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Association of pathological and volumetric biomarker changes with cognitive decline in clinically normal adults: Harvard Aging Brain Study

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ABSTRACT

• **Background:** Hippocampal volume (HV) atrophy is a well-known biomarker of memory impairment. However, compared to amyloid-beta (A β) and tau imaging, it is less specific for Alzheimer's disease (AD) pathology. This lack of specificity could provide indirect information about potential co-pathologies that cannot be observed *in vivo*. In this prospective cohort study, we aimed to assess the associations among A β , tau, HV, and cognition, measured over a ten-year follow-up period with a special focus on the contributions of HV atrophy to cognition after adjusting for A β and tau.

• **Methods:** We enrolled 283 older adults without dementia or overt cognitive impairment in the Harvard Aging Brain Study. In this report, we only analyzed data from individuals with available longitudinal imaging and cognition data. Serial MRI [follow-up duration: 1.3-7.0y], neocortical A β imaging on PiB PET scans [1.9-8.5y], entorhinal and inferior temporal tau on Flortaucipir PET scans [0.8-6.0y], and the Preclinical Alzheimer Cognitive Composite [3.0-9.8y] were prospectively collected. We evaluated the longitudinal associations between A β , tau, volume, and cognition data and investigated sequential models to test the contribution of each biomarker to cognitive decline.

• **Results:** We analyzed data from 128 clinically normal older adults, including 72 (56%) women and 56 (44%) men; median age at inclusion was 73 years old (range: 63-87). Thirty-four participants (27%) exhibited an initial high-A β burden on PET imaging. Faster HV atrophy was correlated with faster cognitive decline ($R^2=0.28$, $p<0.0001$). When comparing all biomarkers, HV slope was associated with cognitive decline independently of A β and tau measures, uniquely accounting for 10% of the variance. Altogether, 45% of the variance in cognitive decline was explained by combining the change measures in the different imaging biomarkers.

• **Discussion:** In older adults, longitudinal hippocampal atrophy is associated with cognitive decline, independently of A β or tau, suggesting that non-AD pathologies (e.g., TDP-43, vascular) may contribute to hippocampal-mediated cognitive decline. Serial HV measures, in addition to AD-specific biomarkers, may help evaluate the contribution of non-AD pathologies that cannot be measured otherwise *in vivo*.

INTRODUCTION

In Alzheimer's disease (AD), amyloid-beta (A β) and tau pathologies gradually accumulate in the brain¹, leading to neuronal loss, cognitive decline, and ultimately, dementia². According to post-mortem studies, the extent of tau pathology correlates with morphometric changes, specifically in the hippocampus³, and with pre-mortem cognitive impairment⁴, suggesting causal relationships between AD pathology, brain volume loss, and dementia. In the past two decades, neuroimaging techniques, including molecular positron emission tomography⁵ (PET) and volumetric magnetic resonance imaging (MRI), have made it possible to measure AD pathological and morphological changes in living individuals. Early accumulation of both A β and tau pathologies have been detected in clinically normal (CN) older adults⁶, defining a preclinical stage of AD preceding symptomatic AD⁷. Previous MRI studies demonstrated close associations between the regional patterns of tau deposition and atrophy⁸. In CN older adults, this association is mainly observed in the (medial) temporal lobe⁹, where the origin of tau neurofibrillary tangles has been identified¹⁰. Further, cognitive decline in CN adults is more closely associated with AD pathology, specifically tau biomarkers, than with volumetric measures^{9, 11}; and longitudinal studies have shown the rate of tau accumulation to be predictive of both cognitive decline⁶ and rates of volume loss¹². There is thus good evidence of an association between AD pathology and brain atrophy. However, brain atrophy, including in the hippocampus, is also observed in the context of non-AD pathologies, such as TDP-43¹³⁻¹⁵, vascular¹⁶ lesions, or primary age-related tauopathy¹⁷ (PART). Although TDP-43 cannot yet be imaged *in vivo*, increasing evidence suggests that non-AD pathologies contribute to age-related cognitive decline, both in

isolation and in combination with AD pathology, making volumetric data difficult to interpret without specific analyses disentangling the respective contributions of longitudinal amyloid and tau accumulation to explain the association between progressive atrophy to cognitive decline.

To provide an insight into the complexity of age-related neuropathologies, we aimed to observe the temporal sequence of changes in pathological and volumetric biomarkers and evaluate their synergistic or independent contributions to cognitive decline.

Determining the typical sequence of pathological and volumetric changes in the medial temporal lobe and neocortex is important for understanding AD-related versus non-AD related clinical progression. This in turn can inform the planning of therapeutic trials in the most appropriate individuals, using the best possible outcome measures.

METHODS

Participants

In this report, we analyzed data from the Harvard Aging Brain study (HABS), a longitudinal study of aging conducted at Massachusetts General Hospital (Boston, MA) with the following inclusion criteria⁶: age from 60 to 90 years old, Global Clinical Dementia Rating (CDR)=0, Mini Mental State Examination (MMSE) and Wechsler Logical Memory II delayed recall (LM) within 1 standard-deviation of education-adjusted norms (MMSE $\geq$ 27 and LM $\geq$ 11 if $\geq$ 16 years of education). Exclusion criteria included recent drug or alcohol abuse, head trauma, and serious medical or psychiatric condition (Geriatric Depression Scale $>$ 10/30). Annual consensus meetings evaluated progression to mild cognitive impairment (MCI) or dementia. Here, we report prospective observations

collected from January 1, 2010 to April 1, 2020 in 128 individuals who had at least two Flortaucipir (FTP) and two Pittsburgh Compound B (PiB) PET scans, assessing tau and A β pathology, and at least two brain MRI scans to evaluate longitudinal volumetric changes.

