Received: 23 September 2020 | Revised: 1 February 2021 | Accepted: 8 February 2021

DOI: 10.1002/alz.12324

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

SHORT REPORT

Elevated plasma neurofilament light predicts a faster rate of cognitive decline over 5 years in participants with objectively-defined subtle cognitive decline and MCI

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*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 the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

Introduction: Neurofilament light (NFL) reflects neuroaxonal damage and is implicated in mild cognitive impairment (MCI) and Alzheimer's disease (AD). Little is known about NFL in pre-MCI stages, such as in individuals with objectively-defined subtle cognitive decline (Obj-SCD).

Methods: Two hundred ninety-four participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) underwent baseline blood draw and serial neuropsychological testing over 5 years of follow-up.

Results: Individuals with Obj-SCD and MCI showed elevated baseline plasma NFL relative to the cognitively normal (CN) group. Across the sample, elevated NFL predicted faster rate of cognitive and functional decline. Within the Obj-SCD and MCI groups, higher NFL levels predicted faster rate of decline in memory and preclinical AD composite score compared to the CN group.

Discussion: Findings demonstrate the utility of plasma NFL as a biomarker of early AD-related changes, and provide support for the use of Obj-SCD criteria in clinical research to better capture subtle cognitive changes.

KEYWORDS
Alzheimer's disease, early detection, mild cognitive impairment, neurofilament light, subtle cognitive decline

1 | INTRODUCTION

Alzheimer's disease (AD) biomarkers can assist in characterizing disease presence and severity and monitoring the effects of disease-modifying treatments. Blood-based measures have strengths including being minimally invasive, cost-effective, and feasible across settings.[1,2]

Neurofilaments (NFs), a structural component of the neural cytoskeleton, are present in dendrites and perikaryal and are especially abundant in axons.[3] Given that any pathological process resulting in neuronal death or axonal damage should lead to NF proteins being released into extracellular fluid, increased biofluid concentrations of NF proteins are not specific to one disease but rather represent a

general index of neurodegeneration.[1] NFs have subunits (heavy, medium, and light), and most research in neurodegenerative conditions has focused on the light subunit (NFL)[1]. Few studies, however, have examined the associations of NFL with neuropsychological performance[4] and it remains unknown how NFL relates to longitudinal cognitive decline.

Subtle objective cognitive changes can be captured during the preclinical phase of AD using sensitive neuropsychological measures, and these measures add prognostic value in predicting decline above and beyond traditional AD biomarkers.[5] Neuropsychological process scores quantify the number and types of errors that an individual produces on a neuropsychological test, or the approach used on a task, and are distinct from the traditionally used overall total score.[6] Process scores have been used to detect cognitive inefficiencies prior to dementia onset.[5] Our previous work using process scores to classify objectively-defined subtle cognitive decline (Obj-SCD) shows that participants with Obj-SCD have cerebrospinal fluid (CSF) and positron emission tomography (PET) AD-biomarker abnormalities intermediate between cognitively normal (CN) and mild cognitive impairment (MCI) participants,[7,8] suggesting that Obj-SCD can be detected coincident with accumulating amyloid and tau pathology. However, how Obj-SCD status relates to blood-based biomarkers including plasma NFL is unknown. Therefore, we examined whether individuals with Obj-SCD show elevated plasma NFL cross-sectionally, and whether baseline plasma NFL predicts cognitive trajectories.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional sources (PubMed, cited articles). Neurofilament light (NFL) is implicated in mild cognitive impairment (MCI) and Alzheimer's disease (AD), however, less is known about NFL in pre-MCI stages. Relevant studies have been reviewed comprehensively and appropriately cited.
2. **Interpretation**: Elevated plasma NFL is associated with a faster rate of change in cognition over 5 years in at-risk groups diagnosed with objectively-defined subtle cognitive decline (Obj-SCD) and MCI. Findings further demonstrate the utility of plasma NFL as a biomarker of early AD-related changes, and also provide support for the use of Obj-SCD criteria in clinical research to better capture subtle cognitive changes.
3. **Future Directions**: Future studies should examine the observed associations in a more representative community-based sample. Future research focused on NFL and other plasma-based biomarkers that predict cognitive decline during pre-MCI stages are important for early identification of individuals at risk as well as future drug development and will facilitate earlier and more personalized therapies.

