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Cerebrospinal fluid β-amyloid$_{42}$ and neurofilament light relate to white matter hyperintensities

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ABSTRACT

White matter hyperintensities (WMHs) are associated with poorer brain health, but their pathophysiological substrates remain elusive. To better understand the mechanistic underpinnings of WMHs among older adults, this study examined in vivo cerebrospinal fluid biomarkers of β-amyloid$_{42}$ deposition (Aβ$_{42}$), hyperphosphorylated tau pathology, neurodegeneration (total tau), and axonal injury (neurofilament light [NFL]) in relation to log-transformed WMHs volume. Participants free of clinical stroke and dementia were drawn from the Vanderbilt Memory & Aging Project (n = 148, 72 ± 6 years). Linear regression models adjusted for age, sex, race/ethnicity, education, intracranial volume, modified Framingham Stroke Risk Profile (excluding points assigned for age), cognitive diagnosis, and *APOE*-ε4 carrier status. Aβ$_{42}$ ($\beta = -0.001$, $p = 0.007$) and NFL ($\beta = 0.0003$, $p = 0.01$) concentrations related to WMHs but neither hyperphosphorylated tau nor total tau associations with WMHs reached statistical significance (p-values > 0.21). In a combined model, NFL accounted for 3.2% of unique variance in WMHs and Aβ$_{42}$ accounted for an additional 4.3% beyond NFL, providing novel evidence of the co-occurrence of at least 2 distinct pathways for WMHs among older adults, including amyloid deposition and axonal injury.

1. Introduction

White matter hyperintensities (WMHs) are nonspecific radiographic markers of fluid accumulation that appear on T2-weighted magnetic resonance imaging (MRI). Prevalent among community-dwelling older adults (Garde et al., 2000; Ylikoski et al., 1995), WMHs relate to an increased incidence of clinical dementia (Benedictus et al., 2015; Debette et al., 2010; Provenzano et al., 2013) and stroke (Debette et al., 2010). Cerebral small vessel disease is traditionally the most common etiology attributed to WMHs in older adults (Provenzano et al., 2013), but emerging evidence suggests multiple pathological pathways are likely (Gouw et al., 2011; Lee et al., 2016). Among older adults with prodromal and clinical Alzheimer's disease (AD), increased WMHs relate to in vivo amyloid aggregation as measured by positron emission tomography (Grimmer et al., 2012; Kandel et al., 2016; Marnane et al., 2016; Provenzano et al., 2013) and cerebrospinal fluid (CSF) β-amyloid$_{42}$ (Aβ$_{42}$) (Marnane et al., 2016). Increased WMHs are found in autosomal-dominant AD before the onset of clinical symptoms, suggesting a link between WMHs and AD pathophysiology (Lee et al., 2016). Increased tau aggregation has also been linked to WMHs (Hertze et al., 2013; Marnane et al., 2016; Tosto et al., 2015), albeit less consistently than amyloid aggregation (Kester et al., 2014; van Westen et al., 2016). Collectively, these data suggest there may be an AD-specific pathway contributing to WMHs among older adults.

CSF biomarkers have become increasingly recognized for their diagnostic and prognostic utility in the study of AD and related dementia (Olsson et al., 2016). CSF comes in direct contact with the extracellular compartment of the brain. Therefore, analysis of CSF

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can provide in vivo information about biochemical changes associated with pathophysiological processes and may enhance insight into the neural correlates of WMHs. $A\beta_{42}$ and hyperphosphorylated tau (p-tau) are well-established CSF biomarkers associated with AD while total tau (t-tau) is a well-established CSF biomarker of neurodegeneration (Blennow et al., 2010). Neurofilament light (NFL) is a nondisease-specific CSF biomarker for large-caliber axonal injury (Skillback et al., 2014). Fig. 1 provides an illustration of the pathophysiology of AD and neuronal injury associated with changes in concentrations for each of these 4 CSF biomarkers of interest (Aβ42, p-tau, t-tau, and NFL). Despite emerging evidence that reduced CSF $A\beta_{42}$ (Kester et al., 2014; Marnane et al., 2016) and increased CSF NFL (Bjerke et al., 2014; Jonsson et al., 2010) may correlate with higher WMHs volume among older adults, it is unknown whether the variance explained by these 2 biomarkers is unique or overlapping. Furthermore, p-tau and t-tau associations with WMHs warrant further investigation given inconsistent findings to date (Kester et al., 2014).

The present study relates in vivo CSF biomarkers of AD pathophysiology ($A\beta_{42}$, p-tau), neurodegeneration (t-tau), and axonal injury (NFL) to fluid-attenuated inversion recovery (FLAIR)—assessed cerebral WMHs. We hypothesized that $A\beta_{42}$ and NFL would relate to WMHs among older adults. If WMHs reflect heterogeneous AD-specific and non—AD-specific pathophysiological substrates, then biomarkers of AD pathogenesis ($A\beta_{42}$) and non—AD-specific axonal damage (NFL) should account for separate variance in WMHs. Therefore, in secondary analyses, we hypothesized that $A\beta_{42}$ and NFL would account for unique variance in WMHs. Given the mixed literature regarding p-tau and t-tau associations with WMHs (Kester et al., 2014; Marnane et al., 2016), we hypothesized that p-tau and t-tau would have weak associations with WMHs. The novelty of our work lies in our inclusion of competitive analytical models incorporating both $A\beta_{42}$ and NFL. These models assess whether each biomarker is associated with WMHs and whether the variance in WMHs accounted for by each biomarker is overlapping or independent of the other. This approach provides a more integrated understanding of the underlying CSF biochemical changes that occur in the context of WMHs among older adults. Our research also adds to emerging evidence linking CSF NFL to brain health outcomes among participant samples enriched for prodromal AD.

