Cognition Mediates the Association Between Cerebrospinal Fluid Biomarkers of Amyloid and p-Tau and Neuropsychiatric Symptoms

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ABSTRACT

Background: Neuropsychiatric symptoms (NPS) can be an early manifestation of Alzheimer's disease (AD). However, the associations among NPS, cognition, and AD biomarkers across the disease spectrum are unclear.

Objectives: We analyzed cross-sectional mediation pathways between cerebrospinal fluid (CSF) biomarkers of AD ($A\beta_{1\text{-}42}$, p-tau_{181}), cognitive function, and NPS.

Methods: Primary models included 781 participants from the National Alzheimer's Coordinating Center (NACC) data set who had CSF analyzed for AD biomarkers using Lumipulse. NPS were assessed with the Neuropsychiatric Inventory Questionnaire (NPI-Q). We assessed cognition with the harmonized MMSE/MoCA, as well as neuropsychological tests sensitive to AD pathology: story recall, naming, animal fluency, and Trails B. The Clinical Dementia Rating (CDR®) scale assessed dementia severity. Mediation models were estimated with Kemeny metric covariance in a structural equation model framework, controlling for age, education, sex, and *APOE ε4*.

Results: The sample was older adults (*M*=73.85, *SD*=6.68; 49.9% male, 390; 27.9% dementia, 218) who were predominantly white (*n*=688, 88.1%). Higher p-$tau_{181}/A\beta_{1\text{-}42}$ ratio predicted higher NPI-Q, which was partially mediated by the MMSE/MoCA and, in a second model, story recall. No other pathway was statistically significant. Both the MMSE/MoCA and NPI-Q independently mediated the association between p-$tau_{181}/A\beta_{1\text{-}42}$ ratio and CDR global impairment. With dementia excluded, p-$tau_{181}/A\beta_{1\text{-}42}$ ratio was no longer associated with the NPI-Q.

Conclusion: NPS may be secondary to cognitive impairment and AD pathology through direct and indirect pathways. NPS independently predict dementia severity in AD. However, AD pathology likely plays less of a role in NPS in samples without dementia.

Keywords: Alzheimer's disease, Neuropsychiatric Symptoms, Cognition, Cerebrospinal Fluid, Biomarkers, Amyloid, P-tau

INTRODUCTION

Neuropsychiatric symptoms (NPS) are a common feature experienced by patients diagnosed with dementia and mild cognitive impairment (MCI) due to Alzheimer's disease (AD)[1,2]. NPS are associated with early pathological changes, including disruption in various neurotransmitter systems [3], and brainstem involvement may be instrumental in AD pathogenesis [4]. NPS are also predictors of cognitive decline, and thus are of growing interest to clinicians and caregivers [2,5–7]. NPS in AD include changes to personality as well as mood and behavioral disturbances with the most prevalent symptoms including apathy [8,9], anxiety [10,11], and depression [12]. Some authors have proposed mild behavioral impairment as a distinct syndrome of prodromal dementia [5,13,14]. However, the etiology of NPS in dementia remains unclear. A number of studies have suggested that NPS are driven by AD pathology including the aggregation of tau neurofibrillary tangles and amyloid plaques [15–17]. There may even be region specific mechanisms for NPS profiles in AD. For example, apathy appears related to AD pathology impacting the anterior cingulate-subcortical circuit, whereas depression and anxiety appear related to impact on frontal-limbic circuits, hallucinations appear related to impact on frontal and temporal lobes, and delusions appear related to impact on anterior-posterior networks and anterior insular regions (see [18]). Other studies have shown that NPS are a prodrome for incident cognitive impairment among healthy community-dwelling participants [19–21]. However, the etiology of NPS in individuals across disease stages is not entirely understood (e.g., preclinical, MCI, and AD dementia) [22,23].

NPS in dementia have been linked to AD pathology in numerous studies of fluid biomarkers [11,15,24–26]. For example, a study with a large AD sample showed patients with a slightly elevated and subsequently increasing score on the Cornell Scale for Depression in Dementia (CSDD) had significantly lower cerebrospinal fluid amyloid beta (CSF $A\beta_{1\text{-}42}$) level compared to patients who scored consistently low on the CSDD, suggesting that symptoms of depression may be linked to higher disease burden [25]. Further, a study of patients with MCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort showed that the presence of anxiety was associated with abnormal CSF $A\beta_{1\text{-}42}$ and total tau (t-tau) concentrations [11]. A recent review study found a large degree of heterogeneity in findings related to CSF correlates of NPS in patients with AD and MCI, emphasizing the need for further exploration into these relationships [27]. Most of the research done in this area has focused on or included patients with cognitive impairment, leading to a gap in knowledge regarding the etiology of NPS in individuals without substantial disease burden. It remains undetermined if AD pathology causes NPS directly or if NPS are indirectly mediated by a decline in cognitive function. That is, NPS could be exacerbated by AD-related cognitive decline without a direct relationship to the underlying pathology (e.g., through secondary effects such as diminished ability to engage in hobbies and social interaction).

