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Associations of neuroinflammatory IL-6 and IL-8 with brain atrophy, memory decline, and core AD biomarkers – in cognitively unimpaired older adults

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ABSTRACT

Concentrations of pro-inflammatory cytokines –interleukin-6 (IL-6) and interleukin-8 (IL-8) – are increased with age and in Alzheimer's disease (AD). It is not clear whether concentrations of IL-6 and IL-8 in the central nervous system predict later brain and cognitive changes over time nor whether this relationship is mediated by core AD biomarkers. Here, 219 cognitively healthy older adults (62–91 years), with baseline cerebrospinal fluid (CSF) measures of IL-6 and IL-8 were followed over time – up to 9 years – with assessments that included cognitive function, structural magnetic resonance imaging, and CSF measurements of phosphorylated tau (p-tau) and amyloid-β (Aβ-42) concentrations (for a subsample). Higher baseline CSF IL-8 was associated with better memory performance over time in the context of lower levels of CSF p-tau and p-tau/Aβ-42 ratio. Higher CSF IL-6 was related to less CSF p-tau changes over time. The results are in line with the hypothesis suggesting that an up-regulation of IL-6 and IL-8 in the brain may play a neuroprotective role in cognitively healthy older adults with lower load of AD pathology.

1. Introduction

Aging is characterized by increased neuroinflammation, which may contribute to the etiology of Alzheimer's disease (AD) (Leng and Edison, 2021) and cognitive decline (Franceschi et al., 2007). Yet, neuro-inflammation could also represent beneficial responses in successful aging (Wang et al., 2022) and in preclinical AD, e.g., by clearance of amyloid (Leng and Edison, 2021). It is thus crucial to understand the effects of neuroinflammation on brain and cognitive decline over time, especially in cognitively healthy older adults (OA) (Albrecht et al., 2021; Singh-Manoux et al., 2014). The cytokine cascade is one of the key mechanisms of neuroinflammation in aging relating to cognitive (Bradburn et al., 2018; Fard et al., 2022; Weaver et al., 2002) and brain structural decline over time (Baune et al., 2008; McCarrey et al., 2014). Specifically, concentrations of two pro-inflammatory cytokines, interleukin-6 (IL-6) and interleukin-8 (IL-8) are increased with age and in Alzheimer's disease (AD) and also have been reported to relate to the accumulation of amyloid-β (Aβ) (Alvarez-Rodríguez et al., 2012; Bettcher et al., 2018; Blum-Degen et al., 1995; Hu et al., 2019; McLarnon, 2016). However, it is still poorly understood whether, how, and

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under which conditions IL-6 and IL-8 are related to brain and memory decline. In the present study, we tested whether cerebrospinal fluid (CSF) concentrations of IL-6 and IL-8 were associated with cognitive, and brain decline in OA and whether this relationship was mediated by the core AD CSF biomarkers Aβ-42 and phosphorylated tau (p-tau). Further, we also tested whether baseline concentrations of CSF IL-8 and IL-6 related to higher accumulation of these core CSF AD biomarkers over time.

The cascade of these cytokines regulates the interaction between glial cell activation and neurons (Wilson et al., 2002). Transient neuroinflammation is fundamental for normal brain functioning and may counteract harmful effects following a brain insult (DiSabato et al., 2016). Age-related changes may prompt glial cells into a chronic state of low-level activation associated with an increased amount of pro-inflammatory cytokines released, which in turn may lead to harmful effects on the brain, with down-stream effects on cognition (Edler et al., 2021; McCarrey et al., 2014). Moreover, it is hypothesized that chronic inflammation plays a role in AD, years before clinical symptoms (Leng and Edison, 2021; Perry and Holmes, 2014). Although the direction of effects between IL-6, IL-8, and the core AD biomarkers Aβ and p-tau is poorly understood, it is hypothesized that pro-inflammatory cytokines are involved in different and opposite processes in a detrimental cycle. Amyloid aggregation may induce the overproduction of IL-6 and IL-8 (Leng and Edison, 2021). At the same time, pro-inflammatory cytokines may in turn play a role in Aβ plaque deposition by contributing to amyloid precursor protein (APP) processing (Domingues et al., 2017; Weisman et al., 2006) and regulation of Aβ clearance (Chakrabarty et al., 2010; Wang et al., 2015). Moreover, pro-inflammatory cytokines could promote hyper-phosphorylation of tau (Quintanilla et al., 2004; Vaz et al., 2020). Albrecht and colleagues (2021) found that higher concentrations of cerebrospinal fluid (CSF) IL-6 and IL-8 were associated with less Aβ and IL-8 with less tau accumulation measured by PET, suggesting a protective role of early neuroinflammation in OA. Contrary, another study (Flores-Aguilar et al., 2021) on assessing brain tissue of older adults without any cognitive symptoms, observed that higher levels of IL-6 protein expression (assessed in brain homogenate) were related to more Aβ pathology. It is thus necessary to better understand the relationship between IL-6 and IL-8, brain atrophy, and cognitive decline in relation to the accumulation of core AD biomarkers Aβ and p-tau.

