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Associations between plasma neurofilament light, in vivo brain pathology and cognition in non-demented individuals with autosomal- dominant Alzheimer's disease

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Abstract

Background: Neurofilament light (NfL) is a promising biomarker of early neurodegeneration in Alzheimer's disease (AD). We examined whether plasma NfL was associated with *in vivo* amyloid-β and tau, and cognitive performance in non-demented Presenilin-1 (PSEN1) E280A mutation carriers.

Methods: Twenty-five mutation carriers and 19 non-carriers (age range: 28 to 49 years) were included in this study. Participants underwent 11C Pittsburgh compound B (PiB)-PET (positron emission tomography), flortaucipir–PET, blood sampling, and cognitive testing.

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Results: Mutation carriers exhibited higher plasma NfL levels than non-carriers. In carriers, higher NfL levels were related to greater regional tau burden and worse cognition, but not amyloid-β load. When adjusting for age, a proxy of disease progression, elevated plasma NfL levels were only correlated with worse memory recall.

Conclusions: Findings support an association between plasma NfL, cognition, and tau pathology in non-demented individuals at genetic risk to develop AD-dementia. Plasma NfL may be useful for selecting individuals at increased risk and tracking disease progression in AD.

Keywords

Alzheimer's disease; presenilin-1; preclinical; pathology; NfL; biomarkers

INTRODUCTION

There is an urgent need for widely available and inexpensive biomarkers of Alzheimer's disease (AD) that can be used in clinical trials to evaluate the efficacy of disease-modifying drugs. One promising candidate is neurofilament light (NfL) chain, a sensitive marker of early neuronal injury and axonal degeneration that has been shown to be elevated in preclinical AD [1–4]. We recently reported that plasma NfL levels were significantly elevated in individuals from a Colombian kindred with autosomal-dominant AD (ADAD) who are nearly certain to develop early-onset dementia [5]. Plasma NfL levels subtly started diverging between ADAD mutation carriers and non-carrier family members approximately 22 years before the kindred's estimated median age of clinical symptom onset [5]. Our data also showed that higher baseline levels of plasma NfL predicted greater cognitive decline in the preclinical stage of the disease. These findings are in line with studies from the Dominantly Inherited Alzheimer's Network (DIAN), which have reported that serum NfL levels can distinguish mutation carriers from non-carriers approximately 7 to 16 years before the expected age of clinical symptom onset [6,7]. The disparity between cohorts in the estimated time in which NfL levels begin to differentiate carriers from non-carriers may be due to sample characteristics. Specifically, the DIAN studies a heterogeneous multi-center sample composed of families with distinct mutations in different genes, whereas the Colombian kindred is a homogenous sample of individuals with a single mutation (E280A) in the Presenilin-1 (*PSEN1*) gene who share a similar clinical profile and sociocultural factors. Notwithstanding, together these studies suggest that blood-based NfL levels are sensitive to early neuronal degeneration in ADAD.

These findings are further supported by recent studies examining the relationship between blood-based NfL levels and other brain imaging markers of neurodegeneration in individuals in the preclinical stage of AD. Specifically, cross-sectional studies have reported that greater plasma NfL levels are related to increased hippocampal atrophy and cortical thinning, precuneus cortical thickness and whole-brain volume, as well as reduced metabolism in those same regions [4,6–8]. Similarly, longitudinal studies in both familial and sporadic AD have shown that higher baseline NfL concentrations in the blood are associated with greater subsequent rates of reduction in precuneus cortical thickness, faster white matter intensity changes, and greater decline in glucose metabolism and cognitive performance [6,9–11].

More recent studies have investigated the association between plasma NfL levels and markers of AD-related pathology in the cerebrospinal fluid (CSF), blood (serum and plasma), and *post-mortem* tissue. One of these studies showed that symptomatic ADAD mutation carriers with greater serum NfL levels had significantly higher total and phosphorylated tau levels in the CSF, compared to non-carriers [12]. Consistent with these findings, higher plasma NfL levels have been related to increased neurofibrillary tangle accumulation in *post-mortem* tissue of older adults with a clinical diagnosis of AD dementia, and greater severity of the disease [13]. Further, a population-based longitudinal study found that elevated plasma NfL and low plasma amyloid-β_{42} levels, individually and in combination at baseline, and not total tau, significantly predicted risk for progression to AD dementia in older adults [14]. Altogether, the few available studies have provided some insight into the utility of blood-based NfL for tracking AD progression. However, very little is known about whether plasma NfL could be useful for tracking AD pathology accumulation in the living brain (especially neurofibrillary tau burden) in non-demented individuals at high risk for AD. Understanding how plasma NfL is related to AD pathology can inform future clinical trials, assist with participant selection and track disease progression, and treatment outcomes.