2. Materials and methods

2.1. Participants

The Vanderbilt Memory & Aging Project (Jefferson et al., 2016) is a longitudinal study investigating vascular health and brain aging in a cohort enriched for mild cognitive impairment (MCI). The inclusion criteria of the cohort required participants be aged 60 years and older, speak English, have adequate auditory and visual acuity for testing, and have a reliable study partner. At enrollment, participants were excluded for MRI contraindication, history of neurological disease (e.g., dementia, multiple sclerosis), stroke, heart failure, major psychiatric illness (e.g., schizophrenia), head injury with loss of consciousness >5 minutes, and systemic or terminal illness (e.g., cancer) that could impact follow-up examination participation. Based on a detailed medical history and record review, clinical interview, and neuropsychological assessment, participants were labeled at baseline with normal cognition (NC), early MCI (Aisen et al., 2010), or MCI (Albert et al., 2011). At enrollment, participants

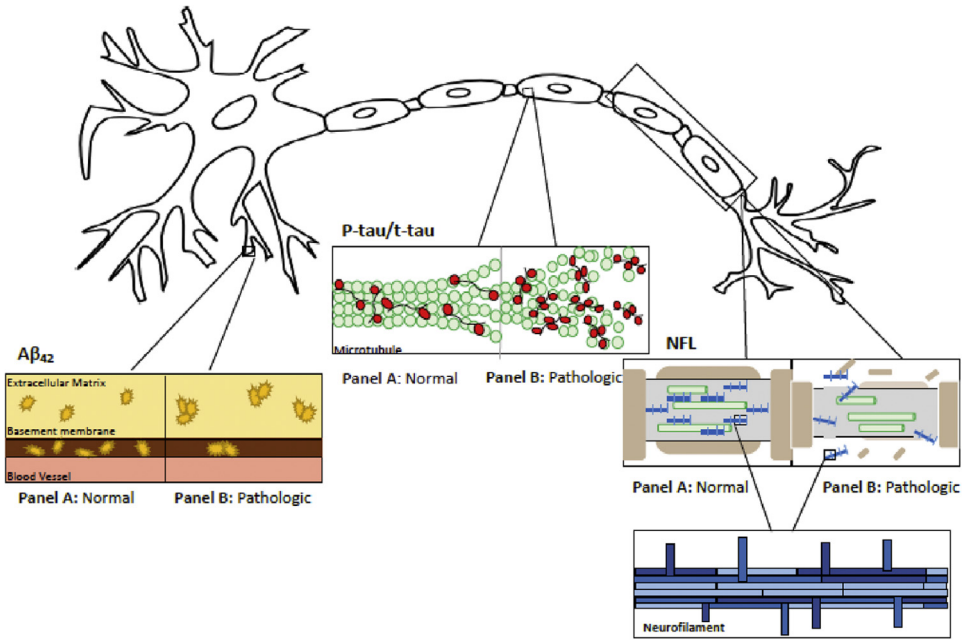

Fig. 1. Pathophysiology associated with CSF biomarkers. Depictions of pathophysiology associated with each CSF biomarker of interest: (1) $A\beta_{42}$ is a peptide made up of 42 amino acids, which results from cleavage of the amyloid precursor protein by beta and gamma secretase, forming larger peptide chains than its alpha secretase pathway. These larger peptides misfold into oligomers that form the amyloid plaques characteristic of AD. Panel A depicts effective clearance of smaller amyloid peptides through perivascular basement membranes. Panel B depicts impaired clearance of large Aβ peptides corresponding to increased amyloid deposition in the brain, resulting in Aβ oligomers in the extracellular matrix and lower concentrations of $A\beta_{42}$ in the CSF. (2) Tau is a protein found on microtubules that form the intracellular neurofibrillary tangles characteristic of AD. Higher CSF concentrations of tau occur in response to neurodegeneration. Hyperphosphorylated tau is measured by marking a specific phosphorylation site on the tau protein. Hyperphosphorylated tau measurements are more specific to Alzheimer's pathology than total tau due to the hyperphosphorylation of tau that occurs in AD. As depicted on panel A, tau may be phosphorylated in its normal state and is involved in the dynamic instability of microtubules. Panel B illustrates how tau proteins become hyperphosphorylated in AD, causing tau to prematurely detach from microtubules and disrupt the balance of assembly and disassembly of microtubules. (3) Neurofilament light is the smallest and most abundant of 3 polypeptides that form neurofilament proteins found in large-caliber, myelinated axons. As depicted in panel A, neurofilaments exist in the axon alongside microtubules, increasing the axon's diameter and conduction velocity. When axonal damage occurs as illustrated in panel B, neurofilaments spill into extracellular space and are cleared as cellular waste into the CSF. Higher CSF concentrations of neurofilament light reflect the acute occurrence of axonal injury. Abbreviation: AD, Alzheimer's disease.

completed a comprehensive evaluation over 2 or 3 days, including (but not limited to) fasting blood draw, medical history and medication review, physical examination, and multimodal brain MRI. Participation in a fasting lumbar puncture was optional. Participants were excluded from the present study if they were missing CSF, covariate, or brain MRI data (see Fig. 2 for inclusion/exclusion details). The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Written informed consent was obtained from participants before data collection.