A small number of studies have considered cognition when examining the potential relationship between NPS and AD pathology [24,28,29]. Krell-Roesch et al. found that lower CSF $A\beta_{1\text{-}42}$ and higher t-tau/ $A\beta_{1\text{-}42}$ and phosphorylated tau (p-tau)/ $A\beta_{1\text{-}42}$ ratios were associated with clinical symptoms of depression and anxiety in older non-demented adults, suggesting that NPS expression may result from AD pathology and potentially independent of cognitive status [28]. Analyses did not control for cognitive function; however, a stronger association between lower

CSF $A\beta_{1-42}$ and clinical symptoms of anxiety and depression was found in individuals with MCI (versus normal cognition). This stresses the need for further investigation into the role of cognitive status in preclinical AD. Babulal et al. [29] examined the presence of NPS and mood changes in a mixed cohort from the WU Knight ADRC (cognitively normal patients, some with positive AD biomarkers). Results showed that participants with higher CSF tau/ $A\beta_{1-42}$ ratio had a greater increase in overall mood disturbance across a one year follow up compared to participants with lower values. Higher values also predicted specific increases in symptoms of anxiety and depression. However, there was no significant correlation between change in scores on the Mini-Mental State Examination (MMSE) and total mood disturbance, NPS, or depression. In contrast, Banning et al. [24] found that lower levels of CSF $A\beta_{1-42}$ and higher levels of CSF p-tau and t-tau were associated with the presence of NPS, and that these associations were mediated by MMSE scores. The results suggest NPS in dementia are partially mediated by cognitive functioning. However, the study failed to assess psychometric properties of NPS in the sample and combined different measures of CSF biomarker analysis. Although an agreement between methods has been established, this relationship is not absolute and could lead to skewed results [30]. Likewise, it is unclear whether these findings will only hold for AD dementia, versus earlier stages in the disease spectrum.

In this study, we investigated the associations between CSF biomarkers ($A\beta_{1-42}$, p-tau_{181}), NPS, and cognitive function across the disease spectrum. We leveraged a large cross-sectional cohort from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) but restricted our primary analyses to participants with a single CSF assay method (Lumipulse). This study includes only cross-sectional data because of the complexity of the models and the lack of consistent data across timepoints. We included multiple neuropsychological tests that are sensitive to AD pathology and conducted factor analyses to assess the structure of the NPS measure. Along with models examining NPS as the outcome, we assessed a secondary model to see whether cognition and NPS independently mediate the relationship between CSF biomarkers and dementia severity.

METHODS

Participants and Design

The sample included data from 2009 participants from the NACC who completed UDS visits between 2005 and 2020, and who had baseline CSF biomarker data from within a year of their UDS visit. Of these, 781 had CSF analyzed by Lumipulse, which was the primary analytic sample used for this study. This was chosen because it was the most common CSF collection method, and originated from a single site (the Knight Alzheimer Disease Research Center (ADRC) at Washington University in St. Louis, MO). Of note, all participants from the Knight ADRC are offered biomarker testing, including lumbar puncture (LP) with CSF analysis. Approximately 76.8% of all Knight ADRC participants receive a baseline LP in place of or along with another biomarker method (e.g., amyloid positron emission tomography). While almost all participants agree to LP in principle, many are excluded due to physician objection or known contraindication (e.g., ongoing anticoagulant therapy or space-occupying cerebral lesion). In addition, LP participation is optional for participants from under-represented groups and

participants with advanced dementia do not receive LP. Despite this, the majority of *eligible* participants receive at least a baseline LP (see [31]).

Since 2005, >30 ADRCs have participated in the NACC-UDS, a database of standardized cognitive, behavioral, and functional evaluations (full description can be found elsewhere [32,33]). Of these, nine sites had available CSF biomarker data. We included a larger sample from all nine sites in secondary models (to increase the generalizability of the findings; see analytic plan). Supplemental Figure 1 provides a CONSORT flow diagram of participants included.

