Neurobiology of Aging 135 (2024) 39–47

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Cerebrospinal fluid neurofilament light chain mediates age-associated lower learning and memory in healthy adults

Mathilde Suhr Hemminghyth [a,b,c,*], Luiza Jadwiga Chwiszczuk [a,d], Monica Haraldseid Breitve [a,b,d], Berglind Gísladóttir [e,f], Gøril Rolfseng Grøntvedt [g,h], Arne Nakling [c], Arvid Rongve [a,c,d], Tormod Fladby [e,i], Bjørn-Eivind Kirsebom [j,k]

[a] Department of Research and Innovation, Research Group for Age-Related Medicine, Helse Fonna, Haugesund Hospital, Haugesund, Norway
[b] Department of Neuropsychology, Helse Fonna, Haugesund Hospital, Haugesund, Norway
[c] Department of Clinical Medicine (K1), University of Bergen, Bergen, Norway
[d] Department of Age-related Medicine, Helse Fonna, Haugesund Hospital, Haugesund, Norway
[e] Department of Neurology, Akershus University Hospital, Lørenskog, Norway
[f] Clinical Molecular Biology (EpiGen), Medical Division, Akershus University Hospital and University of Oslo, Norway
[g] Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway
[h] Department of Neurology and Clinical Neurophysiology, University Hospital of Trondheim, Trondheim, Norway
[i] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[j] Department of Neurology, University Hospital of North Norway, Tromsø, Norway
[k] Department of Psychology, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

ARTICLE INFO

Keywords:
Normal aging
Cognition
Learning and memory
Total-tau
Neurofilament light chain

ABSTRACT

Multiple cognitive domains, including learning, memory, and psychomotor speed, show significant reductions with age. Likewise, several cerebrospinal fluid (CSF) neurodegenerative biomarkers, including total tau (t-tau, a marker of neuronal body injury) and neurofilament light chain (NfL, a marker of axonal injury) show age-related increases in normal aging. In the current study, we aimed to investigate whether the age-effect within different cognitive domains was mediated by age-associated CSF markers for neurodegenerative changes. We fitted 10 mediation models using structural equation modeling to investigate this in a cohort of 137 healthy adults, aged 40–80 years, from the Norwegian Dementia Disease Initiation (DDI) study. Here, t-tau and NfL were defined as mediators between age and different cognitive tests. The models showed that NfL mediated the age-effect for CERAD learning and memory recall (learning: $\beta = -0.395$, $p < 0.05$; recall: $\beta = -0.261$, $p < 0.01$). No such effect was found in the other models. Our findings suggest that the age-related lower performance in verbal learning and memory may be linked to NfL-associated neurodegenerative changes in cognitively healthy adults.

1. Introduction

Healthy adults show age-related decline within multiple cognitive domains, including learning, memory, and psychomotor speed (Eliassen et al., 2022; Espenes et al., 2020; Kirsebom et al., 2019). These changes are commonly defined as part of normal and healthy cognitive aging. Consequently, age is the main demographic adjustment included in normative reference data for most neuropsychological tests.

Despite proliferating data, the biology of aging and the nature of the cognitive changes are not properly understood. We do however know that pathological biological changes are common in aging brains that remain fully functional (Jack et al., 2017). Several of these pathological changes can be measured via different biomarkers, e.g. on MRI scans, in the blood or in the cerebrospinal fluid (CSF).

Many of these biomarkers are linked to specific diseases, where amyloid beta (Aβ) and phosphorylated tau (p-tau) reflect the hallmark pathology of amyloid plaques and neurofibrillary tangles in Alzheimer's disease (AD) (McKhann et al., 2011). On the other hand, some biomarkers, including total tau (t-tau) and neurofilament light chain (NfL), are not disease specific and are altered in several diseases. T-tau is thought to be a marker of neuronal body damage and intensity of neurodegeneration, and higher CSF t-tau is seen in many age-related

* Correspondence to: Department of Research and Innovation/Department of Neuropsychology, Helse Fonna, Haugesund Hospital, Post box 2170, N-5504 Haugesund, Norway.
E-mail addresses: mathildesh@hotmail.com, mathem@ihelse.net (M.S. Hemminghyth).

https://doi.org/10.1016/j.neurobiolaging.2023.12.005
Received 25 May 2023; Received in revised form 15 December 2023; Accepted 21 December 2023
Available online 27 December 2023

neurodegenerative diseases (Llorens et al., 2018). NfL is on the other hand linked to subcortical, large-caliber axonal degeneration and neuronal damage (Norgren et al., 2003). Higher NfL concentrations is associated with more advanced cortical atrophy, reduced white matter integrity, and increased volume of white matter lesions, often referred to as white matter hyperintensities (WMH) in radiological terms (Khalil et al., 2018; Mattsson et al., 2017; Meeker et al., 2022).

WMH is in turn largely driven by small vessels disease (SVD) (Pålhaugen et al., 2021; Stewart et al., 2021) and age, and prevalence rates for WMH are ranging from 60 to 80% in those above 65 years of age (De Leeuw et al., 2001; Longstreth et al., 1996). However, WMHs are also present in younger people, with a recent prevalence estimate of 25.9% for people under 45 years of age (Debette and Markus, 2010; Wang et al., 2019). As studies also have found WMH volume to be one of the most important predictors of higher CSF NfL concentrations (Meeker et al., 2022), these findings altogether suggests that NfL may be a marker for brain aging and small vessel brain injury, rather than neurodegeneration per se.

Further, both NfL and t-tau have been found to be associated with cognitive decline (Mattsson et al., 2016). These pathological changes also represent risk factors for progression to dementia for people with mild cognitive impairment (MCI) (Villemagne et al., 2011). Thus, both neurodegenerative markers and cognition change during aging, but we still do not know the mechanisms of these changes. As the general population grows older, there is an increasing need to understand these observed age-related changes and how to tackle these in an everyday clinical setting.

When deciding whether a set of performances are normal or impaired, we base our judgment upon normative reference data. Today most of these are adjusted according to age, but as markers of neurodegeneration both increases with age and are associated with cognitive decline, one might question whether this kind of adjustment is the most suitable one for a sensitive detection of impairment. These norms are principally based on cross-sectional data, with a very few exceptions (i.e. change norms), and we must therefore rely on the same type of data if when answering questions regarding alternative interpretations of the observed relationships. Thus, using cross-sectional data we aimed to investigate whether the age-effect within different cognitive domains could be explained by general, and AD non-specific, markers of neurodegeneration. Specifically, whether levels of either t-tau or NfL, as markers of gray and white matter degeneration respectively, mediate the relationship between age and performance on cognitive tests. We hypothesized that the cross-sectional relationship between age and cognition is partly explained by proxy CSF biomarkers of underlying age-related brain changes. This is important to study, as it has crucial implications for the use of normative reference data and for the very definition of normality in cognitive assessments. However, our study cannot answer questions regarding cognitive change and the effect of neurodegenerative markers in this process.

2. Materials and methods

2.1. Study design

This study is a part of the ongoing Norwegian multicenter study, *Dementia Disease Initiation* (DDI), which is an observational study that focuses on early detection of dementia and neurodegenerative diseases (Fladby et al., 2017). Since the study started in 2013, both people with cognitive complaints and healthy controls have been recruited from all the health regions in Norway. Inclusion criteria are age between 40–80 years and a native language of Norwegian, Swedish, or Danish. Exclusion criteria are severe brain trauma or disorders such as epilepsy, multiple sclerosis, tumors or other neurodegenerative disorders, severe psychiatric disorders, developmental disorders, or other severe somatic diseases that might influence cognition. Participants with SCD were recruited from two main sources: 1) self-referrals following advertisements in media, newspapers, and news bulletins; and 2) referrals to local memory clinics. The healthy controls (HC) were spouses or patients who completed lumbar puncture for orthopedic surgery that had no cognitive complains. In addition, some HCs volunteered following advertisement as described.

