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SHORT COMMENTARY

Prediction of cognitive decline in healthy aging based on neuropsychiatric symptoms and PET-biomarkers of Alzheimer's disease

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Abstract

Neuropsychiatric symptoms (NPS) have been associated with a risk of accelerated cognitive decline or conversion to dementia of the Alzheimer's Disease (AD) type. Moreover, the NPS were also associated with higher AD biomarkers (brain tau and amyloid burden) even in non-demented patients. But the effect of the relationship between NPS and biomarkers on cognitive decline has not yet been studied. This work aims to assess the relationship between longitudinal cognitive changes and NPS, specifically depression and anxiety, in association with AD biomarkers in healthy middle-aged to older participants. The cohort consisted of 101 healthy participants aged 50–70 years, 66 of whom had neuropsychological assessments of memory, executive functions, and global cognition at a 2-year follow-up. At baseline, NPS were assessed using the Beck Depression and Anxiety Inventories while brain tau and amyloid loads were measured using positron emission topography. For tau burden, THK5351 uptake is used as a proxy of tau and neuroinflammation. Participants, declining or remaining stable at follow-up, were categorized into groups for each cognitive domain. Group classification was investigated using binary logistic regressions based on combined AD biomarkers and the two NPS. The results showed that an association between anxiety and prefrontal amyloid burden significantly classified episodic memory decline, while the classification of global cognitive decline involved temporal and occipital amyloid burden but not NPS. Moreover, depression together with prefrontal and hippocampal tau burden were associated with a decline in memory. The classification of participants based on executive decline was related to depression and mainly prefrontal tau burden. These findings suggest that the combination of NPS and brain biomarkers of AD predicts the occurrence of cognitive decline in aging.

Keywords Neuropsychiatric symptoms · Aging · Cognitive decline · Alzheimer's PET biomarkers

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Introduction

Neuropsychiatric symptoms (NPS) are present in the older population with and without cognitive impairment [1–3]. Among the most common symptoms are depression, apathy, and anxiety. When they manifest in mild cognitive impairment (MCI), they increase the risk of dementia [4]. When present in aging in the absence of cognitive impairment, they increase the risk of future cognitive impairment [5]. Notably, they have been associated with accelerated overall decline or decline in a specific cognitive domain (memory, executive functions, attention, language, praxis, and visuospatial functions) [5, 6].

In addition, several studies have focused on the relationships between NPS and Alzheimer disease (AD) biomarkers (i.e., β-amyloid and tau). Currently, the results are divergent. Notably, the use of anti-β-amyloid therapy can increase depression, suicide attempts, anxiety, and sleep disturbances in individuals with AD [7]. The authors suggested that increased β-amyloid in the brain would contribute to attenuate or repair neuronal damage. Thus, sudden reduction of β-amyloid could worsen cognition and NPS. In contrast, other work with Positron Emission Tomography (PET) examination using radiotracers of β-amyloid has found greater amyloid burden in association with the severity of certain NPS. Mori et al. found more β-amyloid in bilateral frontal regions in AD patients with apathy [8]. Bensamoun et al. reported more whole-brain β-amyloid in patients exhibiting more severe anxiety or irritability. Both symptoms were also linked to higher β-amyloid burden in frontal and cingulate regions, while irritability also stood out with a higher burden in parietal regions [9].

At the MCI stage, patients with amyloid-positive status exhibited a higher probability of NPS, including depression, anxiety, apathy, irritability, or disturbances in nocturnal behaviors [10]. Patients with Amyloid-positive MCI and depression have a higher amyloid burden in insular and frontotemporal regions and have a higher rate of conversion to AD [11]. Some associations could also be demonstrated in older cognitively healthy individuals. While single NPS such as depression, apathy, and anxiety were positively correlated with global β-amyloid burden [12, 13], the clinical state of mild behavioral disorder, as defined by Ismail et al., was also correlated with global and striatal burden [14–16]. Moreover, having higher depression and anxiety scores increased the risk of having a positive amyloid PET scan in cognitively healthy individuals [10].

In addition to the amyloid burden, tau burden measured with PET has also been associated with NPS in early AD. Different NPS were sometimes associated with the same burden locations. For example, affective (depression, anxiety) and hyperactive (agitation, aberrant motor behaviors) type symptoms were similarly associated with dorsolateral prefrontal, entorhinal, inferior temporal, posterior cingulate, supramarginal, and precuneus tau burden [17]. Affective symptoms were also characterized by orbitofrontal tau burden [17]. Even in older cognitively healthy individuals, the probability of depression was associated with tau burden, but not with amyloid burden [18]. Similarly, total and affective NPS assessed with the NeuroPsychiatric Inventory were correlated with transentorhinal tau burden [19]. More recently, Tissot et al. undertook to analyze these relationships in a broad spectrum of NPS both in individuals without cognitive impairment, with MCI or AD [20]. In individuals without cognitive impairment, most NPS (agitation, depression, euphoria, hallucinations, motor disturbances and nocturnal behaviors) were associated with frontal and/or temporal tau burden. In cognitively impaired individuals, the overall severity of NPS was associated with temporal, medial frontal, precuneus and cuneus tau burden. Results were also broadly similar when corrected for β-amyloid status.