Study design

The study design of HABS has been previously described in detail⁶. In short, longitudinal data were acquired for PiB, MRI, and cognition from 2010. Because FTP was not available before 2013, the initial FTP was defined as 'baseline' (time_{t=0}), and the terms 'baseline FTP_{t=0}' and 'initial FTP_{t=0}' are equivalent. The initial PiB (and MRI) sessions were acquired on average three years before baseline and are termed 'initial_{t=-3}', with 'baseline_{t=0}' referring to PiB or MRI at approximately the time of initial FTP_{t=0}. Participants had two to four FTP observations (median=2), over a median follow-up of 2.1 years [0.8-6.0]. Participants had two to six PiB observations (median=3) over a median follow-up of 5.1 years [1.9-8.4], two to five MRI scans (median=3) over a median follow-up of 4.8 years [1.3-7.0], and four to nine annual cognitive evaluations (median=8) over a median follow-up of 7.3 years [3.0-9.8]. PiB, MRI, and cognition were thus evaluated both before and after baseline FTP_{t=0}, allowing us to distinguish between successive and concurrent changes between biomarkers.

Neuropsychological evaluation

Participants in HABS are evaluated yearly with a battery of cognitive assessments, including tests of episodic memory, executive function, processing speed, and language. In this study, we evaluated cognition with the Preclinical Alzheimer Cognitive Composite (PACC5), an average of z-scored performances on five tests sensitive to cognitive decline in at-risk individuals⁶: LM, MMSE, Category Fluency (Animals, Names, Furniture), Digit-Symbol Coding, and the Free and Cued Selective Reminding Test, which uses three versions with different items, each version repeated every three years¹⁸.

Brain Imaging

Three-dimensional (3D) structural T1-weighted MRI scans were acquired using a Siemens 3 Tesla Tim Trio (Siemens, Erlangen, Germany). T1 images were segmented and parcellated using FreeSurfer software (v6.0). Hippocampal (HV) and total cortical (CV) volumes, adjusted for intracranial volumes, were used as proxies for allocortical and neocortical atrophy, respectively. Precuneus thickness was also tested for neocortical atrophy; and the volume of white matter hypointensities (WMH) was used as a proxy for cerebrovascular burden. C^{11} -PiB and F^{18} -FTP tracers were synthesized onsite. PET images were acquired using a Siemens HR+ scanner. Both PiB and FTP measures were computed as standardized-uptake-value-ratios (SUVR, four frames of five minutes: 75-105min for FTP; 40-60min for PiB) using cerebral white matter as reference region, as in previous works⁶. PET data were co-registered to each participant's base MRI. Partial volume correction was applied using geometric transfer matrix. PiB signal was extracted from a neocortical aggregate and FTP from entorhinal cortex (EC), an allocortical region,

and inferior temporal (IT), a neocortical region where tau is commonly observed in preclinical AD.⁶ Primary analyses used continuous PET values. PiB groups (high and low) were used for figures and secondary analyses. PiB threshold was set at 0.72 SUVR ($\sim$ Centiloid=25) using a Gaussian mixture model on the initial PiB data.

Statistics

Mixed-effect models with random intercept and time slope per participant predicting PACC, HV, WMH, FTP, and PiB were computed over time in separate models. Individual slopes of change were calculated by summing the estimated fixed and random effects of time. For PACC, PiB, and volume data, slopes were estimated over the entire follow-up ($PACC_{t=-3 \text{ to } t=+4}$, $PiB_{t=-3 \text{ to } t=+2}$, $HV_{t=-3 \text{ to } t=+2}$), and over shorter periods (referred to as $PiB_{t=-3 \text{ to } t=0}$ before baseline and $PiB_{t=0 \text{ to } t=+2}$ after baseline as in ⁶). Cross-sectional measures and slope data were correlated and entered as predictors or outcomes in linear regressions evaluating the associations between PACC, HV, WMH, FTP, and PiB, and their respective slopes, covarying, age, education, sex, and Apolipoprotein E (APOE) e4 genotype status. We did not correct for multiple comparisons to interpret the data, but we provided the threshold for correcting p-values using the Bonferroni method for each table of results. Results were summarized in a serial mediation model, providing evidence for sequential biomarker changes in preclinical AD and other age-related conditions. All possible indirect pathways between PiB, FTP, HV, and final $PACC_{t=+4}$ scores were tested. Direct, indirect, and total effects were tested with a 5000-iteration bootstrap. All models were fit in Matlab v9.3 except mediations, which used R v3.4.2 (Lavaan package).

Standard Protocol Approvals and Patient Consent

The Mass General Brigham Institutional Review Board has approved the HABS protocol and participants provided written informed consent before undergoing any procedures.

DATA AVAILABILITY

Dr. Hanseeuw and Johnson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Request for data can be sent to the following email address: habsdata@mgh.harvard.edu.

RESULTS

Characteristics of the study participants

Table 1 provides the demographics, cognitive, and imaging data of the 128 participants. Based on the initial $\text{PiB}_{t=-3}$ observation, 94 participants (73%) were classified as low-PiB and 34 (27%) were classified as high-PiB participants. Initial cognitive performance and demographics (age, sex, education) were not significantly different between groups, but high-PiB had lower initial $\text{HV}_{t=-3}$ ($p=0.02$), greater $\text{WMH}_{t=-3}$ ($p=0.027$), and greater baseline $\text{FTP}_{t=0}$ ($p<0.001$) than low-PiB participants. During the follow-up, WMH, PiB and FTP demonstrated significant increase and HV, CV, and cognition significant decrease, including in the low-PiB participants only (see CI95% for change data in Table 1). High-PiB participants had faster rates of change for all imaging markers (PiB, FTP, HV, CV, WMH) and faster cognitive decline than low-PiB participants. At the end of the study, eight high-PiB participants (24%) had progressed to either MCI ($n=6$) or AD dementia ($n=2$), whereas all low-PiB participants remained CN.

