Original research

Neuropsychiatric symptoms in cognitive decline and Alzheimer's disease: biomarker discovery using plasma proteomics

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ABSTRACT

Background and objectives Neuropsychiatric symptoms (NPS) are common in older people with cognitive impairment and Alzheimer's disease (AD). No biomarkers to detect the related pathology or predict the clinical evolution of NPS are available yet. This study aimed to identify plasma proteins that may serve as biomarkers for NPS and NPS-related clinical disease progression.

Methods A panel of 190 plasma proteins was quantified using Luminex xMAP in the Alzheimer's Disease Neuroimaging Initiative cohort. NPS and cognitive performance were assessed at baseline and after 1 and 2 years. Logistic regression, receiver operating characteristic analysis and cross-validation were used to address the relations of interest.

Results A total of 507 participants with mild cognitive impairment (n=396) or mild AD dementia (n=111) were considered. Selected plasma proteins improved the prediction of NPS (area under the curve (AUC) from 0.61 to 0.76, p<0.001) and future NPS (AUC from 0.63 to 0.80, p<0.001) when added to a reference model. Distinct protein panels were identified for single symptoms. Among the selected proteins, ANGT, CCL1 and IL3 were associated with NPS at all three time points while CCL1, serum glutamic oxaloacetic transaminase and complement factor H were also associated with cognitive decline. The associations were independent of the presence of cerebral AD pathology as assessed using cerebrospinal fluid biomarkers.

Conclusions Plasma proteins are associated with NPS and improve prediction of future NPS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ No biomarkers to detect neuropsychiatric symptom (NPS) and predict their evolution in patients with cognitive decline are available, yet.

WHAT THIS STUDY ADDS

⇒ This study identified specific protein biomarker panels for overall NPS and for the most common single NPS as well as for the prediction of future NPS, with good predictive performance. The associations were mostly independent from the core Alzheimer's disease pathology suggesting distinct alterations underlying the manifestation of NPS and related clinical progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Pending further validation, these easily accessible biomarkers could be used in clinical practice to detect pathologies underlying NPS and inform decision-making on NPS treatment and prevention.

INTRODUCTION

Neuropsychiatric symptoms (NPS) are common in older people with cognitive decline and are associated with worse long-term outcomes, including faster cognitive decline and earlier death.[1 2] NPS include a wide range of symptoms such as depression, anxiety, apathy and agitation and are particularly common in individuals with cognitive impairment, including Alzheimer's disease (AD) dementia with rates up to 97%.[3 4] Diagnosis of NPS is mostly based on clinical assessments and proxy questionnaires, and little is known about the related molecular and biological pathway alterations. Making an aetiological assignment based on the clinical evaluation of NPS remains difficult. Easily accessible and reliable biomarkers could be helpful for the clinician to understand the aetiology of NPS, and to treat NPS in patients with cognitive decline. Such biomarkers may also help to identify patients at risk for persistence of NPS over time and associated cognitive and functional decline.

Only a few studies have investigated potential biomarkers of NPS, in most cases focusing on a priori selected molecules like markers of inflammation or cortisol.[4 5] Some studies investigated associations of NPS with biomarkers of the core AD pathology, but most findings were yet inconsistent.[6 7] For single symptoms such as depression and apathy, interleukin-6,[8] chemokines,[8] homocysteine[9] or vitamin B[10] have been investigated. However, the findings have not been replicated yet and the usefulness of these molecules as biomarkers of NPS remains uncertain.

Recent advances in proteomic approaches have identified blood-based biomarker candidates for different chronic disorders, including AD.[11 12] However, previous studies very rarely investigated proteome alterations in relation to NPS. Using untargeted proteomics in a single-centre memory clinic cohort we previously identified a

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Table 1 Characteristics of the study participants grouped by the presence of NPS

	Total n=507	NPS+ n=234	NPS− n=273	P value
Demographic data				
Sex, female (%)	187 (36.9)	83 (35.5)	104 (38.1)	0.580
Age, years	74.3±7.5	74.1±7.3	74.5±7.7	0.546
Education, years	15.5±3.1	15.3±3.0	15.7±3.1	0.090
White race (%)	480 (94.7)	223 (95.3)	257 (94.1)	0.353
Clinical data				
NPI-Q	2.2±2.9	4.4±2.9	0.3±0.5	<0.001
CDR	0.6±0.2	0.6±0.2	0.5±0.1	<0.001
CDR-SB	2.2±1.5	2.7±1.8	1.7±1.2	<0.001
MMSE	26.3±2.3	26.0±2.5	26.5±2.1	0.007
AD diagnosis	111 (21.9)	73 (31.2)	38 (13.9)	<0.001
Amyloid pathology (%)	240 (79.7)	125 (83.9)	115 (75.6)	0.086
APOEe4 carrier (%)	286 (56.4)	138 (59.0)	148 (54.2)	0.323

Criteria for the NPS positive group (NPS+) were NPI-Q score >1, for the NPS negative group (NPS−) NPI-Q score <2.
AD, Alzheimer's disease; APOEe4, apolipoprotein E epsilon 4; CDR, clinical dementia rating; CDR-SB, CDR sum-of-boxes; MMSE, mini mental status examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptom.

panel of 15 plasma proteins associated with current NPS and future NPS.[13]

Herein, using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database,[14] our main objective was to identify further plasma protein biomarker candidates for NPS in subjects with cognitive impairment and to test their performance to predict the persistence of NPS and cognitive decline over time.