In this study, we sought to test whether baseline levels of plasma NfL were associated with brain markers of cortical amyloid-β and tau pathology burden, as well as cognition, in *PSEN1* E280A cognitively-unimpaired carriers and carriers with mild cognitive impairment (MCI) from the world's largest ADAD kindred. The disease in *PSEN1* E280A carriers is estimated to progress to MCI at a median age of 44 years (95% confidence interval: 43-45) and dementia at the age of 49 (95% confidence interval: 49-50) [15,16]. Mutation carriers also have a well-characterized disease trajectory with cortical amyloid-β accumulation beginning over a decade before the onset of MCI, elevated tau burden in medial temporal lobe regions (e.g. entorhinal cortex and inferior temporal gyrus) an average of six years before the onset of MCI as measured by positron-emission tomography (PET) [17], and cortical atrophy an average of six years before clinical symptom onset [17–19]. We hypothesized that higher plasma NfL concentration would be associated with greater AD pathology burden, including mean cortical amyloid-β and tau burden in an aggregate of regions that are vulnerable to early pathology accumulation[17,20,21]. We also hypothesized that higher plasma NfL concentration would be related to worse cognitive performance in mutation carriers.

METHODS AND MATERIALS

Study design and participants

Baseline plasma NfL concentrations were characterized in 25 *PSEN1* E280A mutation carriers (19 cognitively-unimpaired mutation carriers and 6 mutation carriers with MCI), and 19 age- and education-matched non-carriers from the same kindred who are enrolled in the Massachusetts General Hospital (MGH) COLBOS (Colombia-Boston) longitudinal biomarker study. Participants were recruited from the Alzheimer's Prevention Initiative registry of familial AD, which currently includes more than 6,000 living members of the kindred and approximately 1,200 mutation carriers[22]. Those with a diagnosis of dementia or with a significant medical, psychiatric, or neurological disorder (e.g., stroke, seizures,

substance abuse, and other disorders that affect motor, visuospatial or cognitive abilities) were excluded from this study. Participants and raters were not informed of the participants' genetic test results.

The study was approved by both the institutional ethics review boards of the University of Antioquia in Medellín, Colombia and the MGH in Boston, MA. All participants provided written informed consent before participating in any procedures.

Clinical and Cognitive Assessments

Clinical assessments were performed at the University of Antioquia in Medellín, Colombia. Participants underwent a clinical interview and were administered the Mini Mental State Examination (MMSE) [23], a Spanish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list test, which has been adapted for this Colombian population [15,24], and the functional assessment staging test (FAST) [25]. In the CERAD word list delayed recall, participants were asked to recall as many words as they could remember from a previously learned list (10 items) after a 10-minute delay. Testing was conducted in Spanish by neuropsychologists or by psychologists trained in neuropsychological assessment. Neurological examinations were performed by a neurologist or by a physician trained in the assessment of neurodegenerative disorders.

Imaging acquisition and processing

All participants in this study travelled from Colombia to Boston (USA) and underwent amyloid and tau PET imaging, as well as MRI at the MGH.

11C Pittsburgh compound B and [F18] flortaucipir PET

As reported previously [17], 11C Pittsburgh compound B (PiB) PET was acquired with a 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12×15 seconds, 57×60 seconds). [F18] Flortaucipir (FTP) was acquired between 80 and 100 minutes after a 9.0 to 11.0 mCi bolus injection in 4 separate 5-minute frames.

11C PiB PET data were expressed as the distribution volume ratio (DVR) with cerebellar grey as reference tissue; regional time-activity curves were used to compute regional DVRs for each region of interest (ROI) using the Logan graphical method applied to data obtained between 40 and 60 minutes after injection [26]. 11C PiB retention was assessed using a large cortical ROI aggregate that included frontal, lateral temporal and retrosplenial cortices as described previously [27].

[F18] FTP specific binding was expressed in FreeSurfer ROIs as the standardized uptake value ratio (SUVR) to cerebellum, similar to a previous report [28]. The spatially transformed SUVR PET data was smoothed with an 8mm Gaussian kernel to account for individual anatomic differences [29]. SUVR values were represented graphically on vertices at the pial surface. A tau summary metric was calculated by averaging regional SUVRs of the entorhinal cortex, amygdala, lateral occipital cortex, and inferior temporal cortex, as previously reported [17,20,21,30]. PET data were not partial volume corrected.

