Amyloid and tau PET burden are associated with white matter bundle abnormalities in asymptomatic individuals at risk of Alzheimer's disease

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BACKGROUND AND OBJECTIVES

Aβ and tau proteins follow distinct patterns of regional accumulation in the brain. Regions preferentially affected by one protein or the other are connected with well-defined major white matter bundles. However, if pathology affects white matter fibers early in the course of Alzheimer's disease (AD) is still unclear. In cognitively unimpaired older adults at risk of AD, we investigated relationships between Aβ and tau burden and various diffusion metrics in bundles typically affected in AD, namely the anterior and posterior cingulum, the uncinate fasciculus and the fornix.

PARTICIPANTS

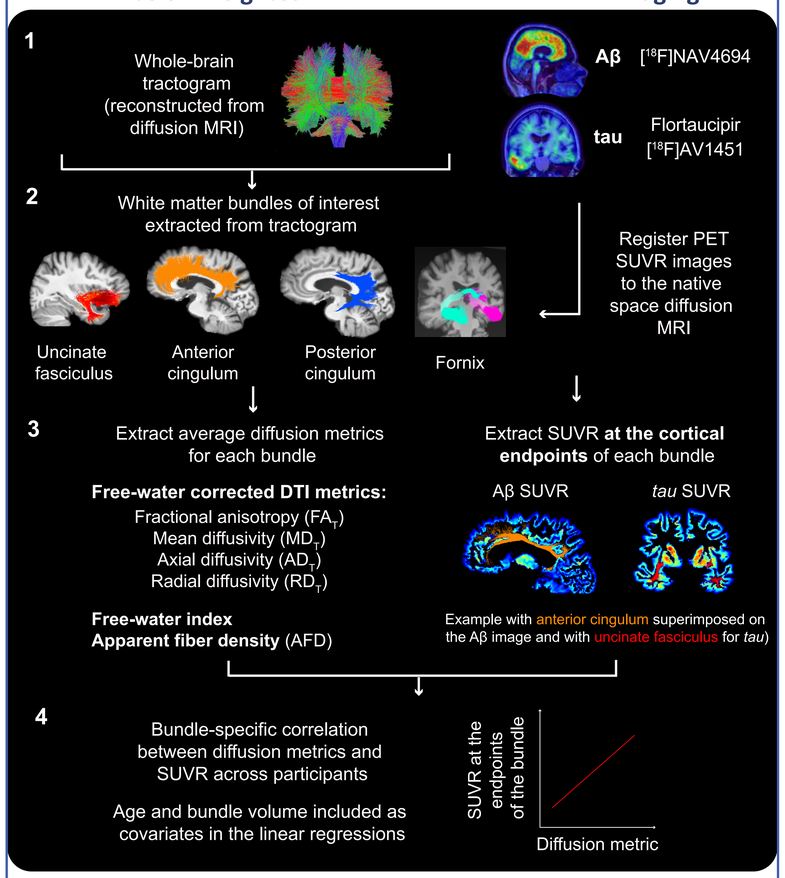
126 asymptomatic older adults with a family history of AD

Age, mean ± sd (range)	67 ± 5 (59-83)
Sex, F:M (%F)	94:32 (75%)
APOE4 (%)	50 (40%)
Education, mean ± sd (range)	15 ± 3 (7-24)

PROCESSING PIPELINE

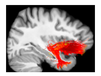
Diffusion-weighted MRI

PET imaging

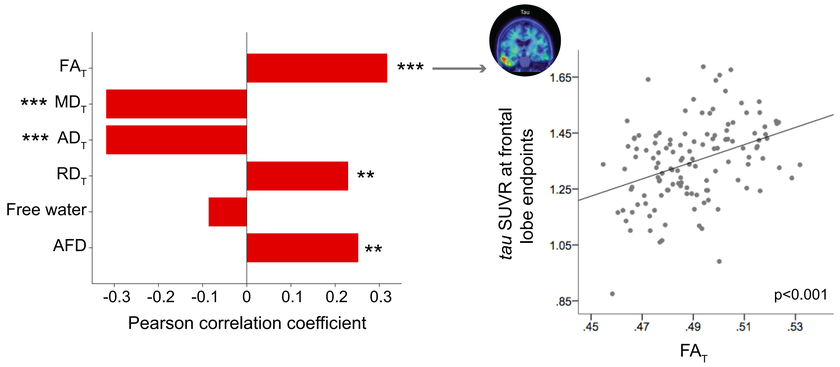


- Diffusion-weighted MRI (64 directions, b=1000 s/mm^2) was acquired 1-2 years prior to PET and preprocessed using the pipeline *Tractoflow* (Theaud et al., *biorXiv*, 2019)
- Bundles were exacted using Recobundle (uncinate and cingulum; Garyfallidis et al., 2018), TractQuerier (posterior cingulum; Wassermann et al., 2016), and bundle-specific tracto-graphy (fornix; Rheault et al., 2019).