After inclusion, participants are followed up biannually and examined following a standardized protocol, which included medical history, neurological and neuropsychological examinations, brain MRI, and blood and cerebrospinal fluid (CSF) samples. The neuropsychological test battery included Consortium to Establish a Registry for Alzheimer's Disease Word List test (CERAD-WL) (Fillenbaum et al., 2008), Visual Object and Space Perception (VOSP) silhouettes (Warrington and James, 1991), Trail Making Test part A and B (TMT-B) (Reitan and Wolfson, 1985), Controlled Oral Word Association Test (COWAT-FAS) (Benton et al., 1994). Disease-stage classification, i.e. into SCD, MCI or dementia, are based on published criteria (Albert et al., 2011; Jessen et al., 2014; McKhann et al., 2011). Abnormal cognition is defined as performances 1.5 standard deviation below the normative mean ($T < 35$) on either COWAT FAS, CERAD recall, TMT B or VOSP silhouettes. Applied norms are regression based (Eliassen et al., 2022; Espenes et al., 2020; Kirsebom et al., 2019; Lorentzen et al., 2021).

2.2. CSF biomarker collection, handling, and measurement

All lumbar punctures were performed following a standardized protocol (Fladby et al., 2017). Commercial enzyme-linked immunosorbent assays (ELISAs) from Innotest (Fujirebio, Ghent, Belgium) based on monoclonal antibodies was used to determine CSF concentrations of total tau (t-tau, hTau Ag kits). The QuickPlex SQ 120 system from Meso Scale Discovery (MSD, MD, USA) was used to measure $A\beta_{1–42}$, $A\beta_{1–40}$ and NfL. $A\beta_{1–42}$ and $A\beta_{1–40}$ was measured in a multiplex setup using V-plex Aβ Peptide Panel 1 (6E10) kit (K15200E-1) and Nfl in a R-plex format using Human Neurofilament L Assay (K1517XR-2). Abnormal CSF concentrations for $A\beta42/40_{ratio}$ ($\leq$0.077) was determined using ROC analysis with visual read of [18 F]-Flutemetamol PET scans as the standard of truth (Siafarikas et al., 2021).

2.3. Participants

For the purpose of the current study, only cognitively normal participants (CN), with or without SCD, were included. All included participants had normal concentrations of CSF $A\beta42/40_{ratio}$ at baseline and remained CN at follow-up (*mean* years=3.96, *SD*=1.71). This was done to rule out prodromal dementia symptoms and to ensure that we studied healthy individuals. All together the sample consisted of n = 137 participants whereof 50 HCs and 87 SCD. Please see supplementary materials for further details on the sample.

2.4. Statistical analyses

All statistical analyses were performed in R Studio version 4.1.2. Firstly, we performed between-group comparisons of test performances and demographic characteristics in HCs and SCDs. We chose to use demographically adjusted standardized scores, i.e. T-scores, for the group comparisons as these scores are the ones used to classify participants as either CN or MCI. We used independent samples t-test for the normally distributed data, Pearson's Chi-squared test for categorical data and Mann-Whitney U tests for the non-normal data. NfL and t-tau group differences were examined using linear regression with log transformed variables and controlling for age. Their association was examined with Pearson correlation.

Then, we fitted mediation models using structural equation modeling (SEM) with maximum likelihood (ML) estimation using the lavaan package. HCs and SCDs were merged together in the SEM analyses. CSF NfL or t-tau were defined as mediators between age and CERAD learning, CERAD recall, TMT-A, TMT-B and VOSP. Together

making up a total of 10 different models. COWAT-FAS was not included in the analyses as age does not significantly influence performance (Egeland et al., 2006; Lorentzen et al., 2021). Raw scores for all the cognitive tests were used in the SEM analyses.

Model fit data was examined using the chi-square test (χ^2), Comparative Fit Index (CFI), Tucker-Lewis Fit Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR). Standard cut-off values for the different indices were applied: CFI and TLI > 0.95; RMSEA < 0.06; and SRMR < 0.08 (Hu and Bentler, 1999). Standard errors and p-values were calculated using bootstrapping with 1000 resampling iterations. The path diagrams were constructed using an open source web application (Mai et al., 2022).

3. Results

3.1. Clinical and demographic characteristics and between-group comparisons

The demographic and clinical characteristics of our cohort are summarized in Table 1. As seen here, there were no between-group differences between the HC and SCD group concerning most demographic and clinical characteristics. However, we observed a slight, albeit significant group difference concerning the MMSE score, where the HC group had slightly better scores ($p = .04$), even though both the group medians and IQRs were the same (30 and 1 respectively). In addition, the HC group had CERAD learning T-scores 0.48 SD above the expected normative mean, whereas the SCD group had T-scores near the expected norm (0.13 SD above), resulting in a 0.25 SD mean difference between the groups ($p = .02$). Importantly, no between-group differences in neither CSF t-tau or NfL concentrations were observed (both n.s.), and they showed a moderate correlation with each other (r = 0.356, p = .000). Furthermore, 40 subjects (29%) showed elevated NfL levels (cut off >2875) and 19 subjects (13%) showed elevated t-tau levels (cut off >378). Taken together these results indicate that the two groups were quite similar. Given the small size of the observed differences, merging the two groups for the SEM analyses was deemed adequate.

3.2. NfL as mediator between age and cognition

All models had good fit (χ^2(df=0) = 0.0; CFI= 1.0; TLI= 1.0, RMSEA= 0.0; SRMR= 0.0). Inclusion of sex and education as covariates did not improve the model (i.e. the fit indices were poor) and was thus left out. Hence, even though both age and sex are theoretically meaningful they did not improve the model prediction sufficiently to be included.

3.2.1. Age and CERAD learning via NfL

As seen in Fig. 1, age was positively related to NfL ($\beta = 0.565$, boot SE = 0.072, $p < 0.001$), which in turn was negatively related to CERAD learning ($\beta = -0.699$, boot SE = 0.307, $p < 0.05$). The direct effect from age to CERAD learning was in the expected direction but non-significant when NfL was included in the model ($\beta = -0.378$, boot SE = 0.302, $p > 0.05$). The indirect effect via NfL was significant and in the same

Table 1
Demographic and Clinical Characteristics.

	Total	HC	SCD	Group comparison HC - SCD
N (% of total)	137 (100)	50 (36.5)	87 (63.5)	
Age in years mean (SD) [range]	59.7	58.6	60.3	P = 0.25[a]
missings	(8.54) [41,78]	(8.54) [41,77]	(8.53) [41,78]	
	0	*0*	*0*	
Female (%)	72 (52.6)	32 (64.0)	40 (46.0)	P = 0.06[b]
Missings	*0*	*0*	*0*	
Education in years mean (SD) [range]	14.1	14.5	13.8	P = 0.20[a]
missings	(2.76) [8,21]	(2.61) [10,21]	(2.83) [8,21]	
	0	*0*	*0*	
MMSE score median (IQR) [range]	30	30	30	**P = 0.02**[c]
missings	(1) [24,30]	(1) [25,30]	(1) [24,30]	
	0	*0*	*0*	
CERAD learning T-score mean (SD) [range]	51.3	53.8	49.8	**P = 0.03**[a]
missings	(9.93) [29,73]	(9.47) [32,72]	(9.95) [29,73]	
	2	*1*	*1*	
CERAD recall T-score mean (SD) [range]	51.3	53.2	50.2	P = 0.06[a]
missings	(8.78) [36,71]	(8.56) [36,69]	(8.77) [36,71]	
	0	*0*	*0*	
TMTA T-score mean (SD) [range]	50.6	51.8	50.0	P = 0.32[a]
missings	(9.81) [30,75]	(10.6) [30,73]	(9.32) [30,75]	
	2	*1*	*1*	
TMTB T-score mean (SD) [range]	50.9	52.2	50.2	P = 0.23[a]
missings	(9.18) [36,75]	(9.27) [37,75]	(9.10) [36,75]	
	2	*1*	*1*	
COWAT FAS T-score mean (SD) [range]	52.0	53.8	51.0	P = 0.10[a]
missings	(9.39) [36,78]	(10.3) [36,78]	(8.71) [36,71]	
	2	*1*	*1*	
VOSP silhouettes T-score mean (SD) [range]	54.1	55.2	53.5	P = 0.31[a]
missings	(9.57) [36,73]	(9.15) [37,72]	(9.81) [36,73]	
	6	*1*	*5*	
	2564 (1337) [876,10846]	2562 (1557) [1118,10846]	2566 (1203) [876,7726]	P = 0.78[d]
NfL mean (SD) [range]	*1*	*1*	*1*	
missings				
t-tau mean (SD) [range]	271	280	266	P = 0.23[d]
missings	(92.1) [100,490]	(96.0) [102,468]	(89.9) [100,490]	
	0	*0*	*0*	