Genotyping

Genomic DNA was extracted from blood by standard protocols, and *PSEN1* E280A characterization was done at the University of Antioquia using methods previously described [31]. Genomic DNA was amplified with the primers PSEN1-S 5′ AACAGCTCAGGAGAGGAATG 3′ and PSEN1-AS 5′ GATGAGACAAGTNCCNTGAA 3′. We used the restriction enzyme BsmI for restriction fragment length polymorphism analysis. Each participant was classified as a *PSEN1* E280A carrier or non-carrier. Participants and investigators were blinded to the genetic status of the individual.

Plasma NfL assay

As previously reported[32], plasma was collected in the morning (non-fasting collection). Three aliquots of 1ml were collected. Samples were stored at −80°C. For NfL analysis, one plasma aliquot was shipped on dry ice to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, Sweden. NfL concentration was measured using an in-house Single molecule array (Simoa) assay, as previously described in detail (manufacturer: Quanterix, Billerica, MA) [33]. Measurements were performed by board-certified laboratory technicians who were blinded to clinical data, genetic status, and demographic characteristic.

Statistical Analyses

We used independent samples t-tests and Chi-square to test group differences in demographic and clinical variables. We conducted a univariate analysis of variance to examine group differences in NfL and cognitive performance with age as a covariate. We used Cohen's *d* to calculate effect sizes and the Bonferroni correction to account for multiple comparisons. We then conducted linear regressions to examine the association between plasma NfL and markers of pathology, and cognition. Specifically, we tested the cross-sectional associations between plasma NfL with the following variables: mean cortical amyloid- β; tau summary measure; the MMSE; and the CERAD word list delayed recall score. Further, as age in *PSEN1* E280A mutation carriers is predictive of disease progression, we also conducted multiple regressions, with age as a covariate. Analyses used a family-wise significance threshold of $p<0.05$ and were performed using statistical software (SPSS V.24.0; SPSS Inc, Chicago, Illinois, USA).

In follow-up analyses, we carried out an exploratory whole-brain analysis examining the relationship between plasma NfL level and amyloid and tau pathology burden in all mutation carriers. Regions were $p < 0.01$ after cluster-wise correction for multiple comparisons (minimum cluster extent k=100mm2).

RESULTS

Demographic and neuropsychological data

Demographic and neuropsychological data are presented in Table 1. Mutation carriers and non-carriers did not significantly differ in age, years of formal education, or sex. Compared to non-carriers, mutation carriers performed significantly worse than non-carriers in the CERAD word list delayed recall ($F(1,41) =10.95$, p=.002, d=1.14) and the MMSE (F

(1,41)= 5.72, p=.021, d=0.90). Differences remained significant after correcting for multiple comparisons.

Plasma NfL levels in carriers and non-carriers

As expected [32], we found that mutation carriers had greater levels of plasma NfL relative to non-carriers (F(1,41)=14.73, p<.001, d=0.81) (Table 2) (Figure 1A). Higher plasma NfL levels were associated with greater age in carriers (B=0.389, p=.003, CI [0.149,0.629]), such that those who had higher NfL levels were older and, hence, closer to the median age of onset of MCI in this cohort (Figure 1B). There were no significant relationships between age and plasma NfL in non-carriers. Further, plasma NfL levels and the relationship between plasma NfL levels and age, did not significantly differ between women and men.

Association between plasma NfL levels, mean cortical Aβ, and regional tau

Amyloid-β and tau burden for each group are presented in Table 2. Consistent with what we previously reported[17], carriers had greater levels of amyloid-β (F(1,41)=69.04, p<.001, d=2.39) and tau pathology (F(1,41)=13.94, p=.001, d=1.38), compared to non-carriers. These differences remained significant after correcting for multiple comparisons.

Plasma NfL levels were not related to mean cortical amyloid-β (p=.137), even after controlling for age (p=.170) (Figure 1C). In contrast, NfL levels were significantly related to the tau summary measure (B=0.026, p=.017, CI [0.005,0.047]). This association with tau did not survive when adjusted by age (p=.966) (Figure 1D). No associations between NfL and PET markers were observed in the non-carrier group.

We also examined the relationship between plasma NfL levels and brain pathology in the whole brain within mutation carriers. Consistent with findings using the summary measures, greater plasma NfL levels were related to higher tau burden in the precuneus and temporal lobe regions, including the entorhinal cortex (Figure 2). There were no associations between NfL and amyloid-β burden in mutation carriers. We also did not find sex differences in the relationship between plasma NfL levels and pathology.