Based on the fact that NPS were shown as risk factors for cognitive decline, and their association with AD PET biomarkers, the objective of our study was to investigate the role of two NPS, specifically depression and anxiety, as well as their association with tau and β-amyloid burden in global and specific cognitive decline in cognitively healthy individuals. Moreover, given that a critical window to detect future decline due to Alzheimer's pathology is in middle age [21], we focus on middle-aged to young-old participants. To our knowledge, this is the first study to examine the effect of association between depression and anxiety and AD biomarkers on cognitive decline and at the same time to explore the full range of cerebral amyloid and tau burdens. The analyses aim to explore the full range of cerebral amyloid and tau burdens, more important implications of temporal (especially medial), prefrontal, cingulate or parietal burdens in predicting memory, executive or global cognitive decline could be expected.

Methods

Participants

This work relied on a cohort of 101 healthy French-speaking participants aged 50–70 years (68 women; $M \pm SD = 59.4 \pm 5.3$ years) who were enrolled between June 15, 2016, and October 2, 2019, for a multimodal cross-sectional study taking place at the University of Liège, Belgium (COFITAGE study; EudraCT: 2016-001436-35) [22]. They gave their written informed consent and received financial compensation. This research was approved by the ethical

committee of the Faculty of Medicine at the University of Liège, Belgium.

Exclusion criteria were as follows: body mass index (BMI) < 18 and > 29; smoking; excessive alcohol consumption (> 15 units/week); excessive caffeine consumption (> 6 cups/day); clinical symptoms of cognitive impairment indicated by Dementia Rating Scale < 130 [23] and/or Mini-Mental State Examination ≤ 27 [24]; recent severe brain trauma; shift work in the past 6 months; transmeridian travel in the past 2 months; high levels of anxiety (21-item self-rated Beck Anxiety Inventory ≥ 17 [25]) and depression (21-item self-rated Beck Depression Inventory ≥ 17 [26]); recent psychiatry history; chronic medication affecting the central nervous system (stable treatment for more than 6 months for hypertension or hypothyroidism were included); and periodic sleep limb movements (PLMS ≥ 15). Participants with sleep apnea (apnea–hypopnea index ≥ 15/h) were screened and excluded during an in-lab screening night of polysomnography. Based on a published analysis of the same sample, two participants were excluded due to incomplete or undosable biological tests [27]. Moreover, clinical MRIs were inspected by a neurologist who found no major anomalies, allowing to exclude other potential pathologies (vascular, Lewy Bodies Disease).

Considering that this work is concerned with cognitive decline, the sample of interest was selected from participants with available neuropsychological data ($N = 66$). Among them, some participants had missing data that made it impossible to determine their indices for executive (final $N = 65$), memory (final $N = 61$) and global (final $N = 59$) decline. Moreover, among the 66 participants with available neuropsychological data, the subsample with amyloid and tau data understood, respectively, 64 and 48 participants. The demographic characteristics of these subsamples are shown in Table 1.

Neuropsychiatric symptoms

Anxiety and depression were assessed respectively using the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI). The BAI consists of a self-administered instrument with 21 items that cover the most frequent anxiety symptoms seen in clinical practice. Each item is scored 0, 1, 2 and 3 denoting increasing severity of symptoms. The BDI includes 21 self-rated items that cover a variety of depressive symptoms including feelings of sadness, concerns about the future, suicidal ideation, tearfulness, sleep, fatigue, interests, worries about health, sexual interest, appetite, weight loss and general enjoyment, with each response scored on a scale from 0 to 3. Higher total scores indicate more severe depressive symptoms.

Neuropsychological data

Of all participants, 66 underwent neuropsychological assessments at baseline and at a 2-year follow-up visit. For episodic memory performance, our analyses focused on the total recall score from the FCSRT due to its associations with medial temporal lobes in MCI and AD [28, 29]. An executive composite score was computed including scores from verbal fluency, digit span in reverse order, Trail Making Test B, 3-back task, and Stroop by summing the task's z-scores. A global composite score was obtained by the sum of z-scores from all tasks except the Mattis Dementia Rating Scale (For more details about the neuropsychological assessment from the COFITAGE study, see [22, 30]). For each of these scores (memory, executive and global), decline indices were established according to the formula: $(\text{score}_{T0} - \text{score}_{T1})/\text{score}_{T0}$. These indices were interpreted as follows: index = 0: performance was similar between baseline and follow-up, Index < 0: performance was improved at follow-up, Index > 0: performance was decreased at follow-up compared to baseline. It should be noted that in cases where performance decreases over time, it remains within the norms.