Correlation between baseline and change data

The eTable 1 provides Pearson's R^2 correlations between PiB, FTP in EC and IT, HV, CV, WMH, and PACC scores. PACC change was most closely associated with IT FTP change ($R^2=0.30$) and HV change ($R^2=0.28$, Fig.1C). CV change was strongly associated with precuneus thickness change ($R^2=0.61$), and to a lesser extent, with HV change ($R^2=0.15$), but it was only weakly associated with change in cognition ($R^2=0.09$), an association entirely explained by HV change. Therefore, we focused on HV change and did not include CV or precuneus thickness in subsequent analyses. WMH changes were associated with older ages and the initial volume of WMH. The association with change in cognition was weak after adjusting for age ($R^2=0.05$), but independent of HV change.

Multiple regressions predicting longitudinal hippocampal atrophy

We next aimed to evaluate how these correlations were modified when adjusting for multiple biomarkers. We first focused our analyses on understanding the predictors of HV change (Table 2, Fig.1); and then the sequence of PiB and FTP change (Table 3, Fig.2). We did so as these were the predictors most strongly correlated with PACC change. Focusing on the predictors of HV was also motivated by the fact that HV may reflect both AD and non-AD pathology, such as LATE or PART.

We first evaluated the effects of covariates in models testing the associations of HV change with age, sex, APOE4 status, and initial HV (Table 2, model #1). Older ages and lower initial HV were associated with faster reductions in HV (Fig.1A), but sex and APOE4 status were not. Consequently, only age and initial HV were included in the next

models of Table 2 evaluating the associations of PiB and FTP with HV changes. We then observed that high PiB SUVr was associated with faster HV reductions in the next five years (#2). However, PiB change was not associated with contemporaneous (#3) or subsequent (#4) HV reductions, suggesting that amyloid pathology and hippocampal atrophy progress independently of each other. EC FTP was strongly correlated with HV change ($R^2=0.35$), while the association between initial PiB and HV change was non-significant when adjusting for EC FTP (#5), indicating that EC FTP mediated the effect of PiB on HV change (Sobel-test=3.8, $p<0.001$). The association between EC FTP and HV change was significant in both the low PiB (#6) and the high PiB (#7) groups, and the estimates were of similar magnitude, indicating that the close association between EC FTP and HV change was independent of PiB. Faster HV reductions were also observed in individuals with faster EC FTP change, adjusting for the initial EC FTP measure (#8-9 and Fig.1B). Finally, we observed that the association of EC FTP and HV change was stronger than that of IT FTP and HV change, both with cross-sectional (#10) and longitudinal (#11) FTP measures. In summary, the association of HV with EC FTP was stronger than that of HV with PiB or IT FTP.

Sequential models predicting associations between pathology, volume, and cognition

We first observed that initial measures of FTP signal in the EC were associated with subsequent increase in PiB (Table 3, model A). In contrast, baseline PiB did not predict subsequent FTP change in the EC (A'), although it predicted FTP change in the IT (B). These *in vivo* observations are consistent with post-mortem observations suggesting that entorhinal, unlike neocortical, tauopathy occurs before neocortical amyloidosis.

Another observation suggested that IT FTP change was subsequent to PiB and EC FTP: PiB change and EC FTP change were both predicted by their own baseline values (A-A', highlighted on Fig.2 using black circling arrows); however, IT FTP change was better predicted by previous PiB change and initial EC FTP measures than by initial IT FTP (B'). PiB changes partially mediated the effect of the initial EC FTP measure on subsequent IT Tau changes (Sobel^{#1} = 2.6, p=0.008, schematic representation of models A-B in Fig.2).

We then predicted the final HV measure with previous cross-sectional and longitudinal measures of PiB and FTP, and confirmed the strong association between EC FTP and HV (Table 3, model C). Both PiB and IT FTP (cross-sectional or change measures) were not significantly associated with final HV, adjusting for initial HV measured five years earlier. In this sequential model, we predicted final HV -and not HV change- to dissociate the timing of the outcome and the predictors, but the results are entirely consistent with the observations made when predicting HV change (Table 2).

EC FTP measures were not significantly associated with final PACC when taking into account final HV and cross-sectional and change measures in IT FTP (D). Indeed, both IT FTP change (Sobel^{#2}=2.8, p=0.006; models B-D) and final HV (Sobel^{#3}=2.6 p=0.008, models C-D) mediated the effect of initial EC FTP SUVr on the final PACC score. WMH measures were not associated with cognition after adjusting for all biomarker changes. Fig.2 summarizes the sequential associations between biomarkers, demonstrating two paths: one from initial PiB to final PACC score via successive increase in PiB and IT FTP (red); and another from initial EC FTP to final PACC score via an increase in IT FTP and

HV loss (blue). The three significant mediations (#1: A-B, #2, B-D, #3 C-D) suggest that PiB and EC FTP are biomarkers that are detected earlier in the preclinical AD course than IT FTP and HV that are more closely related to cognition.