2.2. Lumbar puncture and biochemical analyses

At baseline, participants were invited to complete an optional fasting lumbar puncture procedure. CSF was collected with polypropylene syringes using a Sprotte 25-gauge spinal needle in an intervertebral lumbar space. Samples were immediately mixed and centrifuged, and supernatants were aliquoted in 0.5 mL polypropylene tubes and stored at −80°C. Samples were analyzed in batch using commercially available enzyme-linked immunosorbent assays (Fujirebio, Ghent, Belgium) to determine the levels of $A\beta_{42}$ (INNOTEST β-AMYLOID$_{(1-42)}$), p-tau (INNOTEST PHOSPHO-TAU$_{(181P)}$), and t-tau (INNOTEST hTAU). P-tau was measured by tagging a tau phosphorylation site at amino acid Thr181. This form of phosphorylated tau appears most specific to AD and correlates with tangle pathology (Buerger et al., 2006; Seppala et al., 2012). NFL was measured using a commercially available enzyme-linked immunosorbent assay (UmanDiagnostics). Board-certified laboratory technicians processed data blinded to clinical information, as previously described (Palmqvist et al., 2014). Intra-assay coefficients of variation were <10 percent.

2.3. Brain MRI

Participants were scanned at the Vanderbilt University Institute of Imaging Science on a 3T Philips Achieva system (Best, the Netherlands) with an 8-channel SENSE receive head coil (Pruessmann et al., 1999). T1-weighted (repetition time = 8.9 ms, echo time = 4.6 ms, spatial resolution = 1 × 1 × 1 mm^3) and T2-weighted FLAIR (repetition time = 11000 ms, echo time = 121 ms, spatial resolution = 0.45 × 0.45 × 4 mm^3) images were acquired as part of the larger multimodal neuroimaging protocol. As previously published (Jefferson et al., 2016), FLAIR images were postprocessed using the Lesion Segmentation Tool toolbox for Statistical Parametric Mapping (SPM8) (Schmidt et al., 2012), excluding the cerebellum and brainstem. FLAIR images were bias-corrected for field inhomogeneities and registered to the T1-weighted images. FLAIR intensity distribution of white matter, gray matter, and CSF were assigned, enabling detection of outliers. Neighboring voxels were classified iteratively and analyzed and assigned to lesion, white matter, or gray matter until no more voxels were assigned to a lesion. Scans were individually reviewed and manually corrected for any mislabeling. Manual corrections were then confirmed by a board-certified neuroradiologist (LTD) blinded to clinical information using the Medical Image Processing, Analysis, and Visualization application (http://mipav.cit.nih.gov). Intracranial volume was calculated based on a summation of participant-specific gray matter, white matter, and CSF using T1-weighted images with SPM8.

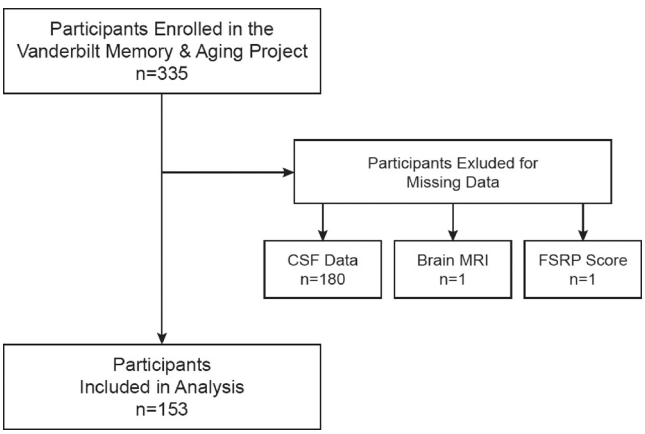

Fig. 2. Participant inclusion/exclusion details. Missing data categories are mutually exclusive. Abbreviations: CSF, cerebrospinal fluid; FSRP, Framingham Stroke Risk Profile.

2.4. Analytical plan

Systolic blood pressure was the mean of 2 measurements obtained before the echocardiogram. Diabetes mellitus was defined as current fasting blood glucose ≥126 mg/dL, hemoglobin A1C ≥6.5%, or current oral hypoglycemic or insulin medication usage. Medication review determined antihypertensive medication use. Left ventricular hypertrophy was defined on echocardiogram as left ventricle mass index >115 g/m^2 in men or >95 g/m^2 in women. Self-report atrial fibrillation was corroborated by echocardiogram, cardiac MRI, documentation of prior procedure/ablation for atrial fibrillation, or medication usage for atrial fibrillation. Current cigarette smoking (yes/no within the year before baseline examination) was ascertained by self-report. Self-report prevalent cardiovascular disease with supporting evidence from medical records included coronary heart disease, angina, or myocardial infarction (note, heart failure was an exclusion for the parent study). The Framingham Stroke Risk Profile (FSRP) score was calculated by applying points by sex for age, systolic blood pressure accounting for antihypertensive medication usage, diabetes mellitus, current cigarette smoking, left ventricular hypertrophy, prevalent cardiovascular disease, and atrial fibrillation (D'Agostino et al., 1994). We excluded points assigned for age because age was included as a separate covariate in our statistical models. *APOE* genotyping was performed on whole blood samples. Apolipoprotein E ε4 (*APOE4*) status was defined as positive (ε2/ε4, ε3/ε4, ε4/ε4) or negative (ε2/ε2, ε2/ε3, ε3/ε3). *APOE2* status was defined as positive (ε2/ε2, ε2/ε3, ε4/ε4) or negative (ε3/ε3, ε3/ε4, ε4/ε4). Intracranial volume was calculated using methods described above in the Section 2.3. WMHs (cm^3) were log-transformed before analyses.