2 | METHOD

2.1 | ADNI Data set

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. For up-to-date information, see www.adni-info.org.

2.2 | Participants

The current study included 294 participants from ADNI1.[9] Participants were included if they were free of dementia at their first study visit; had available NFL, neuropsychological, and covariate data at their baseline visit; and had serial neuropsychological data. ADNI was approved by institutional review boards at participating institutions and written informed consent was obtained.

2.3 | Cognitive groups

Jak/Bondi actuarial neuropsychological MCI criteria were applied to classify participants as CN or MCI.[10] Actuarial neuropsychological Obj-SCD criteria were then applied to participants without MCI. Participants were considered to have Obj-SCD if they performed >1 (standard deviation (SD) below the age-/education-/sex-adjusted mean on (1) one impaired total test score in two different cognitive domains (memory, language, attention/executive), *or* (2) two impaired neuropsychological process scores from Rey Auditory Verbal Learning Test, *or* (3) one impaired total test score and one impaired process score.[7,8] (Detailed descriptions of criteria are presented in supplementary materials.)

2.4 | Plasma NFL measurements

Plasma NFL was analyzed with the Single Molecule Array (Simoa) technique. All samples were measured in duplicate, except for one (due to technical reasons). Analytical sensitivity was <1.0 pg/mL. Values are presented as pg/mL.

2.5 | Neuropsychological Composite Scores

Composite scores for specific domains of memory, language, executive functioning, and visuospatial abilities were developed within ADNI.[11,12] In addition, a composite score measuring early cognitive changes in AD thought to reflect amyloid-related decline (modified

Preclinical Alzheimer's Cognitive Composite [mPACC])[13] was calculated. (Detailed descriptions of composites are presented in supplementary materials.)

2.6 | Everyday Functioning

The Functional Activities Questionnaire (FAQ), an assessment of instrumental activities of daily living (IADLs), was completed by each participant's study partner at baseline and annual follow-up visits. The partner rated each participant's difficulties in the past 4 weeks on 10 tasks (eg, paying bills) using a 4-point scale: 0 (*normal*), 1 (*has difficulty but does by self*), 2 (*requires assistance*), or 3 (*dependent*). FAQ total score was calculated as the sum of the 10 individual scores, with higher scores indicating greater difficulty.[14]

2.7 | Covariates

Apolipoprotein E (*APOE*) ε4 allele frequency (0, 1, 2) was determined. CSF markers were processed using Elecsys immunoassays; AD biomarker positivity was determined using a published CSF p-tau/amyloid beta (Aβ) ratio cut-score.[15]

2.8 | Statistical analyses

The distribution of plasma NFL was skewed, so a natural log transformation was used. An analysis of covariance (ANCOVA) examined group differences in baseline NFL adjusting for age, sex, *APOE* ε4 allele frequency, and CSF p-tau/Aβ positivity.

Multivariable linear mixed-effects (LME) modeling using full information maximum likelihood estimation was used to examine 5-year trajectories of change in cognition and IADLs as a function of baseline NFL in nested models. Longitudinal models adjusted for age, education, sex, *APOE* ε4 allele frequency, and CSF p-tau/Aβ positivity and included main effects of group (CN, Obj-SCD, or MCI), baseline NFL, and time, as well as the baseline NFL x time interaction. We then ran models adding the three-way interaction of baseline NFL x group x time as well as the two-way interactions of group x time, baseline NFL x time, and baseline NFL x group. Random intercept and slope were included.