Fig.3 illustrates how the variance in PACC decline was explained by biomarkers change. In total, 48% of the variance was explained by a model combining IT FTP change (unique variance explained: 11%), HV change (10%), PiB slope (2%), and WMH slope (3%). Only 2% of the variance in cognitive changes was still explained by age at baseline after taking into account biomarker changes, indicating that most of the age-related cognitive decline was explained by this model. Change in EC FTP signal did not add any explanatory power when both IT FTP change and HV change were entered in the model, confirming that its association to cognitive decline was only indirect. Of note, 22% of the explanation of cognition provided from shared variance between biomarkers, indicating synergy between A β , tau, and atrophy that suggests AD as the cause for decline. In contrast, the variance uniquely explained by WMH and HV suggest non-AD pathologies, such as cerebrovascular disease and LATE, as the likely cause of clinical decline. When plotting the two most predictive biomarkers, HV change and IT FTP change, versus PACC decline in a 3D-plot, the two independent effects are clearly visible (Fig.4). Individuals with a large HV atrophy but little IT FTP signal were older than individuals with the opposite pattern, confirming the possibility of LATE.

DISCUSSION

In this cohort study, we followed clinically normal adults over a decade, including individuals in the preclinical phase of AD, and observed a sequence of events, starting with entorhinal tauopathy, which was associated with subsequent hippocampal atrophy; and neocortical A β , which was associated with subsequent neocortical tauopathy. Hippocampal atrophy and neocortical tauopathy were both independent predictors of lower cognition at final follow-up, mediating the effects of initial entorhinal tau and A β pathology. Our results suggest two pathways leading to cognitive impairment in older adults, one restricted to the medial temporal lobe (blue arrows in Fig.2), the second involving A β and tau in neocortex (red arrows). These pathways are partially independent, with HV loss explaining part of the variability in cognitive decline at similar levels of neocortical tau. Measuring longitudinal changes in HV as a secondary outcome in clinical trials, in addition to A β and tau pathologies may thus be important to better predict individual trajectories of cognitive decline and the response (or lack of response) to AD drugs. Specifically, regarding anti-A β immunotherapies that were recently approved, the current data lead to the following observations: It is likely these drugs will provide the greatest clinical benefits in individuals with amyloidosis and only limited neocortical tauopathy and hippocampal atrophy, as these two pathologies are associated with cognitive decline independently of A β . The mechanisms behind the reduced benefits may be different though, as the effect of neocortical tau on cognition is initially mediated by A β , suggesting AD as the cause of cognitive impairment at a stage where tauopathy has become independent of A β , whereas major hippocampal atrophy

in the absence of neocortical tauopathy suggests non-AD pathologies, such as LATE or PART.

The observation that HV strongly correlates to cognition has been made for at least thirty years¹⁹. However, it is only recently that the contributions of different age-related neuropathologies responsible for hippocampal atrophy are disentangled. In our study, we observed that HV loss was predicted by older ages, and that the impact of HV loss on cognition was greater at older ages. As these observations were made adjusting for A β and tau pathologies, they suggest the contribution of non-AD neuropathologies²⁰. Some of these pathologies, such as Limbic age-related TDP43 encephalopathy¹³⁻¹⁵ (LATE) or cerebrovascular disorders¹⁶, are known to be associated with hippocampal atrophy and could contribute to the strong correlation observed between HV and cognition, even after adjusting for AD pathologies. Measuring HV may thus provide information on the possibility of non-AD pathologies, either as the main cause²¹ (low-A β /tau) or as a co-pathology (high-A β /tau) contributing to cognitive decline. It is nevertheless important to acknowledge that even after including A β , tau, WMH, and atrophy in our predictive models, half the variance in cognitive decline could not be explained, suggesting that some neuropathologies (e.g., alpha-synuclein) or other contributions to cognitive decline (e.g., genetics or lower cognitive reserve) cannot be detected by measuring HV. Yet, a global measure of cortical volume did not improve the prediction of cognitive decline. More detailed structural changes or specific biomarkers for non-AD neuropathologies should therefore be developed to improve our ability to predict, and ultimately prevent, age-related cognitive decline.

Of note, we did not observe a strong correlation between cognitive decline and total cortical volume (or parietal atrophy), highlighting the regional specificity of the medial temporal lobe for cognitive decline in sporadic AD, whereas early parietal atrophy has been observed as a prominent feature in autosomal dominant AD studies^{22, 23}.

Besides age, HV was mostly predicted by entorhinal tauopathy, an early event in preclinical AD that was associated with subsequent A β and neocortical tauopathy. Structural and metabolic dysfunctions of the medial temporal lobe are well-known predictors of subsequent cognitive impairment in preclinical AD²⁴. However, HV was also associated with entorhinal tau when restricting analyses to the low-A β subgroup, suggesting that PART¹⁷ contributes to hippocampal atrophy and cognitive decline. Of note, the impact of entorhinal tau on cognition in the low-A β subgroup was entirely mediated by HV, indicating that HV could serve as a biomarker for monitoring this medial temporal lobe pathology after AD pathology is excluded. Similarly, medial temporal hypometabolism on FDG-PET was recently suggested as a biomarker of LATE, based on both autopsy-validated and a large cross-sectional FDG dataset²⁵. Increasing evidence suggests that medial temporal atrophy and dysfunction occurring in the absence of A β ²⁶ or tau²⁷ pathology are associated with cognitive decline. Further work should better determine the sensitivity of different tau-PET tracers to PART in order to better distinguish the respective contributions of PART and LATE to hippocampal atrophy and cognitive decline.

Limitations

Our conclusions are limited by the convenience sample that has been included in HABS. Participants are indeed highly educated and mostly white, limiting the generalizability of the findings. Also, the results are partially driven by a few individuals who progressed to MCI or dementia during the study. Removing these individuals from the analyses did not modify the results other than reducing the total amount of cognitive variance explained to 31%. The respective contributions of hippocampal atrophy and neocortical tau accumulation remained unchanged, suggesting that both AD and non-AD pathologies contribute to cognitive decline before clinical impairment is detectable.

