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The Association Between Biomarkers and Neuropsychiatric Symptoms Across the Alzheimer's Disease Spectrum

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ABSTRACT

Objective: *To investigate the relationship between Alzheimer's disease biomarkers and neuropsychiatric symptoms.* ***Methods:*** *Data from two large cohort studies, the Dutch Parelsnoer Institute – Neurodegenerative Diseases and the Alzheimer's Disease Neuroimaging Initiative was used, including subjects with subjective cognitive decline (N = 650), mild cognitive impairment (N = 887), and Alzheimer's disease dementia (N = 626). Cerebrospinal fluid (CSF) levels of $A\beta_{42}$, t-tau, p-tau, and hippocampal volume were associated with neuropsychiatric symptoms (measured with the Neuropsychiatric Inventory) using multiple logistic regression analyses. The effect of the Mini-Mental State Examination (as proxy for cognitive functioning) on these relationships was assessed with mediation analyses.* ***Results:*** *Alzheimer's disease*

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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biomarkers were not associated with depression, agitation, irritability, and sleep disturbances. Lower levels of CSF $A\beta_{42}$, higher levels of t- and p-tau were associated with presence of anxiety. Lower levels of CSF $A\beta_{42}$ and smaller hippocampal volumes were associated with presence of apathy. All associations were mediated by cognitive functioning. ***Conclusion:*** *The association between Alzheimer's disease pathology and anxiety and apathy is partly due to impairment in cognitive functioning.* (Am J Geriatr Psychiatry 2020; 28:735−744)

INTRODUCTION

Neuropsychiatric symptoms (NPS) occur in nearly all patients with Alzheimer's disease (AD) dementia over the disease course and have prognostic consequences.[1−4] Although AD pathology differs between patients with and without certain NPS, the etiology of NPS remains unclear.[5] An increased understanding of the underlying biological mechanisms of NPS in AD would result in better understanding and improve earlier treatment of these multifactorial symptoms.[6]

AD pathology is reflected by biomarkers, such as cerebrospinal fluid (CSF) levels of amyloid-β ($A\beta_{42}$) protein, total tau (t-tau) and phosphorylated-tau (p-tau),[7] and reduced hippocampal volume (HCV).[8,9] Previous research showed that symptoms of depression and anxiety are related to lower CSF $A\beta_{42}$[5,10] and higher t-tau[11] levels, although others have not supported this finding.[12−17] These inconsistent findings apply to other NPS as well, such as apathy, agitation, and irritability, and might be explained by differences in study design such as sample size, sample characteristics, or differences in the measurement of both biomarkers and NPS.

The association of AD pathology with NPS as reported in several studies suggests that these NPS are either a noncognitive manifestation of underlying AD pathology or that NPS result in AD pathology. When AD pathology was not associated with NPS, hypotheses were posed that the presence of NPS might result in cognitive impairment (e.g. where NPS deplete cognitive resources). Another hypothesis might be that awareness of cognitive decline results in NPS. Possibly, the explanation for the presence of NPS differs per disease stage, that is, the association between NPS and AD pathology might be dependent on cognitive functioning.[18]

The primary aim of the present study was to study (inter)relations of AD biomarkers (CSF $A\beta_{42}$, t-tau, and p-tau; hippocampal volume) and the most common NPS in mild cognitive impairment and AD dementia (depression, anxiety, agitation, apathy, irritability, and sleep/night-time behavior disturbances[2,4,19]). This study also examines how global cognitive functioning might impact this relationship, in a large clinically representative sample of subjects with subjective cognitive decline, mild cognitive impairment, and AD dementia.

MATERIALS AND METHODS

Sample

Individuals were included from two large, multicenter and longitudinal studies, the Dutch Parelsnoer Institute − Neurodegenerative Diseases (PSI-NDZ,[20] parelsnoer.org) and the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu). The PSI-NDZ study is a collaborative cohort study of the Memory Clinics of eight Dutch University Medical Centers, focusing on the role of biomarkers in early and differential diagnosis and course monitoring of neurodegenerative diseases.[20] The ADNI study has 59 acquisition sites in the United States and primarily evaluates whether magnetic resonance imaging (MRI), positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure progression of mild cognitive impairment and AD. ADNI phases 1, GO and 2 were used for the present study. These three ADNI phases are consecutive cohorts with slightly different data collection protocols (see adni-info.org).