METHODS

Study population

We included all participants from the ADNI database (adni.loni.usc.edu) with available plasma proteomic data (V.2013-08-02). Cognitively unimpaired individuals (n=58, 10.3% of the participants, of which n=5 having NPS) were excluded. This resulted in a total number of 508 participants with either amnestic mild cognitive impairment (MCI) or mild AD dementia.[15 16] Subjects taking concomitant psychotropic medication except for the following were excluded: stable doses of antidepressants lacking significant anticholinergic side effects, oestrogen replacement therapy and Ginkgo biloba. Demographic data, apolipoprotein E epsilon 4 (APOEe4) status and cerebrospinal fluid (CSF) AD biomarkers were available at baseline. Other clinical data (Neuropsychiatric Inventory Questionnaire (NPI-Q),[17] Clinical Dementia Rating (CDR), CDR–sum of boxes (CDR-SB)[18]) was used corresponding to the time points proteomic analysis was performed for baseline and 1 and 2 years follow-up within a range of ±3 months.

NPSs at baseline and follow-up were assessed using NPI-Q. This is a self-administered questionnaire completed by informants with regular contact with the individual. It includes 12 different symptoms (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioural disturbances and appetite/eating changes), each rated from 1 to 3 based on their severity, and subsequently all 12 scores were summarised in 1 total score. The presence of NPS was defined as NPI-Q>1 (further details are shown in online supplemental section 1). Cognitive decline at follow-up was defined as ΔCDR-SB>0.5.[19]

Biological assessments

A multiplexed immunoassay panel measuring 190 protein analytes with the Luminex xMAP platform (Luminex, Austin, Texas, USA) was used at Rules-Based Medicine (RBM, Austin, Texas, USA). It contained selected proteins previously reported to be associated with inflammation, metabolic disorders, cardiovascular diseases, cancer and with proteins involved in cell signalling and believed to play a role in AD.[20] More details on the methods and the quality control procedures are available from the ADNI website.

CSF samples were available for 301 participants (50.5% in MCI and 90.1% in AD). Concentrations of beta-amyloid 1-42 (Aβ42), total tau (tTau) and tau phosphorylated at threonine-181 (pTau181) were measured using the multiplex xMAP Luminex platform with immunoassay kit-based reagents of Innogenetics (INNO-BIA AlzBio 3; Ghent, Belgium).[21] Each participant was classified according to both the presence of amyloid pathology and the ATN classification system.[22] Three ATN groups were defined as follows: A−/T−/N− were classified as normal, A−/T±/N±as non-AD pathological changes and A+/T±/N± as belonging to the AD continuum. The cut-offs for A, T and N previously derived from the ADNI cohort were Aβ42<192 pg/mL, pTau181>93 pg/mL and tTau>93 pg/mL, respectively.[23]

The APOE genotyping was performed using DNA extracted by Cogenics to determine two single nucleotide polymorphisms (rs429358, rs7412) that define the epsilon (e) 2, 3 and 4 alleles.[24] The APOEe4 status was defined based on the presence of one or more e4 alleles.

Data preparation

One participant with a CDR score of 2 was excluded to include only mild dementia. Therefore, we analysed the data from 507 participants. After quality control, we excluded 44/190 plasma proteins due to too many missing data points (>10%) and 15 analytes with a coefficient of variation >25% to ensure the reliability of the remaining data. Outliers, defined as values ±5 SD from the mean, were adjusted to the value of the nearest non-outlier. Analytes with levels below the least detectable dose (LDD) were imputed as LDD/2. For missing value imputation, we used the mean of the non-missing values for replacement. All variables with a variance inflation factor >5 (n=16) were excluded from further analysis, resulting in a total of 115 proteins (online supplemental table S1). To approach a Gaussian distribution, all proteins were log10 transformed before analysis.

Statistical analysis

For the descriptive statistics and the logistic regression analysis, SPSS (IBM, V.28.0) was used. All other analyses were performed using RStudio V.2022.12.0+353 including the MASS,[25] partial receiver operating characteristic (ROC),[26] caret[27] and glmnet[28] packages. Categorical variables were described showing absolute and relative frequencies, and continuous variables the mean and SD. For cohort characteristics, two-tailed t-test and Mann-Whitney-U-test were performed for continuous and Pearson's χ^2 test for categorical variables. The Shapiro-Wilk test was used to test normality of each variable. Multicollinearity of all variables included in the regression analysis was tested using the variance inflation factor. To verify a possible overfitting of the models, the Hosmer-Lemeshow test for goodness-of-fit was used with

