way interactions followed by within 2-way interactions until the model only included the main effect terms. All the models were then compared by using the consistent Akaike's information criterion (cAIC) (Bozdogan, 1987), and the model with the smallest cAIC was considered the best fitting model.

If the fixed factor Group, or any interaction with it, were found to be significant, two regression models were carried out separately for PwPD or HC, with the same outcomes and predictors as above, except for the Group fixed factor and the related interactions, and controlling for medication status in the PwPD group. Importantly, age of onset in the PwPD group was not considered because of the substantial overlap with the variable age.

If any significant interactions were found between GDS score and any of the three biomarkers examined here, i.e., APOE4 carrier status, CSF Aβ42 or CSF p-tau, post hoc tests were then carried out. Three levels of depressive symptoms were calculated, based on the mean and standard deviation (SD) of the GDS score: low depression (less than - 0.5 SD), medium depression (between −0.5 SD and +0.5 SD), and high depression (over + 0.5 SD); followed by an examination of possible significant interactions in each depression level.

In every model, Bonferroni correction for multiple comparisons was applied.

The model fits of every model are reported in Table S1 in the Supplementary materials.

2.6. Data availability

Data used in the current study was obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data). The present study used Tier 3 Data, obtained from PPMI upon request after approval by the PPMI Data Access Committee. No restricted data was used in the current analysis.

3. Results

3.1. Between group differences at baseline

As shown in Table 1, the two groups were matched for age, gender, and number of *APOE*4 carriers and non-carriers. Even though the HC group had a higher level of education than the PwPD group, this difference was no longer significant after applying Bonferroni correction for multiple comparisons.

Significant differences between groups were also observed in MoCA scores, in which the PwPD group had significantly lower scores than the HC ($p < .001$), and in GDS scores, with PwPD scoring significantly higher than the HC ($p < .001$). Results also showed that the PwPD group had significantly lower CSF levels of p-tau, when compared to the HC group ($p < .001$), as well as lower CSF levels of Aβ42, yet the difference in CSF Aβ42 was no longer significant after applying Bonferroni correction for multiple comparisons.

3.2. Linear mixed effects models

The results of the full model, including both PwPD and HC, showed that, after applying Bonferroni correction, the MoCA score was

Table 1
Demographic and clinical characteristics by group at baseline.

	PwPD ($n = 348$)		HC ($n = 160$)		p^a
	Range	M (SD)	Range	M (SD)	
Gender (Female)		120 (34.5 %)		56 (35.0 %)	0.989
Age (years)	33–85	61.65 (9.58)	31–85	61.05 (11.06)	0.554
Education (years)	5–26	**15.66 (2.92)***	11–24	**16.27 (2.82)***	**.029**
Global cognition (MoCA)	17–30	**27.19 (2.23)***	27–30	**28.27 (1.10)***	**<.001^**
Depression (GDS)	0–14	**2.22 (2.26)***	0–14	**1.14 (1.79)***	**<.001^**
APOE4 (non-carrier)		261 (75.0 %)		124 (77.5 %)	0.617
CSF Aβ42	238.8–3707	**929.59 (410.86)***	239–3297	**1051.73 (507.13)***	**.008**
CSF p-tau	81–467	**169.47 (57.49)***	82–581	**194.84 (82.53)***	**<.001^**
Disease duration (months)	0–36	6.50 (6.35)	–	–	
UPDRS3	4–47	21.05 (8.76)	–	–	

MoCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale. *APOE*4: apolipoprotein E ε4 allele carrier status (yes vs. no). *Significantly different. ^Significant after applying Bonferroni correction for multiple comparisons ($P < .006$). [a] Student's t-tests are reported for all variables except gender and *APOE*4, for which Chi square test is reported.

predicted best by the following variables and interactions: GDS (B = 0.2863, $t = 2.95$, $p = .003$), p-tau × GDS (B = −0.0020, $t = -3.71$, $p < .001$), Group × p-tau (B = −0.0081, $t = -2.94$, $p = .003$), and Group × p-tau × GDS (B = 0.0029, $t = -2.97$, $p = .003$) along with time, age, and gender (see Table S3 in Supplementary materials).

This means that, in both HC and PwPD, MoCA scores were significantly higher in younger and female individuals, and significantly decreased over time, with however only one PwPD who developed dementia at YEAR 1 and 2, and none of the HC who did develop dementia during the considered time window. Also, results of the full model did indicate that MoCA scores were significantly predicted by depressive symptoms, and that this relationship was different in the two groups, PwPD and HC, and was influenced by the level of p-tau.