PET acquisition and processing

At baseline, Aβ-PET imaging was performed with radiotracers [18F]Flutemetamol ($n = 63$) or [18F]Florbetapir ($n = 3$), while tau/neuroinflammation-PET imaging was performed with radiotracer [18F]THK-5351 ($n = 66$), on an ECAT EXACT + HR scanner (Siemens, Erlangen, Germany). For all radiotracers, participants received a single dose of the

Table 1 Demographic characteristics of the amyloid subsample ($N = 64$) and the tau subsample ($N = 48$)

	Amyloid subsample				Tau subsample			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Age	59.84	5.46	50	69	59.71	5.52	50	69
Education	14.88	3.30	9	25	15.08	3.40	9	25
Women %	67.2				62.5			
Neuropsychiatric								
BDI	4.39	4.40	0	16	4.02	4.12	0	16
BAI	2.33	2.50	0	9	2.35	2.46	0	8

respective radioligands in an antecubital vein (target dose app. 185 MBq). Aβ-PET image acquisitions started 85 min after injection, and four frames of 5 min were obtained, followed by a 10-min transmission scan (with Germanium-68), with a total duration spent in the scanner of the app. 30 min. For [18F]THK-5351-PET, a 10-min transmission scan was acquired first, and dynamic image acquisitions started immediately after injection, consisting of 32 frames (with increasing time duration), with a total duration spent in the scanner of approximately 100 min. All PET images were reconstructed using a filtered back-projection algorithm including corrections for measured attenuation, dead time, random events, and scatter using standard software (Siemens ECAT-HR + V7.1, Siemens/CTI, Knoxville, TN, USA). The preprocessing steps are detailed in Rizzolo et al. [22]. Standardized uptake value ratio (SUVR) was calculated using the whole cerebellum as the reference region for Aβ-PET [31], and cerebellum grey matter for [18F]THK-5351-PET [32]. Mean PET SUVr were extracted for regions from the Automated Anatomical Labelling atlas 3 [33].

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 software. Two analytic steps were performed. First, partial correlations between neuropsychiatric symptoms, decline indices and tau/amyloid burden values in AAL regions (with age, sex, and education as covariates) were performed as a validation step to check the potential associations between NPS and PET variables with cognition. Bonferroni correction was used for multiple tests adjustment. These correlation analyses allowed us to check the non-collinearity of predictors (NPS and PET values). The normality checks of the distributions using kurtosis and skewness statistics showed that this assumption is partially met. Given the sample of healthy participants and the inclusion criteria for neuropsychiatric data, the mean and variability of the NPS and brain burden are low, limiting the achievement of normal distributions for all variables. In a second step, logistic regression models based on Wald Forward Selection (stepwise selection method with entry testing based on the significance of the score statistic, and removal testing based on the probability of the Wald statistic) were applied to predict cognitive decline with the decline indices grouped into two categories (1 = positive index indicating a decline in scores, 0 = zero or negative index) as dependent variable, and demographic (age, sex, education), NPS and tau/amyloid burden as predictive covariates. Distinct models were applied to assess the predictive ability of NPS associated with burdens (amyloid, tau) on each decline index (memory, executive, global). A total of six models were run: decline ~ NPS + Amyloid*3, decline ~ NPS + Tau*3. The threshold of significance for all analyses was 0.05. Each model consisted of the iteration with the higher classification accuracy (sensitivity and specificity) (even in cases where the Wald statistics are not significant at $p < 0.05$ [type II error]).

Results

Demographic and clinical group characteristics

Considering the sample according to global cognitive decline, the declining and non-declining subgroups consist of 29 and 30 participants respectively. The groups are equivalent in terms of age, sex distribution, and years of education. Descriptive data and comparison test results are summarized in Table 2.

Correlational analyses

Initial correlation analyses showed relationships between age, education, sex, decline indices and amyloid (Fig. 1) and tau burdens (Fig. 2). The relationships between NPS, decline indices and brain burdens are therefore established using partial correlations corrected for age, sex, and education (Supplementary Table 1). Depression was positively correlated with anxiety. In terms of cognitive decline, depression and anxiety were not correlated with a decline in any domain. In terms of amyloid burden, depression was negatively correlated with right pallidum and cerebellar (except for right cerebellum crus 2 for which correlation was positive), whereas anxiety was positively correlated with left

Table 2 Demographic characteristics in subsamples for global cognitive decline

	Global declining subsample ($N = 29$)		Global non-declining subsample ($N = 30$)		Statistic	p-Value
	Mean	SD	Mean	SD		
Age	60.38	6.04	59.20	4.93	0.823	0.414
Education	14.93	3.58	15.10	3.13	0.193	0.847
Women %	62.1		70		0.414	0.520
Global cognitive decline index	2.86	1.93	−2.86	2.13	10.787	< 0.001