Standard protocol approvals, registrations, and patient consents

The NACC database was approved by the University of Washington Institutional Review Board. Informed consent was obtained at each individual ADC. Involvement of human subjects was done in accord with the Helsinki Declaration of 1975.

CSF Biomarkers

LP is not routine for all ADRCs that contribute to NACC and sharing of CSF data to NACC is voluntary. Nine sites in the current data had available CSF data. In the present sample, we analyzed participants whose CSF biomarker data was analyzed using Lumipulse (*n*=781). All Lumipulse-based samples were collected at a single ADRC, the Knight ADRC. Primary models included p-tau$_{181}$/ A$\beta_{1\text{-}42}$ ratio as the assumed best predictor of underlying AD pathology (i.e., given widespread clinical use and superior concordance with amyloid PET scans compared to individual biomarkers) [34–36]. As a sensitivity analysis, models were recomputed with p-tau$_{181}$ and A$\beta_{1\text{-}42}$ as individual predictors. Of note, t-tau was not a significant predictor in any model (alone or in combination with other biomarkers), and was not included in the analysis to minimize model complexity. Samples were collected and processed as previously described [37]. LP was done after overnight fasting. Samples were collected in a 50 mL polypropylene tube using an atraumatic Sprotte 22-gauge spinal needle. CSF was placed on ice and centrifuged at low speed within two hours. CSF was transferred to another 50 mL tube and aliquoted at 500 uL into polypropylene tubes and stored at −80°C [38]. For biomarker analysis, samples were brought to room temperature, vortexed, and transferred to polystyrene cuvettes. Concentrations of each biomarker were measured by chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE G1200, Fujirebio, Ghent, Belgium). A single lot of reagents were used.

Of the other eight sites, 704 samples were analyzed using Luminex, 512 were analyzed by enzyme-linked immunosorbent assay (ELISA), and 12 were analyzed using Athena ADMark. These last 12 participants were excluded due to the small numbers in the group. These participants were only analyzed in secondary models due to differences in analyte concentrations by assay methods (see Methods).

Neuropsychiatric Symptoms

The Neuropsychiatric Inventory Questionnaire (NPI-Q) was used as a measure of NPS [39]. In the NPI-Q, study partners (collateral sources) are asked to evaluate the patient on 12 symptoms over the past month. Each symptom is rated on a scale from 0 (absent) to 3 (severe). The NPI-Q was intended to produce a composite or summary score. Numerous factor analyses have been conducted in various samples with the NPI-Q, with diverse structures retained across the samples

(see [40]). However, several of these studies (e.g., [41–43]) used principal component analysis, a factor analytic method which hypothesizes the absence of measurement error, and is therefore inappropriate for a Likert scale such as the NPI-Q (see [44]). In this study, we employed a factor analytic method without this limitation (see Measurement and Latent Constructs). We used factor models given the original intention of the NPI-Q [39], and to reduce multiple comparisons.

Neuropsychological Tests and Dementia Severity

Participants receive the UDS neuropsychological battery at approximately annual visits to each ADRC [45–47]. The UDS has had three versions, with the most recent (UDS version 3.0) released in March 2015 [45]. At this most recent update, several tests from the neuropsychological battery were replaced with non-proprietary alternatives. We used results from the Crosswalk study to harmonize scores between versions [46]. From the full UDS battery, we included tests that are sensitive to AD pathology, including tests of episodic memory (i.e., story recall; Logical Memory Delayed Recall and Craft Story Delayed Recall) [48,49], confrontation naming (Boston Naming Test and Multilingual Naming Test) [50–52], semantic fluency (Animals) [53,54], and set shifting (i.e., switching between instructional sets; Trail Making Test Part B [TMT-B]) [55]. We also included a global cognitive screening measure (Mini-Mental State Examination [MMSE] or Montreal Cognitive Assessment [MoCA]) [56,57]. Raw scores were used for these measures. Of note, the full battery of tests did not fit into a latent measurement model (see Results).

Lower scores indicate worse performance for all but one test, TMT-B, where slower speed in seconds indicates worse performance. As noted, for participants who received earlier versions of the NACC UDS, neuropsychological test scores were harmonized with the Crosswalk study [46]. This included scores from Logical Memory, the Boston Naming Test, and the MoCA. Final harmonized cognitive test variables included the MMSE/MoCA, Story Recall, Naming, Animal Fluency, and TMT-B.