[a] Independent samples t-test
[b] Pearson's Chi-squared test
[c] Mann-Whitney U test
[d] Linear regression controlled for age with log transformed variables

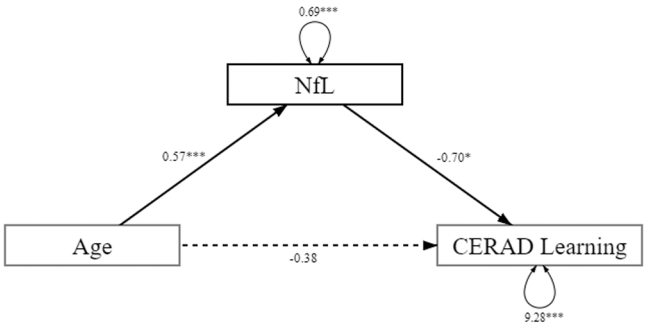


Fig. 1. Mediation Model for CERAD Learning With NfL.

direction as the direct effect ($\beta = -0.395$, boot SE = 0.186, $p < 0.05$) indicating indirect-only mediation (Zhao et al., 2010). The total effect was significant ($\beta = -0.773$, boot SE = 0.273, $p < 0.01$). Hence, NfL fully mediated the relationship between age and CERAD learning.

3.2.2. Age and CERAD recall via NfL

As seen in Fig. 2, age was positively related to NfL ($\beta = 0.564$, boot SE = 0.067, $p < 0.001$), which in turn was negatively related to CERAD recall ($\beta = -0.463$, boot SE = 0.161, $p < 0.01$). The direct effect from age to CERAD learning was in the expected direction but became non-significant when NfL was included in the model ($\beta = -0.252$, boot SE = 0.157, $p > 0.05$). Still, the indirect effect via NfL was significant in the same direction as the direct effect ($\beta = -0.261$, boot SE= 0.099, $p < 0.01$), indicating indirect-only mediation (Zhao et al., 2010). The total effect was significant ($\beta = -0.513$, boot SE = 0.146, $p < 0.01$). Hence, NfL fully mediated the relationship between age and CERAD recall.

3.2.3. Age and TMT-A via NfL

As seen in Fig. 3, age was positively related to NfL ($\beta = 0.567$, boot SE = 0.068, $p < 0.001$). NfL was however positively, but non-significantly related to TMT-A ($\beta = 1.169$, boot SE = 0.825, $p > 0.05$). The direct effect from age to TMT-A was significant and in the expected direction ($\beta = 2.172$, boot SE = 0.882, $p < 0.05$). The indirect effect via NfL was non-significant, but in the same direction as the direct effect ($\beta = 0.663$, boot SE= 0.452, $p > 0.05$). This indicates direct-only non-mediation (Zhao et al., 2010). The total effect was significant ($\beta = 2.835$, boot SE = 0.830, $p < 0.01$). Hence, NfL did not mediate the relationship between age and TMT-A.

3.2.4. Age and TMT-B via NfL

As seen in Fig. 4, age was positively related to NfL ($\beta = 0.567$, boot SE = 0.069, $p < 0.001$). NfL was in turn positively, but non-significantly related to TMT-B ($\beta = 1.468$, boot SE = 2.055, $p > 0.05$). The direct effect from age to TMT-B was significant and in the expected direction ($\beta = 9.252$, boot SE = 1.920, $p < 0.001$). The indirect effect via NfL was non-significant, but in the same direction as the direct effect ($\beta = 0.832$, boot SE= 1.164, $p > 0.05$). This indicates direct-only non-mediation (Zhao et al., 2010). The total effect was significant ($\beta = 10.084$, boot SE = 1.603, $p < 0.001$). Hence, NfL did not mediate the relationship between age and TMT-B.

3.2.5. Age and VOSP Silhouettes via NfL

As seen in Fig. 5, age was positively related to NfL ($\beta = 0.576$, boot SE = 0.070, $p < 0.001$). NfL was in turn negative, but non-significantly related to VOSP Silhouettes ($\beta = -0.237$, boot SE = 0.292, $p > 0.05$). Further, both the direct effect from age to VOSP Silhouettes and the indirect effect via NfL was negative and non-significant (Direct:

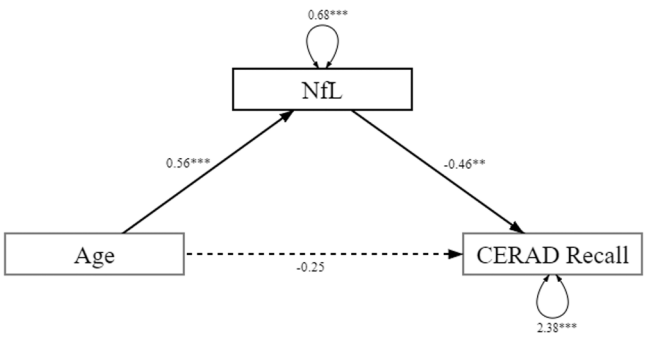


Fig. 2. Mediation Model for CERAD Recall With NfL.

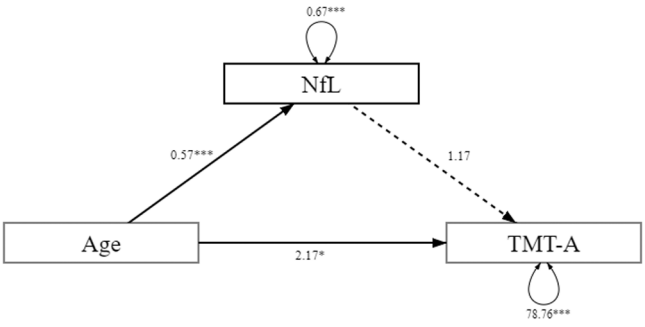


Fig. 3. Mediation Model for TMT-A With NfL.

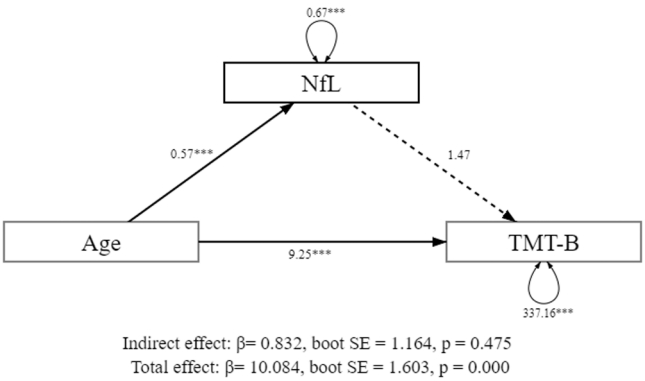


Fig. 4. Mediation Model for TMT-B With NfL.