There is inconclusive evidence regarding the relationships of IL-6 and IL-8 with cognitive and brain decline in OA. The most robust finding appears to be a relationship between higher blood levels of IL-6 and more cognitive decline over time (Singh-Manoux et al., 2014; Weaver et al., 2002; Yaffe et al., 2003), although this has not been consistently replicated (Dik et al., 2005; Schram et al., 2007). Both a *meta*-analysis and a systematic review reported cross-sectional associations between peripheral high concentrations of IL-6 and poorer cognition (Bradburn et al., 2018; Fard et al., 2022). Evidence for an association between cognition and IL-8 in OA is scarcer and limited to cross-sectional data. Baune and colleagues (2008) found that higher serum IL-8 was related to lower memory performance. However, this finding was not replicated (Trollor et al., 2012). The evidence for relationships between IL-6 and IL-8 and brain structure in OA is also inconclusive. Negative, cross-sectional relationships between blood IL-6 and hippocampal volume have been described (Marsland et al., 2015; Satizabal et al., 2012), whereas Baune and colleagues (2009) reported a combined effect of the serum interleukins concentrations (IL-6, IL-8, and sIL-4R) on brain volume in a cross-sectional study. Both serum IL-6 and IL-8, however, have been found to mediate the relationship between brain atrophy and mortality (Hanning et al., 2016). Longitudinally, associations between higher serum concentrations of IL-6 and cortical thinning over time have been found in one study (McCarrey et al., 2014), though no significant association was observed in another study with a shorter follow-up (Satizabal et al., 2012). To our knowledge, the relationship between CSF IL-8 concentrations and longitudinal brain decline has not hitherto been investigated. The varying associations (in terms of direction) between ILs and brain and cognitive outcomes have often been attributed to the dissociative effects of IL-6 and IL-8 (protective vs. neurotoxic). Ultimately, the consequences of released IL-6 and IL-8 may depend on the internal milieu and thus vary throughout the aging-disease continuum and the accumulation of pathology (Albrecht et al., 2021).

In the present study, we tested whether baseline CSF IL-6 and IL-8 are related to brain atrophy and cognitive decline over time in OA (n = 219, followed for up to 9.51 years). Specifically, we focused on the medial temporal lobe structures and the lateral ventricles, as well as episodic memory, which are highly sensitive to both aging and AD (Chincarini et al., 2016; Fjell and Walhovd, 2010; Jahn, 2013; Rönnlund et al., 2005). Given the hypothesized interplay between IL-6 and IL-8 with the core AD biomarkers Aβ-42 and p-tau, we tested whether the associations between the cytokines and brain and cognitive decline were mediated by Aβ-42 and p-tau. Finally, in a subsample with longitudinal measurements of CSF, we assessed the relationship between IL-6 and IL-8 and changes in core AD CSF biomarkers over time.

2. Material and methods

2.1. Participants

A total of 219 cognitively healthy older participants were included in the final sample (113 females, mean age at baseline = 74.63 years, standard deviation [SD] = 5.97, age range = 62.00–91.15). Participants belonged to the COGNORM Cohort (Idland et al., 2017) (n = 114 participants, mean age = 73.77, SD = 6.43) and to the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (n = 105 participants, mean age = 75.55, SD = 5.29) (Mueller et al., 2005) from ADNI1/ADNI GO phases. Both datasets have CSF biomarker information, longitudinal structural magnetic resonance imaging (MRI) of the brain, and cognitive assessments. Participants were required at baseline to be cognitively healthy according to a battery of neuropsychological tests, have available CSF data, and both MRI and cognitive data information. See specific inclusion criteria for COGNORM and ADNI in Supplementary Info (SI). Longitudinal structural MRIs were available for up to 9.51 years (mean = 2.16, SD = 2.18) and cognitive data for up to 6.89 years (mean = 2.38, SD = 1.93). See Table 1 and Supplementary Fig. 1 for sociodemographic and sample details for each dataset. All participants gave informed written consent, and the studies were approved by the relevant ethical committees (**SI** for more details) and conducted in accordance with the Declaration of Helsinki.

2.2. MRI acquisition and preprocessing

For COGNORM, structural T1-weighted (T1w) MPRAGE scans were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner, with the following parameters: TR = 2400 ms, TE = 3.79 ms, TI = 1000, flip angle = 8°, voxel size = 1.25 × 1.25 × 1.20 mm, FOV = 240 mm. For ADNI, we included 1.5 T images from multiple scanners. See http://adni.loni.usc.edu/methods/mri-tool/mri-analysis for information on scanner models and sequences. Critically, each participant was scanned by use of the same scanner over time, hence, the possible variance associated with different scanners for the cohort will likely be captured by the random intercept for the participant. Images were transformed into the Brain Imaging Data Structure (BIDS) format (Gorgolewski et al., 2016), using Clinica for ADNI data (Routier et al., 2021; Samper-González et al., 2018). Images from ADNI and COGNORM underwent identical preprocessing pipelines. We used the longitudinal FreeSurfer v.7.1.0 stream (Reuter et al., 2012) for cortical reconstructions of the structural T1w scans (https://surfer.nmr.mgh.harvard.edu/fswiki) (Dale et al., 1999; Fischl et al., 1999). First, the images were processed using the cross-sectional stream, which includes the removal of nonbrain tissue, Talairach transformation, intensity

Table 1
Cohort characteristics at baseline and CSF follow-up information.

	COGNORM	ADNI	Total	Cohort diff.	Effect size
Characteristics					
N (F:M)	114 (60:54)	105 (53:52)	219 (113:106)	0.10 (0.75)	0.02
Age	73.77 (6.43)	75.55 (5.29)	74.63 (5.97)	2.24 (0.08)	0.30
Age range	64.74–91.15	62.00–89.60	62.00–91.15	–	–
MRI obs (n)	356 (3.12 [1.33])	551 (5.25 [1.32])	907 (4.14 [1.70])	–	–
Memory obs (n)	677 (5.94 [1.75])	574 (5.47 [1.19])	1251 (5.71 [1.52])	–	–
MMSE	29.07 (1.17)	29.06 (1.05)	29.06 (1.11)	−0.09 (0.93)	0.11
Education (years)	14.81 (3.95)	15.66 (2.87)	15.21 (3.49)	1.83 (0.10)	0.24
***APOE* ε4** (-/+)	57:42	79:26	136:68	7.15 (<0.005)	0.18
Baseline MRI values (mm, mm^3)					
Hippocampal mm^3	3540 (410.32)	3523 (410.34)	–	–	–
Entorhinal mm	3.20 (0.25)	3.16 (0.27)	–	–	–
Lateral ventricles mm^3	18,721 (10189.04)	17,238 (9097.19)	–	–	–
Baseline memory values					
Memory composite score	20.46 (3.38)/6.60 (1.79)†	0.93 (0.49)	–	–	–
Baseline cytokines and AD CSF values (pg/mL)					
CSF Aβ-42	710.30 (211.42)	1256.3 (655.20)	–	–	–
CSF p-tau	61.28 (19.82)	21.82 (9.12)	–	–	–
CSF IL-8	47.51 (11.50)	1.66 (0.12)	–	–	–
CSF IL-6	1.06 (0.49)	4.48 (2.31)	–	–	–
CSF follow-up subsample					
N follow-up	35	105	140	–	–
CSF follow-up obs	35	177	212	–	–
Time from baseline	4.55 (0.50)	2.18 (1.34)	2.57 (1.53)	–	–
Interval (range in years)	2.88–5.69	0.75–5.15	0.75–5.69	–	–