For the present study, baseline data was used from subjects with subjective or objective cognitive complaints (i.e., subjective cognitive decline, mild cognitive impairment, and AD dementia) who had information

on NPS and at least one of the following biomarkers available: Aβ_{42}, t-tau and p-tau in CSF, and HCV on MRI. Exclusion criteria were 1) the presence of any psychiatric or neurological disorders other than dementia that could cause cognitive impairment and 2) a diagnosis of dementia due to non-AD etiology (n = 143, 28 subjects for whom this information was missing).

Clinical Assessment

The comprehensive assessment procedures included a clinical interview, standardized physical and neurological examinations, and neuropsychological assessments. Assessment of cognitive functioning was assessed using the Mini-Mental State Examination (MMSE).[21] In both studies, the clinical diagnosis of dementia was based on DSM-IV criteria and etiological diagnosis of AD according to standardized clinical criteria (NINCDS-ADRDA criteria for probable AD[22]). Diagnosis of mild cognitive impairment was made in accordance to the Petersen criteria,[23] that is, 1) memory complaints, 2) abnormal memory function based on norm-based cut scores, and 3) normal activities of daily living. Participants were diagnosed with subjective cognitive decline when significant memory concerns could not be objectified.

Neuropsychiatric symptoms

In the PSI-NDZ cohort and ADNI 2, the presence of NPS was assessed with the full Neuropsychiatric Inventory (NPI), a commonly used informant-based scale that examines 12 neuropsychiatric domains through a structured interview with the caregiver.[24] In the ADNI 1 and ADNI GO studies, the informant-based NPI-Questionnaire (NPI-Q) was used.[25] Both formats assess the presence and severity (1−3, mild-severe) of each domain, but only the full NPI assesses the frequency (1−4, rarely-very often) of the symptoms, where multiplying the severity by frequency results in a continuous domain score (1−12) per NPS. In order to harmonize the different datasets, NPS were dichotomized simply as present (severity score ≥1) or absent (severity score = 0). For the present study, the most prevalent symptoms in mild cognitive impairment and AD dementia were selected − depression, anxiety, apathy, agitation, irritability, and night-time behavior disturbances.[2,4,19,26,27]

Information on NPS was available for 1,313 (99.6%) ADNI subjects and for 756 (89.5%) PSI-NDZ subjects (95.7% for whole sample). Subjects for whom NPS data were available differed from subjects for whom these were not available with regard to age (72.1 versus 66.8 years, Welch's $t_{(df)} = -4.6_{(95.3)}$, $p < 0.001$), and education (14.0 versus 12.2 years, Welch's $t_{(df)} = -4.9_{(103)}$, $p < 0.001$). Distribution of gender (56.5 versus 56.0% females, $\chi^2_{(df)} = 0.0_{(1)}$, $p = 0.9$) and MMSE scores (26.4 versus 26.2, Welch's $t_{(df)} = -0.8_{(69.1)}$, $p = 0.4$) were similar in both groups.

Biomarker Assessment

CSF

CSF was collected by lumbar puncture. The CSF procedures have been described in detail elsewhere for PSI-NDZ[20] and ADNI.[7] To measure Aβ42, t-tau, and p-tau levels, PSI-NDZ used commercially available single-parameter enzyme-linked immunosorbent assay methods whereas ADNI used Roche Elecsys and cobas e immunoassay analyzer system. To combine both measures of CSF, scores were converted into z-scores based on the means and standard deviations of the subjective cognitive decline subjects, as these were considered as control group.