3 | RESULTS

3.1 | Participant Characteristics

Table 1 shows characteristics by group (CN: $n = 81$, Obj-SCD: $n = 46$, MCI: $n = 167$). As expected, at baseline, across most neuropsychological measures, MCI performed worst, followed by Obj-SCD, and then CN. In addition, MCI had greater functional difficulties, although CN and Obj-SCD groups did not differ from each other. In terms of annual change, MCI showed a greater decline compared to Obj-SCD and CN groups on memory, executive function, language, and mPACC and IADLs. The Obj-SCD group showed greater annual decline in IADLs relative to the CN group.

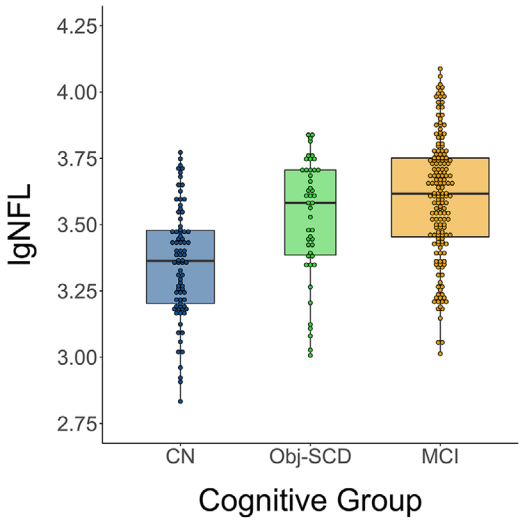

FIGURE 1 Baseline NFL by cognitive group. Dot-box plot showed predicted NFL from analysis of covariance (ANCOVA) models adjusting for age, sex, apolipoprotein E (*APOE*) ε4 allele frequency, and cerebrospinal fluid (CSF) p-tau/amyloid beta (Aβ) positivity. lgNFL = log transformed neurofilament light; CN = cognitively normal; Obj-SCD = objectively-defined subtle cognitive decline; MCI = mild cognitive impairment

3.2 | Baseline NFL

With adjusting for age, sex, *APOE* ε4 allele frequency, and CSF p-tau/Aβ positivity, there was a main effect of cognitive group on baseline NFL ($F_{2, 293} = 7.50$, $P = .001$). Pairwise comparisons showed that, relative to the CN group, the MCI group had significantly higher NFL ($P < .001$) and the Obj-SCD group had marginally significantly higher NFL ($P = .050$). Obj-SCD and MCI groups did not differ from each other ($P = .227$)(Figure 1).

3.3 | Cognitive Trajectories

With adjusting for age, sex, education, *APOE* ε4 allele frequency, and CSF p-tau/Aβ positivity, there was a significant interaction between baseline NFL and time such that elevated baseline NFL predicted faster rate of decline on memory, language, executive function, and preclinical composite scores as well as increasing functional difficulties (P's ≤ .013). The interaction between NFL and time was not significant for the visuospatial composite ($P = .997$). (See supplementary materials Table S1 and Figure S1.)

We then ran models to determine whether cognitive group moderated the NFL x time interaction. There was a significant three-way interaction between group, NFL, and time such that, relative to CN