Unadjusted Spearman rank correlations among CSF biomarkers were assessed. For hypothesis testing, linear regression models with ordinary least square estimates related each CSF biomarker ($A\beta_{42}$, p-tau, t-tau, and NFL) to log WMHs. Models were adjusted for age, sex, race/ethnicity, education, intracranial volume, cognitive diagnosis, and *APOE4*. Given extensive literature suggesting vascular risk factors increase the risk of WMHs (Fazekas et al., 1988; Lazarus et al., 2005) and clinical AD (Borenstein et al., 2005; Kivipelto et al., 2005), models were also adjusted for adverse vascular risk using a modified version (excluding points assigned for age) of the FSRP (D'Agostino et al., 1994) to avoid arbitrarily detecting a connection between $A\beta_{42}$ and WMHs that might be due to shared vascular risk factors. A post hoc linear regression model related those CSF biomarkers with significant associations to WMHs as competing predictors using identical covariates as the primary models. This competitive model approach assessed the extent to which the variance accounted for by an individual biomarker was unique or overlapping with another biomarker. Competitive models were repeated including all remaining CSF biomarkers as additional covariates in separate models. Post hoc linear regression models related an $A\beta_{42}$ × NFL interaction term to WMHs. $A\beta_{42}$ interaction terms were also separately run for age, *APOE4* allele status (dichotomized by presence of at least one ε4 allele), *APOE2* allele status (dichotomized by the presence of at least

one ε2 allele), and cognitive diagnosis (NC, MCI) on WMHs. Each model with $A\beta_{42}$ as the predictor was repeated including NFL, NFL + p-tau, and NFL + t-tau as covariates in separate models. All models were then repeated stratified by cognitive diagnosis (NC, MCI). Significance was set a priori at $p < 0.05$. Analyses were conducted using R 3.1.2 (www.r-project.org).

3. Results

3.1. Participant and CSF biomarker characteristics

Participants included 148 adults aged 60–90 years (72 ± 6 years), 68% were men, and 93% self-identified as non-Hispanic white. $A\beta_{42}$ levels correlated with p-tau ($r = -0.22$, $p < 0.01$) and t-tau levels ($r = -0.27$, $p < 0.001$). P-tau and t-tau levels correlated ($r = 0.98$, $p < 0.001$). NFL levels correlated with p-tau ($r = 0.51$, $p < 0.001$) and t-tau ($r = 0.57$, $p < 0.001$) levels. NFL was not associated with $A\beta_{42}$ ($r = -0.06$, $p = 0.49$). Participant and biomarker characteristics are presented in Table 1.

3.2. CSF biomarkers as individual and interactive predictors of WMHs

In linear regression models, $A\beta_{42}$ ($p = 0.007$) and NFL ($p = 0.01$) concentrations related to WMHs. $A\beta_{42}$ did not interact with NFL on WMHs ($p = 0.36$; see Table 2 for effect sizes and Fig. 3A and B for illustrations). Neither p-tau nor t-tau concentrations were significantly related to WMHs (p-values>0.34; see Supplemental Fig. 1A and B for illustrations).

$A\beta_{42}$ interacted with cognitive diagnosis on WMHs ($p = 0.03$), a finding that persisted when NFL was added as a covariate ($p = 0.009$). Stratified analyses revealed $A\beta_{42}$ related to WMHs only in the NC participants (NC $p = 0.0007$; MCI $p = 0.49$), which also persisted when NFL was added as a covariate (NC $p = 0.0004$; MCI $p = 0.38$). $A\beta_{42}$ did not interact with age ($p = 0.71$), APOE4 allele status ($p = 0.65$), or APOE2 allele status ($p = 0.10$) on WMHs. These interaction models remained null when NFL was added as a covariate (all p-values > 0.06). NFL did not interact with cognitive diagnosis ($p = 0.62$), age ($p = 0.995$), APOE4 allele status ($p = 0.87$), or APOE2 allele status ($p = 0.43$) on WMHs. Results were similar when including p-tau or t-tau as an additional covariate (see Table 3 for details).

3.3. CSF biomarkers as competing predictors of WMHs

In a combined model including the 2 CSF biomarkers with associations with WMHs (i.e., $A\beta_{42}$ and NFL), both $A\beta_{42}$ ($\beta = -0.001$, $p = 0.004$) and NFL ($\beta = 0.0003$, $p = 0.008$) related to WMHs. Beta values for $A\beta_{42}$ ($\beta = -0.001$, $p = 0.007$) and NFL ($\beta = 0.0003$, $p = 0.01$) in individual models were unchanged when both biomarkers were included in a single model. Covariates accounted for 28.5% of