CSF data were available for 941 (71.4%) ADNI subjects and for 205 (24.3%) PSI-NDZ subjects (53.0% for whole sample). Subjects for whom CSF data were available differed from subjects for whom these were not available with regard to gender (58.7 versus 53.9% females, $\chi^2_{(df)} = 4.8_{(1)}$, $p = 0.03$), education (15.2 versus 12.6 years, Welch's $t_{(df)} = -16.4_{(2033)}$, $p < 0.001$), and MMSE score (26.7 versus 26.0 years, Welch's $t_{(df)} = -4.7_{(1433)}$, $p < 0.001$). Age was similar in both groups (71.7 versus 72.1 years, Welch's $t_{(df)} = 0.9_{(1992)}$, $p = 0.4$).

MRI

Both PSI-NDZ and ADNI used standardized acquisition protocols performed at 1.5 and 3.0 Tesla, which are described in detail elsewhere.[20,28] Total intracranial volume and HCV were measured centrally at the Biomedical Imaging Group Rotterdam (BIGR, Erasmus MC, Rotterdam, Netherlands) using a multiatlas segmentation procedure, according to

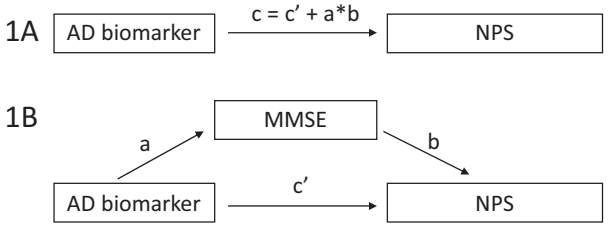
methods described previously,[29] and obtaining gray matter volumes from the T1-weighted image using the unified tissue segmentation method[30] of SPM8 (Statistical Parametric Mapping, London, UK). To correct for head size, HCV was divided by intracranial volume, then further normalized to have zero mean and unit variance.

MRI data were available for 1,304 (98.9%) ADNI subjects and for 556 (65.8%) PSI-NDZ subjects (86.0% for whole sample). Subjects for whom MRI data were available differed from subjects for whom these were not available with regard to age (72.3 versus 69.2 years, Welch's $t_{(df)} = -4.9_{(368)}$, $p < 0.001$), education (14.4 versus 11.5 years, Welch's $t_{(df)} = -13.0_{(423)}$, $p < 0.001$), and MMSE score (26.5 versus 25.9, Welch's $t_{(df)} = -2.3_{(198)}$, $p < 0.001$). Gender distribution was similar in both groups (56.4 versus 56.8% females, $\chi^2_{(df)} = 0.002_{(1)}$, $p = 0.9$).

Statistical Analyses

Statistical analyses were performed with R version 3.3.2.,[31] with significance set at $p < 0.01$ in two-sided tests. A relatively stringent p-value was chosen to reduce the Type I error. Group differences (i.e., between ADNI and PSI, between subjects with versus without available biomarker data and NPS, between diagnostic groups) were analyzed using t tests, one-way analysis of variance (in case more than two groups) or Kruskal-Wallis test by rank (nonparametric) for continuous variables and χ^2 tests for categorical variables. Logistic regression models were used to estimate odds ratios (ORs) of biomarker levels for predicting the presence of individual NPS, corrected for age, gender, and study cohort. To further understand these relationships, the effect of amyloid independent of neuronal injury (i.e., tau and HCV) and vice versa (i.e., neuronal injury independent of amyloid) was tested. In addition, mediation models were ran to test the hypothesis that cognitive functioning (i.e., MMSE score) mediates the relationship between biomarkers and NPS, following the Baron & Kenny approach.[32] It must be noted however that, because these are cross-sectional data, it cannot be shown that biomarker abnormality temporally precedes NPS.[33] We must therefore be careful with the interpretation of causality. In the first step of this approach, the total association between biomarker and NPS was assessed (Fig. 1A, path c). In the second step, the direct associations between biomarker and MMSE (Fig. 1B, path a), MMSE and NPS (Fig. 1B, path b) and biomarker and NPS (Fig. 1B, path c') was assessed. The indirect mediating effect of MMSE (a × b) was tested in case both path a and path b from the first steps showed significant associations. All analyses were corrected for age, gender, and study cohort. The scaling issue that occurred in these mediation models, due to a linear mediator and binary outcome, was addressed by standardizing the coefficients. The standard error parameters were bootstrapped (5,000 resamples). The 95% confidence intervals (CIs) were determined using the adjusted bootstrap percentile method to correct for bias in the distribution of bootstrap estimates.