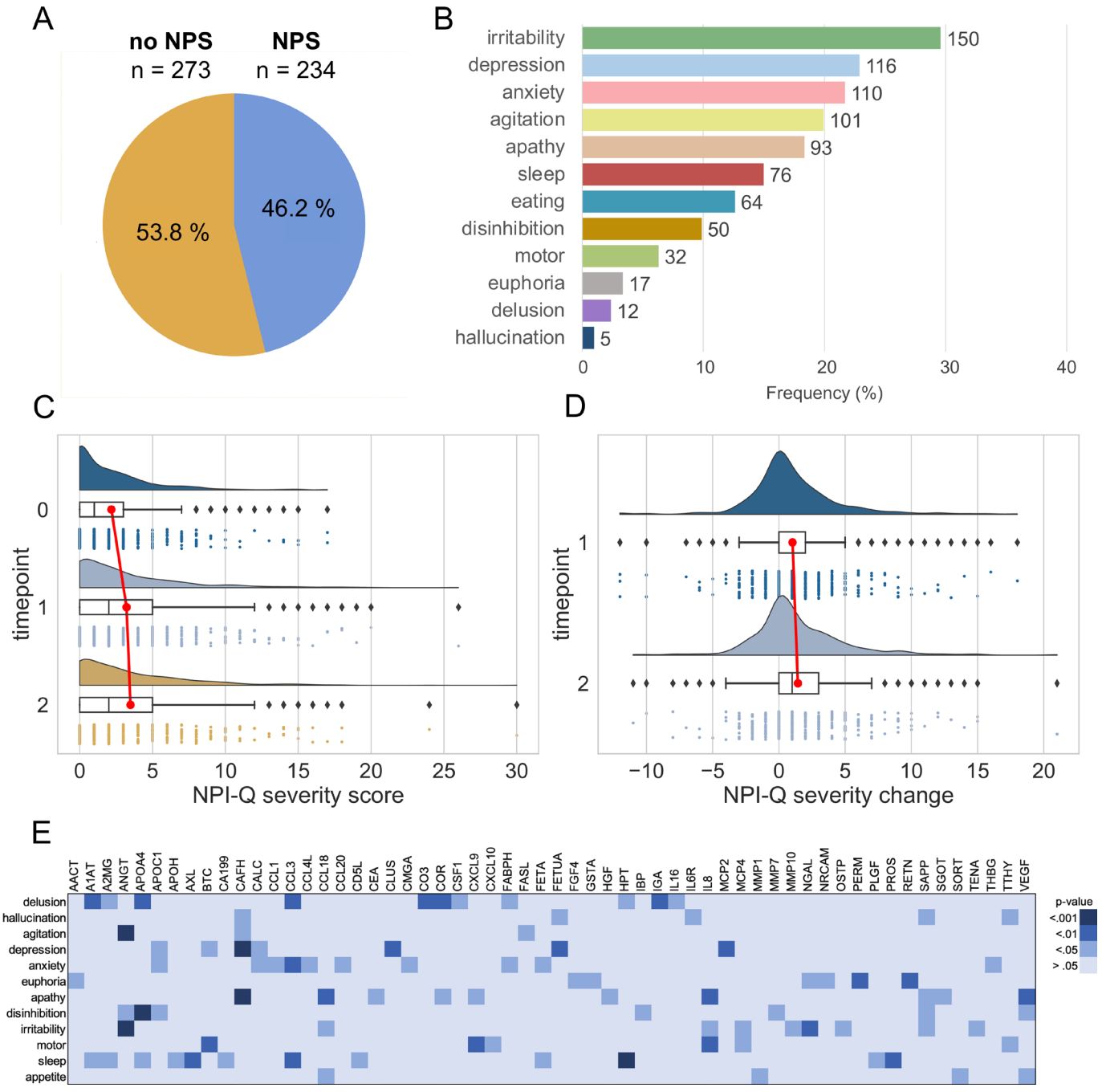

Figure 1 (A) Grouping of the study cohort (n=507) into participants with NPS (NPIQ>1) and without NPS (NPI-Q<2). (B) Frequency of the single items (symptoms) of the NPI-Q in the whole cohort. (C) Raincloud plot showing the distribution of NPI-Q total severity scores in the whole cohort at baseline (0), at 1-year follow-up (1) and 2-year follow-up (2). (D) Raincloud plot showing the distribution of NPS severity change (ΔNPI-Q from baseline to 1 or 2-year follow-up. Higher values show an increasing (ie, worsening) NPI-Q score. (E) Spearman's rank correlation of plasma proteins with all symptoms measured by the NPI-Q. P values of significant correlations are highlighted with colours according to the legend on the right. n, number; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptoms.

the cut-off of a p>0.05. For all statistical tests, two-tailed tests were used and the alpha value was set at 0.05.

Associations of protein levels with the presence of NPS at baseline

To determine the proteins that may independently be associated with the presence of NPS at baseline and determine the best predictive model, we applied binary logistic regression analysis using baseline NPS (NPI-Q>1) as the dependent variable and the 115 proteins as independent variables along with age, sex, education years, APOEe4 status and diagnosis, with a backward stepwise selection method. Variables were chosen based on p values, and a p value threshold of 0.1 was used to set a limit on the total number of variables included in the final model. Before regression analysis, all continuous variables were transformed into standardised z-scores to ensure equal variance.

To further confirm the protein selection, we applied a cross-validation approach considering the proteins selected by the last step of backwards regression. The study population was randomly partitioned into a training (n=409, 80% of participants) and testing (n=98, 20% of participants) dataset. The

Table 2 Best models for different NPS-related prediction outcomes

Prediction outcome	Included variables	χ^2 (df)	P value	R^2
Baseline NPS	AD dementia 25 proteins	117.81 (26)	<0.001	0.28
Irritability	Male sex 19 proteins	113.92 (26)	<0.001	0.19
Depression	AD dementia 10 proteins	59.10 (11)	<0.001	0.17
Anxiety	Young age AD dementia 35 proteins	141.15 (38)	<0.001	0.38
Agitation	13 proteins	57.44 (13)	<0.001	0.17
Apathy	AD dementia 15 proteins	92.27 (17)	<0.001	0.27
NPS after 1 year	Young age male sex APOEe4 carrier AD dementia 12 proteins	90.88 (16)	<0.001	0.23
NPS after 2 years	AD dementia 29 proteins	122.19 (31)	<0.001	0.34

Table shows the best predictive models for different outcomes including all variables resulting from logistic regression analysis. For all models age, sex, education years, APOEe4 carrier status and diagnosis (MCI or AD dementia) were considered. χ^2 (df), R^2 and p values are shown for all models.
AD, Alzheimer's disease; APOEe4, apolipoprotein E allele e4; df, degrees of freedom; MCI, mild cognitive impairment; NPS, neuropsychiatric symptom.

training dataset was used to perform fivefold cross-validation before evaluating the model using the testing dataset.

