Medial temporal lobe gray matter microstructure alterations provide improved sensitivity to detect neurodegeneration associated with Alzheimer's disease biomarkers

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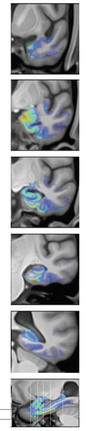
NODDI-based gray matter microstructural measures in areas of early tau deposition in the medial temporal lobe provide the earliest marker of Alzheimer's associated neurodegeneration in cognitively unimpaired individuals

INTRODUCTION

- Early detection of neurodegeneration in Alzheimer's disease is limited cross-sectionally in cognitively unimpaired (CU) individuals
- Recent advances in diffusion MRI (dMRI) allow for measurement of gray matter microstructure using Neurite Orientation Dispersion and Density Imaging (NODDI) [1]
- Earliest neurodegenerative changes occur in MTL regions associated with early tau deposition [2]
- Ex vivo atlas of tau deposition allows for investigation of these areas in vivo (Right, adapted from [3])
- Aim: To investigate Age and AD-related microstructural changes in early sites of tau deposition in the MTL using neuroimaging and plasma biomarkers



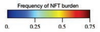
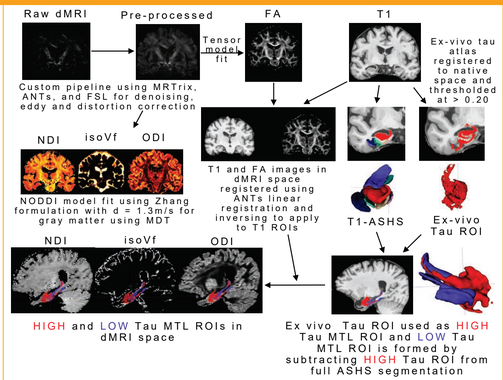


Table 1. Demographics and biomarkers

	All (n = 304)	CU (n = 219)	MCI (n = 60)	AD (n = 25)
Age (yrs)	67.04 (22-92)	65.03 (15.27)	73.03 (6.66)	70.24 (7.57)
Sex (M:F)	122:182	79:140	27:33	16:9
Race (W:B:A:M:U)	223:70:3:6:2	152:58:3:5:1	48:12:0:0:0	23:0:0:1:1
Education (yrs)	16.4 (2.52)$_{n=302}$	16.5 (2.44)$_{n=217}$	16.4 (2.59)$_{n=60}$	15.3 (2.84)$_{n=25}$
Amyloid Positivity	69/223 (31%)	28/159 (17.6%)	27/46 (58.7%)	18/18 (100%)
Amyloid SUVR	1.12 (0.25)$_{n=182}$	1.04 (0.188)$_{n=125}$	1.24 (0.28)$_{n=46}$	1.43 (0.23)$_{n=17}$
Plasma pTau$_{181}$ (pg/mL)	3.08 (1.85)$_{n=225}$	2.60 (1.45)$_{n=142}$	3.58 (1.95)$_{n=47}$	5.16 (2.30)$_{n=21}$
Plasma GFAP (pg/mL)	148.9 (77.23)$_{n=225}$	130.0 (58.20)$_{n=142}$	168.1 (88.06)$_{n=47}$	232.8 (99.56)$_{n=21}$

Mean (S.D.) given for all continuous measures aside from Age where range is provided. Subscript denotes number of participants for which measure was available. M: Male, F: Female, W: White, B: Black or African American, A: Asian, M: Multiple Races, U: Unknown or Did Not Report

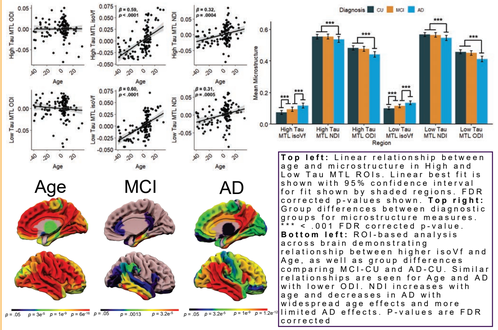
METHODS



- Amyloid PET with [^{18}F]florbetapen and SUVR measures calculated using cerebellar reference region
- Plasma p-tau-181 and GFAP measured using SiMoA® SR-X Platform (Quanterix, Billerica, MA, USA)
- Statistical analyses performed using R v4.3.1. All analyses control for age, sex, education, race, time between biomarker and MRI, and macrostructure (volume or thickness)

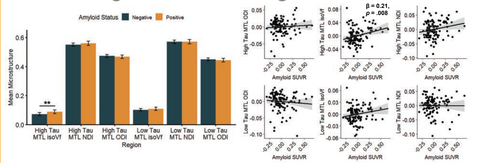
RESULTS

Widespread age and disease-specific effects



Top left: Linear relationship between age and microstructure in High and Low Tau MTL ROIs. Linear best fit is shown with 95% confidence interval for fit shown by shaded regions. FDR corrected p-values shown. **Top right:** Group differences between diagnostic groups for microstructure measures. *** < .001 FDR corrected p-value.
Bottom left: ROI-based analysis across brain demonstrating relationship between higher isoVf and Age, as well as group differences comparing MCI-CU and AD-CU. Similar relationships are seen for Age and AD with lower ODI. ODI increases with age and decreases in AD with widespread age effects and more limited AD effects. P-values are FDR corrected

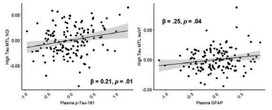
Amyloid effects in CU individuals only within high Tau MTL regions



Left: Group differences between amyloid positive and amyloid negative CU individuals demonstrating significant increase in isoVf in high tau MTL within amyloid positive individuals; **FDR-corrected $p <$ .01. **Right:** Linear relationship between global Amyloid SUVR and isoVf in high tau MTL ROI; line of best fit shown with shaded region representing 95% CI for fit. P-values FDR corrected

RESULTS

Similar effects seen with plasma biomarkers



Linear relationship between Plasma p-tau$_{181}$ and higher NDI in high tau MTL regions **(Left)** and between plasma GFAP and higher isoVf in high tau MTL regions in CU individuals **(Right)**. Linear best fit is shown with shaded area representing 95% CI for fit. Analyses control for demographics, time between samplea and MRI, and macrostructure

No relationships between any measure and biomarkers outside of MTL in CU individuals or with macrostructure

More widespread relationships when looking across all diagnostic groups

Preliminary results in subset with Tau PET show similar relationships

REFERENCES

1. Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., & Alexander, D. C. (2012). NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *Neuroimage*, *61*(4). https://doi.org/10.1016/j.neuroimage.2012.03.072
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3. Yushkevich, P. A., Muñoz López, M., et. al. (2021). Three-dimensional mapping of neurofibrillary tangle burden in the human medial temporal lobe. *Brain*, *144*(9). https://doi.org/10.1093/brain/awab262

CONCLUSIONS

- Age and Alzheimer's disease disrupt gray matter microstructure throughout the MTL and across the cortex
- Gray matter microstructure alterations in high tau MTL regions are seen in amyloid positive CU individuals prior to macrostructural changes
- MTL microstructural changes are associated with plasma AD biomarkers in CU individuals

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