Association between plasma NfL levels and cognition

In mutation carriers, higher plasma NfL levels were related to worse CERAD word list delayed recall scores (B=−0.607, p<.001, CI [−0.820,−0.394]) (Figure 3A) and MMSE scores (B=−0.475, p=.004, CI [−0.782,−0.169]) (Figure 3B). The association between plasma NfL levels and memory performance remained significant after controlling for age (B=−0.376, p=.001, CI [−0.574, −0.178]), amyloid-β (B=−0.527, p<.001, CI [−0.726, −0.329]), and tau burden (B=−0.408, p<.001, CI [−0.571, −0.245]). Plasma NfL levels were associated with MMSE scores when adjusting for amyloid-β (B=−0.373, p=.016, CI [−0.668, −0.078]), but not for age (p=.188) or tau burden (p=.111). We then examined age, NfL levels, amyloid-β and tau burden as predictors of CERAD word list delayed and MMSE scores in the same model. We found that NfL levels and tau were significantly associated with CERAD word list delayed recall scores (F(4,20)=29.183, p<.001, R^2=.854), while tau was significantly related to MMSE scores (F(4,20)=12.520, p<.001, R^2=.715). There were

no sex differences in the relationship between plasma NfL levels and cognitive performance. Plasma NfL levels were also not associated with cognitive performance in non-carriers.

DISCUSSION

This study examined the associations between plasma NfL levels, *in vivo* amyloid-β and tau pathology burden, and cognitive performance in non-demented ADAD mutation carriers who will develop dementia with virtually 100% certainty. As we previously reported, amyloid-β begins to accumulate in the brain of *PSEN1* E280A carriers in their late 20s, 15 to 20 years before clinical onset, and regional tau pathology is evident 5 to 10 years before dementia onset [17]. Whereas PET imaging has been proven to be valuable for the early identification of AD-related pathology, blood-based biomarkers of AD have gained increasing attention given their potential diagnostic value, accessibility, and utility for tracking disease progression and monitoring treatment response. NfL, in particular, has been proposed as a promising biomarker of early neuronal injury, axonal degeneration, and synapse loss, as it has been shown to distinguish individuals at risk for AD dementia many years before clinical onset. In fact, we recently reported that plasma NfL levels began to distinguish *PSEN1* mutation carriers from non-carriers nearly 22 years before expected symptoms onset, and were strongly correlated with cognitive decline [5]. Yet, very little is known about how plasma NfL levels relate to *in vivo* AD neuropathology and cognition in individuals with ADAD who will go on to develop dementia.

Consistent with our previous report, mutation carriers had significantly greater plasma NfL levels compared to non-carriers, supporting that there might be early axonal and neural injury in preclinical AD [32]. Our results also showed that compared to age-matched non-carriers, non-demented carriers exhibited a significant relationship between higher plasma NfL levels and greater tau burden. However, plasma NfL levels were not associated with mean cortical amyloid-β burden or tau in an aggregate of regions of interest when covarying for age, a proxy of disease progression in this kindred. In contrast, we found that greater plasma NfL levels were related to worse verbal memory, even beyond the effects of age and other markers of disease progression. Contrary to what we previously reported [5], plasma NfL levels were not associated with age in non-carriers, which may be due to the limited age range in the current sample relative to the much larger dataset in our previous report with plasma NfL and cognitive data (but no PET imaging).

To date, the relationship between tau pathology and NfL in AD has only been reported in CSF, *post-mortem* tissue, and blood. Specifically, studies have found that elevated blood-based NfL levels are associated with greater CSF total and phosphorylated tau levels in symptomatic carriers of an ADAD mutation [12], and with greater neurofibrillary tangles in *post-mortem* tissue of older adults with AD dementia [13], but not plasma tau [34]. While no study to our knowledge has reported on the relationship between plasma NfL levels and PET tau in AD, one recent study [35] showed that in five of ten veterans with blast injuries who displayed high levels of tau binding also exhibited elevated plasma NfL levels. This suggests a link between plasma NfL and aggregated neurofibrillary tangles measured by [F18] FTP PET. In our study, we found that plasma NfL did not relate to tau PET burden after controlling for age, suggesting that these two markers are asynchronous and that increases in

plasma NfL are evident earlier than tau pathology measured by PET. It is also possible that plasma NfL is a good predictor of downstream tau pathology, a question that will be better addressed with longitudinal data.