To investigate the correlations of the selected protein levels with NPS severity (NPI-Q severity score), we used Spearman's rank correlation.

To test whether the selected protein panels can improve the prediction of NPS we added the proteins selected before ('full model') and after cross-validation ('parsimonious model') to a reference model including age, sex, education years, APOEe4 status and diagnosis. To compare the predictive performance of the different models, we calculated the area under the curve (AUC) of ROC. We applied the DeLong method[29] to compare all models.

To further determine the best models predictive for single symptoms of NPS, we applied the same approach except for the cross-validation.

Prediction of future NPS and of cognitive decline

To determine the best model for the prediction of future NPS (NPI-Q>1) at 1 and 2 years follow-up, we used the same approach as described above. In a further exploratory step, we determined the best predictive models for the worsening of the NPI-Q (ΔNPI-Q>1) and for NPS severity change (ΔNPI-Q score) between baseline and follow-up visits, with the same independent variables as above.

To investigate whether the proteins selected after cross-validation were predictive of cognitive decline at 1 or 2 years follow-up, we used the Mann-Whitney U test.

Associations with AD pathology

To explore the associations between NPS and the presence of AD pathology as measured by CSF biomarkers, we performed binary logistic regression analysis using baseline NPS (NPI-Q>1) as dependent variable and possible confounders (age, sex, education years, APOEe4 status and diagnosis) together with either amyloid pathology or ATN groups as independent variables.

Pathways related to overall NPS and to individual symptoms of NPS

Details on the pathway enrichment analysis can be found in online supplemental section 2.

RESULTS

Study participants

Table 1 displays the subject characteristics of the 507 participants grouped according to the presence of NPS at baseline (NPI-Q>1).

Details on the group differences regarding the core AD biomarkers can be found in online supplemental table S2. Figure 1 displays the frequency of all 12 symptoms, the distribution of NPI-Q severity scores at baseline and both follow-up visits, the NPI-Q severity change over time, as well as an overview on correlations between all measured proteins with total NPS and the single symptoms at baseline.

Proteins associated with NPS at baseline

Results of the best model to predict NPS at baseline are shown in table 2 and online supplemental table S3. After cross-validation, 15 proteins were selected (figure 2A, right) with an accuracy of 69% (specificity of 76% and sensitivity of 61%). ROC curves of the models are shown in figure 2A, left. When compared with the reference model, both models improved the prediction of NPS. Five of the 15 proteins additionally correlated with higher NPS severity at baseline, as shown in online supplemental figure S1.

Associations with single symptoms of NPS at baseline

We investigated the five most common single symptoms of NPS in this cohort. The co-occurrence of two or more symptoms per participant is shown in the Venn diagram in figure 3A. The determined models each included a different number of associated proteins and covariables, as shown in table 2. Angiotensinogen (ANGT) was the most commonly shared protein, which was found to predict all symptoms except for depression. Figure 3B shows a Venn diagram with the number of shared proteins. For all symptoms, adding the selected proteins to the reference model improved the prediction when compared with the reference model ($p<0.01$). The selected proteins from all models as well as the ROC curves for all five symptoms are shown in figure 4 and are listed in detail in online supplemental tables tables S4–S8.

Prediction of future NPS

Follow-up data for future NPS based on the NPI-Q score were available in 488/507 after 1 year and 426/507 after 2 years.

Results of the best model to predict future NPS at 1-year follow-up (full model) are shown in table 2 and online supplemental table S9. After cross-validation, eight proteins were selected for the 'parsimonious model' (figure 2B, right) with an accuracy of 65% (specificity of 52% and sensitivity of 75%). ROC curves of both models are shown in figure 2B, left. When compared with the 'reference model', both models improved the prediction of NPS at 1-year follow-up.

Results of the best model to predict future NPS at 2-year follow-up (full model) are shown in table 2 and online supplemental table S10. After cross-validation, 20 proteins were selected for the 'parsimonious model' (figure 2C, right) with an accuracy of 68% (specificity of 49% and sensitivity of 81%). ROC curves of the models are shown in figure 2C, left. When compared with the 'reference model', both models improved the prediction of NPS at 2-year follow-up.

ANGT, interleukin-3 (IL3) and T lymphocyte-secreted protein I-309 (CCL1) were the only proteins from the 'parsimonious models' that were associated with NPS at baseline and both follow-up visits (figure 5). Results on the prediction models of