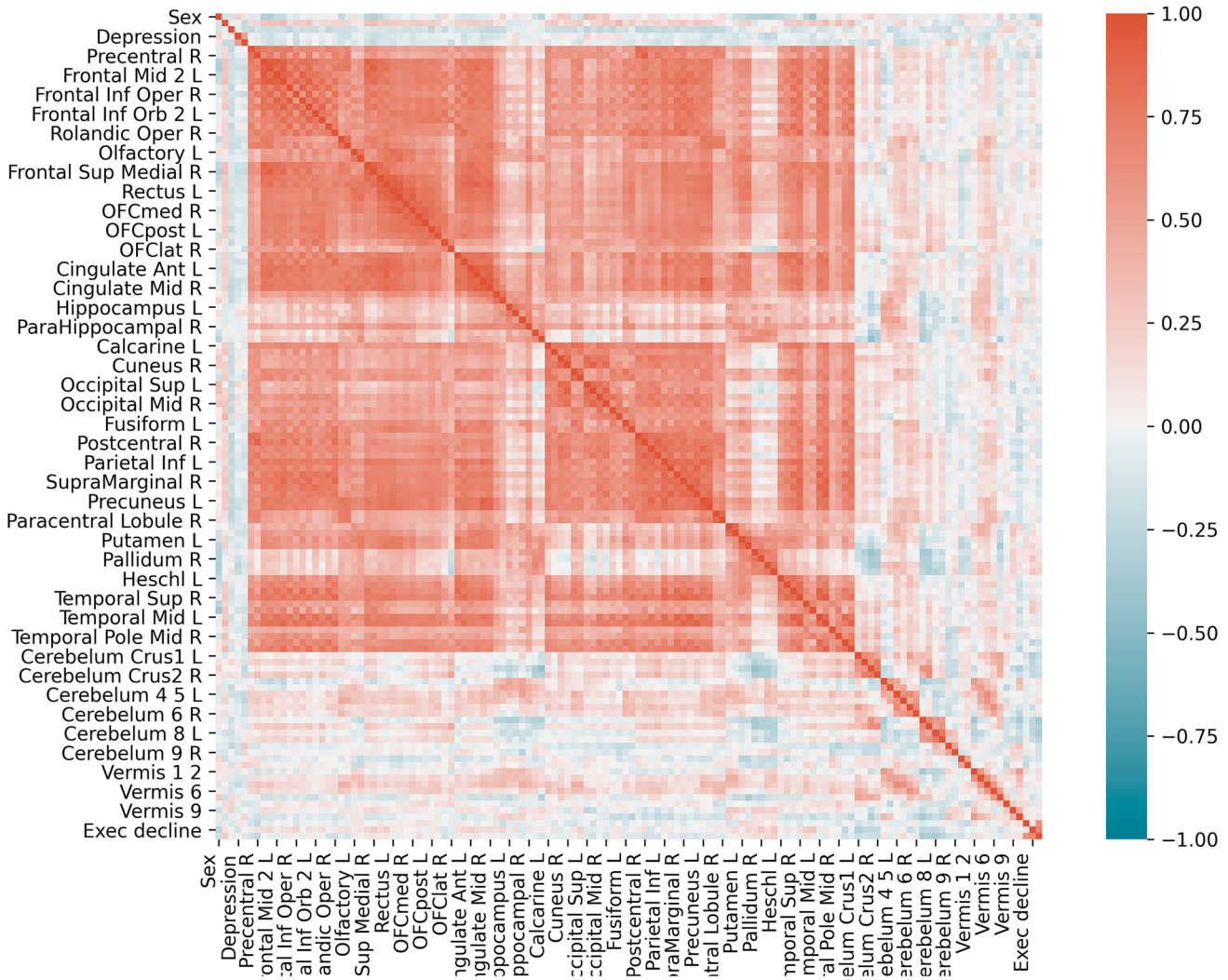

Fig. 1 Correlation matrix for demographic, amyloid and cognitive factors. List of variables: sex, age, education, depression, anxiety, precentral (L: left and R: right, for each structure), frontal superior, frontal middle, frontal inferior opercularis, frontal inferior triangularis, frontal inferior orbitalis, rolandic opercularis, supplementary motor, frontal superior medial, frontal medial orbital, rectus, orbitofrontal medial, orbitofrontal anterior, orbitofrontal posterior, orbitofrontal lateral, insula, cingulate anterior, cingulate middle, cingulate posterior, hippocampus parahippocampal, amygdala, calcarine, cuneus, lingual, occipital superior, occipital middle, occipital inferior, fusiform, postcentral, parietal superior, parietal inferior, supramarginal, angular, precuneus, paracentral lobule, caudate, putamen, pallidum, thalamus, heschl, temporal superior, temporal pole superior, temporal middle, temporal pole middle, temporal inferior, cerebellum (Crus1, 2, 3, 4–5, 6, 7b, 8, 9, 10), Vermis (1–2, 3, 4–5, 6, 7, 8, 9, 10), memory decline, executive decline, global decline. For more details on the variables, please see Supplementary Table 1

temporal pole and vermis, and negatively correlated with cerebellar burdens. In terms of tau burden, depression was positively correlated with bilateral hippocampus and cuneus, cerebellar and vermis, whereas anxiety was negatively correlated with left anterior cingulate burden.