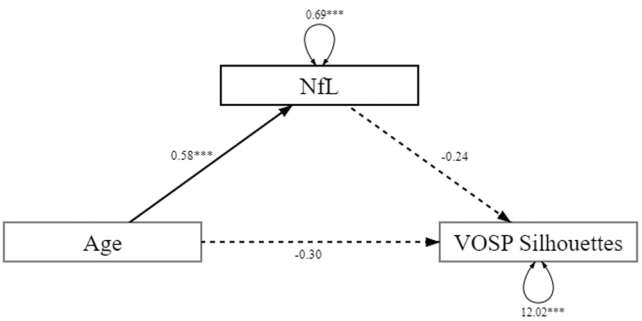


Fig. 5. Mediation Model for VOSP Silhouettes With NfL.

$\beta = -0.295$, boot SE = 0.375, $p > 0.05$; Indirect: $\beta = -0.136$, boot SE= 0.168, $p > 0.05$). This indicates no-effect non-mediation (Zhao et al., 2010). The total effect was also non-significant ($\beta = -0.431$, boot SE = 0.3, $p > 0.05$). Hence, neither age nor NfL was significantly associated with the performance on VOSP Silhouettes.

3.3. t-tau as mediator between age and cognition

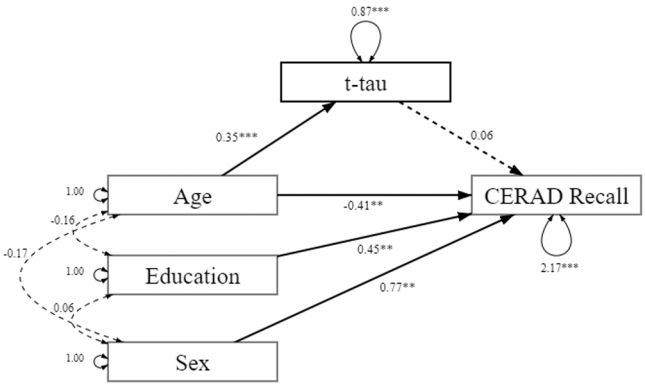
The SEM mediation models with t-tau as mediator and sex and education as covariates showed good fit. In addition, inclusion of these covariates did also substantially alter some of the mediation model relationships, and we therefore chose to include both sex and education in the models with t-tau.

3.3.1. Age and CERAD learning via t-tau

All model fit indices indicated a good model fit, χ^2(df=2) = 1.81 ($p = .404$); CFI= 1.000; TLI= 1.017, RMSEA= 0.000; SRMR= 0.028. As seen in Fig. 6, age was positively related to t-tau ($\beta = 0.364$, boot SE = 0.072, $p < 0.001$). t-tau was in turn positive, but non-significantly related to CERAD learning ($\beta = 0.074$, boot SE = 0.265, $p > 0.05$). Further, the direct effect from age to CERAD learning was negative and non-significant ($\beta = -0.538$, boot SE = 0.278, $p > 0.05$). The indirect effect via t-tau was positive, but non-significant ($\beta = 0.027$, boot SE= 0.097, $p > 0.05$). This indicates no-effect non-mediation (Zhao et al., 2010). The total effect was also non-significant ($\beta = -0.510$, boot SE = 0.270, $p > 0.05$). On the other hand, both education and sex had a positive and significant effect on CERAD learning. (Education: $\beta = -0.741$, boot SE = 0.267, $p < 0.01$; Sex: $\beta = 1.598$, boot SE = 0.526, $p < 0.01$). Hence, sex (i.e., women performed better) and education were significantly associated with CERAD learning performance, whereas age and t-tau was not.

3.3.2. Age and CERAD recall via t-tau

All model fit indices indicated a good model fit, χ^2(df=2) = 2.12 ($p = .347$); CFI= 0.998; TLI= 0.991, RMSEA= 0.021; SRMR= 0.029. As seen in Fig. 7, age was positively related to t-tau ($\beta = 0.348$, boot SE = 0.074, $p < 0.001$). t-tau was in turn positive, but non-significantly related to CERAD recall ($\beta = 0.055$, boot SE = 0.138, $p > 0.05$). The direct effect from age to CERAD recall was negative and significant ($\beta = -0.410$, boot SE = 0.142, $p < 0.01$), but the indirect effect via t-tau was positive and non-significant ($\beta = 0.019$, boot SE= 0.049, $p > 0.05$). This indicates direct-only non-mediation (Zhao et al., 2010). The total effect was significant ($\beta = -0.391$, boot SE = 0.138, $p < 0.01$). In addition, both education and sex had a positive and significant effect on CERAD recall. (Education: $\beta = 0.449$, boot SE = 0.138, $p < 0.01$; sex: $\beta = 0.767$, boot SE = 0.259, $p < 0.01$). Hence, both age, sex (i.e. women performed better) and education were significantly associated with CERAD recall performance, but no mediation effect was found for t-tau.



Indirect effect: β= 0.019, boot SE= 0.049, p= 0.695
Total effect: β= -0.391, boot SE= 0.138, p= 0.004

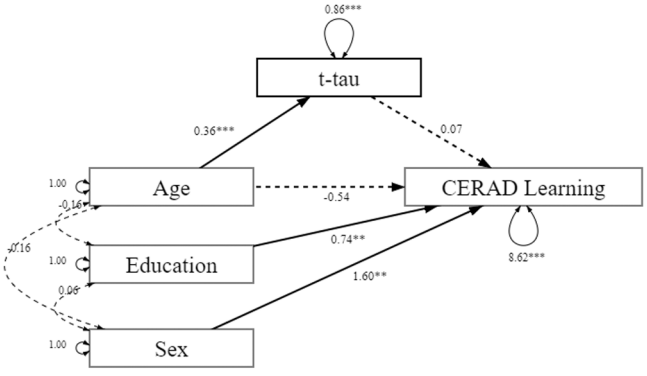
Fig. 7. Mediation Model for CERAD Recall With t-tau.

3.3.3. Age and TMT-A via t-tau

All model fit indices indicated a good model fit: χ^2(df=2)= 2.29 ($p = .319$); CFI= 0.992; TLI= 0.973, RMSEA= 0.033; SRMR= 0.032. As seen in Fig. 8, age was positively related to t-tau ($\beta = 0.348$, boot SE = 0.076, $p < 0.001$). t-tau was in turn positive, but non-significantly related to TMT-A ($\beta = 1.315$, boot SE = 0.742, $p > 0.05$). The direct effect from age to TMT-A was positive and significant ($\beta = 2.288$, boot SE = 0.816, $p < 0.01$), but the indirect effect via t-tau was positive and non-significant ($\beta = 0.458$, boot SE= 0.282, $p > 0.05$). This indicates direct-only non-mediation (Zhao et al., 2010). The total effect was significant ($\beta = 2.745$, boot SE = 0.839, $p < 0.01$). In addition, sex had a negative and significant effect on TMT-A ($\beta = -4.407$, boot SE = 1.523, $p < 0.01$). The effect of education was non-significant ($\beta = 0.802$, boot SE = 0.864, $p > 0.05$). Hence, age and sex (i.e. women performed better) were significantly associated with performance on TMT-A. Education and t-tau were not.