TABLE 1 Demographic and clinical characteristics by cognitive group status

	Total Sample N = 294		CN N = 81		Obj-SCD N = 46		MCI N = 167		F or χ^2	P
Baseline characteristics	**Mean or %**	**SD**	**Mean or %**	**SD**	**Mean or %**	**SD**	**Mean or %**	**SD**		
Age	74.88	6.75	75.65	6.14	75.59	6.80	74.31	6.99	F = 1.39	.252
Education	15.78	2.89	15.88	2.79	16.22	2.72	15.61	2.99	F = 0.86	.426
Female, %	38.4%	–	45.7%	–	32.6%	–	36.5%	–	$\chi^2 = 2.71$	.258
APOE ε4 allele frequency									$\chi^2 = 22.04$	<.001
0	56.8%	–	75.3%	–	63.0%	–	46.1%	–	–	–
1	35.3%	–	21.0%	–	34.8%	–	42.5%	–	–	–
2	7.8%	–	3.7%	–	2.2%	–	11.4%	–	–	–
CSF p-tau/Aβ+, %	59.5%	–	33.3%	–	45.7%	–	76.0%	–	$\chi^2 = 45.66$[a,b]	<.001
mPACC	−4.97	4.64	−0.63	3.23	−3.22	3.22	−7.56	3.73	F = 115.52[a,b,c]	<.001
Memory	0.26	0.76	1.06	0.50	0.50	0.47	−0.20	0.54	F = 165.57[a,b,c]	<.001
Language	0.20	0.20	0.88	0.66	0.29	0.51	−0.15	0.70	F = 66.46[a,b,c]	<.001
Executive Function	0.16	0.86	0.82	0.62	0.29	0.57	−0.19	0.83	F = 51.48[a,b,c]	<.001
Visuospatial Abilities	−0.07	0.75	0.22	0.64	0.00	0.65	−0.23	0.78	F = 10.97[b,c]	<.001
FAQ	2.52	4.02	0.32	0.79	0.80	1.42	4.08	4.73	F = 35.35[b,c]	<.001
Follow-up characteristics (annual change)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
mPACC	−0.89	0.91	−0.29	0.50	−0.62	0.89	−1.26	0.89	F = 43.04[b,c]	<.001
Memory	−0.09	0.08	−0.05	0.07	−0.06	0.08	−0.11	0.08	F = 21.48[b,c]	<.001
Language	−0.10	0.08	−0.06	0.06	−0.08	0.08	−0.13	0.08	F = 23.71[b,c]	<.001
Executive Function	−0.10	0.07	−0.06	0.05	−0.08	0.05	−0.12	0.07	F = 31.10[b,c]	<.001
Visuospatial Abilities	−0.05	0.04	−0.04	0.03	−0.05	0.03	−0.06	0.04	F = 3.44	.033
FAQ	1.45	1.38	0.52	0.66	1.21	1.29	1.97	1.42	F = 38.91[a,b,c]	<.001

F statistic reported for one-way ANOVAs, χ^2 statistic report for chi-square tests.
[a]Significant differences between CN and Obj-SCD.
[b]Significant differences between CN and MCI.
[c]Significant difference between Obj-SCD and MCI.
CN = Cognitively normal; Obj-SCD = objectively-defined subtle cognitive decline; MCI = mild cognitive impairment; APOE = apolipoprotein E; CSF = cerebrospinal fluid; p-tau = phosphorylated tau; Aβ = amyloid beta; mPACC = modified Preclinical Alzheimer's Cognitive Composite; FAQ = Functional Activities Questionnaire.

participants, elevated baseline NFL predicted faster rates of decline in memory and preclinical composite scores in participants with Obj-SCD (P's < .05) and MCI (P's < .05). The memory composite and mPACC trajectories did not differ between the Obj-SCD and MCI groups. Cognitive group did not moderate the NFL x time interaction for language, executive function, or visuospatial scores or for FAQ (*P*s > 0.05) (Table 2 and Figure 2).

4 | DISCUSSION

The results extend prior work investigating biomarker associations with the Obj-SCD classification by examining associations with NFL. Findings are consistent with prior work showing elevated NFL levels in participants at risk for progression to AD, but who are not yet considered to have clinical dementia,[4,16] and expands this work to a longitudinal study of Obj-SCD. Once significant cognitive impairment has been identified, irreversible neurodegenerative changes have commonly occurred.[16] Thus biomarkers that predict cognitive decline during pre-MCI stages are important for early identification of individuals at risk as well as future drug development, and may facilitate personalized therapies.[16]

Our study is limited in generalizability beyond ADNI's mostly White, highly educated sample. Strengths include adjustment for traditional AD risk factors such as *APOE* ε4 allele frequency and CSF p-tau/Aβ that relate to cognition. Given that the effects of plasma NFL persisted after these adjustments suggests robust effects and that plasma NFL may be an independent risk factor rather than a byproduct of other risk factors. In addition, NFL has been shown to increase with age,[17] and it is worth noting that our cognitive groups did not differ in mean age.