FIGURE 1. Schematic model of analyses.



Notes: Panels [A] and [B] show the schematic model of mediation analyses. Panel [A] shows the total effect of biomarker on NPS, denoted by path c. Panel [B] shows the direct effect of biomarker on affective symptom, which is denoted by path c', and the indirect effect of biomarker on affective symptom through cognitive functioning (path a×b). Analyses were adjusted for age, gender, and cohort.

RESULTS

In total, 2,163 subjects were included (mean age: 71.9, SD: 9.1; 56.5% females). Baseline characteristics, per clinical diagnosis, are presented in Table 1 (maximum available data). Between the cohorts, there were significant differences, with ADNI being older, higher educated, having lower CSF values of t-tau and p-tau, lower hippocampal volumes, and having less often NPS. CSF $A\beta_{42}$ levels, MMSE scores, percentage of females, and APOE-ε4 carriers were similar across the cohorts (characteristics per cohort and test statistics are presented in supplemental data Table 1).

TABLE 1. Baseline Characteristics Per Clinical Diagnosis

	Total (N = 2,163)	SCD (N = 650)	MCI (N = 887)	AD Dementia (N = 626)	Test Statistic $\chi^2_{(df)}$ or $F_{(df)}$*	p Value	Post Hoc Differences
Cohort (ADNI/PSI), %	60.9/39.1	64.3/35.7	63.7/36.3	53.5/46.5	$\chi^2_{(2)} = 20.4$	<0.001	SCD = MCI < AD
Female	1220 (56.5)	363 (55.8)	530 (60.0)	327 (52.2)	$\chi^2_{(2)} = 9.0$	0.011	SCD = MCI > AD
Age, years, m (sd)	71.9 (9.1)	68.7 (9.6)	72.8 (8.2)	73.9 (8.8)	$F_{(2, 2157)} = 64.6$	<0.001	SCD < MCI = AD
Education, years, m (sd)	14.0 (3.9)	14.5 (3.7)	14.2 (3.9)	13.1 (3.9)	$F_{(2, 2160)} = 25.5$	<0.001	SCD = MCI > AD
MMSE, m (sd)	26.4 (2.8)	28.4 (1.7)	27.0 (2.0)	23.4 (2.2)	$F_{(2,1760)} = 881.0$	<0.001	SCD > MCI > AD
Biomarkers							
CSF present	1,131 (52.3)	422 (64.9)	421 (47.5)	288 (46.0)	$\chi^2_{(2)} = 59.8$	<0.001	SCD > MCI = AD
Aβ_{42}, m (sd)[a]	−0.5 (1.0)	0.0 (1.0)	−0.6 (1.0)	−1.0 (0.7)	$F_{(2,1143)} = 115.0$	<0.001	SCD > MCI > AD
t-tau, m (sd)[a]	0.5 (1.4)	0.0 (1.0)	0.6 (1.3)	1.2 (1.6)	$F_{(2,1143)} = 84.1$	<0.001	SCD < MCI < AD
p-tau, m (sd)[a]	0.5 (1.4)	0.0 (1.0)	0.6 (1.3)	1.2 (1.6)	$F_{(2,1142)} = 85.0$	<0.001	SCD < MCI < AD
Aβ_{42}, abnormal[b]	687 (59.9)	169 (38.7)	280 (67.0)	238 (81.8)	$\chi^2_{(2)} = 149.0$	<0.001	SCD < MCI < AD
t-tau, abnormal[b]	657 (57.3)	169 (38.7)	259 (62.0)	229 (78.7)	$\chi^2_{(2)} = 120.0$	<0.001	SCD < MCI < AD
p-tau, abnormal[b]	682 (59.6)	177 (40.6)	267 (63.9)	238 (81.8)	$\chi^2_{(2)} = 128.0$	<0.001	SCD < MCI < AD
MRI scan present	1,860 (86.0)	547 (84.2)	785 (88.5)	528 (84.3)	$\chi^2_{(2)} = 7.9$	0.020	NS
Hippocampal volume, % ICV[c]	3.4 (0.6)	3.7 (0.6)	3.4 (0.6)	3.1 (0.6)	$F_{(2, 1857)} = 135.0$	<0.001	SCD > MCI > AD
APOE-ε4 carrier	1061 (52.6)	251 (40.5)	438 (53.0)	372 (64.8)	$\chi^2_{(2)} = 70.4$	<0.001	SCD < MCI < AD
Neuropsychiatric symptoms							
NPI present	2,069 (95.7)	618 (95.1)	849 (95.7)	602 (96.2)	$\chi^2_{(2)} = 0.9$	0.630	NS
Depression	646 (31.5)	182 (29.6)	241 (28.7)	223 (37.4)	$\chi^2_{(2)} = 13.7$	<0.001	SCD = MCI < AD
Anxiety	472 (23.0)	101 (16.4)	166 (19.8)	205 (34.3)	$\chi^2_{(2)} = 63.1$	<0.001	SCD = MCI < AD
Apathy	573 (28.1)	115 (18.8)	192 (23.0)	266 (44.9)	$\chi^2_{(2)} = 120.0$	<0.001	SCD = MCI < AD
Agitation	461 (22.6)	96 (15.7)	182 (21.8)	183 (30.8)	$\chi^2_{(2)} = 39.7$	<0.001	SCD < MCI < AD
Irritability	699 (34.2)	203 (33.1)	260 (31.2)	236 (39.7)	$\chi^2_{(2)} = 11.8$	0.003	SCD = MCI < AD
Sleep/night-time behavior disturbances	455 (22.3)	161 (26.3)	157 (18.7)	137 (23.1)	$\chi^2_{(2)} = 12.0$	0.002	NS
(History of-) any psychiatric diagnosis	673 (55.7)	246 (65.6)	258 (55.7)	169 (45.6)	$\chi^2_{(2)} = 30.4$	<0.001	SCD > MCI > AD
(History of-) depression^	475 (64.0)	159 (71.3)	185 (65.1)	131 (55.7)	$\chi^2_{(2)} = 12.3$	0.002	NS
(History of-) anxiety^	92 (62.6)	41 (59.4)	27 (60.0)	24 (72.7)	$\chi^2_{(2)} = 1.9$	0.392	NS
(History of-) diagnosis, other	169 (7.8)	64 (9.8)	67 (7.6)	38 (6.1)	$\chi^2_{(2)} = 6.5$	0.040	NS