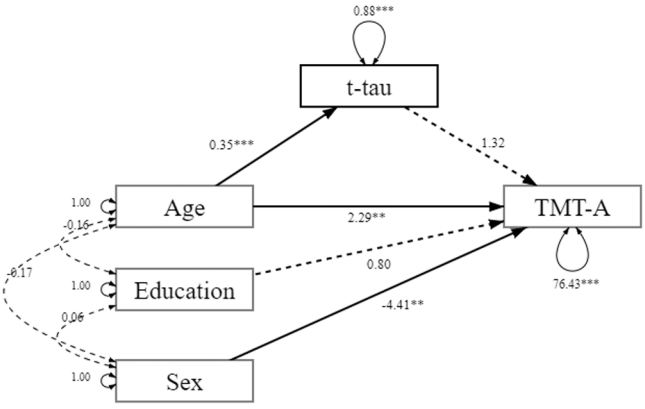
3.3.4. Age and TMT-B via t-tau

All model fit indices indicated a good model fit, χ^2(df=2)= 2.29 ($p = .319$); CFI= 0.996; TLI= 0.985, RMSEA= 0.033; SRMR= 0.031. As seen in Fig. 9, age was positively related to t-tau ($\beta = 0.348$, boot SE = 0.073, $p < 0.001$). t-tau was in turn positive, but non-significantly related to TMT-B ($\beta = 1.252$, boot SE = 1.765, $p > 0.05$). The direct effect from age to TMT-B was positive and significant ($\beta = 8.970$, boot



Indirect effect: β= 0.027, boot SE= 0.097, p= 0.780
Total effect: β= -0.510, boot SE= 0.270, p= 0.059

Fig. 6. Mediation Model for CERAD Learning With t-tau.



Indirect effect: β= 0.458, boot SE= 0.282, p= 0.105
Total effect: β= 2.745, boot SE= 0.839, p= 0.001

Fig. 8. Mediation Model for TMT-A With t-tau.

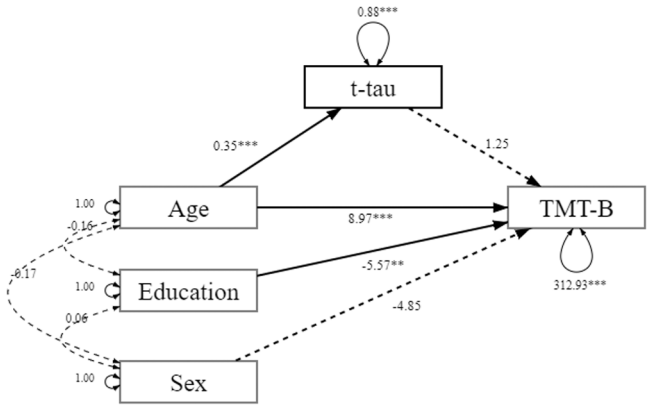


Fig. 9. Mediation Model for TMT-B With t-tau.

SE = 1.580, $p < 0.001$), but the indirect effect via t-tau was positive and non-significant ($\beta = 0.436$, boot SE= 0.621, $p > 0.05$). This indicates direct-only non-mediation (Zhao et al., 2010). The total effect was significant ($\beta = 9.406$, boot SE = 1.541, $p < 0.001$). In addition, education had a negative and significant effect on TMT-A ($\beta = -5.570$, boot SE = 1.790, $p < 0.01$), but the sex effect was non-significant ($\beta = -4.851$, boot SE = 3.314, $p > 0.05$). Hence, age and education were significantly associated with performance on TMT-A. Sex and t-tau were not.

3.3.5. Age and VOSP Silhouettes via t-tau

All fit indices indicated a good model fit, χ^2(df=2) = 1.58 ($p = .454$); CFI= 1.000; TLI= 1.075, RMSEA= 0.000; SRMR= 0.026. As seen in Fig. 10, age was positively related to t-tau ($\beta = 0.363$, boot SE = 0.070, $p < 0.001$). T-tau was in turn positive, but non-significantly related to VOSP Silhouettes ($\beta = 0.230$, boot SE = 0.329, $p > 0.05$). Both the direct effect from age to TMT-B and the indirect effect via t-tau was non-significant (Direct: $\beta = -0.431$, boot SE = 0.350, $p > 0.05$; Indirect: $\beta = 0.083$, boot SE= 0.123, $p > 0.05$). The total effect was also non-significant ($\beta = -0.347$, boot SE = 0.339, $p > 0.05$), and all together this indicates no-effect non-mediation (Zhao et al., 2010). In addition, both education and sex had a non-significant effect on VOSP Silhouettes (Education: $\beta = 0.567$, boot SE = 0.299, $p > 0.05$; sex: ($\beta = 0.235$, boot SE = 0.605, $p > 0.05$). Hence, neither age, t-tau, education nor sex were significantly associated with performance on VOSP Silhouettes.

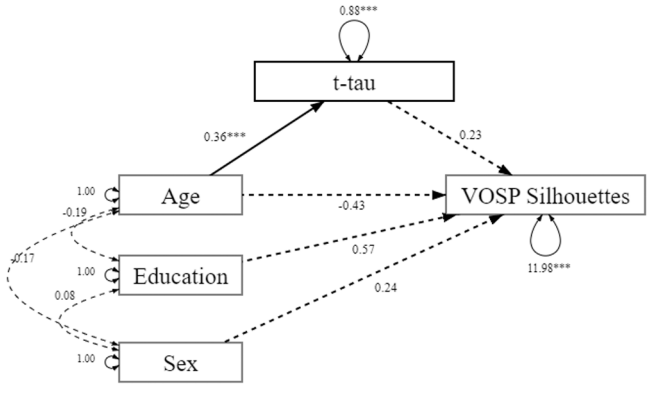


Fig. 10. Mediation Model for VOSP Silhouettes With t-tau.

3.4. Summarized results

Our cohort is young and well-educated in this study context. Further, our results showed only minor differences between the HC and SCD group, implicating that they were quite alike. Thus, the groups were merged in the SEM analyses.

We did not include age and sex as covariates in the SEM models with NfL as the model fit for these models was poor, i.e. inclusion of covariates worsened the model fit. This was probably because these variables did not explain enough variance in the dependent variable to justify increasing the model's complexity. Nevertheless, the models we fitted showed that NfL mediated the relationship between age and both CERAD learning and CERAD recall in our cohort. The direct age effect became non-significant with the inclusion of NfL as a mediator, making it an indirect-only mediation effect. No such effect was found for NfL and the other neuropsychological tests.

Regarding t-tau, all the models with covariates showed good fit. Thus, inclusion of age and sex did substantially improve the model's prediction and they were therefore included. In contrast, the models did not reveal any significant relationships between t-tau and the neuropsychological tests. Consequently, we did not find any mediation effects for t-tau in our models.

4. Discussion

In the current study, we found that NfL mediated the age effect on both verbal learning and verbal memory in a group of highly selected, middle-aged and well-educated adults. As NfL is suggested as a marker of axonal injury (Norgren et al., 2003), these results indicate that some of the normal age-related differences in memory may be due to white matter changes in the brain. Further, white matter lesions seem to be more important than those in gray matter, given that we did only find these effects for NfL and not for t-tau. Hence, our findings are in line with our hypotheses; the cross-sectional age-effect on cognition was mediated by CSF degenerative markers, albeit this effect was restricted to verbal learning and memory. In addition, the presence of SCD seems less important, as we did not detect any crucial cognitive differences between the group with and without SCD.

Few studies have conducted mediation analyses between age, t-tau or NfL and cognition using SEM. However, a recent study did and found that serum NfL did not mediate the relationship between age and cognitive test scores in any domains (Collins et al., 2023). The discrepancy between these findings and ours can be related to several factors. First, it is important to note that their battery did not include tests of list learning and that they used latent cognitive domains variables in their analyses. Thus, one cannot isolate the effect on performance on specific tests. Second, they also used longitudinal data, and the patterns found in using cross-sectional and longitudinal analyses need not to correspond. In addition, CSF and serum NfL may not be equally sensitive (Alagaratnam et al., 2021). Other studies using cross-sectional data, have also found an association between CSF NfL and neuropsychological test performance in healthy older adults (Osborn et al., 2019). Such associations between NfL and cognition have also been found for different neurological diseases, including dementia (Olsson et al., 2019).