We did not obtain tau PET scans at study start, because the FTP tracer was not yet available. Although we provided some evidence in favor of entorhinal FTP preceding PiB signal, we could thus not observe the sequence between early tau changes and subsequent A β . Also, the present work did not use specific regional data or a low threshold to detect early A β making it difficult to exclude an early contribution of A β pathology to entorhinal tau. Future work should include younger individuals to specifically focus on the onset of early AD pathology.

Group studies may be insensitive to atypical patterns of biomarker progression, and larger studies are required to evaluate inter-individual variations in biomarkers trajectories. The present study was not designed to detect atypical presentations of AD or non-AD pathologies. Studying genetic and lifestyle variations across individuals may also shed light on the different cognitive trajectories and explain part of the variance in

HV and AD pathology. Longer studies or including more observations per participant might lead to different conclusions.

Developing biomarkers of non-AD pathology, whether through imaging or in bio-fluids, is of utmost importance to better understand cognitive decline in aging and pathological conditions. Therefore, the utility of measuring morphometric changes, such as HV, will need to be re-evaluated when such novel biomarkers become available.

CONCLUSION

In this longitudinal study of clinically normal older adults, we observed that decline in cognition after a ten-year follow-up resulted (1) from successive changes in A β and tau in the neocortex, and (2) from medial temporal lobe pathologies, including entorhinal tauopathy, leading to hippocampal atrophy. Cerebrovascular disease, as measured using WMH, did not contribute much to cognitive decline. Larger and more diverse samples are needed to support the proposed sequential pathways. Biomarkers targeting non-AD pathologies such as TDP43 or alpha-synuclein are required to confirm the contributions of such pathologies to hippocampal atrophy. In the meantime, measuring HV in trials together with A β and tau may help identify individuals who are more likely to present with non-AD co-pathologies and therefore potentially respond differently to AD drugs.

Table 1: Characteristics of the participants

Mean value (<i>SD</i>)	All N=128	Low PiB N=94	High PiB N=34	p-value
Age at inclusion: t=-3 years	72.6 (6.0)	72.0 (6.2)	74.0 (5.1)	Non sig.
Education years	16.2 (3.0)	16.0 (3.1)	16.7 (2.6)	Non sig.
Female (%)	56.3%	56.4%	55.9%	Non sig.
E4 carriers (%)	30.0% missing=1	17.0% missing=1	65.0% missing=0	<0.001
Initial PiB: t=-3 SUVr	0.63 (0.27)	0.49 (0.07)	1.02 (0.20)	<0.001
Annual PiB Change: t=-3 → t=+2 SUVr/year	0.02 (0.02) CI95: 0.01-0.02	0.01 (0.01) CI95: 0.01-0.01	0.04 (0.02) CI95: 0.03-0.04	<0.001
Baseline EC FTP: t=0 SUVr	1.22 (0.29)	1.14 (0.17)	1.47 (0.39)	<0.001
Annual EC FTP Change t=0 → t=+2 SUVr/year	0.02 (0.01) CI95: 0.02-0.03	0.02 (0.01) CI95: 0.02-0.02	0.03 (0.02) CI95: 0.02-0.04	0.003
Baseline IT FTP: t=0 SUVr	1.29 (0.19)	1.25 (0.10)	1.43 (0.29)	<0.001
Annual IT FTP Change t=0 → t=+2 SUVr/year	0.02 (0.02) CI95: 0.02-0.03	0.02 (0.02) CI95: 0.02-0.03	0.04 (0.03) CI95: 0.03-0.05	<0.001
Initial HV: t=-3 cm ³	7.23 (0.72)	7.32 (0.70)	6.99 (0.72)	0.020
Annual HV Change t=-3 → t=+2 cm ³ /year	-0.07 (0.04) CI95: -0.08-0.06	-0.06 (0.03) CI95: -0.07-0.05	-0.09 (0.05) CI95: -0.11-0.08	<0.001
Initial Cortical Volume: t=-3 cm ³	443 (43)	442 (41)	445 (50)	Non sig.
Annual Cortical Vol. Change t=-3 → t=+2 cm ³ /year	-2.43 (0.78) CI95: -2.56-2.29	-2.31 (0.74) CI95: -2.46-2.16	-2.74 (0.81) CI95: -3.03-2.46	0.001
Initial WMH Volume: t=-3 cm ³	4.10 (6.09)	3.33 (2.50)	6.22 (10.91)	0.027
Annual WMH Vol. Change t=-3 → t=+2 cm ³ /year	0.33 (0.32) CI95: 0.27-0.39	0.30 (0.27) CI95: 0.25-0.36	0.40 (0.41) CI95: 0.26-0.55	0.053
Initial PACC: t=-3 z-score	0.16 (0.60)	0.17 (0.62)	0.15 (0.66)	Non sig.
Annual PACC Change t=-3 → t=+4 SD/year	-0.05 (0.11) CI95: -0.03-0.07	-0.02 (0.06) CI95: -0.003-0.03	-0.15 (0.16) CI95: -0.09-0.20	<0.001

Legend: Low- and high-PiB participants are compared using T-tests (χ^2 for E4 and sex). Significant p-values surviving Bonferroni correction (uncorrected $p < 0.004$, adjusting for the 14 lines) are highlighted in bold. CI95 = 95% confidence intervals are provided for one-sample t-test, testing whether the rates of changes are different from zero.