Descriptive statistics represent mean (SD). N = number of subjects. Obs = total number of observations. *MRI obs* and *Memory obs* rows contain info related to the (mean [SD]) number of observations per participant. *APOE* ε4 = non-carriers: carriers. MMSE = Mini Mental State Examination. Cohort differences are assessed using chi-squared test (χ^2[p]) for dichotomous variables and *t*-test (t [p]) for continuous. False discovery rate (pFDR) correction was applied to the *t*-test models. Effect size for cohort differences is assessed using Cohen's D for continuous variables and Cramer's V for dichotomous. Brain measures reflect thickness and volume averaged across hemispheres. † Memory composite score for COGNORM refers to the raw scores of Immediate and Delayed in the Word List Memory Task (CERAD). N follow-up = number of subjects at follow-up.

correction, tissue and volumetric segmentation, cortical surface reconstruction, and cortical parcellation. Next, an unbiased within-subject template space based on all cross-sectional images was created for each participant, using a robust, inverse consistent registration (Reuter et al., 2010). To increase the reliability and statistical power of the cortical thickness estimates, the processing of each time point was then reinitialized with common information from the within-subject template. Entorhinal thickness and volume of the hippocampi and lateral ventricles averaged across hemispheres, were selected as regions of interest (ROIs). In extended analyses, we also included ROI-based cortical thickness (|n| = 34) (Desikan et al., 2006) and subcortical volumetric (|n| = 7) analyses (*aseg* atlas) (bilateral accumbens, amygdala, caudate, pallidum, putamen, thalamus and supratentorial volume). These additional analyses are reported in SI in [Zenodo] at https://doi.org/10.5281/zenodo.7896648, for a visual representation see Supplementary Figs. 2 and 3.

2.3. APOE genotyping

For COGNORM, blood samples were genotyped for *APOE* (gene map locus 19q13.2) using TaqMan Allelic Discrimination technology (Applied Biosystems). Genotypes were obtained for the 2 SNPs that are used to unambiguously define the ε2, ε3, and ε4 alleles (rs7412 and rs429358). For ADNI, *APOE* genotyping was based on DNA extracted by Cogenics from a 3 mL aliquot of EDTA blood as fully described in https://adni.loni.usc.edu/methods/genetic-data-methods/. We dichotomized the participants either into ε4 carriers or non-carriers (68:136).

2.4. CSF collection and analysis

For COGNORM, the CSF collection is thoroughly described elsewhere (Idland et al., 2017; Sajjad et al., 2020). Briefly, the CSF samples were analyzed at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital (Mölndal, Sweden). CSF concentrations of IL-6 and IL-8 were measured using a Mesoscale Discovery (MSD) immunoassay (V-PLEX Human Proinflammatory Panel I), and CSF Aβ42 and p-tau concentrations using INNOTEST enzyme-linked immunosorbent assay (ELISA; Fujirebio, Ghent, Belgium). For ADNI, CSF IL-6 concentrations were measured using commercially available multiplex immunoassays (Millipore Sigma, Burlington, MA) (*ADNI_HULAB.csv*), CSF IL-8 using Luminex immunoassay technology (Rules Based Medicine MyriardRBM) (*Biomarkers Consortium ADNI CSF QC Multiplex data.csv*), and CSF Aβ42 and p-tau concentrations using Elecsys phosphorylated-tau 181 (p-tau), and β-amyloid (1–42) CSF immunoassays (*UPENNBIOMK9.csv* ADNI file). Values above the upper technical limit were recalculated based on the calibration curve (≥ 1700 pg/ml for Aβ-42 [n = 19]). Available CSF data were n = 194 for IL-6 and n = 198 for IL-8. Each outlier outside the range set was replaced by a NA value (we identified 2 outliers in each cohort). Longitudinal CSF Aβ-42 and p-tau data were available for a subset of participants (COGNORM: n = 35, mean interval = 4.55 years,

SD = 0.50; ADNI: n = 105, mean interval = 2.18 years, SD = 1.34). CSF values were scaled within cohort. The CSF follow-up subsample was representative of the main baseline sample as the main characteristics were not significantly different from the baseline sample. See Table 1 and Supplementary Table 1.

2.5. Analyses to establish comparability of samples and the unique role of IL-6 and IL-8 relative to other biomarkers

Prior to the main analyses, two preliminary tests were carried out to 1) determine whether the COGNORM and ADNI samples could be merged and 2) test whether at baseline IL-6 and IL-8 contributions were independent from those of other relevant markers in the context of the aging-disease continuum. For both analyses, we used a set of additional CSF biomarkers available in both datasets at baseline (sTREM2, neurogranin, FABP3, total tau, NFL, YKL-40, Aβ-42, p-tau). See **SI** for the CSF collection and analysis. In the first analysis, we checked whether the CSF correlation matrices between cohorts were comparable using Mantel tests with |n| = 1000 replicates ($r = 0.84$, $p < 0.001$) (Dray and Dufour, 2007). In the second analysis, we used an Independent Component Analysis (ICA), as implemented in the *fastICA* package (Marchini and Ripley, 2021), on all the additional available biomarkers described above, including IL-6 and IL-8. We tested whether IL-6 and IL-8 effects were mostly captured by components which are independent of those supposed to capture amyloidosis and tau pathology and neurodegenerative processes.