While prior studies in ADAD have reported a relationship between serum NfL levels and PET amyloid-β in symptomatic mutation carriers, we did not find an association between plasma NfL and amyloid-β burden [6]. The absence of a significant association between plasma NfL levels and amyloid-β burden may be related to the fact that NfL is a marker of neurodegeneration, and amyloid-β has been found to be a weaker predictor of neurodegeneration and cognitive decline compared to tau pathology[21,36,37]. However, we must also consider that findings may have been influenced by having only a few mutation carriers in the lower end of the amyloid-β range, which in turn may have dampened the relationship between amyloid-β and plasma NfL levels. Further, our data show that plasma NfL levels are associated with memory functioning beyond the effects of age, amyloid-β and tau pathology burden. As such, our findings raise the possibility that measuring plasma NfL could be very useful for recruiting participants for clinical trials who are at risk for dementia, and for tracking treatment response to disease-modifying drugs, in the absence of tau PET imaging. That is, that plasma NfL could be an accessible and less invasive measure of neurodegeneration and cognitive decline, that may also provide information about tau pathology in the brain.

The current study has multiple strengths. First, we did not rely on presenting symptoms or cognitive data to infer whether individuals will go on to develop dementia. Instead, we examined blood-based NfL levels in a group of individuals who have a well-characterized clinical trajectory with MCI starting at a median age of 44 years and dementia at 49 years [15–17]. Studying ADAD provides a unique opportunity to study biomarkers of AD in the preclinical stage, as we can estimate how far mutation carriers are from the clinical symptom onset based on the mutation that they carry. In addition, we examined *in vivo* amyloid-β and tau pathology using PET imaging, which is considered the gold standard for quantifying and examining brain pathology in AD. Additionally, to our knowledge, this is the first study to assess how plasma NfL levels relates to the disease continuum by examining the two pathologies that characterize AD *in vivo*. Mutation carriers were also young and otherwise healthy, which minimizes potential confounding variables that are more common in advanced age and contribute to cognitive decline (e.g., cardiovascular disease). Finally, the nearly homogeneous clinical profile of mutation carriers allows us to infer how NfL levels may change as the disease progresses, supporting the utility of this blood-based biomarker for tracking disease progression.

The present study also has limitations which must be discussed. First, our sample size is relatively small compared to other studies of AD and cognitive aging, and is possible that some of the effects may be driven by the symptomatic MCI participants. However, individuals with these mutations are relatively rare and all our participants had a single mutation (*PSEN1* E280A), which makes our sample highly homogeneous compared to other cohorts, and one of the larger single mutation ADAD samples with NfL and PET imaging. Further, there is a limited range of tau accumulation in mutation carriers, as many were over 6 years away from the estimated age at which significant tau burden is observed in PET.

Future studies should consider recruiting individuals with a wider range of tau accumulation to better characterize the relationship between plasma NfL levels and tau pathology. Altogether, research with a larger sample and greater variability in pathology measured by PET is needed to better characterize the relationships between plasma NfL levels and AD-related pathology in the preclinical stage. More research is also needed to examine whether our findings in ADAD generalize to preclinical late-onset sporadic AD. Similarly, the utilization of plasma NfL as an early marker of brain pathology and risk for dementia needs to be validated in other cohorts before it is used in clinical settings, as learning about this risk may significantly impact the decisions that individuals make about their health and daily lives. We are currently conducting the first longitudinal biomarker study with this kindred, which will provide greater insight into how annual change in plasma NfL levels relates to *in vivo* pathology burden and cognitive decline over time.

Taken together, our findings suggest that higher plasma NfL is associated with, and may even be an earlier marker of, brain pathology as measured by PET and memory performance in *PSEN1* E280A mutation carriers who are still years away from their estimated age of dementia onset. These results support the potential value of plasma NfL for tracking early disease progression and monitoring treatment response in clinical trials of disease-modifying drugs for AD.

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HIGHLIGHTS

- Higher plasma neurofilament light (NfL) was related to greater in vivo tau pathology burden in preclinical Alzheimer's disease (AD).
- Plasma NfL levels did not predict amyloid beta positron emission tomography (PET) load in preclinical AD.
- Higher NfL levels related to worse memory performance beyond the effects of age
- More research is needed to assess if these findings may generalize to sporadic AD

RESEARCH IN CONTEXT

Systemic review: We reviewed the literature on neurofilament light (NfL), pathology, neurodegeneration and cognition in Alzheimer's disease (AD), using traditional sources (e.g., PubMed). Our search yielded that very little is known about whether plasma NfL predicts AD pathology burden in the living brain in individuals at high risk for AD.