Notes: Data are n (%), unless specified otherwise. SCD: subjective cognitive decline; MCI: mild cognitive impairment; AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; PSI: Parelsnoer Institute − Neurodegenerative Diseases; MMSE: mini-mental state examination; CSF: cerebrospinal fluid; Aβ_{42}: amyloid-β protein; t-tau: total tau; p-tau: phosphorylated-tau; MRI: magnetic resonance imaging; NPI: neuropsychiatric inventory; ICV: intracranial volume; APOE-ε4: Apolipoprotein E.

[a] z-scores.

[b] For ADNI, concentrations below 980 pg/mL for Aβ_{42}, above 245 pg/mL for t-tau and above 21.8 pg/mL for p-tau were classified as abnormal (correspondence with L. M. Shaw, 2018). For PSI-NDZ, concentrations below 551 pg/mL for Aβ_{42}, above 375 pg/mL for t-tau and above 52 pg/mL for p-tau were classified as abnormal [Vos et al., 2015]. Information on psychiatric history was available for 742 (depression) and 147 (anxiety) patients.

[c] Total hippocampal volume (left + right) divided by total intracranial volume.

* χ^2 test for categorical variables and one-way analysis of variance for continuous variables were performed, with p set at <0.01, respectively with post hoc Bonferroni correction and Tukey HSD; df: degrees of freedom.