2.6. Cognitive function over time

We used two composite scores for assessing memory performance and memory decline. For ADNI, we selected ADNI-MEM (Crane et al., 2012). We scaled the longitudinal ADNI-MEM scores based on the mean and SD at the first timepoint. For COGNORM, we computed a composite score based on the Immediate and Delay scores in the Word List Memory Task (CERAD) (Morris et al., 1989) at the first timepoint using principal component analysis (PCA). The scores at follow-up were predicted using the components found at the first timepoint. Each memory composite score was standardized within each cohort. The Cohort variable was regressed out from all the statistical analyses performed. See Supplementary Fig. 4 for a visual representation of the cognitive trajectories of episodic memory for each cohort.

2.7. Statistical analysis

All analyses were run in the R-environment (R Core Team, 2022). Linear mixed-effects models (LME), as implemented in the lme4 R-package (Bates et al., 2015), were used to assess the effect of IL-6 and IL-8 × Time (from baseline) on brain structural and memory performance decline, and core AD CSF change. The biomarker × Time interaction represented the effect of baseline biomarker concentrations on change. Additional models were computed to assess the interaction of IL-6 and IL-8 with the core AD biomarkers (Aβ-42, p-tau, p-tau/Aβ-42 ratio). IL-6 and IL-8 were analyzed separately throughout. Before performing the analyses, we confirmed that data were – grossly – normally distributed. The models were corrected for multiple comparisons using false discovery rate, Benjamini-Hochberg correction (pFDR) (Benjamini and Hochberg, 1995), when multiple dependent variables were tested. Specifically, we corrected the p-value from all the models, separately for each dependent domain (brain, memory, CSF change) and each LME level of complexity.

2.7.1. Relationship between IL-6 and IL-8 and brain structural and memory decline over time

We tested whether baseline CSF IL-6 and IL-8 were associated with entorhinal thinning, hippocampal atrophy, and lateral ventricle expansion over time by running a series of separate LME models. See Supplementary Table 2 for Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) of the different models. First, LME models were run as a function of IL-6 and IL-8, Time, and the IL-6 and IL-8 × Time interaction. Sex, Cohort (ADNI, COGNORM), Age at baseline (mean-centered), intracranial volume (only for volumetric outcomes), and *APOE* ε4 were introduced as covariates. Random intercepts per individual were included. Next, we tested whether the effect of IL-6 and IL-8 in the model was moderated by the concentrations of core AD biomarkers. Hence, second, we re-ran the LME models with the addition of Aβ-42 together with the IL-6 and IL-8 × Time interaction. Third, we added p-tau to the interaction of the basic LME model. Fourth, we added a p-tau/Aβ-42 ratio term and its interactions with IL-6 and IL-8 and Time to the basic model. Note that the main effects and lower-level interactions of Aβ-42 and p-tau were also added in the corresponding models. The same procedure described above was run to assess the relationship of baseline CSF IL-6 and IL-8 with longitudinal memory scores with the additional introduction of education as a covariate. In addition, when results were significant, we re-ran the analyses tentatively controlling for test–retest effects including a single dummy regressor (which encodes whether the participants have taken the test before or not) denoting the second visit onwards, since most test–retest effects occur between the first and the second visit (Rabbitt et al., 2001; Wilson et al., 2006).

2.7.2. Relationship between IL-6 and IL-8 and change in core AD CSF biomarkers over time

We assessed, in a subsample (n = 140), whether baseline concentrations of CSF IL-6 and IL-8 predicted change in CSF Aβ-42, p-tau, and p-tau/Aβ-42 ratio over time. To avoid batch effects, the CSF values at baseline were re-analyzed in the same batch as the follow-up CSF values for the COGNORM dataset. We scaled the core AD CSF biomarkers based on their mean and SD at the first timepoint. We ran LME analyses where Aβ-42, p-tau, and p-tau/Aβ-42 ratio CSF were fitted by IL-6 and IL-8, Time, and the IL-6 and IL-8 × Time interaction. In the p-tau model, we additionally included baseline CSF Aβ-42 and its interaction terms in the model. Sex, Cohort, Age at baseline (mean-centered), and *APOE* ε4 were used as covariates.

3. Results

3.1. Cohort characteristics

The baseline characteristics of the cohort are presented in Table 1.

3.2. Results of the analyses to establish comparability of samples and the unique role of IL-6 and IL-8 relative to other biomarkers

This first analysis showed that biomarker matrices were highly comparable based on the output of the Mantel test. Since the samples also have similar sociodemographic characteristics (shown in Table 1), it was deemed suitable to combine the two cohorts. The second analysis showed three meaningful components: the first one weighted on tau pathology and neurodegenerative processes; for the second one interleukins had a higher contribution, whereas the third component weighted strongly on Aβ-42. Hence, IL-6 and IL-8 are captured by a unique ICA component, suggesting IL-6 and IL-8 contributions can be largely dissociated from those of amyloid and tau pathology. See Supplementary Table 3 for the ICA output.

3.3. Associations between IL-6 and IL-8 and brain atrophy

The results are presented in Table 2 (n = 219 participants, MRI observations = 907). No significant relationships between CSF IL-6 and IL-8 and brain structure survived corrections for multiple comparisons using pFDR. For space consideration, we reported the stats of all the variables included in the models in [Zenodo] at https://doi.org/10.

Table 2
Associations between CSF IL-6 and IL-8 and brain atrophy.

