β-amyloid pathology and hippocampal atrophy are independently associated with memory function in cognitively healthy elderly

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The independent effects of different brain pathologies on age-dependent cognitive decline are unclear. We examined this in 300 cognitively unimpaired elderly individuals from the BioFINDER study. Using cognition as outcome we studied the effects of cerebrospinal fluid biomarkers for amyloid-β (Aβ42/40), neuroinflammation (YKL-40), and neurodegeneration and tau pathology (T-tau and P-tau) as well as MRI measures of white-matter lesions, hippocampal volume (HV), and regional cortical thickness. We found that Aβ positivity and HV were independently associated with memory. Results differed depending on age, with memory being associated with HV (but not Aβ) in older participants (73.3–88.4 years), and with Aβ (but not HV) in relatively younger participants (65.2–73.2 years). This indicates that Aβ and atrophy are independent contributors to memory variability in cognitively healthy elderly and that Aβ mainly affects memory in younger elderly individuals. With advancing age, the effect of brain atrophy overshadows the effect of Aβ on memory function.

The prevailing hypothesis of the pathophysiology of Alzheimer’s disease (AD) suggests β-amyloid (Aβ) deposition in the brain as the primary event followed by tau pathology, neuronal dysfunction, neurodegeneration, and cognitive symptoms1. To understand the pathophysiology of AD and to improve design of clinical trials, more information is needed about the sequential order of and associations between AD biomarkers, and their relationship with other age-associated brain changes. It is especially important to clarify the roles of different biomarkers in early stages of AD, since trials of disease-modifying drugs in late stages of AD have failed and focus is now shifting towards targeting the disease early, even before symptoms develop.

Aβ pathology, detected by amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) levels of Aβ peptides, is common in cognitively unimpaired elderly2–5. A person with Aβ pathology can be said to be on the Alzheimer continuum6, and the asymptomatic presence of Aβ pathology in cognitively unimpaired persons may be called preclinical AD7. The direct effects of Aβ pathology on cognitive performance in the preclinical stages are not fully understood, with some studies showing an association between Aβ pathology and worse memory performance cross-sectionally8–12 and others not13–15. However, recent studies conclude that Aβ negative cognitively unimpaired subjects perform better on tests of overall cognition, as well as tests of memory function, compared to Aβ positive, and, more notably, Aβ positive cognitively unimpaired show a faster cognitive decline over time16–21.

Besides Aβ pathology, other AD-related brain changes have also been associated with cognitive decline. Post-mortem studies have shown that the degree of cognitive impairment is closely related to the amount of neurofibrillary tangles, consisting of hyperphosphorylated tau (P-tau), in patients with AD dementia22. Associations have been shown in cognitively unimpaired persons between memory performance and CSF levels of total tau

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All methods were performed in accordance with the relevant guidelines and regulations. A cut-off for Aβ positivity was defined using mixture modelling in a larger sample of the BioFINDER study (n = 889 in total) consisting of a group of cognitively unimpaired subjects, including the sample included in this study and an additional 235 subjects (n = 325), as well as a group of subjects with subjective cognitive decline (SCD; n = 204), MCI (n = 276), or dementia (n = 84), using the R package “mixtools”. Mixture modelling is a 2-step procedure based on an expectation maximization algorithm, which assumes that the CSF β42/40 ratio is a mixed sample from two different normal distributions (in this case one with a normal Aβ deposition and one with an abnormal Aβ deposition). Mixture modelling has previously successfully been used to identify cut-offs for Aβ biomarkers.

To compare differences between groups, the chi-square test was used for dichotomous variables and the independent samples t-test for numerical variables. Linear regression models were tested to assess the effects of different biomarkers on cognition, with and without covariates (age, sex, and years of education, and HV was also adjusted for ICV). Interaction terms were tested for biomarkers and age. To facilitate interpretation of interactions and main effects, we used z scores of continuous variables. Test of statistical mediation was performed using the
causal steps approach. WML volume was used after logarithmic transformation (ln), because of skewed distribution. Statistical significance was defined by p < 0.05. Correction for multiple comparisons was performed by the false discovery rate when indicated. Statistical analyses were performed with R (version 3.3) and SPSS Statistics for Mac (version 24).

Results

Out of the 361 participants of the cohort of cognitively unimpaired in the Swedish BioFINDER Study, 300 had complete baseline MRI and CSF analyses and were included in the present study. Demographics are shown in Table 1 and Supplementary Fig. 1 shows a histogram of the age distribution in the sample. The cut-off for Aβ positivity was defined as Aβ42/40 < 0.051 (Supplementary Fig. 2). The proportion of amyloid positive subjects in each group used for mixture modelling is shown in Supplementary Table 1.