Table 2: Linear regressions investigating the associations between demographics, amyloid (PiB-PET), tau (FTP-PET), and longitudinal change in hippocampal volume (HV)

Model #	Outcome	Predictors	Estimate (SE)	2-tail p
1 N=128 Five-year follow-up	HV change (t=-3 to t=+2)	Age (t=-3) Initial HV (t=-3) E4 status Female Sex	-1.7 (0.6) 0.01 (0.005) -9.6 (7.1) -5.0 (6.6)	0.01 0.01 0.18 0.45
2 N=128 Five-year follow-up	HV change (t=-3 to t=+2)	Age (t=-3) Initial HV (t=-3) PiB SUVr (t=-3)	-1.6 (0.6) 0.01 (0.005) -40 (12)	0.02 0.01 0.001
3 N=128 Five-year follow-up	HV change (t=-3 to t=+2)	Age (t=-3) Initial HV (t=-3) PiB SUVr (t=-3) PiB change (t=-3 to t=+2)	-1.6 (0.6) 0.01 (0.005) -35 (13) -171 (199)	0.02 0.01 0.01 0.39
4 N=128 Two-year follow-up	HV change (t=0 to t=+2)	Age (t=-3) Initial HV (t=-3) PiB SUVr (t=-3) PiB change (t=-3 to t=0)	-0.3 (0.5) 0.01 (0.004) -27 (10) -161 (933)	0.60 0.01 0.01 0.86
5 N=128 Five-year follow-up	HV change (t=-3 to t=+2)	Age (t=0) Initial HV (t=-3) PiB SUVr (t=0) EC FTP SUVr (t=0)	-1.0 (0.6) 0.01 (0.005) -3 (11) -69 (12)	0.07 0.12 0.75 <0.0001
6 N=94 Low-PiB Five-year follow-up	HV change (t=-3 to t=+2)	Age (t=0) Initial HV (t=-3) PiB SUVr (t=0) EC FTP SUVr (t=0)	-1.3 (0.6) <0.001 (0.005) 13 (33) -74 (20)	0.03 0.86 0.69 0.0002
7 N=34 High-PiB Five-year follow-up	HV change (t=-3 to t=+2)	Age (t=0) Initial HV (t=-3) PiB SUVr (t=0) EC FTP SUVr (t=0)	0.3 (1.3) 0.03 (0.01) 22 (33) -54 (18)	0.84 0.01 0.63 0.01

8 N=128 Five-year follow-up	HV change (t=-3 to t=+2)	Age (t=0)	-0.9 (0.5)	0.08
		Initial HV (t=-3)	0.01 (0.005)	0.17
		EC FTP change (t=0 to t=+2)	-585 (219)	0.01
		EC FTP SUVr (t=0)	-53 (11)	<0.0001
9 N=128 Two-year follow-up	HV change (t=0 to t=+2)	Age (t=0)	-0.1 (0.5)	0.87
		HV (t=0)	0.01 (0.004)	0.05
		EC FTP change (t=0 to t=+2)	-513 (199)	0.01
		EC FTP SUVr (t=0)	-20 (11)	0.06
10 N=128 Two-year follow-up	HV change (t=0 to t=+2)	Age (t=0)	-0.3 (0.5)	0.54
		HV (t=0)	0.01 (0.004)	0.01
		IT FTP SUVr (t=0)	42 (20)	0.04
		EC FTP SUVr (t=0)	-44 (12)	<0.0001
11 N=128 Two-year follow-up	HV change (t=0 to t=+2)	Age (t=0)	-0.2 (0.5)	0.74
		HV (t=0)	0.01 (0.004)	0.01
		IT FTP change (t=0 to t=+2)	-103 (131)	0.43
		EC FTP change (t=0 to t=+2)	-600 (198)	0.003

Legend: Significant p-values surviving Bonferroni correction (uncorrected $p < 0.004$, adjusting for the 11 independent models in the table) are highlighted in bold.

Table 3: Linear regressions investigating the longitudinal associations between amyloid (PiB-PET), tau (FTP-PET), hippocampal volume (HV), and cognition (PACC performances)

Model #	Outcome	Predictors	Estimate (SE)	2-tail p
A	PiB change (t=0 to t=+2)	PiB SUVR (t=0)	0.014 (0.006)	0.02
		EC FTP SUVR (t=0)	0.015 (0.006)	0.02
A'	EC FTP change (t=0 to t=+2)	PiB SUVR (t=0)	<0.001 (0.005)	0.92
		EC FTP SUVR (t=0)	0.02 (0.005)	<0.001
B	IT FTP change (t=0 to t=+2)	PiB SUVR (t=0)	0.02 (0.01)	0.01
		IT FTP SUVR (t=0)	0.03 (0.01)	0.002
B'	IT FTP change (t=0 to t=+2)	Initial PiB (t=-3)	0.01 (0.01)	0.51
		PiB change (t=-3 to t=0)	1.55 (0.58)	0.01
		IT FTP SUVR (t=0)	0.01 (0.01)	0.44
		EC FTP SUVR (t=0)	0.03 (0.01)	0.002
C	Final HV (cm ³) (t=+2)	Initial PiB (t=-3)	-0.07 (0.10)	0.44
		PiB change (t=-3 to t=+2)	-0.15 (1.34)	0.91
		EC FTP SUVR (t=0)	-3.01 (1.10)	0.01
		EC FTP change (t=0 to t=+2)	-3.41 (1.59)	0.03
		IT FTP SUVR (t=0)	-0.14 (0.15)	0.36
		IT FTP change (t=0 to t=+2)	-0.16 (1.14)	0.89
D	Final PACC (t=+4)	Initial PiB (t=-3)	-0.59 (0.28)	0.04
		PiB change (t=-3 to t=+2)	-1.11 (4.04)	0.78
		EC FTP SUVR (t=0)	0.31 (0.33)	0.34
		EC FTP change (t=0 to t=+2)	-2.88 (4.68)	0.54
		IT FTP SUVR (t=0)	-1.93 (0.46)	0.001
		IT FTP change (t=0 to t=+2)	-13.03 (3.63)	<0.001
		Final HV (t=+2)	0.23 (0.09)	0.01
		Final WMH (t=+2)	0.01 (0.01)	0.39

Legend: Significant p-values surviving Bonferroni correction (uncorrected p<0.01, adjusting for six models) are in bold. Unstandardized estimates are provided with standard errors, adjusting for initial age, sex and e4 genotype. All models are sequential, i.e., the outcome and predictors are measured at different time-points. Model C, predicting final HV, is adjusted for initial HV. Model D is adjusted for initial PACC.