Hence, separate analyses were carried out in PwPD and HC. In the model with PwPD only, results indicated that, after applying Bonferroni correction, time, age, gender, and GDS × CSF p-tau significantly predicted MoCA scores, as described in Table 2. Post hoc tests conducted separately by level of depressive symptoms showed that, in PwPD with the highest GDS scores, CSF levels of p-tau significantly predicted MoCA scores (B = −0.0136, $t = -3.54$, $p < .001$), but not in those with medium (B = −0.0004, $t = -0.16$, $p = .871$) or low (B = −0.0013, $t = -0.54$, $p = .593$). depressive symptoms; see Fig. 2 for a scatterplot of the three groups.

In the model with HCs only, results showed that, after applying Bonferroni correction, the best model was the one considering only time and age as significant predictors of MoCA scores (see Table S4 in Supplementary materials).

These results are in line with the ones reported in Table 1, showing higher GDS scores in PwPD at baseline, as well as with the results reported in Table S2 of the supplementary materials. This last table reports in fact the demographic of the three subgroups created based on the GDS scores in both HC and PwPD, and shows that 80 PwPD and 12 HC showed a GDS score equal or higher than the cut-off, indicating clinically relevant scores.

Importantly, we also conducted a post-hoc analysis of GDS scores over the three years following baseline, in order to evaluate if GDS scores changed over time. Results of this analysis revealed that, although PwPD had significantly higher scores than HC at each time point, scores did not significantly change over time neither in PwPD nor HC (for details, see Tables S5 and S6 in Supplementary materials).Finally, we also conducted additional analysis to assess any potential role of medication status in the PwPD group, and results show no significant role of medication in predicting MoCA scores over the three years time window (see Table S7 in Supplementary materials).

Table 2
Results of the mixed models' analyses conducted to assess MoCA scores predictors in PwPD only, over the three-year's time window.

Predictors	PwPD ($n = 348$)				
	B	SE	*t*	*p*	*95 % CI [LL, UP]*
Time 1 (Year 1 vs. Baseline)	−0.8025	0.1467	−5.47	**< .001^**	[-1.0900, −0.5150]
Time 2 (Year 2 vs. Baseline)	−0.8286	0.1574	−5.26	**< .001^**	[-1.1371, −0.5201]
Time 3 (Year 3 vs. Baseline)	−0.4752	0.1793	−2.65	0.008	[-0.8266, −0.1238]
Age (years)	−0.0748	0.0125	−6.00	**< .001^**	[-0.0992, −0.0503]
Gender (0 = female, 1 = male)	−0.6720	0.2404	−2.80	**.005^**	[-1.1432, −0.2008]
Education (years)	0.0802	0.0400	2.01	0.046	[0.0018, 0.1586]
APOE4 (0 = no, 1 = yes)	−0.1926	0.2726	−0.71	0.480	[-0.7269,0.3417]
CSF Aβ42	0.0001	0.0003	0.40	0.689	[-0.0005, 0.0007]
CSF p-tau	0.0044	0.0026	1.73	0.084	[-0.0006, 0.0094]
Depression (GDS score)	0.2818	0.1027	2.74	0.006	[0.0805, 0.4831]
CSF p-tau × Depression	−0.0019	0.0006	−3.44	**< .001^**	[-0.0030, −0.0008]

B = unadjusted estimate; SE = standard error of the estimate; *t* = test t; CI=Confidence Interval; LL = Lower Limit; UL=Upper Limit; *APOE4*: apolipoprotein E ε4 allele carrier status; GDS: Geriatric Depression Scale. ^ significant after applying Bonferroni correction ($p < .0056$).

4. Discussion

The aim of the current study was to identify possible biological mechanisms underlying the relationship between depressive symptoms and global cognition in individuals affected by PD, a neurodegenerative disorder characterised by high risk of depression (Ahmad et al., 2023), and of cognitive decline and dementia (Severiano E Sousa et al., 2022). Our hypothesis was that CSF levels of either Aβ42 or p-tau, or *APOE4* carrier status, would interact with depressive symptoms in predicting global cognition in PwPD. To test this hypothesis, we examined cognitive, affective, and biomarkers data collected from a group of individuals with Parkinson's disease, and a matched group of healthy controls, over a three-year period, using linear mixed effects regression models.

The main findings from the stratified linear mixed effects regression analyses revealed a significant interaction between depressive symptoms and CSF levels of p-tau in predicting global cognition longitudinally in PwPD. Specifically, lower cognitive performance was significantly associated with higher CSF p-tau levels, but only in PwPD with the highest levels of depressive symptoms. No significant interactions were found with CSF Aβ42, *APOE4*, or in the HC group.