Disruption of mechanisms of neuroplasticity, resulting in a net loss of synapses over time, is thought to be an early event in the AD

TABLE 2 Estimates for change in cognitive domain composites as a function of baseline NFL and cognitive group

	Memory			Language			Executive Function			Visuospatial Skills			Preclinical Composite			Daily Functioning		
	b	S.E.	*P*	b	S.E.	*P*	b	S.E.	*P*	B	S.E.	*P*	B	S.E.	*P*	b	S.E.	*P*
Intercept	**1.042**	**0.083**	**<.001**	**0.974**	**0.100**	**<.001**	**1.042**	**0.106**	**<.001**	**0.243**	**0.086**	**.005**	0.985	0.636	.123	−0.127	0.820	.878
Age	0.038	0.037	.307	−0.079	0.044	.072	−0.079	0.046	.085	0.034	0.036	.340	0.367	0.277	.188	−0.455	0.368	.217
Education	**0.091**	**0.036**	**.012**	**0.115**	**0.043**	**.008**	**0.135**	**0.045**	**.003**	**0.145**	**0.035**	**<.001**	**0.642**	**0.271**	**.019**	0.237	0.358	.509
Female	**0.175**	**0.073**	**.018**	−0.015	0.087	.863	0.046	0.091	.613	0.075	0.070	.288	0.805	0.550	.146	−0.302	0.726	.678
APOE ε4 allele frequency																		
0 (ref)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
1	**−0.241**	**0.084**	**.004**	−0.187	0.099	.061	0.013	0.104	.903	−0.093	0.081	.251	**−1.990**	**0.629**	**.002**	1.292	0.833	.122
2	**−0.426**	**0.143**	**.003**	−0.315	0.169	.064	0.055	0.177	.756	−0.058	0.137	.670	**−3.077**	**1.073**	**.005**	**2.933**	**1.409**	**.038**
CSF p-tau/AB	**−0.288**	**0.087**	**.001**	−0.174	0.102	.092	**−0.514**	**0.108**	**<.001**	−0.139	0.083	.095	**−3.141**	**0.649**	**<.001**	**3.484**	**0.857**	**<.001**
Cognitive group																		
CN (ref)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SCD	**−0.411**	**0.115**	**<.001**	**−0.580**	**0.140**	**<.001**	**−0.554**	**0.148**	**<.001**	−0.181	0.126	.153	**−2.886**	**0.891**	**.001**	**2.464**	**1.136**	**.031**
MCI	**−1.292**	**0.093**	**<.001**	**−1.354**	**0.113**	**<.001**	**−1.354**	**0.119**	**<.001**	**−0.566**	**0.100**	**<.001**	**−9.893**	**0.718**	**<.001**	**7.867**	**0.922**	**<.001**
Time	−0.059	0.033	.078	−0.058	0.041	.163	−0.001	0.045	.980	−0.010	0.051	.840	0.029	0.287	.919	0.665	0.413	.109
NFL	−0.040	0.073	.585	−0.010	0.089	.910	0.033	0.094	.723	0.060	0.077	.433	−0.191	0.566	.736	0.584	0.722	.419
NFL x Time	0.028	0.032	.382	−0.017	0.040	.680	−0.007	0.044	.880	0.042	0.049	.398	−0.004	0.283	.999	0.230	0.412	.578
Cognitive group x NFL																		
CN x NFL (ref)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SCD x NFL	−0.131	0.113	.247	−0.186	0.137	.178	−0.095	0.145	.519	0.021	0.127	.869	−1.511	0.873	.085	1.034	1.106	.350
MCI x NFL	**−0.242**	**0.085**	**.005**	**−0.341**	**0.103**	**.001**	**−0.283**	**0.110**	**.010**	−0.172	0.091	.059	**−2.455**	**0.659**	**<.001**	1.554	0.839	.065
Cognitive group x Time																		
CN x Time (ref)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SCD x Time	−0.003	0.056	.953	−0.036	0.070	.606	−0.097	0.077	.212	−0.017	0.087	.845	−0.731	0.482	.132	**1.777**	**0.684**	**.010**
MCI x Time	**−0.238**	**0.041**	**<.001**	**−0.301**	**0.052**	**<.001**	**−0.394**	**0.057**	**<.001**	**−0.192**	**0.063**	**.003**	**−3.322**	**0.356**	**<.001**	**4.135**	**0.509**	**<.001**
Cognitive group x NFL x Time																		
CN x NFL x Time (ref)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SCD x NFL x Time	**−0.118**	**0.057**	**.038**	−0.107	0.072	.136	0.023	0.078	.767	0.013	0.089	.881	**−1.003**	**0.481**	**.039**	0.937	0.673	.165
MCI x NFL x Time	**−0.101**	**0.040**	**.012**	−0.075	0.049	.133	−0.054	0.055	.320	−0.057	0.061	.356	**−0.825**	**0.346**	**.019**	0.867	0.500	.084