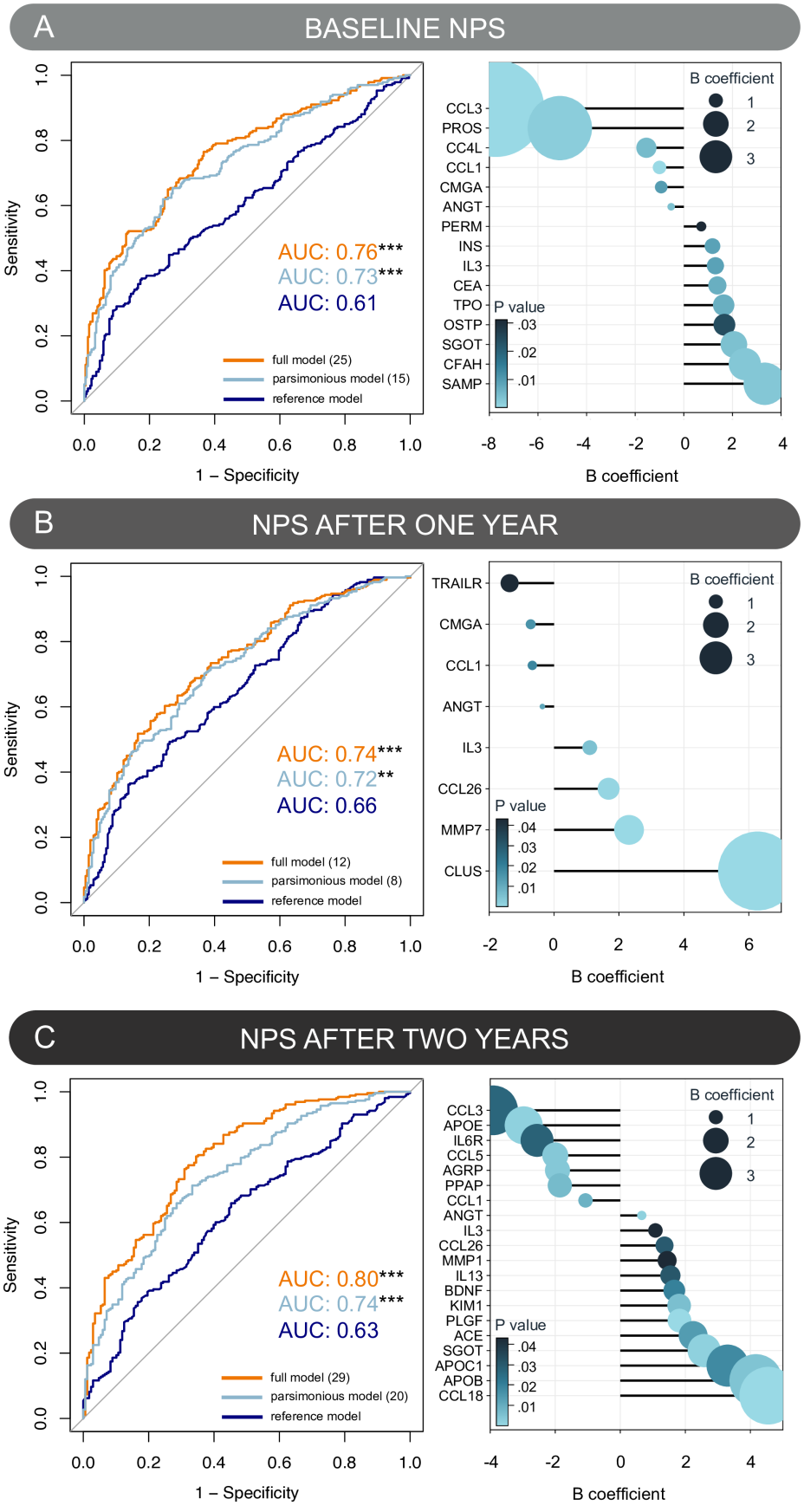

Figure 2 Prediction of overall NPS at baseline (A) and follow-up visits after 1 year (B) and after 2 years (C). On the left side ROC curves indicating the AUC of the three different predictive models are shown. In brackets, the number of included proteins is shown. On the right side, the correlation dot plot is shown including all cross-validated proteins from the parsimonious model with their beta coefficients. The size of each dot corresponds to the B coefficient of the single protein. **p<0.01, ***p<0.001. AUC, area under the curve; NPS, neuropsychiatric symptoms; ROC, receiver operating characteristics.