Associations between biomarkers and memory. In univariable analyses, Aβ positivity (β = −0.15; p = 0.009), higher P-tau (β = −0.15; p = 0.012), higher T-tau (β = −0.13; p = 0.021), and higher YKL-40 (β = −0.13; p = 0.026) were associated with worse memory performance. When controlling for age, sex, and education, only Aβ positivity (β = −0.14; p = 0.013) remained significantly associated with memory (Table 2). Larger WML volume (β = −0.14 (p = 0.020), smaller total HV (β = 0.21; p < 0.001), and thinner cortex of all regions studied (β = 0.13–0.28; p = 0.001–0.030) were associated with worse memory, in the unadjusted analyses. When controlling for age, sex, and education (and for HV also ICV), smaller HV (β = 0.27; p < 0.001) and thinner entorhinal/parahippocampal (β = 0.22; p < 0.001), temporal (β = 0.16; p = 0.012), and frontal (β = 0.14; p = 0.022) cortical thickness were associated with worse memory (Table 2). The results did not differ if total HV was replaced with left (β = 0.25; p < 0.001) or right HV (β = 0.24; p < 0.001).

When including all the biomarkers that were significant (not adjusted for multiple comparisons) after controlling for demographic variables in the same model, Aβ positivity (β = −0.14; p = 0.010) and smaller HV

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Table 1. Descriptive characteristics. Descriptive characteristics in the total population and split into two age groups by the median age (73.3 years). Mean (SD) if not otherwise specified. ***p < 0.001, **p < 0.01, *p < 0.05. Abbreviations: CSF, cerebrospinal fluid; Aβ40, amyloid-β 40; Aβ42, amyloid-β 42; MRI, magnetic resonance imaging; WML, white matter lesion; ctx, cortex; ADAS, Alzheimer’s disease assessment scale; AQT, A quick test of cognitive speed; SDMT, symbol digit modalities test; TMT-A, trailmaking test A.
\(\beta\) measures of cortical thickness, neither unadjusted (\(\beta\) sex, and ICV, the results were similar. Likewise, there were no associations between \(A\beta\) and education (and for HV also ICV), only HV remained significantly associated (\(0.14; p < 0.001\)) and adjusting for age, sex, and education (and for HV also ICV), only HV remained significantly associated (\(0.14; p < 0.001\)) and adjusting for age, sex, and ICV, the results were similar.

**Associations between biomarkers and attention/executive function.** Higher P-tau (\(3 = -0.13; p = 0.027\)) and T-tau (\(3 = -0.14; p = 0.018\)) were associated with worse performance on the composite attention/executive score unadjusted, but not when controlling for age, sex, and education (Table 2). No associations were seen between attention/executive function and \(A\beta\) positivity or any of the biomarkers and cognition. Linear regression models with cognitive measures as dependent variables and CSF/MRI measures as independent variables. Model 1: unadjusted.

**Associations between \(A\beta\) and brain structure.** There was no association between \(A\beta\) positivity and HV, neither unadjusted (\(3 = -0.033; p = 0.57\)) nor when adjusting for age, sex, and ICV (\(3 = 0.011; p = 0.81\)). When replacing total HV with left \(3 = -0.011; p = 0.81\) or right HV (\(3 = 0.031; p = 0.52\) and adjusting for age, sex, and ICV, the results were similar. Likewise, there were no associations between \(A\beta\) positivity and any of the measures of cortical thickness, neither unadjusted (\(3 = -0.071–0.026; p = 0.22–0.91\)) nor when adjusting for age and sex (\(3 = 0.038–0.051; p = 0.36–0.74\)).
Interactions between biomarkers and age to predict cognition. A significant interaction effect between total HV and age (used as a continuous predictor) on memory was seen ($p = 0.040$). Secondarily, we performed an exploratory analysis with the sample divided into younger and older participants, split by the median age (73.3 years). When using age as a dichotomous predictor, similar results were seen for the interaction effect ($p = 0.007$). When stratifying into the two age groups, the relationship between HV and memory was not statistically significant in the younger group ($p = 0.066$), but in the older group there was a highly significant relationship when controlling for demographic variables ($\beta = 0.40; p < 0.001$; Figs 1B and 2A, Suppl. Table 3).

No significant interaction was detected between Aβ positivity and age on memory ($p = 0.38$), but when stratifying into the two age groups, the relationship between HV and memory was not statistically significant in the younger group ($p = 0.066$), but in the older group there was a highly significant relationship when controlling for demographic variables ($\beta = 0.40; p < 0.001$; Figs 1B and 2A, Suppl. Table 3).

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No significant interaction was detected between Aβ positivity and age on memory ($p = 0.38$), but when stratifying into the two age groups, the opposite from HV was seen, i.e. there was an association between Aβ positivity and worse memory in the younger group ($\beta = -0.23; p = 0.003$), but not in the older group ($p = 0.38$; Figs 1B and 2B, Suppl. Table 3). Based on the theoretical model of amyloid pathology preceding tau pathology in AD, we tested if the association between Aβ positivity and memory was mediated by P-tau. When adding P-tau in the model in the younger group, a statistical mediation effect was seen, i.e. higher P-tau ($\beta = -0.17; p = 0.045$) but not Aβ positivity ($\beta = -0.15; p = 0.079$) was significantly associated with worse memory (Fig. 1B, Suppl. Table 4), and Aβ positivity was associated with higher P-tau ($\beta = -0.39; p < 0.001$; Fig. 1B, Suppl. Table 5) when controlling for age and sex.