	Brain Region	(t [pFDR])	Estimate [CI]
IL-6 × Time	Entorhinal thickness	−1.39 (0.26)	-2.18×10^{-3} [-5.25×10^{-3} -8.96×10^{-4}]
	Hippocampal volume	−1.00 (0.32)	−1.53 [-4.53–1.47]
	Lateral Ventricles volume	−1.35 (0.26)	−27.03 [-66.32–12.27]
IL-8 × Time	Entorhinal thickness	0.37 (0.71)	6.04×10^{-4} [-2.52×10^{-3}–3.74×10^{-3}]
	Hippocampal volume	1.65 (0.29)	2.56 [-0.46–5.60]
	Lateral Ventricles volume	−0.79 (0.64)	−17.14 [-59.41–25.06]
IL-6 × Time × Aβ	Entorhinal thickness	−0.02 (0.99)	-2.73×10^{-5} [-3.27×10^{-3}–3.20×10^{-3}]
	Hippocampal volume	0.25 (0.99)	0.41 [-2.72–3.52]
	Lateral Ventricles volume	−0.007 (0.99)	−0.15 [-39.49–39.35]
IL-8 × Time × Aβ	Entorhinal thickness	−1.94 (0.16)	-2.82×10^{-3} [-5.68×10^{-3}–4.02×10^{-7}]
	Hippocampal volume	0.14 (0.89)	0.20 [-2.52–2.90]
	Lateral Ventricles volume	0.18 (0.89)	3.31 [–33.07–39.74]
IL-6 × Time × p-tau	Entorhinal thickness	0.81 (0.42)	8.90×10^{-4} [-1.26×10^{-3}–3.03×10^{-3}]
	Hippocampal volume	−1.37 (0.32)	−1.45 [-3.53–6.26]
	Lateral Ventricles volume	1.24 (0.32)	17.50 [-9.99–45.00]
IL-8 × Time × p-tau	Entorhinal thickness	−0.21 (0.84)	-4.11×10^{-4} [-4.29×10^{-3}– 3.51×10^{-3}]
	Hippocampal volume	−0.66 (0.76)	−1.27 [-5.01–2.49]
	Lateral Ventricles volume	−1.28 (0.60)	−34.82 [-87.97–18.17]
IL-6 × Time × p-tau/Aβ ratio	Entorhinal thickness	−0.40 (0.69)	-6.90×10^{-4} [-4.02×10^{-3}–2.65×10^{-3}]
	Hippocampal volume	−2.21 (0.08)	−3.61 [-6.80–−0.40]
	Lateral Ventricles volume	1.43 (0.23)	31.30 [-11.45–73.97]
IL-8 × Time × p-tau/Aβ ratio	Entorhinal thickness	0.95 (0.52)	2.11×10^{-3} [-2.22×10^{-3}–6.50×10^{-3}]
	Hippocampal volume	−1.66 (0.29)	−3.52 [-7.64–0.65]
	Lateral Ventricles volume	−0.61 (0.54)	−17.94 [-75.82–39.79]

LME models. Sex, Cohort, Age at baseline (mean-centered), Intracranial volume, and *APOE* ε4 as covariates. Statistics represent t-values, pFDR corrected values, and estimate. CI = confidence interval 95%.

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3.4. Associations between IL-6 and IL-8 and memory changes

We assessed the relationship between CSF IL-6 and IL-8 and the longitudinal trajectories of memory changes (n = 219 participants, memory observations = 1251). IL-8 × Time interaction was significant after controlling for multiple testing (t = 1.97, df = 921.05, pFDR = 0.05): higher concentrations of IL-8 were associated with relatively better memory over time. Moreover, IL-8 × p-tau × Time was also significant (t = -2.02, df = 921.06, pFDR = 0.04) as was IL-8 × p-tau/Aβ-42 ratio × Time (t = -2.21, df = 939.58, pFDR = 0.03). Both interactions were driven by higher concentrations of IL-8 with lower concentrations of p-tau and p-tau/Aβ-42 ratio being associated with better memory over time. In the context of higher levels of p-tau and p-tau/Aβ-42 ratio, the trajectories of memory decline were similar regardless of the neuroinflammatory levels. See Fig. 1 for a visual representation of the significant results and Table 3 for an overview of all the models. *APOE* ε4 and Sex have been suggested to be possible modifiers of the inflammation–cognition relationship. Although statistical power probably is insufficient to detect 4-way interactions, we ran a series of exploratory analyses. See Supplementary Table 4 for the stats and Supplementary