Considering cognitive decline, executive decline was negatively correlated with left inferior temporal and cerebellar amyloid burdens and positively correlated with frontal, cingular, insular, temporal, occipital, parietal and striatal tau burdens measured at baseline; memory decline was negatively associated with frontal, left cingular and right temporal amyloid burden and positively with right orbitofrontal and bilateral rectus tau burdens at baseline; global decline was negatively correlated with precentral, rolandic operculum, supramarginal and cerebellar amyloid burdens, and positively with frontal, anterior cingular, parietal, occipital, and temporal tau burdens at baseline.

However, none of these correlations did survive Bonferroni correction for multiple comparisons, suggesting few or no collinearity between NPS and brain burden.

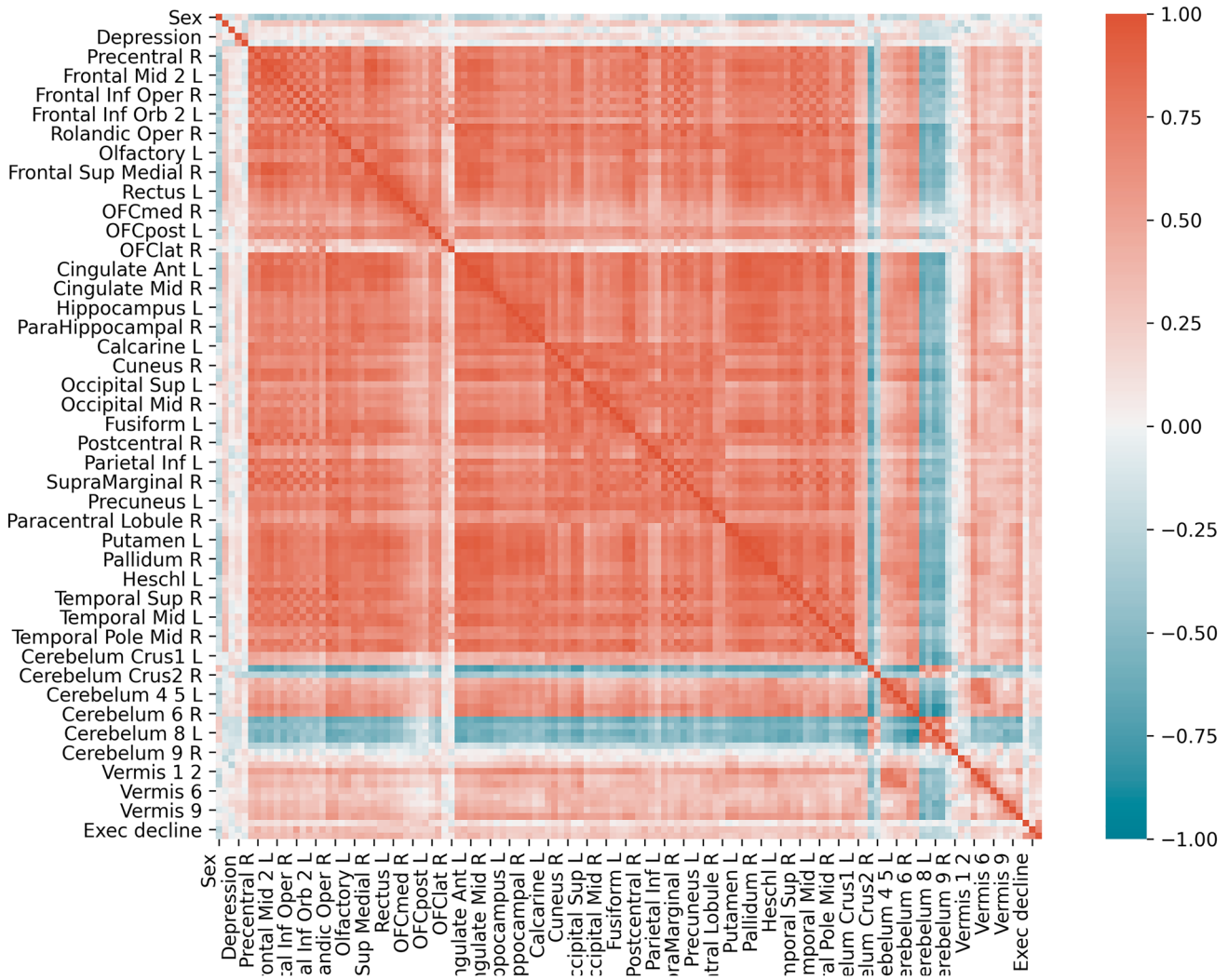

Fig. 2 Correlation matrix for demographic, tau and cognitive factors. List of variables: sex, age, education, depression, anxiety, precentral (L: left and R: right, for each structure), frontal superior, frontal middle, frontal inferior opercularis, frontal inferior triangularis, frontal inferior orbitalis, rolandic opercularis, supplementary motor, frontal superior medial, frontal medial orbital, rectus, orbitofrontal medial, orbitofrontal anterior, orbitofrontal posterior, orbitofrontal lateral, insula, cingulate anterior, cingulate middle, cingulate posterior, hippocampus parahippocampal, amygdala, calcarine, cuneus, lingual, occipital superior, occipital middle, occipital inferior, fusiform, postcentral, parietal superior, parietal inferior, supramarginal, angular, precuneus, paracentral lobule, caudate, putamen, pallidum, thalamus, heschl, temporal superior, temporal pole superior, temporal middle, temporal pole middle, temporal inferior, cerebellum (Crus1, 2, 3, 4–5, 6, 7b, 8, 9, 10), Vermis (1–2, 3, 4–5, 6, 7, 8, 9, 10), memory decline, executive decline, global decline. For more details on the variables, please see Supplementary Table 1

Logistic regression predictive models

Overall, the combination of NPS and amyloid burden was significantly predictive of memory decline (Table 3). Prediction was improved by higher anxiety scores, lower amyloid burden in the right inferior frontal opercularis and triangularis regions and left and right cerebellar crus 1 and 3, as well as by higher amyloid burden in the left supplementary motor area, orbitofrontal cortex, superior parietal, and right inferior temporal regions. The model had a sensitivity of 86.4% and a specificity of 95.2% in predicting participants with a decline in memory performance (Supplementary Table 2).