Anxiety

Lower CSF levels of Aβ_{42} were significantly associated with the presence of anxiety (Table 2). This direct association was independent of t-tau and p-tau but was attenuated after adding MMSE to the model (OR: 1.18, 95% CI: 0.99−1.41, Wald $\chi^2_{(df)} = 3.40_{(1)}$, p = 0.065). Subsequent mediation analyses showed that the association between Aβ_{42} and anxiety indirectly operated through MMSE ($\beta_{indirect} = -0.054$, 95% CI: 0.029−0.079, bootstrap p <0.001), thereby being consistent with the concept of mediation. Higher levels of CSF t-tau were associated with the presence of anxiety (Table 2). This direct association was independent of Aβ_{42} (OR: 1.16, 95% CI: 1.04−1.30, Wald $\chi^2_{(df)} = 7.60_{(1)}$, p <0.001) but was attenuated after adding MMSE to the model (OR: 1.11, 95% CI: 0.98−1.25, Wald $\chi^2_{(df)} = 27.38_{(1)}$, p = 0.098). Subsequent mediation analyses showed that the association between t-tau and anxiety indirectly operated through MMSE ($\beta_{indirect} = 0.051$, 95% CI: 0.026−0.075, bootstrap p <0.001). Higher levels of CSF p-tau were associated with the presence of anxiety (Table 2). This direct association was independent of Aβ42 (OR: 1.17, 95% CI: 1.05−1.31, Wald $\chi^2_{(df)} = 8.13_{(1)}$, p <0.01) but was attenuated after adding MMSE to the model (OR: 1.12, 95% CI: 0.99−1.26, Wald $\chi^2_{(df)} = 3.52_{(1)}$,

TABLE 2. Multivariable Effects of Baseline AD Biomarkers and Presence of NPS in the Pooled Cohort

	AD Biomarker			
NPS	**CSF Aβ_{42}[a]**	**CSF t-tau**	**CSF p-tau**	**AHV[a]**
Depression	1.12 (0.98−1.28), p = 0.101	1.06 (0.97−1.17), p = 0.209	1.08 (0.98−1.19), p = 0.113	0.95 (0.84−1.07), p = 0.406
Anxiety	1.34 (1.14−1.57), p <0.001	1.21 (1.09−1.35), p <0.001	1.22 (1.10−1.36), p <0.001	1.14 (1.01−1.30), p = 0.039
Apathy	1.25 (1.08−1.46), p = 0.003	1.12 (1.01−1.24), p = 0.039	1.11 (1.00−1.23), p = 0.056	1.28 (1.13−1.45), p <0.001
Agitation	1.13 (0.98−1.32), p = 0.101	1.08 (0.97−1.20), p = 0.156	1.12 (1.01−1.24), p = 0.036	1.12 (0.98−1.27), p = 0.084
Irritability	1.08 (0.94−1.23), p = 0.272	1.10 (0.99−1.21), p = 0.071	1.11 (1.00−1.22), p = 0.052	1.10 (0.97−1.23), p = 0.125
Sleep/night-time	0.93 (0.80−1.07), p = 0.281	0.98 (0.88−1.09), p = 0.700	1.01 (0.91−1.12), p = 0.856	0.93 (0.81−1.06), p = 0.258

Notes: Results are displayed as: odds ratios (95% confidence interval), p-value. Analyses are corrected for age, gender, and study cohort. Significance was set at p < 0.01. AD: Alzheimer's disease; NPS: neuropsychiatric symptoms; CSF: cerebrospinal fluid; Aβ_{42}: amyloid-β protein; t-tau: total tau; p-tau: phosphorylated-tau, AHV: adjusted hippocampal volume (total hippocampal volume (left + right) divided by total intracranial volume.
[a] Inversely coded as more pathology means lower scores.

p = 0.061). Subsequent mediation analyses showed that the association between p-tau and anxiety indirectly operated through MMSE ($\beta_{indirect}$ = 0.048, 95% CI: 0.024 −0.073, bootstrap p <0.001). HCV was not associated with the presence of anxiety (Table 2).