No significant interactions were seen between any of the other CSF/MRI biomarkers and continuous age on memory, and no interactions with age were seen for any of the biomarkers on attention/executive function (data not shown). We also looked on interactions on memory function between Aβ positivity and sex and education respectively, as well as between HV and sex and education respectively. None of these interactions were significant (data not shown).

Discussion
In this study of cognitively unimpaired elderly, we found that (1) Aβ positivity, HV, and cortical thickness (temporal and frontal) were associated with worse memory, with independent effects of Aβ and HV on memory; (2) the Aβ effect on memory could be confirmed in the younger part of the sample, while the HV effect on memory was significant in the older part of the sample only; (3) Aβ positivity was not related to atrophy; and (4) biomarkers of white matter lesions and inflammation were not associated with memory or attention/executive function when controlling for demographic covariates. Taken together, our findings indicate that Aβ pathology and brain atrophy are independent contributors to subtle memory decline in cognitively healthy elderly. Furthermore, Aβ pathology mainly influences memory in the younger part of the population, possibly through mechanisms such...
as tau that do not require gross atrophy. With advancing age, the effect of brain atrophy seems to overtake the effect of Aβ on memory function.

Our findings are in agreement with previous studies where brain structure and Aβ pathology also were independently associated with memory performance in cognitively unimpaired, without an association between Aβ and atrophy. Some studies have argued that the Aβ effect on memory is mediated by neurodegeneration, at least to some degree. However, the studies showing that neurodegeneration mediates the effect of Aβ on memory included patients with MCI in their analyses, while the independent effect was seen when analysing cognitively unimpaired separately or adjusting for diagnosis as a co-variates. One interpretation of this is that later on in the AD process, the Aβ effect on memory is in part mediated through atrophy, but in the preclinical stages of the disease, Aβ pathology affects memory performance without being associated with atrophy. Such atrophy-independent effects of Aβ could depend on early tau pathology, causing dysfunction of neurons or loss of synapses, without gross atrophy. This hypothesis is supported by the statistical mediation effect of P-tau in the present study, where Aβ no longer had a significant association with memory when including P-tau in the model. However, the effect of P-tau on memory was not very strong and a trend was still seen for Aβ (p = 0.079) and this mediation effect needs to be studied further.

The age dependent associations between amyloid pathology, hippocampal volume, and memory have in part been described before in cognitively unimpaired subjects, where memory function has been shown to be more vulnerable to hippocampal volume loss at older age. This could imply that the function of other areas important for memory performance is impaired at higher age, contributing to worse memory without the need of as much hippocampal atrophy as in younger individuals. This is plausible considering age as a proxy of known and unknown processes, which can affect brain structure and function, such as TDP-43 accumulation. Aβ was associated with memory in the younger but not the older participants. However, in the absence of a statistically significant interaction effect between amyloid and age on memory, the interpretation of this should be made with caution. This age difference could be explained by other pathologies being more common in the older group, which may overshadow the effect of Aβ pathology on memory.

An association with attention/executive function was seen for HV, but not for any of the cortical thickness measures. This could be due to a larger variability in the HV variable, making it easier to find an existing association. Also, there are substantial interindividul differences between cortical thickness measures, making these analyses hard to interpret in cross-sectional studies.

This study has its limitations. First, as mentioned in the previous paragraph, it is a cross-sectional study, which means you cannot establish temporal changes of the variables. Second, studies have shown P-Tau to only exhibit moderate correlation with tau neuropathology, while the correlation between tau-PET (AV-1451) and tau neuropathology is stronger. Therefore, using tau-PET instead of CSF P-tau in the mediation analysis may give different, and more accurate, results. Third, the memory test used only has ten levels and this in combination with the high overall cognitive performance may result in a ceiling effect. This would make it harder to find an actual association, which is a reason to interpret negative findings with some caution.
In conclusion we found that Aβ positivity in cognitively unimpaired people affects memory function without involvement of brain atrophy. It indicates that, of the pathologies studied here, Aβ pathology contributes the most to memory decline in cognitively unimpaired younger elderly. With increasing age, this effect may be overshadowed by other pathological processes, which lead to brain atrophy. To understand the mechanisms of cognitive impairment in the elderly, future studies would benefit from analyses of other biomarkers that may provide a more detailed characterization of other age-associated brain changes, for example being able to study α-synuclein and TDP-43 pathology in vivo.

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Author Contributions

A.L.S. performed the calculations and wrote the main manuscript. O.H. and S.P. contributed as senior authors and conceived the original idea. All authors provided feedback and helped shape the research, analysis and manuscript.

Additional Information

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