APOE = apolipoprotein E; CSF = cerebrospinal fluid; p-tau = phosphorylated tau; Aβ = amyloid beta; ref = Reference group; CN = cognitively normal; Obj-SCD = objectively-defined subtle cognitive decline; MCI = mild cognitive impairment; NFL = neurofilament light; SE. = standard error. Bold values are statistically significant ($P < .05$). Effect size (*r*-values) interpretation: small = 0.10, medium = 0.30, large = 0.50.
Continuous independent variables and covariates in the model were standardized to have a mean of 0 and standard deviation of 1.
CN status was used as the reference group for the primary analyses; secondary analysis of the model was performed with MCI as the reference group.

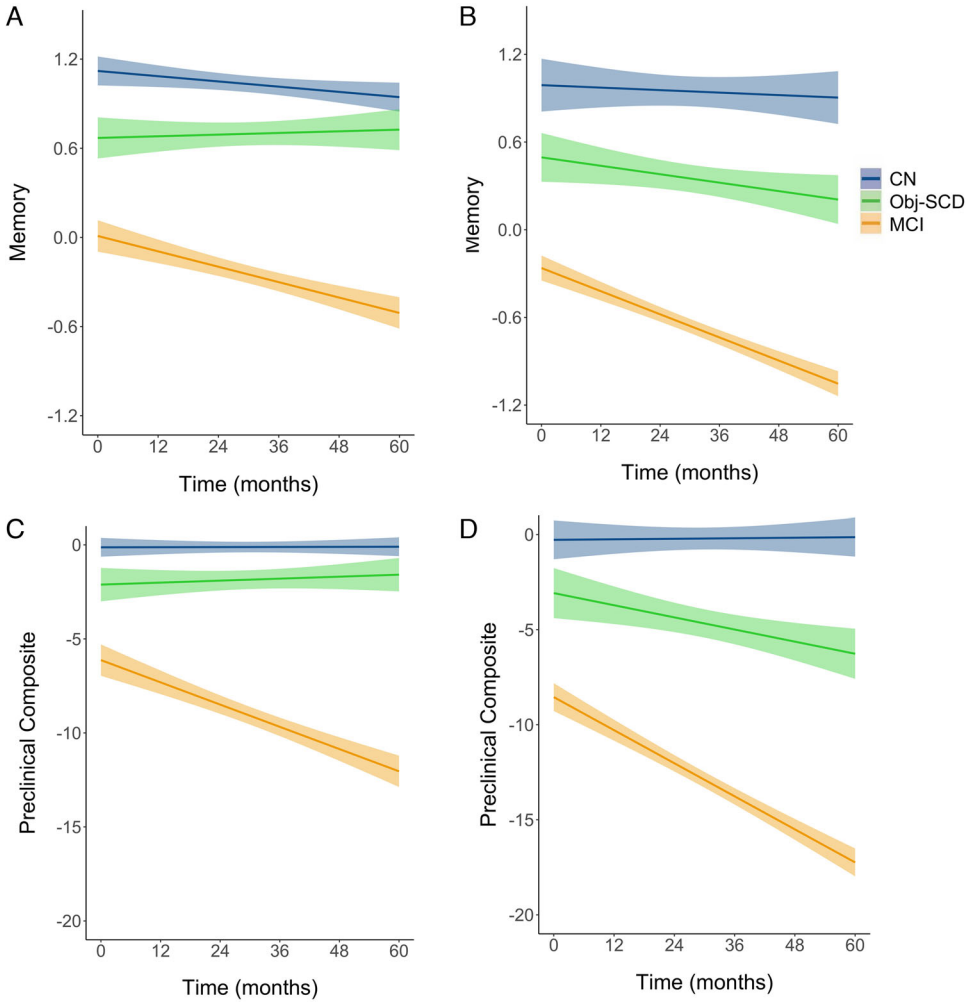

FIGURE 2 Trajectories of cognitive performance and instrumental activities of daily living (IADL) difficulties by baseline NFL and cognitive group model–predicted values of memory performance and the modified Preclinical Alzheimer's Composite (mPACC) score by cognitive group. Graphs illustrate predicted memory performance among those with (A) low baseline NFL and (B) high baseline NFL and mPACC among those with (C) low baseline NFL and (D) high baseline NFL adjusted for age, education, sex, apolipoprotein E (*APOE*) ε4 allele frequency, and p-tau/amyloid beta (Aβ) positivity. Low and high NFL were determined by a median split of the values in the analytic sample. Shaded area represents 95% confidence intervals. NFL = neurofilament light; CN = cognitively normal; Obj-SCD = objectively-defined subtle cognitive decline; MCI = mild cognitive impairment