Amyloid burden but not NPS was predictive of global cognitive decline (Table 4). Prediction was improved by lower amyloid burden in the right superior occipital region, left fusiform, right pallidum, and left cerebellar 7b lobule, as well as by higher amyloid burden in the right olfactory region, left hippocampus, right cuneus, left inferior occipital region, and right cerebellar 6 lobule. The model had a sensitivity of 89.7% and a specificity of 93.1%

in predicting participants with global cognitive decline (Supplementary Table 3).

No significant association with, or improved classification compared with the hazard threshold for, NPS and amyloid burden was found for executive decline. Also, for all models, age, sex, and education covariates were not significantly associated with classification.

Overall, the association of NPS and tau burden was significantly predictive of both memory (Table 5 and Supplementary Table 4) and executive (Table 6 and Supplementary Table 5) decline.

Regarding memory decline (Table 5), prediction was improved by higher depression scores, lower tau burden in the left hippocampal region, and higher burden in the right orbitofrontal cortex and right cerebellum 9. The model had a sensitivity and specificity of 91.7% in predicting participants with memory decline (Supplementary Table 4).

Regarding executive decline (Table 6), prediction was improved by higher depression scores, lower tau burden in

Table 3 Binary logistic regression for memory decline prediction based on NPS and amyloid burden

	Coef	Wald	*p*-Value	Confidence interval 95%	
BAI	1.635	4.856	0.028	0.181	3.089
Right frontal pars opercularis	−129.461	6.196	0.013	−231.397	−27.526
Right frontal pars triangularis	−160.272	5.572	0.018	−293.342	−27.202
Left supplementary motor area	44.519	5.380	0.020	6.902	82.136
Right posterior orbitofrontal cortex	114.011	6.028	0.014	23.000	205.022
Right superior parietal	54.241	3.953	0.047	0.769	107.714
Right inferior temporal	51.883	3.911	0.048	0.461	103.305
Left Crus I of cerebellar hemisphere	−238.614	6.307	0.012	−424.833	−52.395
Right lobule III of cerebellar hemisphere	−81.508	5.478	0.019	−149.765	−13.252
Constant	270.534	5.982	0.014		

BAI Beck anxiety inventory; *R* right; *L* left

Table 4 Binary logistic regression for global cognitive decline prediction based on NPS and amyloid burden

	Coef	Wald	*p*-Value	Confidence interval 95%	
R olfactory cortex	39.433	4.611	0.032	3.4423	75.424
L hippocampus	67.457	3.811	0.051	−0.267	135.180
R cuneus	161.235	5.309	0.021	24.086	298.384
R superior occipital	−230.480	5.996	0.014	−414.956	−46.003
L inferior occipital	211.025	5.841	0.016	39.889	382.161
L fusiform	−322.460	5.873	0.015	−583.258	−61.662
R pallidum	−52.883	5.618	0.018	−96.614	−9.152
R lobule VI of cerebellar hemisphere	229.353	5.165	0.023	31.548	427.157
L lobule VIIb of cerebellar hemisphere	−223.493	5.219	0.022	−415.240	−31.745
Constant	82.489	4.720	0.030		

R right; *L* left

Table 5 Binary logistic regression for memory decline prediction based on NPS and tau burden