We assessed dementia severity using global rating scores from the Clinical Dementia Rating (CDR®) Dementia Staging Instrument [58]. The CDR stages severity of dementia using informant report of orientation, judgment/problem solving, memory, home and hobbies, personal care, and community affairs. Higher scores reflect worse severity of dementia. Participants were excluded from respective models if data on mediators or outcomes were missing, including the MMSE/CDR (n=21) and other neuropsychological tests (n=68). The same participants were missing data from the MMSE/MoCA and CDR.

Measurement and Latent Constructs

Prior to inferential models, we examined the factor structure of the NPI-Q to better understand our primary outcome in this sample. Given diverse factor structures previously documented with the NPI-Q [40], we initially conducted parallel analysis [see 55]. We next assessed the recommended number of retained factors with confirmatory factor analyses (CFAs). For all factor analyses and subsequent structural models, we used the Kemeny metric space to construct a non-parametric covariance matrix with a generalized linear rank framework. These associations are affine-linearly invariant over all monotone transformations, enabling stable linear decomposition and analysis [60]. Loadings were estimated with generalized least squares (GLS). Higher factor scores suggest increased NPS. Confirmatory fit was assessed with the comparative

fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root-mean-square residual (SRMR).[61–63] Satisfactory fit criteria were as follows: CFI > 0.95, RMSEA < 0.06, and SRMR < 0.08 [63]. When relevant, models were compared with the Bayesian information criterion (BIC), with lower values suggesting a better model [64,65].

Missing NPI-Q data were rare in the sample (≤ 1%) and no NPI-Q data were missing in samples included in structural models (i.e., participants without missing relevant moderators). Mean values for NPI-Q items ranged from 0.02 (hallucinations) to 0.37 (irritability/lability). Skewness was high for several items including delusions (5.99), hallucinations (11.97), elation/euphoria (9.49), disinhibition (3.89), motor disturbance (4.91), and appetite/eating (3.21); kurtosis was > 4 for all items, further supporting a nonparametric approach. While many of the factor loadings were low and cannot be validly interpreted as part of the construct, we did not remove these items from structural models because to do so would remove the ability to account for measurement error from these items, and because they were considered an important part of the overall construct when the scale was designed (i.e., items to be interpreted with a summary score; see [39]). In addition, exploratory factor analyses were run to compare unidimensional and multidimensional models. In all cases, the unidimensional model was the preferred model (e.g., $BIC_{factor1}$= -255.7, $BIC_{factor2}$= 38.18, $BIC_{factor3}$ = 286.12).

As a final step, we assessed whether the full battery of neuropsychological tests would fit into a latent measurement model following the same procedure.

Statistical Analyses

Analyses were performed with the lavaan package in the statistical programming language R (version 4.2.3) [66]. Primary models assessed whether cognition, as measured by neuropsychological tests, mediated the relationship between CSF biomarkers and the NPI-Q. As described, harmonized raw scores were used for neuropsychological tests. In addition, p-tau_{181}/ $A\beta_{1\text{-}42}$ ratio was used in primary models and individual CSF biomarkers in sensitivity models. To replicate the most similar past study, and due to discrepancies in missing data, we initially used the MMSE/MoCA as a stand-alone mediator. We then conducted a second model with Story Recall, Naming, Animal Fluency, and TMT-B as independent mediators. Mediation models were assessed in an SEM framework. Unlike the Baron & Kenny approach [67], SEM simultaneously estimates latent variables and mediation pathways while correcting for measurement error; the schema for and definition of mediation analyses can be found in Figure 1. Based on these findings, an exploratory model included NPI-Q factor scores and MMSE/MoCA scores as independent mediators of the relationship between CSF biomarkers and CDR global impairment scores. We did not include additional neuropsychological tests in this model given the sample size differences and the complexity of the model. Age, biological sex, years of education, and Apolipoprotein E (*APOE*) ε4 allele genotyping (ε4 carriers vs. non-carriers) were included as covariates in all models. When multiple mediation pathways were statistically significant, contrasts were used to compare statistical differences between pathways. Statistics of variance are presented as R^2. The absolute value of standardized weights can be directly compared to assess the relative importance of a predictor in a particular model.