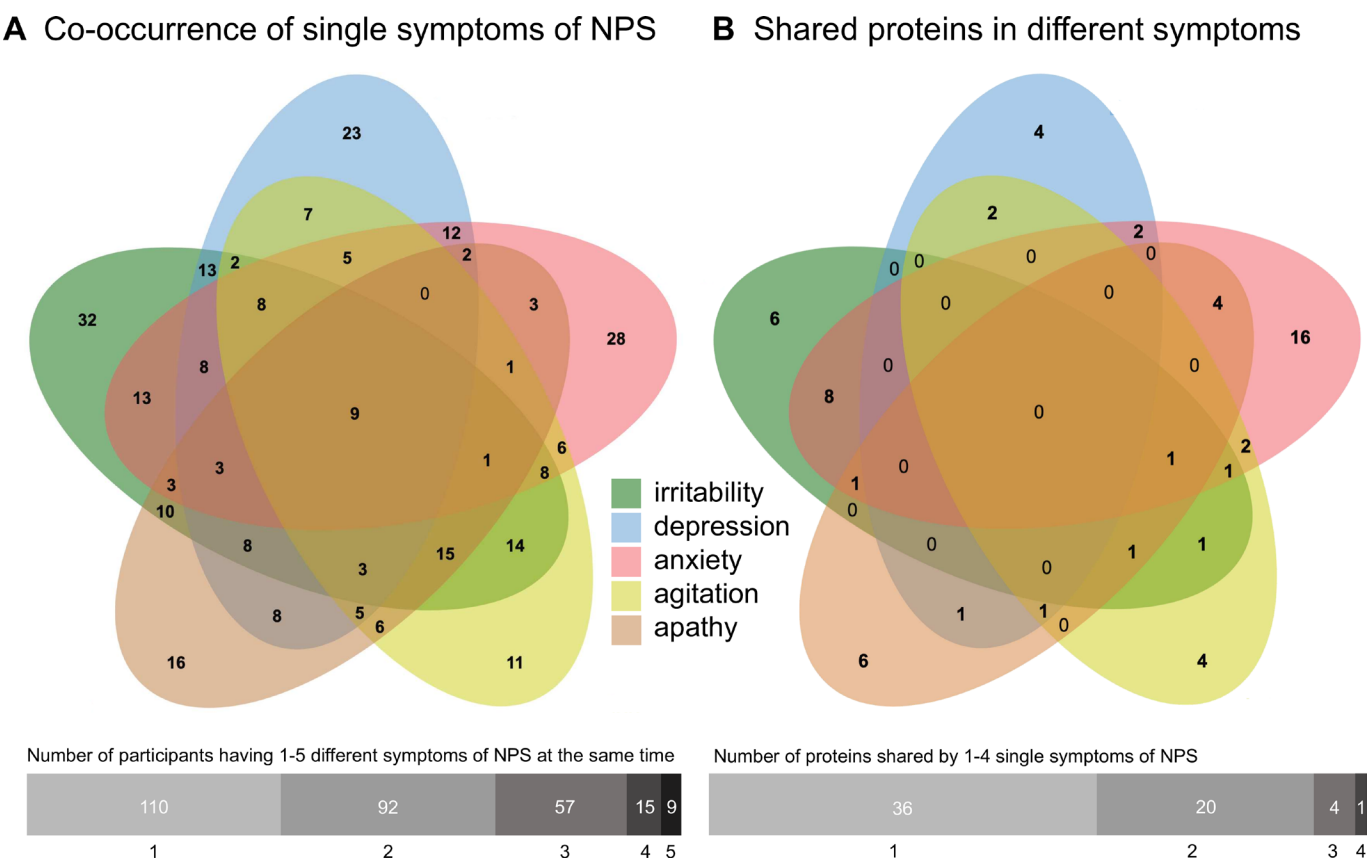

Figure 3 (A) Venn diagram with the number of patients having 1–5 of the most common symptoms (irritability, depression, anxiety, agitation, apathy) at baseline. (B) Venn diagram with the number of associated and shared proteins between single symptoms. NPS, neuropsychiatric symptoms.

NPS severity change and worsening of NPS are shown in online supplemental tables S11–S14.

Prediction of cognitive decline

We found a significant association between the presence of NPS at baseline and cognitive decline after 1 year (68% of the individuals experiencing NPS vs 57% of those without NPS; χ^2 (1, n=487)=5.79, p=0.019) and after 2 years (70% vs 54%, χ^2 (1, n=423)=10.60, p=0.001). From the 15 proteins associated with baseline, 3 were also associated with cognitive decline after 1 year (lower complement factor H (CFAH) (U=27 259.5, Z=−2.84, p=0.005, r=−0.13), lower CCL1 (U=24 899.5, Z=−2.01, p=0.044, r=0.09), and lower serum glutamic oxaloacetic transaminase (SGOT) (U=24 918.0, Z=−2.00, p=0.045, r=0.09)). Only CFAH was associated with cognitive decline after 2 years (U=18 734.0, Z=−2.12, p=0.034, r=0.10).

Associations with AD pathology

CSF biomarkers were available for 64% of the participants with NPS and for 56% without NPS. CSF levels of Aβ42, pTau181 and tTau were not different between the NPS positive and NPS negative groups (online supplemental table S2). Neither the presence of amyloid pathology (OR 1.32, 95% CI 0.65 to 2.70, p=0.442) nor the classification according to ATN groups (OR 1.02, 95% CI 0.55 to 1.90; p=0.947) were associated with the presence of NPS at baseline. Out of the 15 proteins associated with NPS at baseline, only chromogranin A showed an association with all three CSF AD biomarkers, thrombopoietin and macrophage inflammatory protein-1 alpha only with Aβ42 and insulin only with pTau181 (online supplemental table S15).

Pathways related to single symptoms

Distinct enriched pathways were found for single symptoms as shown in online supplemental figure S2. The most common over-represented pathways were signal transduction, immune system and protein metabolism.

DISCUSSION

Using targeted plasma proteomics in the ADNI cohort, we identified and cross-validated a panel of proteins associated with NPS at baseline. In addition, selected proteins improved the prediction of future NPS when compared with a reference model relying on clinical parameters only. Some of these proteins additionally predicted cognitive decline. The observed associations between proteins and NPS were independent of the presence of AD pathology as indicated by CSF biomarkers. Furthermore, for overall NPS and for the most common single symptoms, the identified protein signatures indicated biological pathway alterations involving signal transduction, immune system and transport of small molecules.

While plasma proteomics has been successfully applied in AD,[12 30] very few studies have investigated proteome changes in relation to NPS.[31] Using untargeted proteomics in plasma in a different cohort, we recently reported a panel of proteins that was associated with NPS at baseline and additionally predicted future NPS.[13] To our knowledge, no study has used targeted proteomics, giving also access to lower abundant proteins such as signal proteins, to identify and evaluate biomarker candidates of NPS so far.

After cross-validation, 15 proteins remained associated with NPS. Adding these proteins to a reference model significantly