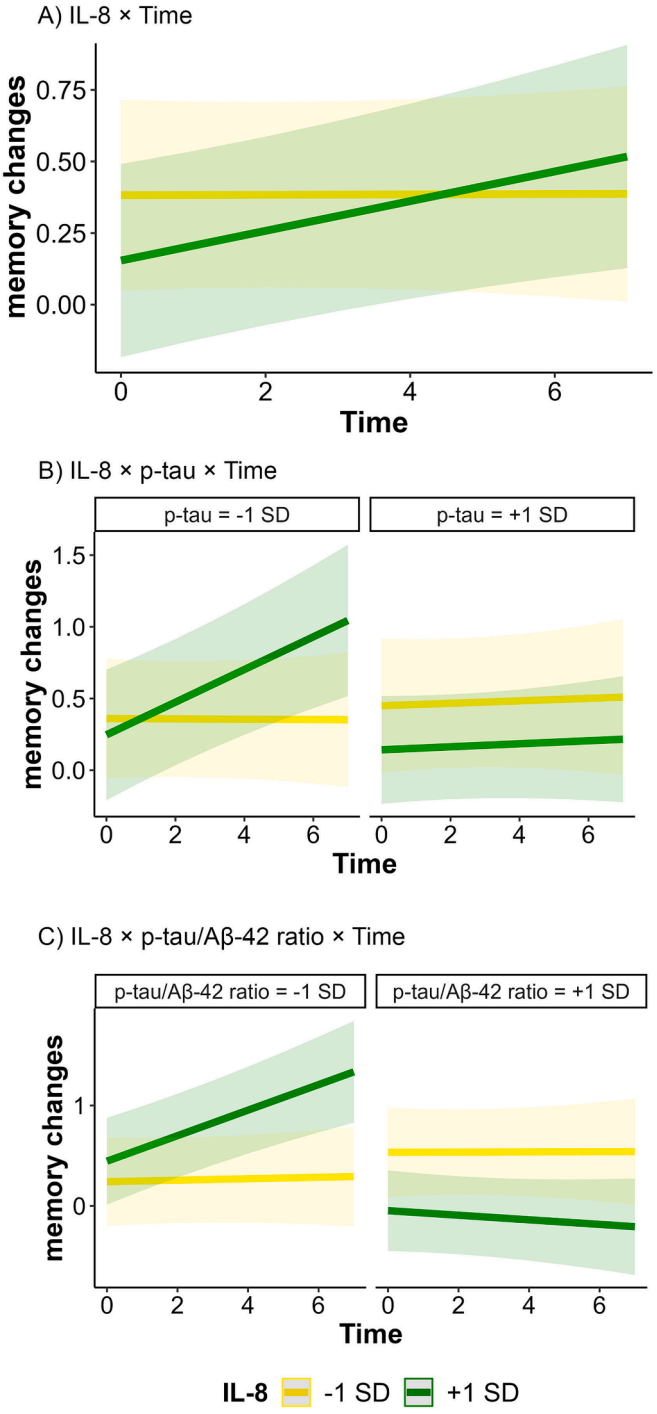

Fig. 1. LME interaction CSF IL-8 on memory changes. Sex, Cohort, Age at baseline (mean-centered), Education, *APOE* ε4, and test-retest effect were included in the analyses as covariates. Number of participants included = 219. For illustrative purposes, green and yellow (+1 SD/-1 SD, i.e., high/low CSF concentrations of IL-8) reflect the trajectories on memory change – as a function of time – at mean ± 1 SD of the CSF biomarker. Results are pFDR corrected. The unit for Time is years. **(A)** CSF IL-8 × Time interaction **(B)** CSF IL-8 × p-tau × Time interaction. **(C)** CSF IL-8 × p-tau/Aβ-42 × Time interaction.

Table 3
Associations between CSF IL-6 and IL-8 and memory changes.

	Memory changes (t [pFDR])	Estimate [CI]
IL-6 × Time	0.42 (0.67)	5.15×10^{-3} [-0.02–0.03]
IL-8 × Time	1.97 (0.05*)	0.02 [2.92×10^{-4}– 0.05]
IL-6 × Time × Aβ	−0.70 (0.48)	-8.82×10^{-3} [-0.03–0.01]
IL-8 × Time × Aβ	0.52 (0.60)	6.52×10^{-3} [-0.02–0.03]
IL-6 × Time × p-tau	−0.50 (0.62)	-4.54×10^{-3} [-0.02–0.01]
IL-8 × Time × p-tau	−2.02 (0.04*)	-0.03 [-0.05–-7.68×10^{-4}]
IL-6 × Time × p-tau/Aβ ratio	−0.94 (0.35)	−0.01 [-0.04–0.01]
IL-8 × Time × p-tau/Aβ ratio	−2.21 (0.03*)	-0.03 [-0.07–-3.71×10^{-3}]

LME models. Sex, Cohort, Age at baseline (mean-centered), Education, *APOE* ε4, and test–retest effect were included in the analyses as covariates. Statistics represent t-values, pFDR corrected values, and estimate. CI = confidence interval 95%.

Fig. 5 for a visual representation. The 4-way interactions IL-6 × p-tau × Time × *APOE* ε4 (t = 2.14, df = 861.75, pFDR = 0.03) and IL-6 × p-tau/Aβ-42 ratio × Time × APOE ε4 (t = 2.46, df = 894.23, pFDR = 0.01) were significant. In the context of lower levels of p-tau and p-tau/Aβ-42 ratio, higher concentrations of IL-6 were associated with better memory over time, only in *APOE* ε4 non-carriers. Note, however, that our sample has limited statistical power to detect 4-way ([likely] attenuated, not reversed) interactions.

3.5. Associations between IL-6 and IL-8 and changes in core AD CSF biomarkers over time

The results are presented in Table 4 (n = 140, CSF observations = 352). Linear mixed models showed that higher baseline IL-6 was related to less CSF p-tau increments, independently of Aβ-42 (t = -2.61, df = 157.80, pFDR = 0.03). See Fig. 2 and Table 4**.** Moreover, we found a significant interaction between IL-6 and Aβ-42 concentrations at baseline on p-tau change (t = 2.89, df = 155.41, pFDR = 0.005); lower concentrations of CSF IL-6 with lower concentrations of CSF Aβ-42 were associated with more CSF p-tau changes.

Table 4
Associations between CSF IL-6 and IL-8 and changes in core AD CSF biomarkers over time.

	CSF changes	(t [pFDR])	Estimate [CI]
IL-6 × Time	Aβ-42	0.19 (0.85)	2.29×10^{-3} [-0.02–0.03]
	p-tau	−2.61 (0.03*)	-0.02 [-0.03–-4.89×10^{-3}]
	p-tau/Aβ-42 ratio	−1.96 (0.08)	-0.01 [-0.03–-1.00×10^{-4}]
IL-8 × Time	Aβ-42	−2.25 (0.07)	-0.03 [-0.06–-4.03×10^{-3}]
	p-tau	0.36 (0.72)	2.85×10^{-3} [-0.01–0.02]
	p-tau/Aβ-42 ratio	1.54 (0.19)	0.01 [-4.15×10^{-3}–0.03]
IL-6 × Time × Aβ	Aβ-42	–	–
	p-tau	2.87 (0.005*)	0.02 [7.87×10^{-3}– 0.04]
	p-tau/Aβ-42 ratio	–	–
IL-8 × Time × Aβ	Aβ-42	–	–
	p-tau	0.08 (0.93)	5.722×10^{-4} [-0.01–0.01]
	p-tau/Aβ-42 ratio	–	–

LME models. Sex, Cohort, Age at baseline (mean-centered), and *APOE* ε4 (and Aβ-42 for p-tau changes models) as covariates. Statistics represent t-values, pFDR corrected values, and estimate. CI = confidence interval 95%.