Table 1
Participant characteristics

Demographics and health characteristics	Total sample	Cognitively normal	Early MCI[a]	MCI	p-value
Sample size, n	148	77	15	56	–
Age, years	72 ± 6	72 ± 7	73 ± 6	73 ± 6	0.73
Sex, % male	68	71	80	61	0.25
Race, % white non-Hispanic	93	94	93	91	0.86
Education, years	16 ± 3	17 ± 2	16 ± 3	15 ± 3	0.002[b]
Montreal Cognitive Assessment, total	26 ± 3	27 ± 2	26 ± 2	24 ± 3	<0.001[b,c,d]
APOE4, % carriers	33	29	13	45	0.03
APOE, % *genotype*					0.19
ε2/ε2	1	1	0	0	–
ε2/ε3	8	9	7	7	–
ε2/ε4	2	1	0	4	–
ε3/ε3	58	61	80	48	–
ε3/ε4	22	23	0	25	–
ε4/ε4	9	4	13	16	–
Framingham Stroke Risk Profile, total[e]	12 ± 4	11 ± 4	13 ± 3	12 ± 4	0.14
Systolic blood pressure, mmHg	142 ± 17	139 ± 15	148 ± 15	145 ± 18	0.04[b,c]
Antihypertensive medication usage, %	46	48	40	45	0.82
Diabetes, %	18	13	27	21	0.28
Cigarette smoking current, %	1	0	7	2	0.12
Prevalent cardiovascular disease, %	3	4	0	2	0.60
Atrial fibrillation, %	3	5	0	0	0.15
Left ventricular hypertrophy, %	3	1	7	5	0.34
CSF biomarkers					
$A\beta_{42}$, pg/mL	718 ± 244	767 ± 225	817 ± 282	624 ± 232	<0.001[b,d]
Amyloid positive (≤530), %	28	18	20	45	0.005[b]
T-tau, pg/mL	432 ± 228	379 ± 175	429 ± 125	504 ± 290	0.02[b]
T-tau positive (≥400), %	44	31	60	57	0.005[b]
P-tau, pg/mL	62 ± 26	57 ± 22	63 ± 17	68 ± 31	0.08
P-tau positive (≥80), %	22	18	13	30	0.17
Neurofilament light[f], pg/mL	1068 ± 581	931 ± 451	1088 ± 465	1250 ± 712	0.002[b]
Neuroimaging characteristics					
Intracranial volume, cm^3	1410 ± 130	1414 ± 138	1449 ± 91	1394 ± 126	0.33
Raw WMHs, cm^3	15 ± 19	14 ± 20	8 ± 5	18 ± 20	0.053[b]
Log-transformed WMHs	2.29 ± 0.93	2.16 ± 0.97	2.07 ± 0.58	2.52 ± 0.91	0.053[b]

Values are denoted as mean ± standard deviation or frequency.
Key: $A\beta_{42}$, amyloid-β_{42}; *APOE4*, apolipoprotein E ε4 allele; MCI, mild cognitive impairment; NC, normal cognition; p-tau, hyperphosphorylated tau; t-tau, total tau; WMHs, white matter hyperintensities.
[a] Participants with early MCI excluded from diagnostic interaction and diagnostic stratified analyses owing to low sample size (n = 15).
[b] For pairwise analyses at $p < 0.05$, NC differed from MCI.
[c] For pairwise analyses at $p < 0.05$, NC differed from early MCI.
[d] For pairwise analyses at $p < 0.05$, early MCI differed from MCI.
[e] A modified Framingham Stroke Risk Profile score was included in statistical models excluding points assigned to age (6.0 ± 2.6).
[f] No cut-point available.

Table 2
Main effect and interaction model results

	R^2	R^2 adjusted	[a]Δ R^2 adjusted	f^2	Partial R^2	[b]*p*-value
[c]Covariates +						
$A\beta_{42}$	0.29	0.24	0.04	0.06	0.05	0.007
T-tau	0.25	0.19	−0.006	0.007	0.007	0.34
P-tau	0.25	0.19	−0.004	0.002	0.002	0.61
NFL	0.28	0.23	0.03	0.04	0.04	0.01
$A\beta_{42}$ × NFL	0.33	0.27	0.03	0.06	0.06	0.36
$A\beta_{42}$ × age	0.29	0.23	−0.005	0.001	0.001	0.71
$A\beta_{42}$ × *APOE4*	0.29	0.23	−0.004	0.002	0.002	0.65
$A\beta_{42}$ × *APOE2*	0.31	0.26	0.02	0.03	0.03	0.10
$A\beta_{42}$ × diagnosis	0.31	0.26	0.02	0.04	0.03	0.03
Covariates + NFL +						
$A\beta_{42}$	0.32	0.27	0.04	0.06	0.06	0.004
T-tau	0.28	0.22	−0.006	0.0002	0.0002	0.87
P-tau	0.28	0.22	−0.006	0.0001	0.0001	0.89
$A\beta_{42}$ × age	0.33	0.27	−0.002	0.004	0.004	0.46
$A\beta_{42}$ × *APOE4*	0.33	0.27	−0.002	0.005	0.005	0.44
$A\beta_{42}$ × *APOE2*	0.35	0.29	0.02	0.04	0.04	0.06
$A\beta_{42}$ × diagnosis	0.36	0.29	0.03	0.05	0.05	0.01
NFL × age	0.28	0.22	−0.006	<0.0001	<0.0001	1.00
NFL × *APOE4*	0.28	0.22	−0.006	0.0002	0.0002	0.87
NFL × *APOE2*	0.29	0.23	−0.001	0.006	0.006	0.43
NFL × diagnosis	0.29	0.23	0.002	0.01	0.01	0.62
Covariates + NFL + P-tau +						
$A\beta_{42}$	0.33	0.27	0.04	0.07	0.06	0.003
T-tau	0.29	0.23	0.002	0.01	0.01	0.24
$A\beta_{42}$ × age	0.33	0.26	−0.002	0.004	0.004	0.44
$A\beta_{42}$ × *APOE4*	0.33	0.26	−0.002	0.004	0.004	0.44
$A\beta_{42}$ × *APOE2*	0.35	0.29	0.02	0.04	0.03	0.07
$A\beta_{42}$ × diagnosis	0.36	0.29	0.02	0.05	0.04	0.01
Covariates + NFL + T-tau +						
$A\beta_{42}$	0.33	0.27	0.04	0.07	0.06	0.003
$A\beta_{42}$ × age	0.33	0.26	−0.002	0.004	0.004	0.46
$A\beta_{42}$ × *APOE4*	0.33	0.26	−0.002	0.005	0.005	0.43
$A\beta_{42}$ × *APOE2*	0.35	0.29	0.02	0.04	0.04	0.10
$A\beta_{42}$ × diagnosis	0.36	0.29	0.03	0.05	0.04	0.01