To examine the impact of early versus late-stage disease, we conducted sensitivity analyses in which we removed all participants with dementia from the models (as diagnosed by the local

ADRC). These models included smaller samples with complete data on the MMSE/MoCA (*n*=546) and complete data on other neuropsychological tests (*n*=539). To ensure that the findings from the sample with Lumipulse CSF collection were not due to undocumented confounds compared to other participants, we replicated primary models in the full sample with any specified CSF collection method (*N*=2009), including participants with complete data on the MMSE/MoCA (*n*=1665) and complete data on other neuropsychological tests (*n*=1478). We added covariates to account for CSF collection method to these models. These variables were converted into binary indicators (i.e., dummy coding) to permit analysis with our generalized linear rank framework. We recognize that adding collection method as a covariate does not fully and properly account for discrepancies in method. For this reason, we only included these models as a sensitivity analysis and focused on a single biomarker method (Lumipulse) for primary models.

RESULTS

Descriptive Characteristics

The primary sample included 781 NACC participants with Lumipulse CSF biomarker collection. Of these, 688 identified as non-Hispanic White (88.1%) and 390 identified as male (49.9%). The sample were older adults (Median = 74, Interquartile range [69, 78]), highly educated (M_{years} = 15.67; *SD* = 2.81), primarily English speaking (*n*=776; 99.4%), and right-hand dominant (*n*=686; 87.8%). Descriptive characteristics stratified by dementia status can be found in Table 1. In the sample with dementia (n = 218), most received a clinical diagnosis of Alzheimer's disease (94.5%). There were two individuals diagnosed with traumatic brain injury (0.9%). Other participants were diagnosed with frontotemporal lobar degeneration (0.5%), depression (0.5%), and anxiety (0.5%). There were seven participants with an unspecified or unclear diagnosis (3.2%).

Overall, moderate to severe NPS were relatively rare in the sample, but this varied by NPI-Q item (see Table 2). Of note, 376 (48.1%) had at least one positive value for at least one symptom (NPI-Q > 0). In the sample without dementia, 199 (35.3%) had at least one positive value.

Factor analyses

For samples with Lumipulse-generated CSF biomarker results and complete data on the MMSE/MoCA/CDR (*n*=760), as well as complete data on neuropsychological tests (*n*=713), parallel analysis suggested that only one factor should be retained from the NPI-Q. A specified unidimensional CFA demonstrated excellent model fit in both samples (χ^2 = 4.27, *df* = 54, *p* = 1.00, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, and, χ^2 = 3.61, *df* = 54, *p* = 1.00, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, respectively). While most factor loadings were significantly different from zero in both samples ($p < 0.05$), several had minimal contribution to the factor (standardized loadings below 0.20; see Table 3). Overall item contribution was similar between both samples. Items were not removed from the model as described in Methods (Measurement and Latent Constructs). All correlation residuals were below |0.10|.

In the sample with Lumipulse-generated CSF biomarker results and complete data on neuropsychological tests (*n*=713), parallel analysis suggested that five factors should be retained for the full battery of neuropsychological tests. A specified unidimensional CFA demonstrated poor fit (χ^2 = 618.82, *df* = 54, $p < 0.002$, CFI = 0.34, RMSEA = 0.12, SRMR = 0.15). No model

with fewer than four factors demonstrated adequate fit with any of these fit indices and there were not sufficient indicators (i.e., neuropsychological tests) to construct a multi-dimensional latent model. As a result, only raw scores for a priori selected tests were used.

Mediation Models

In the sample with Lumipulse-generated CSF biomarker results and complete data on the MMSE/MoCA (*n*=760), we assessed the MMSE/MoCA as mediator for the association between CSF biomarkers and the NPI-Q. The initial (c-path) model had excellent fit, $\chi^2 = 12.13$, $df = 109$, $p = 1.00$, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, $R^2 = 0.09$, as did the full mediation model, $\chi^2 = 14.38$, $df = 120$, $p = 1.00$, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, $R^2 = 0.15$. In the initial model, higher p-tau$_{181}$/A$\beta_{1\text{-}42}$ ratio predicted higher NPI-Q. These effects were present but reduced in the full mediation model, suggesting partial mediation (i.e., the mediator only partially accounts for the initial association). Specifically, the association between p-tau$_{181}$/ A$\beta_{1\text{-}42}$ ratio and the NPI-Q was partially mediated by the MMSE/MoCA, standardized indirect effect (IE_z) = 0.066, 95% CI [0.034, 0.099]. See Table 4a and Figure 2a.