4. Discussion

The main results showed that higher concentrations of CSF IL-8 were associated with better memory performance over time, specifically in the context of lower concentrations of p-tau and p-tau/Aβ-42 ratio, while higher baseline IL-6 were related to less CSF p-tau changes over time in cognitively healthy older adults. This suggests, that, in the context of cognitively healthy aging, up-regulation of pro-inflammatory cytokines may play a beneficial role. However, the "neuroprotective" effects of ILs were largely constrained to low concentrations of pathological biomarkers, indicating a pathology-dependent nature of ILs and suggesting, to some extent, a switch towards a neurotoxic profile of IL-6 and IL-8 with more AD-related pathology.

Higher concentrations of CSF IL-8 were associated with better memory over time with lower levels of p-tau and p-tau/Aβ-42 ratio suggesting a neuroprotective role of the neuroinflammatory response, constrained to a lower load of tau pathology. This result stands in contrast to two previous cross-sectional studies, where higher IL-8 was related to cognitive impairment (Baune et al., 2008; Trollor et al., 2012). However, these studies used cross-sectional data and IL-8 serum values. We speculate that the pathology-dependent effect of IL-8 on cognitive functioning is driven by an early beneficial neuroinflammatory response, exerted by glial cells, before increased accumulation of AD pathology in the brain. During this process, cytokines and chemokines are released, along with neurotrophic factors, to eliminate pathogens, restore homeostasis and promote neuronal survival (Galimberti et al., 2006; Leng and Edison, 2021). Indeed, an initial attempt from glial cells to regulate Aβ clearance is described in preclinical AD phases (Albrecht et al., 2021; Galimberti et al., 2006). However, the neuroprotective function might be exerted by glial cells until a threshold: from that moment on, the neuroinflammatory response may switch its profile to a more neurotoxic one along with an increased accumulation of amyloid plaques (probably also due to an ineffective clearance by glial cells) and neurofibrillary tangles (Calsolaro and Edison, 2016; Leng and Edison, 2021).

Indeed, higher concentrations of CSF IL-8 have been found in patients with MCI compared to AD, independently of the disease duration, suggesting that in early phases of the disease, increased release of IL-8 may be a contributing factor rather than a consequence of AD (Galimberti et al., 2006; Hesse et al., 2016; Willette et al., 2013). As described above, we found a negative interaction of IL-8 and p-tau (and p-tau/Aβ-42 ratio concentrations) on memory changes. This relationship is however not clearly understood in the literature. A human neuronal cell (SH-SY5Y) study suggests a potential role of IL-8 in increasing tau phosphorylation (Vaz et al., 2020), whereas cross-sectional PET evidence suggests that CSF IL-8 is inversely related to tau PET ([18F] flortaucipir FTP) signal (Albrecht et al., 2021). When we included *APOE* ε4 as a possible modifier of the inflammation – cognition relationship in the context of lower levels of AD biomarkers, higher concentrations of IL-6 were associated with better memory performance over time only in *APOE* ε4 non-carriers. Although Schram and colleagues (2007) reported higher blood levels of IL-6 associated with steeper cognitive decline in *APOE* ε4 carriers, several studies reported no evidence for the effect modification of *APOE* ε4 status (Dik et al., 2005; Wennberg et al., 2019), while in our case, the neuroprotective effects of IL-6 levels seem to be constrained to individuals with lower levels of pathology and the *APOE* ε4 non-carrier status. However, the current study has low statistical power to detect complex interactions, and these results must therefore be regarded as preliminary, requiring further investigation.

Moreover, in our study, higher baseline CSF IL-6 was related to less p-tau changes over almost 6 years, hence, relatively lower concentrations of tau protein's phosphorylation over time, also suggesting adaptive mechanisms of early neuroinflammation. Correspondingly, the interaction found pointed towards lower concentrations of IL-6 in the context of higher amyloid-pathological load associated with higher p-tau changes. This result is in contrast with in vitro studies where IL-6

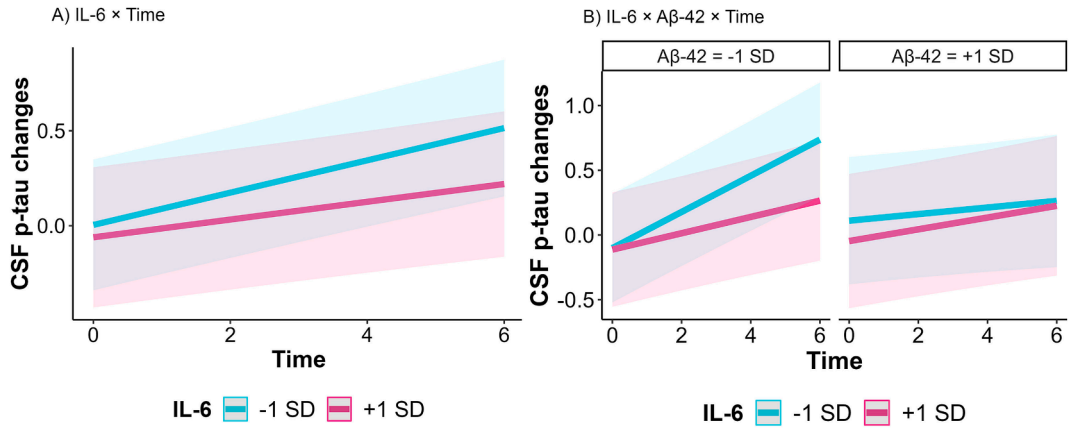

Fig. 2. LME interaction CSF IL-6 on CSF p-tau changes. Sex, Cohort, Age at baseline (mean-centered), and APOE ε4 as covariates. Number of participants included = 140. For illustrative purposes, magenta and cyan (+1 SD/-1 SD, i.e., high/low CSF concentrations of IL-6) reflect the trajectories of AD CSF biomarkers – as a function of time – at mean ± 1 SD of the CSF interleukins. The unit for Time is years. **(A)** CSF IL-6 × Time interaction on p-tau change. **(B)** CSF IL-6 × Aβ-42 × Time on p-tau change.

contributed to APP processing and production and hyperphosphorylation of tau via a cyclin-dependent kinase 5 pathway (Calsolaro and Edison, 2016; Lyman et al., 2014; Wang et al., 2015). On the other hand, significant negative associations between IL-6 and beta-amyloid accumulation, and no significant relationship with tau PET have been reported from in vivo PET studies (Albrecht et al., 2021).