Interpretation: We reported that elevated plasma NfL is an early marker of AD progression. Higher plasma NfL levels were associated with greater PET tau pathology and worse memory in non-demented Presenilin1 E280A carriers with ADAD, who will invariably develop dementia. Therefore, plasma NfL could be valuable for tracking early disease progression and monitoring treatment response in clinical trials.

Future directions: Findings set the stage for studies to investigate the relationship between plasma NfL and *in vivo* pathology in sporadic AD, as well as how change in plasma NfL levels relates to AD-related pathology burden and cognitive decline over time using longitudinal data.

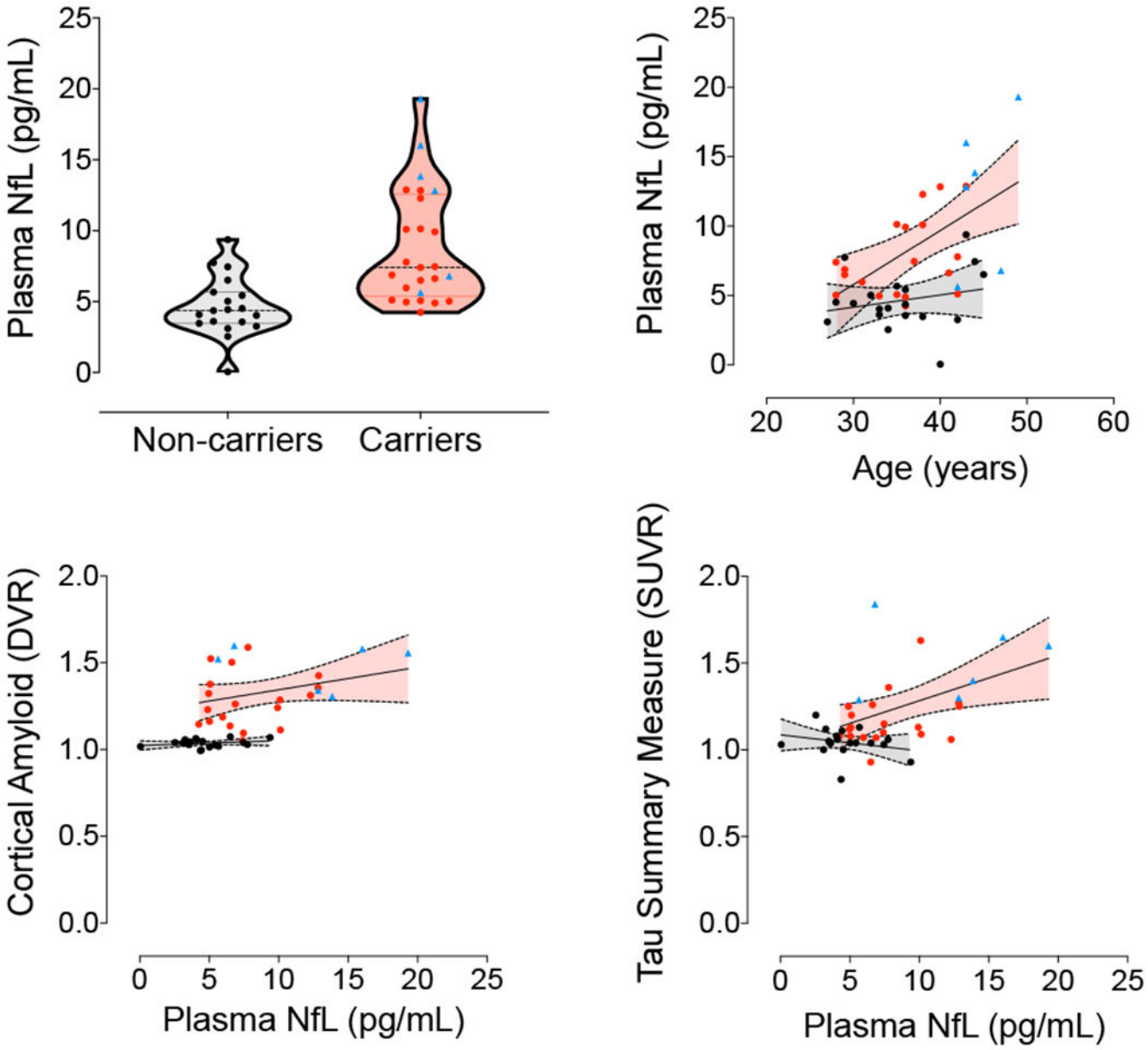

Figure 1. Plasma NfL levels and pathology in mutation carriers and non-carriers.

pg/mL = picograms per milliliter. Graph depicts the mean and standard deviation for each group. Black circles represent raw data for non-carriers, red circles represent cognitively-unimpaired carriers, and blue triangles represent carriers with MCI. Lines represent the best fit line for each group and shadowed areas the confidence intervals. (A) Mutation carriers had significantly higher levels of plasma NfL compared to non-carriers. (B) In mutation carriers only, higher plasma NfL levels were associated with higher age. (C, D) Plasma NfL levels were related to tau burden but not cortical amyloid-β without covarying for age.