All analyses were re-run excluding predictor outliers >4 standard deviations from mean (n = 3), and there were no significant changes in results.
Key: $A\beta_{42}$, amyloid-β_{42}; *APOE4*, apolipoprotein E ε4 allele; *APOE2*, apolipoprotein E ε2 allele; NFL, neurofilament light; p-tau, hyperphosphorylated tau; t-tau, total tau.
[a] Represents change in R^2 from the covariates only model.
[b] For predictor(s) after covariates entered into the model.
[c] Includes age, education, sex, race/ethnicity, intracranial volume, modified Framingham Stroke Risk Profile with points excluded for age, cognitive diagnosis, and separately for *APOE4* and *APOE2* carrier status.

the variance, including 0.5% from the modified FSRP. When $A\beta_{42}$ was added to the model containing just the covariates, it accounted for an additional 3.9% unique variance in WMHs. Adding NFL to the model containing just the covariates contributed an additional 3.2% unique variance. Adding $A\beta_{42}$ to the model already containing covariates and NFL contributed an additional 4.3% unique variance, resulting in 7.5% combined variance accounted for by $A\beta_{42}$ and NFL beyond covariates (see Table 2 for details).

4. Discussion

Among community dwelling older adults free of clinical dementia and stroke, we found lower CSF $A\beta_{42}$ and higher CSF NFL related to increased WMHs. When CSF $A\beta_{42}$ and NFL were included as dual predictors in a single model, each biomarker statistically accounted for unique variance. There was no significant Aβ42 × NFL interaction on WMHs which coupled with both biomarkers contributing unique variance as duel predictors in a single model, further supports the independence of Aβ42 and NFL. The novelty of this study lies in the use of a single, integrated analytical model to concurrently relate multiple CSF biomarkers to WMHs assessing the extent to which the variance accounted for by each biomarker is overlapping with another biomarker. Our inclusion of an older adult cohort, for which two-third of the participants were cognitively normal, also addresses a crucial gap in the literature regarding the need for more comprehensive biomarker models to predict AD and related neurodegeneration in preclinical populations. Prior work has focused primarily on the utility of NFL as an individual biomarker of disease progression in clinical cohorts (Bacioglu et al., 2016). By examining NFL in a competitive analytical model among a nondemented and predominantly cognitively normal sample, we critically extend the literature regarding the additive value of NFL as part of an integrated biomarker model in the neurobiology of aging adults. Although cross-sectional, results provide initial evidence suggesting WMHs may reflect distinct neuropathological pathways, including both amyloid aggregation and axonal injury.

Our observation that CSF $A\beta_{42}$ relates to WMHs (Marnane et al., 2016) after adjusting for common confounds, including systemic vascular risk and genetic susceptibility to AD, strengthens the hypothesis that an independent Aβ pathway contributes to WMHs. The mechanistic link between amyloid and WMHs remains elusive but may reflect impaired amyloid clearance through perivascular interstitial fluid drainage pathways (Iliff et al., 2012; Kress et al., 2014). Emerging evidence suggests that drainage systems within the basement membrane of cerebral vessels constitute important clearance pathways for amyloid. Aβ particles are prone to aggregate and cohere to membrane surfaces, causing them to become trapped alongside immune complexes, barricading the flow of interstitial fluid (Mawuenyega et al., 2010; Potter et al., 2013; Zekonyte et al., 2016). This process may result in fluid accumulation and white matter disruption appearing as WMHs on FLAIR, with co-occurring evidence of cerebral amyloid deposition (Weller et al., 2015). Fig. 1 illustrates functional and pathological versions of this neural system by which waste products, including insoluble Aβ particles, are cleared into interstitial fluid for ultimate removal through the CSF.

Another important observation from this study is that CSF NFL is associated with WMHs even after adjusting for $A\beta_{42}$ levels, suggesting an axonal injury pathway for WMHs unrelated to β-amyloid. Both CSF NFL (Jonsson et al., 2010) and WMHs (Molad et al., 2017; Wardlaw et al., 2013) have been linked to small vessel disease, suggesting small vessel disease may underlie this association. Our older adult sample was free of clinical stroke with limited prevalent cardiovascular disease, and analytical models statistically accounted for systemic vascular risk factors. Therefore, it is unlikely that small vessel disease fully accounted for the observed association reported here. The pathology underlying WMHs is not completely known and requires further research for a more comprehensive understanding. A second possibility is that the co-occurrence of axonal damage (represented by increased CSF NFL) and increased WMHs represents a heterogeneous set of underlying disease states that result in substantial damage to white matter fiber tracts. Regardless of mechanism, CSF NFL elevations correspond temporally with acute axonal injury (Bacioglu et al., 2016), so WMHs among older adults may signify an active process of white matter tissue breakdown. Given the lack of consistent findings regarding histopathological correlates of WMHs (Black et al., 2009; Shoamanesh et al., 2011), future studies should longitudinally track temporal concordance between changes in CSF NFL and WMHs. Such research could improve the understanding of whether WMHs persist following a return to baseline in CSF NFL concentrations with remission of active white matter injury processes and whether WMHs may represent some threshold of clinical importance regarding CSF NFL elevations.