In the sample with Lumipulse-generated CSF biomarker results and complete data on neuropsychological tests (*n*=713), we assessed Story Recall, Naming, Animal Fluency, and TMT-B scores as mediators for the association between CSF biomarkers and the NPI-Q. The initial (c-path) model had excellent fit, $\chi^2 = 9.59$, $df = 109$, $p = 1.00$, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, $R^2 = 0.08$, as did the full mediation model, $\chi^2 = 112.55$, $df = 159$, $p = 0.99$, CFI = 1.00, RMSEA = 0.00, SRMR = 0.04, $R^2 = 0.13$. In the initial model, higher p-tau$_{181}$/ A$\beta_{1\text{-}42}$ ratio predicted higher NPI-Q. These effects were present but reduced in the full mediation model, suggesting partial mediation. The association between p-tau$_{181}$/ A$\beta_{1\text{-}42}$ ratio and the NPI-Q was significantly mediated by Story Recall, $IE_z = 0.049$, 95% CI [0.011, 0.088]. None of the other mediation pathways were statistically significant. However, the mediation effect of TMT-B was near statistical significance, $IE_z = 0.024$, 95% CI [-0.003, 0.051]. See Table 4b and Figure 2b.

In the sample with complete data on the MMSE/MoCA and CDR (*n*=760), we assessed the MMSE/MoCA and NPI-Q as mediators for the association between CSF biomarkers and CDR global impairment scores. The initial (c-path) model had excellent fit, $\chi^2 < 0.01$, $df = 5$, $p = 1.00$, CFI = 1.00, RMSEA = 0.00, SRMR = 0.00, $R^2 = 0.11$, as did the full mediation model, $\chi^2 = 36.08$, $df = 132$, $p = 1.00$, CFI = 1.00, RMSEA = 0.00, SRMR = 0.02, $R^2 = 0.25$. In the initial model, higher p-tau$_{181}$/ A$\beta_{1\text{-}42}$ ratio predicted higher CDR global impairment. These effects were present but reduced in the full mediation model, suggesting partial mediation. The association between p-tau$_{181}$/ A$\beta_{1\text{-}42}$ ratio and CDR global impairment was partially mediated by the MMSE/MoCA, $IE_z = 0.058$, 95% CI [0.034, 0.082], as well as the NPI-Q, $IE_z = 0.091$, 95% CI [0.040, 0.143]. The difference between these pathways was not statistically significant (suggesting neither is the more complete mediator), $\beta_z = 0.034$, 95% CI [-0.021, 0.088]. See Table 4c and Figure 2c.

Sensitivity Models

For all models, including CSF A$\beta_{1\text{-}42}$ and CSF p-tau$_{181}$ as independent predictors replicated findings from models using p-tau$_{181}$/ A$\beta_{1\text{-}42}$ ratio. That is, lower CSF A$\beta_{1\text{-}42}$ and higher CSF p-tau$_{181}$ predicted higher NPI-Q. These effects reduced and/or were no longer statistically significant in full mediation models, suggesting partial to more complete mediation. The same

mediation pathways were and were not statistically significant (see Supplemental Table 1a,b). Statistics of variance were slightly higher (MMSE/MoCA: $R^2 = 0.16$; neuropsychological tests: $R^2 = 0.14$). Likewise, in the sample with complete data on the MMSE/MoCA and CDR (*n*=760), lower CSF $A\beta_{1\text{-}42}$ and higher CSF p-tau_{181} predicted higher CDR global impairment. These effects were present but reduced in the full mediation model, suggesting partial mediation. Statistics of variance were again slightly higher (baseline: $R^2 = 0.12$, mediation: $R^2 = 0.26$). The same mediation pathways were statistically significant (see Supplemental Table 2). Likewise, the difference between these pathways was not statistically significant.

To examine the impact of early versus late-stage disease, we assessed whether the MMSE/MoCA continued to mediate the association between CSF biomarkers and the NPI-Q in participants without dementia (*n*=546). The initial (c-path) model had excellent fit, $\chi^2 = 4.16$, *df* = 109, *p* = 1.00, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01. However, CSF biomarkers were not significant predictors of the NPI-Q in the sample. As a result, a full mediation model was not conducted. We assessed whether Story Recall, Naming, Animal Fluency, or TMT-B mediated the association between CSF biomarkers and the NPI-Q in participants without dementia (*n*=539). The initial (c-path) model had excellent fit, $\chi^2 = 4.09$, *df* = 109, *p* = 1.00, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01. However, CSF biomarkers were again not significant predictors of the NPI-Q in the sample. As a result, a full mediation model was not conducted.