Apathy

Lower levels of Aβ_{42} were associated with the presence of apathy (Table 2). This direct association was independent of t-tau and p-tau but was attenuated after adding MMSE to the model (OR: 1.14, 95% CI: 0.97−1.34, Wald $\chi^2_{(df)} = 2.32_{(1)}$, p = 0.128). Subsequent mediation analyses showed that the association between Aβ_{42} and apathy in the total group indirectly operated through MMSE ($\beta_{indirect}$ = 0.044, 95% CI: 0.020−0.067, bootstrap p <0.001), thereby being consistent with the concept of mediation. Levels of CSF t-tau or p-tau were not associated with the presence of apathy (Table 2). Smaller HCV (here, inversely coded) was associated with the presence of apathy (Table 2). The association was attenuated after adding MMSE to the model (OR: 1.13, 95% CI: 0.97−1.30, Wald $\chi^2_{(df)} = 2.55_{(1)}$, p = 0.110). Subsequent mediation analyses showed that the association between HCV and apathy indirectly operated through MMSE ($\beta_{indirect}$ = −0.053, 95% CI = −0.072; −0.033, bootstrap p <0.001), again consistent with the concept of mediation.

Depression, Agitation, Irritability, Sleep/Night-time Behavior Disturbances

No association between the presence of depression, agitation, irritability, and sleep/night-time behavior disturbances and Aβ_{42} values, t-tau, p-tau, and HCV was found (Table 2).

DISCUSSION

The relationship between AD biomarkers and NPS was examined in 2,163 subjects covering the AD disease spectrum (subjective cognitive decline, mild cognitive impairment, and AD dementia), which were included from two large cohort studies (ADNI and PSI-NDZ). Lower CSF levels of Aβ_{42}, higher CSF levels of t- and p-tau were associated with presence of anxiety. Lower CSF levels of Aβ_{42} and smaller HCV, but not CSF t- or p-tau, were associated with presence of apathy. All associations were shown to operate indirectly through MMSE. That is, the presence of AD pathology seems to have an effect on the presence of anxiety and apathy via a lower MMSE score. This implies that symptoms of anxiety and apathy across the AD spectrum are associated with AD pathology, due to impaired cognitive functioning.

The association of AD biomarkers with anxiety and apathy but not the other symptoms suggests that these symptoms share an underlying mechanism and can possibly be considered as a continuum, where cognitive decline first results in anxious compensating behavior (e.g., emotional vulnerability syndrome[34]), which later in the disease progresses in a apathic state. This needs to be assessed in more detail.

AD biomarkers were not associated with depression, agitation, irritability, and sleep/night-time behavior disturbances. Clinical diagnosis did not act

as a moderator in any of these associations (results not shown), indicating that the effect of AD pathology on presence of NPS did not differ across clinical diagnoses. Although the null-findings with regard to AD pathology and depression in AD were somewhat unexpected given the vast amount of literature on this relationship, these current results are in line with a recent systematic review.[35] Possibly, symptoms of depression, agitation, irritability, and sleep/night-time behavior disturbances are better explained by psychosocial (e.g., awareness and psychological reaction to the disease) or environmental factors (e.g., relationship with caregivers) or other biological factors that were not examined here, such as the influence of the hypothalamic pituitary adrenal axis, (chronic) inflammation, vascular disease or disturbances in neurotransmitter systems.[36-38] On the other hand, it can be hypothesized that possible existing associations are masked by grouping together cognitively impaired individuals with affective symptoms that actually represent heterogeneous phenotypes, for example, having a lifetime history of psychiatry versus those with new onset.[39] In this line of reasoning, early-onset psychiatry (e.g., depression or anxiety) may act as risk factor for dementia, via mechanisms such as chronically elevated cortisol or neuroinflammation levels, which in turn have neurotoxic effects on the brain, leading to AD pathology. NPS might then be attributable to past depressive/anxious episodes rather than current AD pathology. In contrast, late life depression or anxiety might be an early manifestation of AD pathology. Therefore, as a post hoc analysis, we examined the association between AD pathology and NPS while controlling for the confounding effect of life-time history of depression or anxiety. Information on psychiatric history was obtained from patient or caregiver report during intake. Neither a life-time history of depression (present yes/no) nor of anxiety (present yes/no) acted as a moderator in the association between AD biomarker and presence of depression and anxiety, respectively (results not shown). However, it must be noted that this information was available for only a small subset of the sample (missing for life-time history of depression 65.7%; for anxiety 93.2%, see Table 1).