On the other hand, a cross-sectional mediation study by Dupont et al. (2020) found cerebral Aβ deposition, but not WMH to mediate the relationship between age and episodic memory. Further, they did find that both working memory, executive functions and language were fully mediated by the combination of Aβ deposition and WMH. However, this study is not directly comparable to our study, given our differing study population; as we only included participants with normal CSF $A\beta42/40_{ratio}$, we excluded those with Aβ pathology. Furthermore, WMH and CSF NfL are differing biomarkers, with overlapping - yet distinct origins. Whereas WMH represents a radiological biomarker to white matter changes, NfL is a proxy biomarker associated with WMH as well as other pathologies. Indeed, a recent longitudinal study by Dhana et al.

(2023) found that increasing levels of WMH and NfL are similarly associated with cognitive decline, but their ability to detect this decline are different and varies with the level of the other marker. These findings suggest that the underlying mechanisms governing the association with cognition are different for the two markers.

The non-significant effect of t-tau and cognitive performance that we found is somewhat differing from other studies that have demonstrated such an association (e.g., Mielke et al., 2017; Stefani et al., 2006). However, it is important to consider the nature of our cohort: (1) It is substantially younger than that of most of the studies in this study context; and (2) we have screened out Aβ pathology. As t-tau has been found to be a closely related to p-tau (Kasuga et al., 2022) and to be a good marker of general neurodegeneration in AD (Kasuga et al., 2023) our selection criteria might have restricted t-tau's ability to detect effects. In addition, we found a relatively low correlation between NfL and t-tau, which points to a small amount of shared variance ($r^2 = 13\%$). Thus, these biomarkers do not seem to be driven by the same underlying degenerative processes in healthy aging. Altogether these findings indicate that NfL pathology and presumably white matter lesions is an initial feature of normal aging that precedes t-tau accumulation and gray matter lesions.

Thus, our study depicts the potential role of NfL and possibly white matter degeneration, in the lower memory performance seen with aging, while other studies have found other markers of neurodegeneration to contribute to the age-related changes in multiple other domains. As such, the findings from both previous and the current study indicate that the brain alterations responsible for NfL accumulation during the lifespan may be an innate feature of normal aging. Even so, other studies also report marked individual differences to this trend (Nyberg et al., 2020). Taking into consideration that NfL is primarily located in the long, myelinated axons and that NfL levels increase with age, this may suggest that normal aging starts with white matter changes. Additionally, our findings might suggest that NfL - and accordingly white matter degeneration of any etiology - primarily affect memory functions. On the other hand, a recent study found high NfL levels to be associated with poorer global cognition (Mielke et al., 2019). However, they also found this association to be stronger in individuals with MCI and AD compared to healthy controls, suggesting that other disease-related factors might have influenced these observations. Thus, more research is needed to confirm our findings.

Second, even if this cross-sectional mediation cannot be used as evidence for a longitudinal mediation of age-related memory decline (Lindenberger et al., 2011), this might have important implications for the way we conceptualize normality in aging. Normative reference data are what we define normality based upon, and for most neuropsychological tests age is the main adjustment used. However, our study suggest that most of the age effect on memory functions may be driven by normal, NfL associated brain alterations in healthy aging. Hence, if confirmed our findings questions whether age is a suitable adjustment in normative reference data for the adult population, where detecting early signs of neurodegeneration is a main concern. It may be that the definition of normal versus impaired regarding memory functions should be cut-off based rather than being adjusted for age.

Providing that our results are confirmed, age-related lower performance in learning and memory seems related to normal differences in white matter integrity, rather than being a mere effect of age per se. Indeed, while we still observed an age-related drop in performance in other cognitive tests (TMT-A and B), neither CSF t-tau nor NfL were associated to lower performance on these tests. However, others have reported associations between both WMH and cortical thinning and TMT performance in healthy aging (MacPherson et al., 2017), suggestive of age-related white-matter changes as well as neuronal loss. Moreover, fluid and neuroimaging markers of neurodegeneration may not be interchangeable, where e.g., t-tau may reflect a neurodegenerative process, whereas the resulting cortical thinning of this process may be more evident over time (Lin et al., 2021). Thus, while our results suggest an age-related lower cognitive performance independently of CSF biomarkers of neurodegeneration, we may still see age-related associations over time. The interplay between healthy age-related cognitive decline, CSF, and MRI markers of neurodegenerative is important, and we aim to address this in future work.

4.1. Strengths and limitations

One of the major limitations of our study is that we did not include MRI data, or longitudinal cognitive data in the analyses. Our data can therefore not answer whether there is a longitudinal mediation in age-related cognitive decline. This is just as important to clarify, but unfortunately, we do not have repeated CSF measures for these markers and are thus not able to tackle this question at present. As previously mentioned, we do however aim to address these shortcomings in future work.

We also had a restricted neuropsychological test battery, including relatively easy tests. This increases the risk for ceiling effects and false positives, as it is quite normal for healthy people to have some abnormal scores (Heaton, 2004). Ideally, the neuropsychological assessment should have been more diverse, containing more detailed measures of different cognitive functions. This would have given us more robust measures, e.g. by making us able to construct domain-specific composite scores.

Further, our study cohort was relatively small, young, and well-educated. This is important to bear in mind as one might question whether our easy neuropsychological test battery was sensitive enough to capture differences in our cohort. Relatedly, one might also question whether one could expect CSF neurodegenerative markers to be elevated, and to our knowledge, population base rates for abnormal CSF NfL and t-tau in cognitively healthy older adults are lacking. In our sample however, we saw abnormal levels of NfL and t-tau in 29% and 13% respectively. This difference, where abnormal NfL is more common than abnormal t-tau, further supports our theory that brain alterations responsible for increased CSF NfL is an early feature of normal aging. Even so, the findings and trends from this study cannot be inferred as applicable for older groups. In addition, the analyses were based on cross-sectional data. Hence, we were not able to apply an ipsative definition of decline. We rather based our selection on normative, yet rigorous, criteria that might have led to a skewed normality definition missing 7% of healthy people (cf. The Bell curve). This will indeed restrict the generalizability of our findings.

On the other hand, the rigorous selection might also be seen as a strength. With the strict normality definition that was applied, we have a high level of certainty that it is indeed healthy aging we have studied. Applying a looser definition might increase generalizability but will conversely increase the risk for confoundment from prodromal disease development.

Another important strength of our study is that we used a SEM approach to test mediation. Compared to the traditional regression approach, SEM provides less biased and more accurate estimations as it has adjustment for measurement error. Thus, our analyses are statistically sound.

Hence, studies with larger study samples are needed. Longitudinal studies including both MRI and CSF data is preferable. Further, a comparison between healthy older adults, and people with MCI and manifest dementia would be of particular interest, as this would help distinguish what can be attributed to normal versus pathological decline.

5. Conclusions

Cross-sectional age-related differences in verbal learning and memory seems to be linked to NfL-levels and associated to an initial phase of aging or neurodegenerative changes in cognitively healthy adults. This underlines NfL's close link to cognitive performance and may reflect the prominent role of white matter pathology in normal aging, as NfL is a

marker of white matter degeneration. However, more research is needed to confirm these findings.

Funding

This project was supported by funding from The Fonna Hospital Trust, Akershus University Hospital, the Northern Norway regional health authorities (HNF1540–20) and the Norwegian Research Council, and JPND/PMI-AD (NRC 311993).