Consistent with prior literature, neither t-tau (Gold et al., 2014; Kester et al., 2014) nor p-tau (Guzman et al., 2013) related to WMHs in our sample. Given that tau is largely localized in axons, the lack of association may appear counterintuitive. As a nonspecific

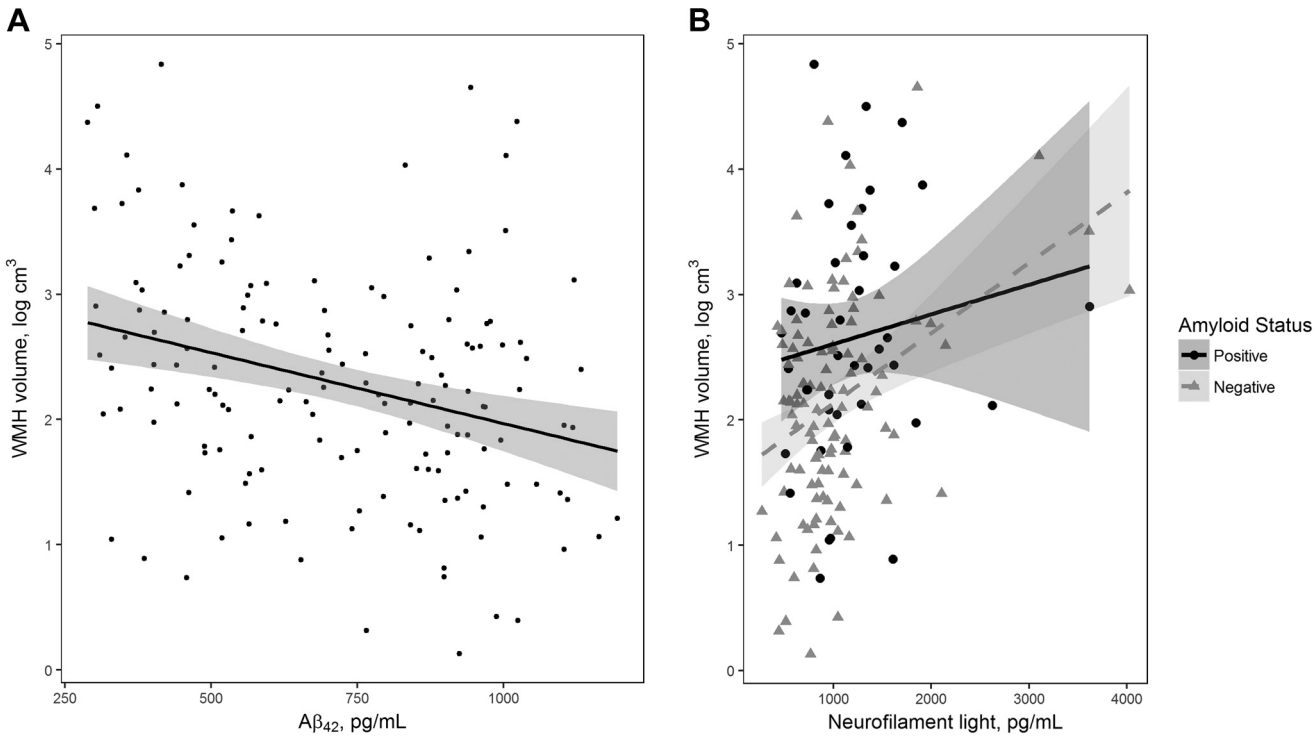

Fig. 3. CSF biomarker concentrations of amyloid-β_{42} and neurofilament light in association with white matter hyperintensities. (A) Amyloid-β_{42} and white matter hyperintensities. Solid black line reflects unadjusted values of CSF Aβ_{42} biomarker concentration (X axis) corresponding to WMH volume (Y axis) for illustration purposes only. When covarying for age, sex, race/ethnicity, education, intracranial volume, cognitive diagnosis, and APOE4, Aβ_{42} related to WMH ($\beta = -0.001$, $p = 0.007$). (B) Neurofilament light and white matter hyperintensities by amyloid status. Solid and dotted lines reflect unadjusted values of neurofilament light CSF biomarker concentrations (X axis) corresponding to WMH volume (Y axis) stratified by amyloid status for illustration purposes only. When covarying for age, sex, race/ethnicity, education, intracranial volume, cognitive diagnosis, and APOE4, neurofilament light related to WMH ($\beta = 0.0003$, $p = 0.01$) but did not interact with Aβ_{42} on WMH ($\beta < 0.00001$, $p = 0.36$). Abbreviations: Aβ_{42}, amyloid-β_{42}; WMHs, white matter hyperintensities; CSF, cerebrospinal fluid.

biomarker of neurodegeneration (Blennow et al., 2010), CSF tau elevations most likely reflect leakage of tau into the CSF following cell death (Schraen-Maschke et al., 2008). Although there are certain clinical populations in which associations between CSF tau levels and white matter disease are observed [e.g., acute ischemic stroke (De Vos et al., 2017), Creutzfeldt-Jakob disease (Cohen et al., 2016), clinical AD (Hertze et al., 2013)], such associations are likely due to the severity of the neurodegenerative processes that co-occur with WMHs in those populations. The WMHs (and co-occurring neurodegeneration) in the present cohort represent a much earlier disease process that has not resulted in substantial neurodegeneration. In contrast to tau, CSF NFL is a direct biomarker of structural axonal damage that is especially reflective of subtle injury to large-caliber, myelinated axons comprising white matter tracks (Skillback et al., 2014). Thus, it may be that NFL is more sensitive than tau to subtle changes in axonal integrity that are driven by early white matter disease. Additional longitudinal data from nondemented cohorts are needed to clarify the point at which white and gray matter changes result in CSF biomarker elevations.