	Coef	Wald	*p*-Value	Confidence interval 95%	
BDI	0.408	3.463	0.063	−0.022	0.838
R medial orbitofrontal cortex	18.899	7.072	0.008	4.970	32.828
L hippocampus	−17.350	7.695	0.006	−29.608	−5.091
R lobule IX of cerebellar hemisphere	50.242	5.422	0.020	7.952	92.531
Constant	−58.810	4.708	0.030		

BDI Beck depression inventory; *R* right; *L* left

Table 6 Binary logistic regression for executive decline prediction based on NPS and tau burden

	Coef	Wald	*p*-Value	Confidence interval 95%	
BDI	0.916	6.346	0.012	0.203	1.629
R frontal pars opercularis	68.086	6.703	0.010	16.542	119.629
R supplementary motor area	58.635	4.720	0.030	5.738	111.532
R lateral orbitofrontal cortex	−12.873	5.880	0.015	−23.277	−2.468
L lingual	−107.474	6.697	0.010	−188.874	−26.073
R precuneus	−51.189	4.346	0.037	−99.315	−3.063
L middle temporal	49.983	5.659	0.017	8.801	91.166
Constant	−3.968	0.283	0.595		

BDI Beck depression inventory; *R* right, *L* left

the right lateral orbitofrontal cortex, left lingual, and right precuneus regions, and higher burden in the right inferior opercularis frontal, right supplementary motor area, and left middle temporal regions. The model had a sensitivity of 96.4% and a specificity of 95% in predicting participants with declining executive performance (Supplementary Table 5).

No significant association with, or improved classification compared with the hazard threshold for, NPS and tau burden was found for global cognitive decline. Also, for every model, age, sex, and education covariates were not significant.

Discussion

The aim was to investigate whether the association of NPS (depression and anxiety) and AD biomarkers (brain β-amyloid and tau burden) predicts cognitive decline (global, memory, executive) in cognitively healthy middle-aged to older individuals. Based on previous work, it was expected that the association between higher NPS and amyloid and tau burden and could be predictive of decline.

Expectations regarding the hypotheses are partially supported by the results. NPS were involved in predicting memory decline when associated with amyloid and tau burden (anxiety and depression respectively), and in predicting executive decline when associated with tau burden (depression). The higher the NPS, the higher the probability of showing a decline. Considering that NPS were below the clinical threshold thanks to inclusion criteria, this suggests that even subtle affective symptoms predict poorer cognitive performance 2 years later in memory and executive functions, the two domains which are the most sensitive to aging [34].

Amyloid and tau burden were both positive and negative associated with declines. The observation that more amyloid burden was linked to a stability of cognitive performance in some regions is not in line with the hypothesis raised by Panza et al. suggesting that an increase in amyloid burden, at the initial phase of rising levels, was an attempt by the brain to mitigate or repair neuronal damage [7]. Although this was work done with patients with AD, whereas here participants were cognitively healthy, it raises the question of a possible protective role of amyloid and tau burden in small amounts. As Paracelsus said, "Everything is poison and nothing is without poison; the dose alone makes something not a poison". Other authors have demonstrated cognitive preservation in people with good cognitive reserve even when developing high tau burden [35] or neuroinflammation in patients with early MCI. Amyloid deposits have been described as generating protective neuroinflammation while neuroinflammation would be toxic when generated by tau deposits [36]. Furthermore, a previous study on the same cohort showed no cross-sectional associations between AD biomarkers and episodic memory performance [22]. The authors emphasized the inconsistency of data in the literature concerning associations between amyloid loadings and cognitive performance, as well as the greater involvement of amyloid loadings in the study of cognitive change over time rather than in cross-sectional studies. Other data suggest that amyloid loads predict tau aggregation before memory decline [37]. Also, Narbutas and colleagues showed a positive association between executive functioning and tau loads in the entorhinal cortex and hippocampus, hypothesizing that this association may be due to a compensatory mechanism in the executive function brain networks [38]. Furthermore, it was shown that a more rapid decline in cognitively normal elderly people was associated with high level of both amyloid and tau pathologies [39]. This confirmed previous findings indicating greater declines when several markers were present in cognitively normal elderly individuals [40]. These studies were carried out over longer follow-up times or with more PET data measurement time points. In the present study, amyloid and tau burden were not pathological, and the level of both in each ROI was not investigated. This approach could contribute to understanding the negative associations between loadings and risk of decline.