Strengths of this study are its large and well-characterized sample, which allowed us to correct for a large number of covariates and the power to detect subtle effects, even with a conservative p-value. Substantial variation in AD biomarker levels and NPS was ensured by the inclusion of individuals across the AD spectrum. However, variability was also induced by merging data of two different cohorts, for example, individuals in PSI-NDZ showing more often NPS but also the use of different biomarker assays, although both cohorts used highly standardized workup procedures. In order to equalize the different CSF assays − each with a different scaling − and to ease interpretation of results, z-scores were utilized which were based on the subjective cognitive decline subgroup. It is important to note that − although not all reached significance in the smaller PSI-NDZ cohort, probably due to power issues − the associations found in the merged cohort were in the same direction as in the cohorts separately (results not shown). That is, the findings were verified in two independent samples. A great amount of NPS comorbidity was observed within subjects (e.g., of individuals with symptoms of depression almost 35% also show symptoms of agitation, 41% symptoms of anxiety, 44% symptoms of apathy, 51% symptoms of irritability, and 34% sleep/night-time behavior disturbances). Investigating the interaction between depression*anxiety and depression*apathy, we observed that AD pathology was associated with anxiety and apathy, independent of whether depression was present. That is, AD pathology was associated with depression only in the presence of anxiety or apathy (results not shown). It might be that more abnormal biomarker levels (i.e., a higher pathological load) may contribute to endorsement of more NPS. This was indeed observed when we related AD biomarker levels to an NPS risk score (range: 0−6, results not shown). In addition, (selection-) bias might have been introduced as it was observed that individuals with biomarker data available at baseline were cognitively healthier, had higher levels of education, were more often females and were older in comparison to those without biomarker data available. In this line, the exclusion of those with a current major depressive disorder at study entry might have resulted in less variability for depression scores, thereby biasing results downward. However, lower CSF levels of $A\beta_{42}$ were associated with mild depressive symptoms, as opposed to moderate and severe depressive symptoms on the severity scale of the NPI (results not shown). This

association with mild depressive symptoms suggests that the null-finding between AD biomarkers and depressive symptoms is not due to the relatively mild severity of depressive symptoms in these cohorts. Also, those who completed the MRI scan were significantly older than those without MRI data − this might have influenced the variability of HCV, possibly biasing our results. A broad age range (29−92) was observed for the PSI-NDZ cohort. However, excluding the 35 subjects younger than 50 years old, did not change the results. NPS were assessed with the NPI. Although this instrument is considered the gold standard in NPS research, its limitations must be acknowledged, for example its dependence on caregiver report which is subject to information bias.[40] Another limitation of the present study is the use of a cross-sectional design as NPS are known to fluctuate over time. This also prevents any conclusions regarding causality as temporality of effects cannot be established. The clinical research setting of the study limits generalizability to population-based or primary care settings.

CONCLUSION

Our findings have implications for the view on NPS in the context of neurodegenerative diseases. The results suggest that anxiety and apathy are indirectly associated with underlying AD pathology and that the presence of these symptoms might be explained by impaired cognitive functioning. Symptoms such as depression might be better explained by psychosocial, environmental, or other biological factors than that was examined in this study. The high prevalence of NPS (22.3%−34.2% in the present study) emphasizes the importance for clinicians to examine and monitor NPS in people across the AD spectrum.

AUTHORS CONTRIBUTION

LB, IR, SK, FV, and PA all contributed to the conception of the research question of this study. LB drafted the manuscript and performed the statistical analyses under the supervision of SK. All other authors participated in the interpretation of the data and revised drafts of the manuscript for important intellectual content. The data collection was performed and coordinated by IR, EB, FV, PPdD, JC, HK, HM, WvdF, AL, and PA. All authors read and approved the final manuscript.

DISCLOSURE

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SUPPLEMENTARY MATERIALS

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