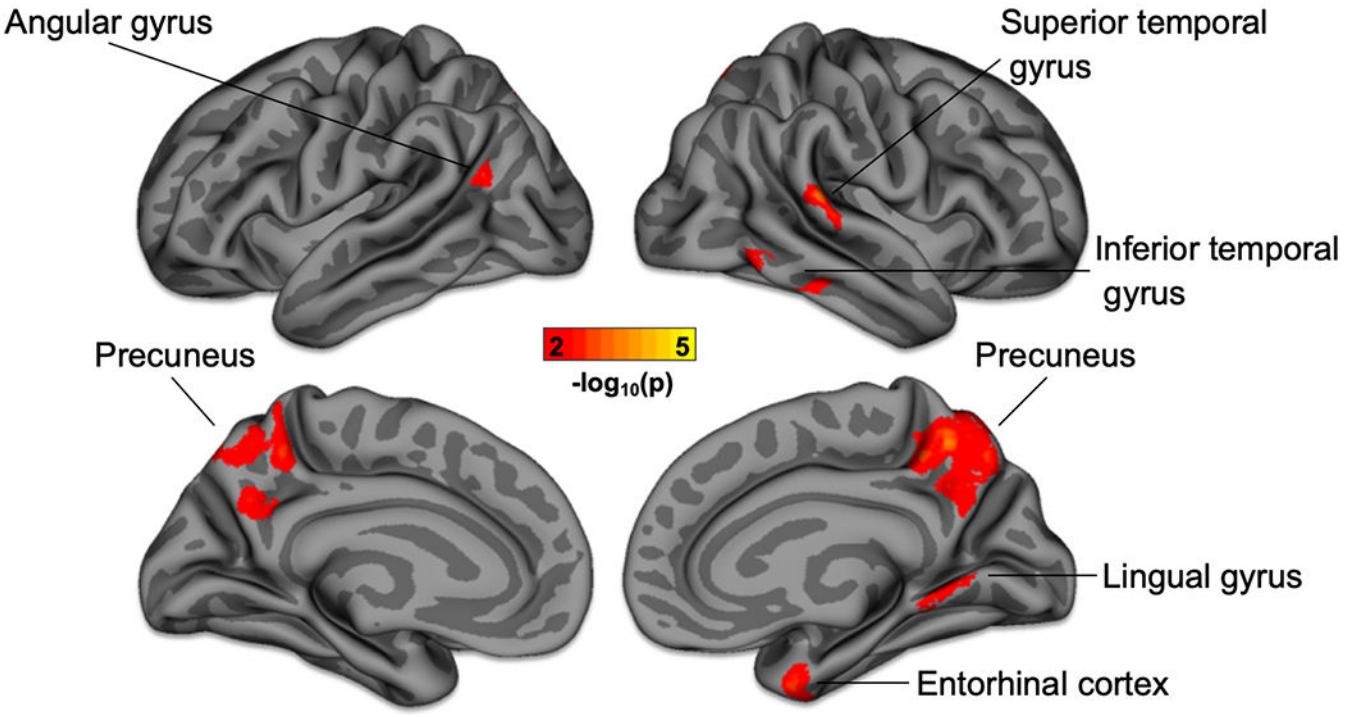

Figure 2. Whole-brain analysis of the relationship between plasma NfL levels and tau pathology.

Higher plasma NfL concentration was related to 18F FTP-binding in the precuneus and temporal regions, including the entorhinal cortex, in mutation carriers. Regions shown are $p < 0.01$ after cluster wise correction for multiple comparisons (minimum cluster extent k=100mm2).