4.1. Depressive symptoms and cognitive performance in PwPD and HC

The significant interaction between depressive symptoms and CSF levels of p-tau in predicting global cognition in PwPD, but not in HC, may be attributed to differences between the groups in mood and cognitive performance.

At baseline, PwPD exhibited significantly higher levels of depressive symptoms compared to age- and gender-matched individuals. In the PPMI cohort, baseline corresponds to the enrolment stage, during which PwPD had been diagnosed within 2 years and were also de novo (i.e., not taking prescribed PD-specific medications yet). These findings are consistent with the literature suggesting that depressive manifestations in PD might appear both as a result of experiencing motor symptoms (Becker et al., 2011; Kazmi et al., 2021) as well as early, or sometimes prodromal PD manifestations.

Current results also showed that PwPD also had significantly lower total MoCA scores, reflecting worse cognitive performance, than HC at baseline and at each time point (for details, see Table S5 in Supplementary materials). Moreover, in the following three years, MoCA scores kept decreasing in the PwPD group, as shown by the mixed effects model (see Table 2). This result is consistent with the literature suggesting that, although some PwPD remain cognitively unimpaired, others develop PD-MCI or PDD, the latter with a prevalence of up to 55 % (Severiano E Sousa et al., 2022).

4.2. CSF p-tau in PwPD and HC

In our cohort, CSF p-tau alone did not significantly predict cognitive performance in the PwPD sample. The present findings might be partly explained by the link between increased tau and depression reported by other studies testing healthy older adults (Babulal et al., 2020; Gatchel et al., 2017; Moriguchi et al., 2021).

Moreover, our findings seem to be consistent with recent evidence suggesting that tau pathology might play a role in the early stages of PD (Chu et al., 2024; Irwin et al., 2013; Zhang et al., 2018). However, it is important to note that the association between CSF tau, either as p-tau or t-tau, and cognitive decline has not been found as consistently as with

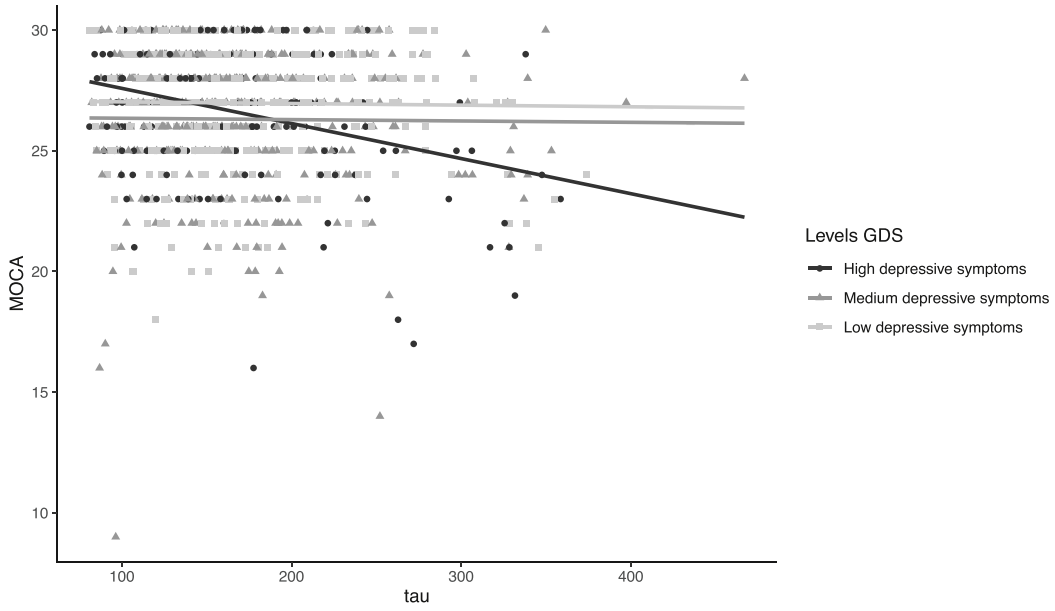

Fig. 2. Scatterplot representing the role of CSF levels of p-tau in predicting MoCA scores in PwPD, stratified by low, medium, and high GDS scores, indicating, respectively, low, medium and high levels of depressive symptoms, over a three-year's time window.

amyloid in PwPD (Johar et al., 2017).

Additionally, it should be mentioned that CSF levels of p-tau were significantly lower in PwPD than in HCs, and while this finding has been reported before (Cousins et al., 2024; Kang, 2013; The Parkinson's Progression Marker Initiative et al., 2016), other studies have not found this difference (Alves et al., 2010; Parnetti et al., 2011).