Under certain conditions, several experimental studies report protective effects of beta-amyloid during development

and in the "young" brain or when present at physiological doses (neuroprotective, antioxidant, and trophic properties, even facilitating synaptic plasticity) [41]. Furthermore, even at higher doses, such as during aging, the effects of amyloid are moderated by people's level of education, as demonstrated in normal cognitive participants, where the relationship between amyloid and episodic memory was not significant in people with a university education [42]. Our sample had particularly high educational characteristics, and this may have had an impact on our results. Other factors may explain the direction of the results: firstly, NPS are reported in Alzheimer's disease either as an underlying manifestation or result of AD pathology. In cases where AD pathology was not associated with NPS, their presence could lead to cognitive impairment. Alternatively, it has been suggested that awareness of cognitive decline may lead to NPS [43]. Ultimately, it is also possible that the origin of NPS differs according to the stage of disease and cognitive functioning [44]. As the participants in this study were healthy with normal cognition, the presence of higher NPS may explain cognitive decline during follow-up without being systematically associated with higher biomarker loads, and these associations may involve different regions due to the different NPS considered in the study.

However, the observation that there was also a link between higher NPS and more amyloid/tau burden in some regions and cognitive decline supports the literature that showed higher tau and amyloid loads associated with higher NPS as risk factors for cognitive decline. For example, the association of depression with a positive amyloid status would increase the risk of MCI incidence by three times, while associated with anxiety, this status would increase the risk of MCI incidence by five times compared to amyloid-negative individuals without NPS [45]. Conversely, it has been shown that higher amyloid loads increase the emergence of NPS, notably anxiety and agitation [46]. Longitudinally, the amyloid-positive status increases the severity of nocturnal and motor behaviors in early-onset AD [47]. Moreover, depression also appears to accelerate cognitive decline in amyloid-positive MCI patients. Interestingly, these participants had greater amyloid loads in frontotemporal and insular regions, as well as coincident hypermetabolism of glucose in frontal regions compared to patients without depression. Furthermore, the progression to AD was faster in amyloid-positive MCI with depression [11]. The current data suggests that such associations between NPS, AD biomarkers and cognitive decline already exist in middle-aged individuals who are cognitively healthy (notably, their scores at follow-up were still within the norms). A longer longitudinal follow-up should inform us about the potential emergence of MCI in some participants and one could predict that this would be more likely in those individuals who had the higher NPS score and the higher amyloid/tau burden. Additionally, within a larger cohort, it would be appropriate to distinguish cognitive trajectories in cognitively healthy individuals according to their protein burden divided into categories for example (first vs fourth quartile), or to define mixed models based on burden and allowing control of subjects as a random factor.

Despite limitations related to the sample size and the short duration of the follow-up, the findings of a link between NPS, AD biomarkers and cognitive decline in a cohort of cognitively healthy middle-aged to young–old individuals underline the importance of further investigations on the relationships between NPS and brain protein burden. It is important to note here that the participants are relatively young (especially for a study of cognitive aging), in very good health condition (still at the end of longitudinal follow-up) with low burdens of brain amyloid and tau proteins. When all these factors are considered, many associations are nonetheless significant, enabling us to classify individuals who show greater reductions in cognitive performance over time. Proportional hazard analyses in healthy individuals according to burden (amyloid positive or not, tau positive or not), genetic risk factor (*APOE*-ε4 or not), and NPS (clinically significant or not) would help to understand the joint risk of the different factors in cognitive decline (normal or pathological). Also, it may be noted that the tau protein radiotracer [18F]THK5351 has been criticized for its off-binding to monoamine oxidase B (MAO-B) in vivo [48]. Thus, [18F] THK5351 is an important marker of neuroinflammatory elements such as reactive astrocytes, which increase along with tau pathology [49]. Previous data showed greater cortical excitability in people with higher THK5351 uptake in the brainstem [50]. The authors pointed out that increased cortical excitability in MCI and AD patients in the early stages of the disease could represent a compensatory mechanism to counter synaptic dysfunction and the accumulation of NFT tau in neuronal networks [51]. Concerning the PET data, another limitation should be mentioned concerning the lack of partial volume correction. Due to the small size of the regions in the AAL atlas, spill-over effects may have affected the results. Also, the neurologist's visual inspection of the MRI scans does not exclude the presence of non-visible lesions. Finally, considering that the inclusion of participants was based on BAI and BDI scores (< 17), the results presented relate only to low levels of depression and anxiety and are therefore not generalizable to moderate/severe levels of these symptoms. However, the anxiety and depression factors were still sufficient variable in the sample to establish statistically significant relationships.

The generalizability of our results refers to the possibility of its implementation in a clinical setting and on an individual basis, to calculate the predictive value of the risk of cognitive decline after 2 years. After the corresponding parameters are being quantified, the

probability of conversion can be calculated using the equation: $P(\text{event}) = 1/(1 + e^{-[\beta 1 * X1 + \beta 2 * X2 + \beta 3 * X3 + \ldots + \beta n * Xn + \text{constant})}$. The regression tablēs (Tables 3, 4, 5, 6) provide the β coefficients of each significant variable in the model and the *X* values are the individual-specific values quantified using corresponding NPS inventory and PET data. The data obtained from the calculation of each equation allows us to estimate, from the data of a given individual, the percentage risk of cognitive decline of this individual.

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Data availability The data that support the findings of this study are not publicly available due to privacy or ethical restrictions but are available upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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