CRediT authorship contribution statement

Nakling Arne: Investigation, Writing – review & editing. **Grøntvedt Gøril Rolfseng:** Investigation, Writing – review & editing. **Fladby Tormod:** Data curation, Investigation, Project administration, Resources, Writing – review & editing. **Rongve Arvid:** Investigation, Supervision, Writing – review & editing. **Gísladóttir Berglind:** Formal analysis, Investigation, Writing – review & editing. **Breitve Monica Haraldseid:** Investigation, Supervision, Writing – review & editing. **Chwiszczuk Luiza Jadwiga:** Investigation, Supervision, Writing – review & editing. **Kirsebom Bjørn-Eivind:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. **Hemminghyth Mathilde Suhr:** Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

BEK has served as a consultant for Biogen. TF has served as a consultant and at the advisory boards for Biogen, Novo Nordisk, Eli Lilly and Roche. MSH, LJC, MHB, BG, GRG, AN, and AR report no conflict of interest.

Acknowledgments

First and foremost, we thank the participants and their relatives who participated in the study. We also thank everyone in the DDI study group for their contribution regarding data collection and handling and the Betanien laboratory for outstanding service.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.12.005.

References

Alagaratnam, J., von Widekind, S., De Francesco, D., Underwood, J., Edison, P., Winston, A., Zetterberg, H., Fidler, S., 2021. Correlation between CSF and blood neurofilament light chain protein: a systematic review and meta-analysis. BMJ Neurol. Open 3 (1). https://doi.org/10.1136/bmjno-2021-000143.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer'S. Dement. 7 (3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008.

Benton, A., Hamsher, K., Sivan, A., 1994. Multilingual Aphasia Examination AJA Associates. Iowa City, IA,

Collins, J.M., Bindoff, A.D., Roccati, E., Alty, J.E., Vickers, J.C., King, A.E., 2023. Does serum neurofilament light help predict accelerated cognitive ageing in unimpaired older adults? Front. Neurosci. 17 https://doi.org/10.3389/fnins.2023.1237284.

De Leeuw, F., de Groot, J.C., Achten, E., Oudkerk, M., Ramos, L., Heijboer, R., Hofman, A., Jolles, J., Van Gijn, J., Breteler, M., 2001. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J. Neurol., Neurosurg. Psychiatry 70 (1), 9–14. https://doi.org/10.1136/jnnp.70.1.9.

Debette, S., Markus, H., 2010. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. Bmj 341. https://doi.org/10.1136/bmj.c3666.

Dhana, A., DeCarli, C., Dhana, K., Desai, P., Wilson, R.S., Evans, D.A., Rajan, K.B., 2023. White matter hyperintensity, neurofilament light chain, and cognitive decline. Ann. Clin. Transl. Neurol. 10 (3), 321–327. https://doi.org/10.1002/acn3.51720.

Dupont, P.S., Bocti, C., Joannette, M., Lavallée, M.M., Nikelski, J., Vallet, G.T., Chertkow, H., Joubert, S., 2020. Amyloid burden and white matter hyperintensities mediate age-related cognitive differences. Neurobiol. Aging 86, 16–26. https://doi.org/10.1016/j.neurobiolaging.2019.08.025.

Egeland, J., Landrø, N.I., Tjemsland, E., Walbækken, K., 2006. Norwegian norms and factor-structure of phonemic and semantic word list generation. Clin. Neuropsychol. 20 (4), 716–728. https://doi.org/10.1080/13854040500351008.

Eliassen, I.V., Kirsebom, B.-E., Fladby, T., Sando, S.B., Hemminghyth, M.S., Aarsland, D., Timón-Reina, S., Wallin, A., Öhman, F., Eckerström, M., 2022. Regression-based cognitive change norms applied in biochemically defined predementia Alzheimer's disease. Neuropsychology. https://doi.org/10.1037/neu0000853.

Espenes, J., Hessen, E., Eliassen, I.V., Waterloo, K., Eckerström, M., Sando, S.B., Timon, S., Wallin, A., Fladby, T., Kirsebom, B.-E., 2020. Demographically adjusted trail making test norms in a Scandinavian sample from 41 to 84 years. Clin. Neuropsychol. 34 (sup1), 110–126. https://doi.org/10.1080/13854046.2020.1829068.

Fillenbaum, G.G., van Belle, G., Morris, J.C., Mohs, R.C., Mirra, S.S., Davis, P.C., Tariot, P.N., Silverman, J.M., Clark, C.M., Welsh-Bohmer, K.A., 2008. Consortium to establish a registry for Alzheimer's disease (CERAD): the first twenty years. Alzheimer'S. Dement. 4 (2), 96–109. https://doi.org/10.1016/j.jalz.2007.08.005.

Fladby, T., Pålhaugen, L., Selnes, P., Bråthen, G., Hessen, E., Almdahl, I.S., Arntzen, K.-A., Auning, E., Eliassen, C.F., Espenes, R., 2017. Detecting at-risk Alzheimer's disease cases. J. Alzheimer'S. Dis. 60 (1), 97–105. https://doi.org/10.3233/JAD-170231.

Heaton, R.K., 2004. Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian adults, Professional Manual. Psychological Assessment Resources,.

Hu, Lt, Bentler, P.M., 1999. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct. Equ. Model.: a Multidiscip. J. 6 (1), 1–55. https://doi.org/10.1080/10705519909540118.

Jack, C.R., Wiste, H.J., Weigand, S.D., Therneau, T.M., Knopman, D.S., Lowe, V., Vemuri, P., Mielke, M.M., Roberts, R.O., Machulda, M.M., 2017. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: a cross-sectional study. Lancet Neurol. 16 (6), 435–444. https://doi.org/10.1016/S1474-4422(17)30077-7.

Jessen, F., Amariglio, R.E., Van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K.A., Van Der Flier, W.M., 2014. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer'S. Dement. 10 (6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001.

Kasuga, K., Kikuchi, M., Tsukie, T., Suzuki, K., Ihara, R., Iwata, A., Hara, N., Miyashita, A., Kuwano, R., Iwatsubo, T., 2022. Different AT (N) profiles and clinical progression classified by two different N markers using total tau and neurofilament light chain in cerebrospinal fluid. BMJ Neurol. Open 4 (2). https://doi.org/10.1136/bmjno-2022-000321.

Kasuga, K., Tsukie, T., Kikuchi, M., Tokutake, T., Washiyama, K., Shimizu, S., Yoshizawa, H., Kuroha, Y., Yajima, R., Mori, H., 2023. The clinical application of optimized AT (N) classification in Alzheimer's clinical syndrome (ACS) and non-ACS conditions. Neurobiol. Aging 127, 23–32. https://doi.org/10.1016/j.neurobiolaging.2023.03.007.

Khalil, M., Teunissen, C.E., Otto, M., Piehl, F., Sormani, M.P., Gattringer, T., Barro, C., Kappos, L., Comabella, M., Fazekas, F., 2018. Neurofilaments as biomarkers in neurological disorders. Nat. Rev. Neurol. 14 (10), 577–589. https://doi.org/10.1038/s41582-018-0058-z.

Kirsebom, B.-E., Espenes, R., Hessen, E., Waterloo, K., Johnsen, S.H., Gundersen, E., Botne Sando, S., Rolfseng Grøntvedt, G., Timón, S., Fladby, T., 2019. Demographically adjusted CERAD wordlist test norms in a Norwegian sample from 40 to 80 years. Clin. Neuropsychol. 33 (sup1), 27–39. https://doi.org/10.1080/13854046.2019.1574902.

Lin, R.-R., Xue, Y.-Y., Li, X.-Y., Chen, Y.-H., Tao, Q.-Q., Wu, Z.-Y., 2021. Optimal combinations of AT(N) biomarkers to determine longitudinal cognition in the Alzheimer's disease. Front. Aging Neurosci. 13 https://doi.org/10.3389/fnagi.2021.718959.

Lindenberger, U., Von Oertzen, T., Ghisletta, P., Hertzog, C., 2011. Cross-sectional age variance extraction: what's change got to do with it? Psychol. Aging 26 (1), 34. https://doi.org/10.1037/a0020525.