In the context of aging and AD, neuroinflammatory response, especially associated with pro-inflammatory cytokines, can be described as a "double-edged sword", depending on the pathological load. Cytokines released by activated glial cells contribute to AD pathology (Heneka et al., 2015). As in a vicious cycle, Aβ aggregates may chronically stimulate glial cells to release toxic products as cytokines, that in turn contribute to Aβ production and could accelerate the pathological cascade of AD events. As described in a *meta*-analysis and systematic review (Shen et al., 2019), in patients with AD, higher concentrations of peripheral IL-6 and IL-8 were associated with the presence of AD biomarkers. However, in our study of healthy older adults, we found a beneficial role of neuroinflammation that may be constrained to lower levels of AD pathology. We hypothesize a shifting profile of pro-inflammatory cytokines towards neurotoxicity, at higher levels of the AD pathological load. A "neurotoxic" profile of ILs may be fully present in individuals with higher pathology than those included in our sample, which showed a quite cognitively healthy profile. Overall, IL-8 and IL-6 might display acute or chronic inflammatory components, and neuroprotective and neurotoxic effects across different stages of the aging-disease continuum (Willette et al., 2013). Further, the ICA analysis showed an independent contribution of ILs from other biomarkers associated with AD such as p-tau and Aβ-42, and neurodegeneration biomarkers. This lack of relationship between ILs and other biomarkers seems to extend to the AD population, in which CSF IL-6 and IL-8 concentrations did not correlate to tau, Aβ-42, neurodegeneration, and gliosis biomarkers (Hesse et al., 2016; Van Hulle et al., 2021). Up-regulation of ILs in both cognitively healthy and impaired aging seems to follow a different trajectory than AD biomarkers and it might not be closely tightened to the AD cascade. This result combined with the protective effects of ILs may warrant more investigation of how ILs are related to cognitively healthy aging and AD.

We interpreted IL-6 and IL-8 together as part of the inflammatory response in the central nervous system. Results from both cytokines generally showed the same profile, showing neuroprotective effects, which were specific to individuals with lower levels of pathology. However, IL-6 and IL-8 also showed specific associations with cognition and neurochemistry. Moreover, in our sample, the correlation between CSF IL-8 and IL-6 was relatively low ($r = 0.25$). This raises the question of whether to analyze and interpret the different pro-inflammatory cytokines together (Baune et al., 2009) or rather dissociate them to better understand their specific associations with brain and cognition in aging (Albrecht et al., 2021). IL-6 is a pleiotropic cytokine, a member of the hematopoietic family, it is associated with B cell differentiation and may play a role in reactive gliosis (Benveniste, 1992). IL-8 is part of the chemokine group, an autocrine agent for microglia that provides a range of pro-inflammatory patterns to the site of injury as chemotaxis of inflammatory cells, recruitment of neutrophils (Franciosi et al., 2005; Remick, 2005) and compared to other interleukins, is produced in the early phases of the inflammatory response with longer lasting effects (Remick, 2005). Thus, although both are indicating aspects of neuroinflammation, they reflect partly different processes, and more complex multimodal analyses are needed to better capture the differential effects of both ILs.

4.1. Limitations and technical considerations

Several limitations need to be considered. We merged two cohorts (ADNI and COGNORM) which may have produced new sources of errors due to differences in the measurements or the populations (Zuo et al., 2019). On the other hand, this merging may constitute a strength providing more robust results that are less likely subject to sampling bias. Since both sociodemographic and biomarker cross-correlations were comparable across cohorts, the benefits of combining the samples include increased statistical power. Another technical consideration of this study is the use of different memory composite scores between both cohorts, which we assumed reflect the same construct. The scores were standardized by initial baseline levels within each cohort and residual effects controlled using Cohort as a covariate. This approach might lead to small biases; however, it was chosen as it has higher statistical power compared to alternative *meta*-analytical approaches. The major strength of this study is the use of longitudinal data, indeed most research on the topic has relied on cross-sectional MRI and cognitive data, which may be problematic when capturing changes that ought to be longitudinally measured. Further, most studies have used serum samples – rather than CSF – to index pro-inflammatory interleukins in healthy older participants (Alvarez-Rodríguez et al., 2012; Maggio et al., 2006). This methodological feature is important since the association between blood and CSF concentrations of interleukins has been found to be modest (Bettcher et al., 2018) or not significant (Hesse et al., 2016), and CSF markers are thought to reflect biochemical changes more closely in the brain (Blennow et al., 2012). Finally, even when using longitudinal data, it remains challenging for neuroimaging studies to pinpoint the specific underlying neurobiological mechanisms behind interleukin associations with brain and cognition, especially when the

mechanisms may be both a response to or a cause of pathology.

5. Conclusions

In conclusion, this study provides novel insights into the interplay between neuroinflammation and brain, memory, and core AD biomarker changes over time. In cognitively healthy older adults, higher concentrations of CSF IL-8 and IL-6 were associated over time with better memory and lesser p-tau accumulation, suggesting a neuroprotective role of the early neuroinflammatory response with lower load of AD pathology.

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Competing interests

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB has served as a consultant, at advisory boards, or on data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. All conflicts of interest are unrelated to the work presented in this paper. The remaining authors declare no competing interests.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The ADNI data is freely available at https://adni.loni.usc.edu/, COGNORM data will be shared upon reasonable requests and necessary data-sharing agreements.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.06.027.

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