In detail, while Cousins and colleagues (2024) suggested that low levels of p-tau are indeed typical of early PD, others explained some of the contradictory results taking into account methodological differences, such as CSF processing, the criteria for the healthy control group, and the elapsed time between diagnosis and CSF collection in PwPD (Kang, 2013; The Parkinson's Progression Marker Initiative et al., 2016). In the current study, the difference in CSF levels of p-tau between PwPD and HC groups did not affect the obtained results, as the interaction between CSF p-tau and GDS scores was significant in the PwPD group, but not in HCs. However, further research that may help in understanding the link between depression, cognition, and tau in PD is necessary.

4.3. CSF Aβ42 and APOE4

We did not find CSF Aβ42 levels to moderate the association between depressive symptoms and cognition, nor to predict cognitive performance alone. This result is consistent with the lack of a link between Aβ42 and depression reported by previous studies (Babulal et al., 2020; Gatchel et al., 2017; Moriguchi et al., 2021), which might partly explain why we found CSF p-tau to be a moderator, but not Aβ42. Yet, current findings contrast with previous research reporting an association between CSF Aβ42 and cognitive decline or dementia in PD (Alves et al., 2010; Hall et al., 2015; Parnetti et al., 2014; Stav et al., 2015; Tan et al., 2021). It is suggested that together with the deposition of misfolded α-synuclein, amyloid plaques and tauopathy are also contributing factors of dementia in PD (Gonzales et al., 2021).

However, considering that the PwPD included in the present study were still at an early stage of the disease and thus, the prevalence of dementia is lower than at later stages (Severiano E Sousa et al., 2022), we investigated cognitive performance, and not dementia. Therefore, it is possible that while CSF levels of Aβ42 keep decreasing, and thus, amyloid-β depositions in the brain increase, the association with cognition might be more clearly observed.

Lastly, our results show that *APOE*4 carrier status did not significantly predict cognitive performance in PwPD or HC, consistent with previous evidence (Bäckström et al., 2022). Nonetheless, because other studies reported an association between depressive symptoms and higher tau PET in APOE4 carriers (Gonzales et al., 2021), whilst others have suggested a link between number of APOE ε4 alleles and cognition in PD (Mata et al., 2014), we believe this requires further investigation.

5. Limitations and future directions

Some limitations should be noted when considering our results. First, as mentioned throughout this manuscript, PwPD at baseline had been diagnosed within two years, and thus, were at an early stage of the disease, and were monitored for only three years after that. While this offers certain advantages, it also has some disadvantages. For example, due to the relatively short time window considered in this study, it is possible that during this period, specific changes might have not occurred yet, at least, to a concerning degree, in depressive symptomatology or CSF biomarkers, such as beta-amyloid.

Future studies considering broader time-windows would be therefore preferable, to replicate and expand current findings concerning the interaction between CSF p-tau, as well as other biomarkers, and depressive symptoms in predicting cognitive performance in PwPD also in later disease stages.

Second, the high level of education of the participants included, which might have been a bias for both cognitive profile and depressive symptoms. Future studies should therefore focus on different groups of individuals, ideally with a lower level of education.

Third, the fact that we did consider the MoCA test as a unique measure of cognitive performance. Despite our choice was motivated by the fact that this instrument is a highly sensitive tool for early detection of MCI, and is therefore widely used both in the research and in the clinical practice, future studies might focus on single cognitive domains using full neuropsychological batteries.

Last, the relatively low percentage of PwPD that, at baseline, did show a GDS score above the recommended clinical cut-off. Despite this suggests that depressive symptoms, and not only a depression diagnosis, do interact with p-tau in predicting cognitive performance at early stages of PD, future studies should definitely consider samples where patients with more severe depressive symptoms are present.

6. Conclusions

In summary, this novel study showed that the interaction between depressive symptoms and CSF levels of p-tau had a significant role in explaining global cognition over a three-year's time window in PwPD. Specifically, current results indicated that in PwPD with high depressive symptoms, CSF p-tau levels influence cognitive performance, but not in those with medium or low symptoms. Overall, current findings highlight the importance of assessing and treating depression in PwPD as early as possible, as it might reduce the likelihood of future cognitive decline. Given the negative impact depression has on prognosis, quality of life, motor abilities, and cognitive performance in PwPD (Jellinger, 2022), and its association with tau pathology, we believe further research is necessary.

CRediT authorship contribution statement

Ainara Jauregi-Zinkunegi: Writing – review & editing, Writing – original draft, Validation. **Lucia Ronconi:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Davide Bruno:** Writing – review & editing, Validation, Supervision. **Elisa Di Rosa:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI and AI-assisted technologies were employed in the writing process.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.05.038.

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