Llorens, F., Villar-Piqué, A., Candelise, N., Ferrer, I., Zerr, I., 2018. Tau protein as a biological fluid biomarker in neurodegenerative dementias. Cognitive Disorders. IntechOpen,.

Longstreth, W., Manolio, T.A., Arnold, A., Burke, G.L., Bryan, N., Jungreis, C.A., Enright, P.L., O'Leary, D., Fried, L., 1996. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: the cardiovascular health study. Stroke 27 (8), 1274–1282. https://doi.org/10.1161/01.STR.27.8.1274.

Lorentzen, I.M., Espenes, J., Hessen, E., Waterloo, K., Bråthen, G., Timón, S., Aarsland, D., Fladby, T., Kirsebom, B.-E., 2021. Regression-based norms for the FAS phonemic fluency test for ages 40–84 based on a Norwegian sample. Appl. Neuropsychol.: Adult 1–10. https://doi.org/10.1080/23279095.2021.1918128.

MacPherson, S.E., Cox, S.R., Dickie, D.A., Karama, S., Starr, J.M., Evans, A.C., Bastin, M. E., Wardlaw, J.M., Deary, I.J., 2017. Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. Cortex 95, 92–103. https://doi.org/10.1016/j.cortex.2017.07.021.

Mai, Y., Xu, Z., Zhang, Z., Yuan, K., 2022. An Open Source WYSIWYG Web Application for Drawing Path Diagrams of Structural Equation Models. ⟨https://semdiag.psychstat.org/⟩. 2023).

Mattsson, N., Insel, P.S., Palmqvist, S., Portelius, E., Zetterberg, H., Weiner, M., Blennow, K., Hansson, O., Initiative, As.D.N., 2016. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. EMBO Mol. Med. 8 (10), 1184–1196. https://doi.org/10.15252/emmm.201606540.

Mattsson, N., Andreasson, U., Zetterberg, H., Blennow, K., Initiative, As.D.N., 2017. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. JAMA Neurol. 74 (5), 557–566. https://doi.org/10.1001/jamaneurol.2016.6117.

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack Jr, C.R., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer'S. Dement. 7 (3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.

Meeker, K.L., Butt, O.H., Gordon, B.A., Fagan, A.M., Schindler, S.E., Morris, J.C., Benzinger, T.L., Ances, B.M., 2022. Cerebrospinal fluid neurofilament light chain is a marker of aging and white matter damage. Neurobiol. Dis. 166, 105662 https://doi.org/10.1016/j.nbd.2022.105662.

Mielke, M.M., Hagen, C.E., Wennberg, A.M., Airey, D.C., Savica, R., Knopman, D.S., Machulda, M.M., Roberts, R.O., Jack, C.R., Petersen, R.C., 2017. Association of plasma total tau level with cognitive decline and risk of mild cognitive impairment or dementia in the mayo clinic study on aging. JAMA Neurol. 74 (9), 1073–1080. https://doi.org/10.1001/jamaneurol.2017.1359.

Mielke, M.M., Syrjanen, J.A., Blennow, K., Zetterberg, H., Vemuri, P., Skoog, I., Machulda, M.M., Kremers, W.K., Knopman, D.S., Jack, C., 2019. Plasma and CSF neurofilament light: relation to longitudinal neuroimaging and cognitive measures. Neurology 93 (3), e252–e260. https://doi.org/10.1212/WNL.0000000000007767.

Norgren, N., Rosengren, L., Stigbrand, T., 2003. Elevated neurofilament levels in neurological diseases. Brain Res. 987 (1), 25–31. https://doi.org/10.1016/S0006-8993(03)03219-0.

Nyberg, L., Lundquist, A., Nordin Adolfsson, A., Andersson, M., Zetterberg, H., Blennow, K., Adolfsson, R., 2020. Elevated plasma neurofilament light in aging reflects brain white-matter alterations but does not predict cognitive decline or Alzheimer's disease. Alzheimer'S. Dement.: Diagn., Assess. Dis. Monit. 12 (1), e12050 https://doi.org/10.1002/dad2.12050.

Olsson, B., Portelius, E., Cullen, N.C., Sandelius, Å., Zetterberg, H., Andreasson, U., Höglund, K., Irwin, D.J., Grossman, M., Weintraub, D., 2019. Association of cerebrospinal fluid neurofilament light protein levels with cognition in patients with dementia, motor neuron disease, and movement disorders. JAMA Neurol. 76 (3), 318–325. https://doi.org/10.1001/jamaneurol.2018.3746.

Osborn, K.E., Khan, O.A., Kresge, H.A., Bown, C.W., Liu, D., Moore, E.E., Gifford, K.A., Acosta, L.M.Y., Bell, S.P., Hohman, T.J., 2019. Cerebrospinal fluid and plasma neurofilament light relate to abnormal cognition. Alzheimer'S. Dement.: Diagn., Assess. Dis. Monit. 11 (1), 700–709. https://doi.org/10.1016/j.dadm.2019.08.008.

Pålhaugen, L., Sudre, C.H., Tecelao, S., Nakling, A., Almdahl, I.S., Kalheim, L.F., Cardoso, M.J., Johnsen, S.H., Rongve, A., Aarsland, D., 2021. Brain amyloid and vascular risk are related to distinct white matter hyperintensity patterns. J. Cereb. Blood Flow. Metab. 41 (5), 1162–1174. https://doi.org/10.1177/0271678X20957604.

Reitan, R., Wolfson, D., 1985. The Halstead-Reitan Neuropsychological Test Battery. Neuropsychology Press,, Tucson, Arizona.

Siafarikas, N., Kirsebom, B.E., Srivastava, D.P., Eriksson, C.M., Auning, E., Hessen, E., Selbaek, G., Blennow, K., Aarsland, D., Fladby, T., 2021. Cerebrospinal fluid markers for synaptic function and Alzheimer type changes in late life depression. Sci. Rep. 11 (1), 20375 https://doi.org/10.1038/s41598-021-99794-9.

Stefani, A., Martorana, A., Bernardini, S., Panella, M., Mercati, F., Orlacchio, A., Pierantozzi, M., 2006. CSF markers in Alzheimer disease patients are not related to the different degree of cognitive impairment. J. Neurol. Sci. 251 (1-2), 124–128. https://doi.org/10.1016/j.jns.2006.09.014.

Stewart, C.R., Stringer, M.S., Shi, Y., Thrippleton, M.J., Wardlaw, J.M., 2021. Associations between white matter hyperintensity burden, cerebral blood flow and transit time in small vessel disease: an updated meta-analysis. Front. Neurol. 12, 647848 https://doi.org/10.3389/fneur.2021.647848.

Villemagne, V.L., Pike, K.E., Chételat, G., Ellis, K.A., Mulligan, R.S., Bourgeat, P., Ackermann, U., Jones, G., Szoeke, C., Salvado, O., 2011. Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. Ann. Neurol. 69 (1), 181–192. https://doi.org/10.1002/ana.22248.

Wang, M.-L., Zhang, X.-X., Yu, M.-M., Li, W.-B., Li, Y.-H., 2019. Prevalence of white matter hyperintensity in young clinical patients. Am. J. Roentgenol. 213 (3), 667–671. https://doi.org/10.2214/AJR.18.20888.

Warrington, E.K., James, M., 1991. A new test of object decision: 2D silhouettes featuring a minimal view. Cortex 27 (3), 377–383. https://doi.org/10.1016/S0010-9452(13)80033-0.

Zhao, X., Lynch Jr, J.G., Chen, Q., 2010. Reconsidering Baron and Kenny: myths and truths about mediation analysis. J. Consum. Res. 37 (2), 197–206. https://doi.org/10.1086/651257.