UNCINATE FASCICULUS



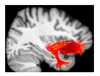
Associations with tau at the endpoints in the frontal lobe (left hemisphere depicted; similar in right hemisphere)



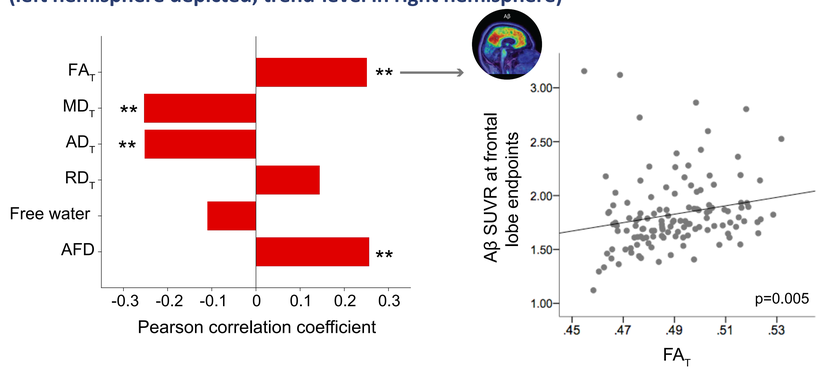
Similar associations were found with the tau SUVR **endpoints in the temporal lobe**, albeit less strong than in the frontal lobe (p<0.05).

The **same pattern of correlations** was found in the **right hemisphere**. Associations were stronger with endpoints SUVR in the frontal lobe than the temporal lobe.

Significant **correlations remained when further adjusting for Aβ SUVR** at corresponding endpoints in both hemispheres.



Associations with Aβ at the endpoints in the frontal lobe (left hemisphere depicted; trend-level in right hemisphere)

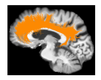


Similar associations were found with the Aβ SUVR **endpoints in the temporal lobe**, albeit less strong than in the frontal lobe (p<0.05).

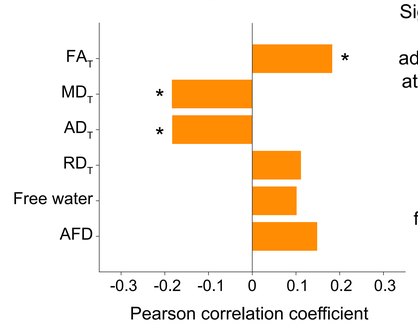
Significant correlations become at trend-level when further adjusting for tau SUVR at corresponding endpoints

In the right hemisphere, only trend-level associations (p=0.07) were found with the endpoints in the temporal lobe (in the same directions as the graph above).

ANTERIOR CINGULUM



Associations with Aβ at the endpoints in the parietal lobe (right hemisphere)



Significant correlations survived further adjusting for tau SUVR at the same endpoints

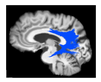
There were trend-level associations with Aβ SUVR endpoints in the frontal lobe (p=0.07)

There were no associations in the left hemisphere

Associations with tau

No associations between any diffusion metric and **tau SUVR** at either endpoints of the anterior cingulum in the left or right hemisphere

POSTERIOR CINGULUM



Associations with Aβ

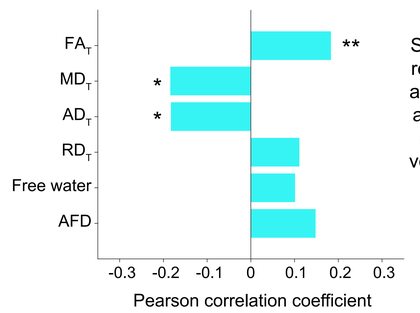
No associations between any diffusion metric and **Aβ SUVR** at either endpoints of the posterior cingulum in the left or right hemisphere

Associations with tau

No associations between any diffusion metric and **tau SUVR** at either endpoints of the posterior cingulum in the left or right hemisphere

FORNIX

Associations with Aβ at the endpoints in the temporal lobe (right hemisphere)



Significant correlations remained when further adjusting for tau SUVR at the same endpoints and for hippocampal volume (divided by TIV)

There were no associations in the left hemisphere

Associations with tau

No associations between any diffusion metric and **tau SUVR** at the temporal endpoints of the fornix in the left or right hemisphere

* p<0.05; ** p<0.01; *** p<0.001. Regression models included age and bundle volume (divided by TIV) as covariates

CONCLUSIONS

Higher free-water corrected FA along with **lower free-water corrected MD and AD** were consistently associated with higher pathology at the cortical endpoints of different white matter bundles known to be affected in AD. The strongest associations were found in the **uncinate fasciculus**, a bundle that connects the orbitofrontal cortex and anterior temporal lobe, where diffusion metrics were related to both Aβ and tau in the left and right hemispheres. Associations in the right hemisphere only were found between Aβ and diffusion metrics in the cingulum and fornix.
The direction of associations is opposite than what is most often reported when studying the full disease spectrum. We hypothesize that pathology might affect white matter metrics differently in the **early asymptomatic phase** vs. later stages, as has been reported previously (Racine et al., 2014; Mito et al., 2018). Diffusion changes might be an early correlate of pathological insults.

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