FIGURE TITLES AND LEGENDS

Fig.1 Associations between hippocampal volume, age, entorhinal tauopathy, and cognition

Legend: Spaghetti plots showing the longitudinal hippocampal volume (HV) data plotted against (A.a) age, (B.a) entorhinal Flortaucipir (FTP) data, and (C.a) Preclinical Alzheimer Cognitive Composite (PACC-5) data. Individuals who progressed to symptomatic AD (MCI or dementia) during the follow-up had fast hippocampal atrophy.

(A.b, B.b, C.b) HV, entorhinal FTP, and PACC slope data are plotted against each other. All associations are significant, demonstrating that HV reduces in size with age, entorhinal tauopathy and poorer cognition. eTable provides the correlations of HV slope with additional slope data. The three most significant ones are illustrated here.

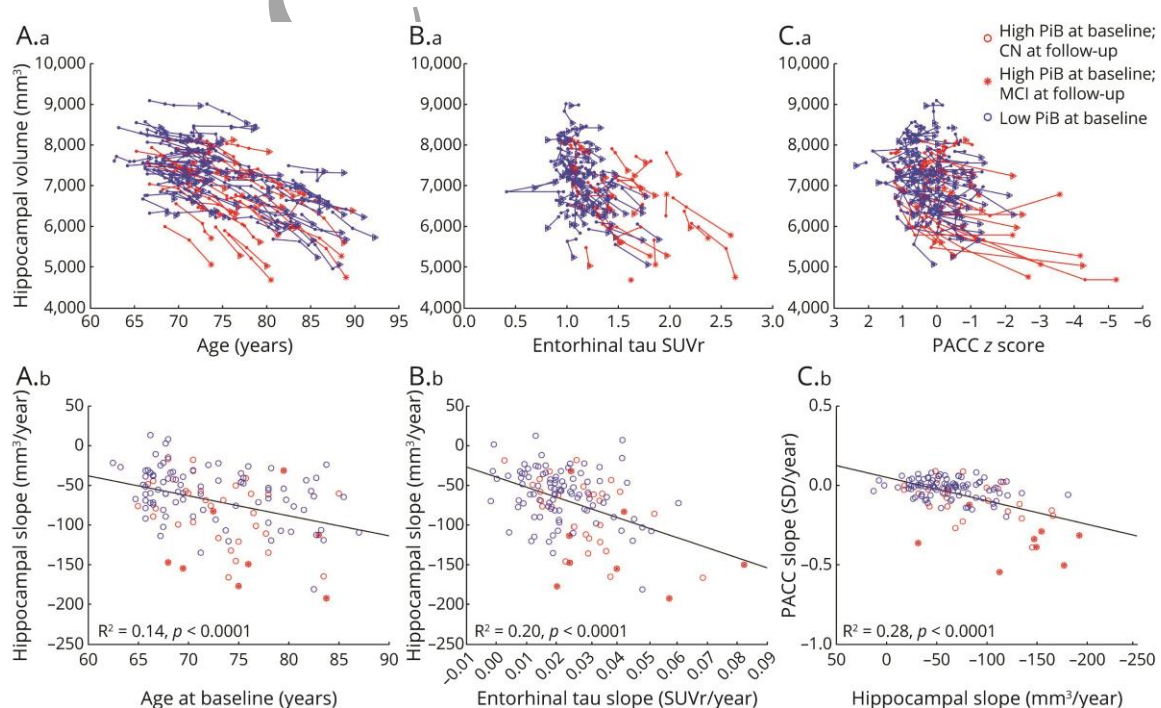


Fig.2 Schematic illustration of the two pathways leading to cognitive decline

Legend: The statistical details of the three sequential models (A-B, B-D, and C-D) are provided in Table 3. All models are adjusted for age, sex, education, and APOE4 genotype. The timing (baseline/change/final) of each observation depends on the specific model. Circling arrows indicate that the baseline data predicts change in the same variable (e.g. baseline A β predicts A β slope) accounting for the other variables. A β accumulation mediates the effect of entorhinal cortex (EC) on inferior temporal (IT) tau, which mediates the effect of EC tau and A β on cognition (double mediation: A-B-D, red). Independently of A β , HV also mediates the effect of EC tau on cognition (C-D, in blue).