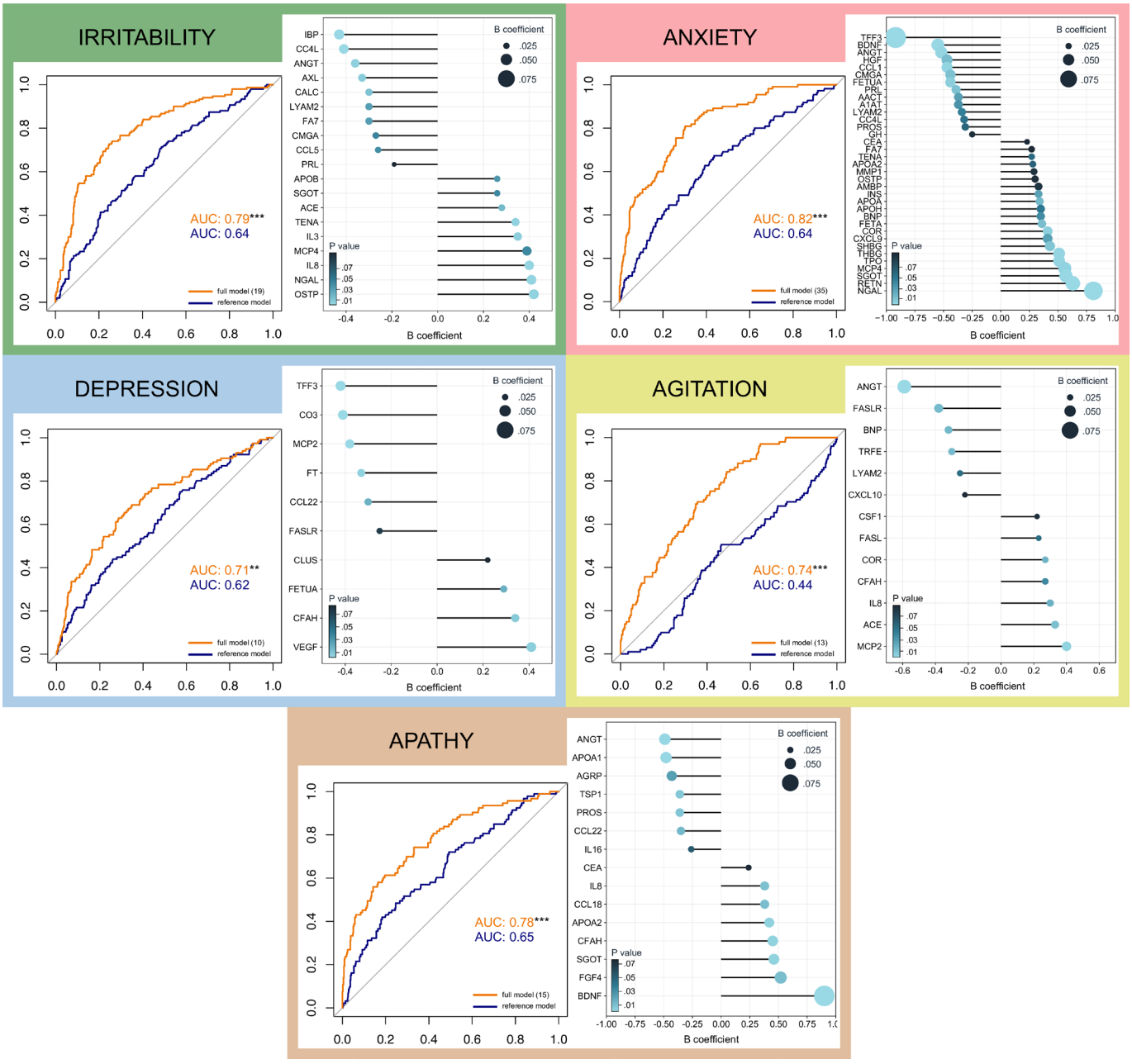

Figure 4 Data for the five most common single symptoms of NPS are displayed. On the left side, ROC curves indicating the AUC of the two different predictive models are shown. The x-axis corresponds to 1−specificity and the y-axis to sensitivity. In brackets, the number of included proteins is shown. On the right side, the correlation dot plot is shown including all proteins from the full model with their beta coefficients. The size of each dot corresponds to the B coefficient of the single protein. **p<0.01, ***p<0.001. AUC, area under the curve; NPS, neuropsychiatric symptoms; ROC, receiver operating characteristics.

improved the prediction of NPS. From the proteins, we previously identified to be associated with NPS applying untargeted proteomics in a small-sized cohort,[13] four were quantified in the present study. All four proteins, that is, CFAH, alpha-1 microglobulin, apolipoprotein H and C reactive protein, were associated with NPS in the current study (online supplemental section 3).

When addressing associations with single symptoms, we found distinct protein panels associated with irritability, depression, anxiety, agitation and apathy. The selected proteins improved the prediction of the respective symptoms when added to the reference model. These findings indicate potential utility of plasma protein biomarkers in identifying and monitoring syndrome-specific pathologies. As co-occurrence of the single symptoms was frequent, in line with previous literature,[32] future studies may investigate biomarker candidates in relation to symptom clusters.

After cross-validation, 8 and 20 proteins measured at baseline were associated with future NPS after 1 year and after 2 years, respectively. Using plasma protein biomarkers could help to identify patients at high risk for persisting or developing NPS over time, which could support personalised decision-making on monitoring and treatment of NPS.

Among the selected proteins, ANGT, CCL1 and IL3 were associated with NPS at all three time points, suggesting an important role of these proteins in persisting NPS. Proinflammatory