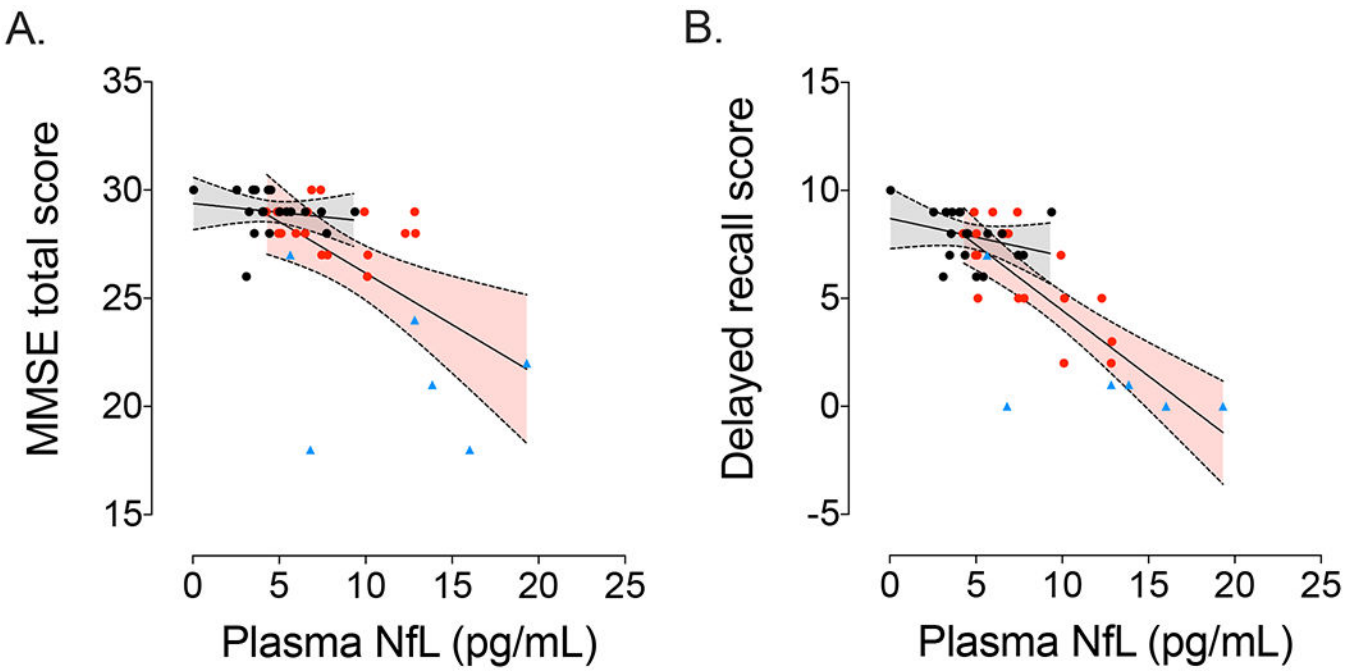

Figure 3. Plasma NfL levels and cognition in mutation carriers and non-carriers.

Black circles represent raw data for non-carriers, red circles represent cognitively-unimpaired carriers, and blue triangles represent carriers with MCI. Lines represent the best fit line for each group and shadowed areas the confidence intervals. Higher NfL levels in mutation carriers were related to lower scores on the CERAD word delayed recall and the MMSE. Only word delayed recall remained significant after adjusting for age.

Table 1.

Demographic and neuropsychological data

	Non-carriers (n=19)	Mutation Carriers (n = 25)	*p*
		M (SD)	
Age (years)	36.36 (5.18)	38.76 (5.98)	.535
Formal education (years)	11.40 (3.95)	9.25 (4.68)	.200
Sex (f/m)	8/11	15/10	.361
MMSE	29 (1)	26.72 (3.43)	.021
FAST			
Stages 1-2	19	19	
Stages >2	0	6	
CERAD delayed recall	7.89 (1.20)	5.16 (3.15)	.002

Note. M = Mean; SD = Standard Deviation; MMSE=Mini Mental State Exam; FAST=Functional Analysis Screening Tool (stages 1 and 2=cognitively normal; stages >2=symptomatic); CERAD= Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery. Differences between cognitively-unimpaired mutation carriers and non-carriers were calculated using independent samples t-test (for age and years of formal education), and univariate analysis of variance controlling for age for the other variables.

Table 2.

Measures of neurodegeneration, amyloid and tau pathology

	Non-carriers (n=19)	Mutation Carriers (n = 25)	*p*
		M (SD)	
Neurofilament Light (pg/mL)	4.65 (2.10)	8.82 (4.01)	<.001
11C PiB PET (DVR)	1.04 (0.02)	1.33 (0.17)	<.001
Tau Summary Measure (SUVR)	1.04 (0.08)	1.25 (0.20)	.001

Note. M = Mean; SD = Standard Deviation; pg/mL = picograms per millilitre; DVR = distribution volume ratio; SUVR = standardized uptake value ratio; PiB = Pittsburgh Compound B. Differences between mutation carriers and non-carriers were calculated using univariate analysis of variance controlling for age for the other variables.