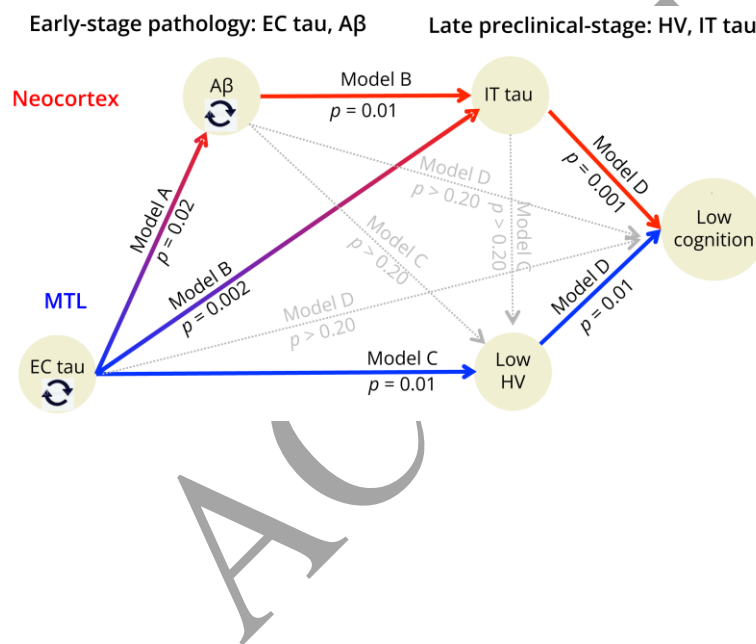


Fig.3 Impact of neuropathologies on cognition, as measured using longitudinal neuroimaging

Legend: Only IT FTP, HV, PiB, and WMH data have been included in the analysis, as the effect of EC FTP on PACC slope was entirely mediated by other biomarkers. Half of the variance explained was shared between two or three (22%) biomarkers, and is suspected to reflect AD pathology ($A\beta$ and tau-driven atrophy and WMH). IT FTP change uniquely explained the greatest amount of variance in PACC decline, and is suspected to reflect a stage of AD pathology where neocortical tauopathy has become independent of $A\beta$ pathology. Ten percent of the variance in cognition is uniquely explained by HV change, and is suspected to reflect Limbic Age-Related TDP-43 encephalopathy (LATE). Cerebrovascular disease (WMH) explained 3% of the variance in cognition, independently of $A\beta$ and tau.

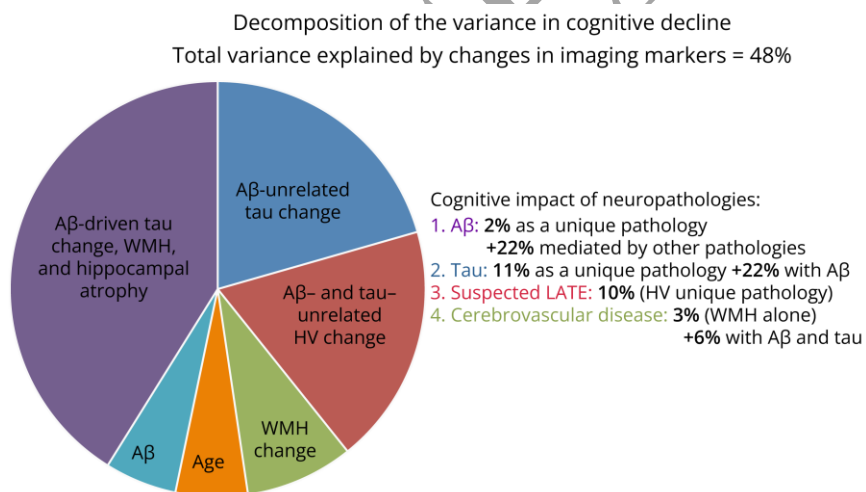
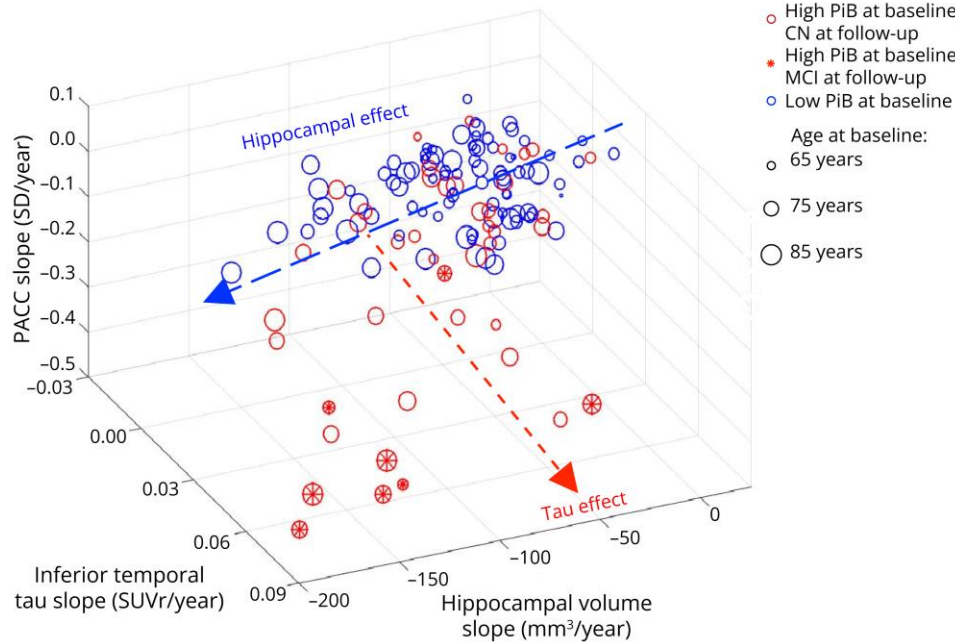


Fig.4 Three-dimensional plot of changes in inferior temporal tau and changes in hippocampal volume predicting changes in cognition

Legend: The effect of hippocampal volume on cognition is clearly observable in both high- and low- A β participants, with a greater effect in older participants (older ages are illustrated by larger dots). Independently of this effect, tau accumulation in the inferior temporal neocortex also has an effect on cognition, with a greater effect in the high-A β participants. Individuals who progressed to symptomatic AD (MCI) are mostly having a combination of hippocampal atrophy and neocortical tauopathy.



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