To ensure generalizability, we assessed whether the MMSE/MoCA continued to mediate the association between CSF biomarkers and the NPI-Q in the sample with relevant complete data and any CSF collection method (*n*=1665). The initial (c-path) model had excellent fit, $\chi^2 = 35.45$, *df* = 142, *p* = 1.00, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, $R^2 = 0.10$, as did the full mediation model, $\chi^2 = 41.30$, *df* = 153, *p* = 1.00, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, $R^2 = 0.19$. Findings were largely the same compared to the sample with Lumipulse-generated CSF biomarker results. Next, we assessed whether Story Recall, Naming, Animal Fluency, or TMT-B scores mediated the association between CSF biomarkers and the NPI-Q in the sample with relevant complete data and any CSF collection method (*n*=1478). The initial (c-path) model had excellent fit, $\chi^2 = 25.61$, *df* = 142, *p* = 1.00, CFI = 1.00, RMSEA = 0.00, SRMR = 0.01, $R^2 = 0.08$. However, there was evidence of poor fit in the full mediation model, $\chi^2 = 318.62$, *df* = 192, $p < 0.001$, CFI = 0.64, RMSEA = 0.02, SRMR = 0.05, $R^2 = 0.14$. There were also a few differences in findings compared to the sample with Lumipulse-generated CSF biomarker results. Along with story recall, which remained a significant mediator, TMT-B was a statistically significant mediator in the larger sample, $IE_z = 0.029$, 95% CI [0.007, 0.051]. See Supplemental Tables 3a,b for full model results from these analyses.

DISCUSSION

The purpose of this study was to investigate whether cognition plays a mediating role in the relationship between CSF biomarkers ($A\beta_{1\text{-}42}$, p-tau_{181}) and NPS across the AD disease spectrum. In addition to analyzing models with NPS as the primary outcome, we also explored whether cognition and NPS act as independent mediators in the association between CSF biomarkers and dementia severity. Findings suggest that higher p-tau_{181}/ $A\beta_{1\text{-}42}$ ratio, the assumed best predictor of underlying AD pathology [34–36], was associated with worse cognitive performance, consequently resulting in more pronounced NPS. Estimates of variance

explained were modest and relatively consistent between models, likely due to the previously stated measurement error within the NPI-Q (see Measurement and Latent Constructs). CSF biomarkers and mediators were relatively stronger predictors than other covariates based on standardized weights. However, cognitive measures only partially mediated the relationship between CSF biomarkers and NPS, suggesting an independent, direct relationship between AD pathology and NPS (i.e., independent of cognitive effects in an AD sample). Among cognitive tests included in this study, story recall emerged as the only retained mediator, with the highest standardized effect. This is consistent with past research that poor recall is a prominent cognitive deficit expected in AD throughout the disease course [68,69]. Global cognition and NPS independently mediated the relationship between CSF biomarkers and dementia severity, with minimal difference between the pathways. As such, AD pathology may disrupt both cognition and mental health, which independently contribute to functional disturbance.

Patients with AD have higher frequency of NPS than general populations [70,71], which can precede cognitive impairment [7,72], and impacts quality of life, daily function, caregiver burden, and institutionalization [13,73,74]. However, the independent and shared pathways between cognition and NPS in AD may lead to different expressions throughout the disease course. Studies have shown that NPS tend to fluctuate within and between patients over time, compared to the relatively steady cognitive decline seen in AD [72,75,76]. Likewise, some studies have found that baseline NPS predicts longitudinal cognitive decline [77–79], but this is not consistent [72,80]. Since psychiatric symptoms impact cognitive test performance (see [81]), it is possible that cognitive functions and NPS create a feedback loop in AD patients over time [82]. That is, cognitive deficits exacerbate NPS and elevated NPS may worsen cognitive deficits.

In our study, when participants with dementia were excluded from models, CSF biomarkers no longer predicted NPS. In contrast to past research ([83] provides a review), this suggests that NPS may not necessarily serve as a better early indicator of AD compared to cognitive measures. However, this observation also supports the directional assumptions made in our primary analyses. In early stages of the disease with less AD pathology, NPS might stem from a variety of factors, including pre-existing psychiatric conditions and psychosocial factors. When pathology builds and disperses in the brain, we observe increased cognitive consequences, potentially exacerbating NPS. It may be that only stable, late onset NPS stemming specifically from AD correlates with worsened cognitive decline (versus transient psychiatric symptoms resulting from factors other than AD; see [84]).