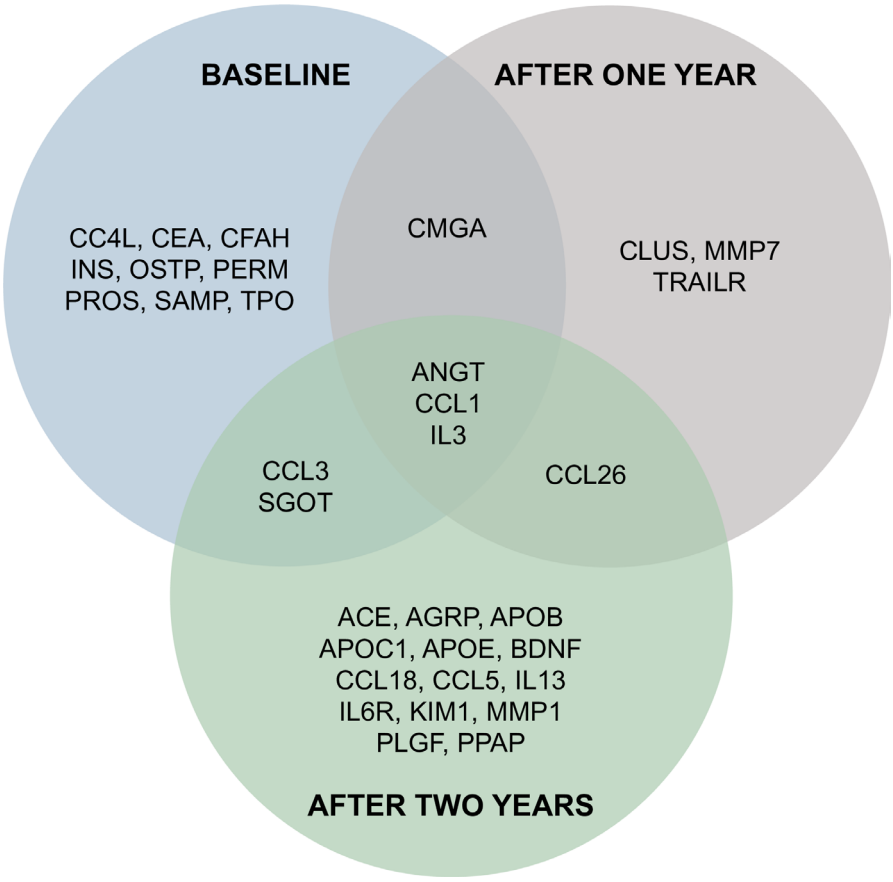

Figure 5 Proteins commonly associated with neuropsychiatric symptoms at baseline, 1 and 2 years follow-up visits.

cytokines, including CCL1 and IL3, have been linked to AD[20 33] but also to NPS before.[34 35] Also, ANGT as part of the renin–angiotensin system has been linked to symptoms like anxiety or emotional stress.[36 37] The association between elevated RAS activity and NPS was also reported to be mediated at least partly through the induction of neuroinflammation, and oxidative stress and may be further pronounced in APOE carriers.[38 39] Additional studies are needed to evaluate the potential of these novel biomarker candidates for the prediction and monitoring of persisting NPS in older people with cognitive decline.

We found CCL1, SGOT and CFAH to be associated with cognitive decline, in line with previous reports,[33 40] together suggesting that these markers may be useful to evaluate the risk of (more rapid) cognitive decline, in particular in patients with NPS.

NPSs were neither associated with amyloid pathology nor with AD pathology in the AD continuum as defined according to the ATN classification. Furthermore, the observed associations of 15 proteins with NPSs were independent of the presence of AD pathology. Among these proteins, only chromogranin A was associated with the single AD CSF biomarkers, in line with a previous report.[41] Of note, the proteomics panel used in this study included proteins previously reported to be associated with (clinically diagnosed) AD. Accordingly, and also considering the high frequency of NPS in AD, it may be expected that the observed associations with NPS are mostly associated with AD pathology. However, previous studies have not addressed the possible role of NPS in the associations of proteins with AD. Previous reports on the associations of NPS with biomarkers of AD were inconsistent.[6 7] Some studies suggested that NPS or mild behavioural impairment may represent an early manifestation of cerebral AD pathology[42] while others, in line with our findings, indicated that NPS may also relate to alterations at least in part independent from the core AD pathology.[13]

In an exploratory approach addressing pathophysiological alterations associated with NPS, we found distinct enriched pathways for the most common symptoms, involving primarily signal transduction, immune system and protein metabolism. Especially, the involvement of the immune system in NPS has been described before and consistently seems to play an important role in NPS.[4 35]

This is, to our knowledge, the first study applying targeted proteomics to identify and test biomarkers of NPS. The sample size for this study was large and allowed for a cross-validation approach. Other strengths of the study are its longitudinal and multicentric design as well as the availability of the CSF AD biomarkers in a subset of the participants. We were also able to evaluate potential biomarker candidates for the most common single NPS separately. However, evaluating associations between proteins and less frequent single symptoms was not possible. Also, we were not able to investigate the effects of concomitant use of psychotropic substances in dept as those medications were an exclusion criterion. However, psychotropic medication may have relevant effects on different clinical outcomes (ie, impact on cognition or NPS) and may lead to molecular changes.[43–45] Importantly, the targeted approach allowed for the quantification of target proteins and is a more suitable approach for the validation of biomarker candidates.[46]

We identified and cross-validated plasma protein panels as biomarker candidates for NPS and related disease progression. ANGT, CCL1 and IL3 were consistently associated with NPS at different time points while CCL1, SGOT and CFAH were also

associated with future cognitive decline. Overall, ANGT showed the most robust associations and was also related to irritability, anxiety, agitation and apathy. Together, our findings suggest that pathological alterations relevant to NPS can be detected with blood-based protein biomarkers. Using easily accessible plasma biomarkers for NPS and related clinical disease progression could open the door to new personalised treatment options in the context of cognitive decline and AD. Pending further validation, these biomarkers could be used in clinical practice not only to detect pathologies related to NPS and differentiate between the aetiology but also to monitor changes in these pathologies over time.

Collaborators 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: Michael Weiner (University of California, San Francisco Northern California Institute for Research and Education), Paul Aisen (University of Southern California), Ronald Petersen (Mayo Clinic, Rochester (co-PI of of Clinical Core)), Clifford R Jack (Mayo Clinic, Rochester), William Jagust (University of California, Berkeley), Susan Landau (University of California, Berkeley), Monica Rivera-Mindt (Fordham University; Mt. 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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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