Covariates in our model accounted for 28.5% of the variance in WMHs, and Aβ_{42} and NFL accounted for an additional 7.5% beyond that. Thus, the majority of the variance in WMHs in our sample is due to unknown factors. This large proportion of unexplained variance limits our ability to draw mechanistic conclusions and speaks to the heterogeneity and ambiguity of WMH substrates in older adults, representing an important area for further study. Given the cohort sample characteristics (e.g., carefully screened community-based cohort without clinical stroke or dementia, most of whom were cognitively normal with a relatively low burden of prevalent cardiovascular disease), we would not expect to see a high degree of explained variance in WMHs. We speculate findings might become more pronounced among more clinically diverse samples of individuals with poorer health characteristics and more advanced neurodegenerative disease, representing an important area of future investigation. Future research should also explore other biomarkers reflecting different pathways of interest (e.g., inflammation, extracellular matrix), which may relate to WMHs and provide further insight into the pathological processes underlying WMHs.

The present study has several strengths. First, MRI data were collected on a single research scanner using T2 FLAIR gold-standard methods for detecting WMHs. Both neuroimaging and CSF measurements were processed in core laboratories where raters were blinded to clinical information. Potential confounders were ascertained in a comprehensive manner, including key covariates that increase cerebral small vessel disease and clinical AD risk. Despite these strengths, several study limitations are noteworthy, including the cross-sectional nature of the methods, which limits drawing conclusions about potential underlying mechanisms. Other limitations include a relatively homogenous participant sample in terms of race/ethnicity and lack of direct method to quantify interstitial fluid drainage impairments.

In summary, our findings support the co-occurrence of at least 2 substrates of WMHs among older adults, including distinct amyloid and non-amyloid pathways. This observation in a dementia-free sample enriched for MCI suggests heterogeneous etiologies underlie development of WMHs before clinical manifestation of AD and related dementia. Our work highlights the importance of investigating neurodegenerative markers in integrative, competitive models rather than studying inherently connected variables in

Table 3
Model results stratified by cognitive diagnosis

	R^2	R^2 adjusted	[a]Δ R^2 adjusted	f^2	Partial R^2	[b]*p*-value
Cognitively Normal						
[c]Covariates +						
$A\beta_{42}$	0.39	0.32	0.11	0.19	0.16	0.0007
T-tau	0.28	0.20	−0.01	0.0003	0.0003	0.89
P-tau	0.28	0.20	−0.01	4.83e-05	4.83e-05	0.95
NFL	0.28	0.20	−0.009	0.004	0.004	0.61
Covariates + NFL +						
$A\beta_{42}$	0.41	0.33	0.13	0.21	0.17	0.0004
T-tau	0.28	0.19	−0.01	8.6e-06	0.8.61e-06	0.98
P-tau	0.28	0.19	−0.01	6.1e-05	6.1e-05	0.95
Covariates + NFL + P-tau +						
$A\beta_{42}$	0.41	0.32	0.13	0.21	0.17	0.0004
T-tau	0.28	0.17	−0.01	0.0005	0.0005	0.86
Covariates + NFL + T-tau +						
$A\beta_{42}$	0.41	0.32	0.13	0.21	0.17	0.0004
Mild Cognitive Impairment						
Covariates +						
$A\beta_{42}$	0.24	0.11	−0.01	0.01	0.01	0.49
T-tau	0.24	0.11	−0.007	0.01	0.01	0.43
P-tau	0.23	0.10	−0.02	0.003	0.003	0.70
NFL	0.32	0.20	0.08	0.13	0.13	0.02
Covariates + NFL +						
$A\beta_{42}$	0.33	0.20	−0.004	0.02	0.02	0.38
-tau	0.32	0.18	−0.02	0.0006	0.0006	0.87
P-tau	0.32	0.18	−0.02	0.0003	0.0003	0.91
Covariates + NFL + P-tau +						
$A\beta_{42}$	0.33	0.18	−0.004	0.02	0.02	0.38
T-tau	0.34	0.19	0.007	0.03	0.03	0.24
Covariates + NFL + T-tau +						
$A\beta_{42}$	0.33	0.18	0.0009	0.02	0.02	0.31

All analyses were re-run excluding predictor outliers >4 standard deviations from mean, and there were no significant changes in results.
Key: $A\beta_{42}$, amyloid-β_{42}; NFL, neurofilament light; p-tau, hyperphosphorylated tau; t-tau, total tau.
[a] Represents change in R^2 from the covariates only model.
[b] For predictor(s) after covariates entered into the model.
[c] Includes age, education, sex, race/ethnicity, intracranial volume, modified Framingham Stroke Risk Profile with points excluded for age, cognitive diagnosis, and *APOE4* carrier status.

an isolated "silo" approach (Jefferson, 2014). It is essential that future research investigate WMHs and emerging dynamic biomarkers to better understand the relative contributions of vascular changes or problems (including both amyloid and non-amyloid pathways), ex vacuo fluid accumulation from neurodegeneration, axonal damage and corresponding demyelination, and other factors yet to be identified in the development of WMHs. Specifically, future research should investigate possible neuropathological mechanisms underlying the link between CSF NFL and WMHs, and leverage human data to corroborate animal models suggesting impaired interstitial fluid clearance of $A\beta_{42}$ may account for the amyloid-dependent WMHs pathway we observed. Finally, future studies should employ longitudinal designs to elucidate how CSF biomarkers relate to changes in WMHs over time and in conjunction with clinical outcomes, including cognitive decline.

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