A difference between transient and stable NPS would explain inconsistent associations between AD pathology and NPS across the disease spectrum, particularly in studies that combine groups [17,24,85]. Prevalence of NPS at a given disease stage may vary by symptom, with each symptom having a distinct atrophy, neuropathologic, and regional cerebral blood activation profile [86–88]. There may also be instrumental limitations impacting findings. For example, the NPI-Q was validated to assess psychopathology in dementia patients, rather than earlier in the disease course [39]. Longitudinal worsening of NPS may be a better indicator of AD pathology [29,81,89,90], which we did not examine in this cross-sectional study. Regardless, our findings are relatively consistent with and expand upon the most similar past study described above [24]. Likewise, these findings have implications for management of NPS in AD patients.

The cognitive sequelae of AD may exacerbate NPS, making it crucial to address cognitive symptoms in treatment of these patients. Memantine, particularly in combination with acetylcholinesterase inhibitors (AChEI), demonstrates improved efficacy for NPS, compared to AChEI alone [91,92]. However, monotherapy with AchEI can also provide relief [93]. Conversely, psychotropic medications in this context have varying support and/or more severe side-effect profiles [94–96]. One meta-analysis found that risperidone and galantamine had the best evidence for treatment of NPS across dementia syndromes [97]. Current investigations explore glycogen synthase kinase-3 (GSK3) inhibitors and other kinase inhibitors [98,99], while monoclonal antibody medications targeting Ab (like lecanemab) await evaluation for NPS impact [100]. For non-responsive or contraindicated cases, emerging evidence supports behavioral, interpersonal, and environmental interventions [101–104]. However, additional studies are needed to identify at-risk AD patients and tailor treatment to specific symptom profiles.

This study has several strengths which contribute to the reliability and significance of findings. First, we addressed non-standardized CSF assay methods by focusing primary analyses on participants with CSF analyzed by Lumipulse, and conducting sensitivity analyses to confirm the consistency of results. Second, our study employed appropriate psychometric analyses of the NPI-Q, which improves upon the existing literature. Third, utilizing innovative nonparametric methods presents a practical alternative for studies employing the NPI-Q (versus assessing items individually or combining items without consideration for measurement error). Fourth, we extended past research by incorporating several neuropsychological tests sensitive to AD pathology. This permits interrogation of the specific aspects of cognition linked to the proposed mediation pathways (e.g., memory). Finally, leveraging data from NACC provided a large, methodologically consistent cohort, further fortifying the credibility of the research.

Our study has several limitations, particularly stemming from analysis of the NPI-Q. We observed that NPI-Q item loadings varied. In some instances, items cannot be reliably interpreted as integral to the construct. In our sample, these items do not operate as intended by the scale's design, which was meant for interpretation with a summary score (see [39]). Despite this, we opted to include these items in analyses. Doing so permits the opportunity to account for measurement error, and these items were considered a crucial part of the construct when the scale was formulated. In primary models, we focused on a single CSF biomarker method, which limits the generalizability of the sample. Likewise, our sensitivity models are limited in addressing variations in CSF assay method. Partialling out variance likely does not fully account for these differences. While mediation suggests potential causality in a cross-sectional study, this represents only one possible explanation. For example, these models do not include all possible covariates; unmeasured variables could be either primary or secondary confounds to the outcome or association being studied (see [105] for a discussion). As noted, we included cross-sectional data for this study because of the complexity of our models and the lack of consistent data across timepoints. Future studies should investigate longitudinal models with NACC samples while perhaps sacrificing psychometric complexity. Finally, the NACC is comprised of individuals from ADRCs across the U.S. and is not representative of the general population. As with any CSF biomarker study, samples from the NACC that choose to undergo LP are not necessarily reflective of all AD patients. For example, participants from the Knight ADRC with advanced

dementia do not receive LP. Regardless, examining NPS in this sample provides value, and ongoing replication will address concerns from any particular study.

Our findings suggest that higher p-tau$_{181}$/ Aβ_{1-42} ratio, a strong indicator of AD pathology, was associated with worse cognitive performance and more pronounced NPS. However, cognitive measures only partially explained the relationship, indicating an independent link between AD pathology and NPS. Global cognition and NPS independently mediated the relationship between CSF biomarkers and dementia severity, suggesting the independent impact of AD pathology on functional disturbance through both cognitive decline and NPS. Early in the disease course, NPS may result from various factors. As AD pathology progresses, cognitive effects may exacerbate NPS, creating complex and varied symptom expressions in patients with AD.

CRediT Author Statement:
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Data Availability: The data supporting the findings of this study are available upon request from the National Alzheimer's Coordinating Center (https://naccdata.org/requesting-data/data-request-process).

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