pathophysiological process and plays a central role in dementia.[18] In the present study, we examined neurocognitive processes related to neuroplasticity (episodic memory processing), which may be more closely related to AD pathology than are CSF or plasma biomarkers. In addition, findings add to an expanding literature showing associations between Obj-SCD criteria and sensitive biomarkers, and provide support for use of these criteria in clinical research to better capture subtle cognitive changes that occur early in the preclinical stage of AD.

ACKNOWLEGEMENTS

This work was supported by the U.S. Department of Veterans Affairs Clinical Sciences Research and Development Service (Merit Award 1I01CX001842 to K.J.B. and Career Development Award-2 1IK2CX001865 to K.R.T. and 1IK2CX001415 to E.C.E.), National Institute on Aging/National Institutes of Health (NIA/NIH) grants (R01 AG063782 to K.J.B.; R01 AG049810 and R01 AG054049 to M.W.B.; R03 AG070435 to K.R.T.; and P30 AG062429), and the Alzheimer's Association (AARF-17-528918 to K.R.T., AARG-18-566254 to K.J.B., AARG-17-500358 to E.C.E.). Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (NIH Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the NIA, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company;

CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICT OF INTEREST

Dr. Bondi receives royalties from Oxford University Press and serves as a consultant for Eisai, Novartis, and Roche Pharmaceutical. The other authors report no disclosures.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Bangen KJ,Thomas KR, Weigand AJ, et al. Elevated plasma neurofilament light predicts a faster rate of cognitive decline over 5 years in participants with objectively-defined subtle cognitive decline and MCI. *Alzheimer's Dement*. 2021;1–7.
https://doi.org/10.1002/alz.12324