

Preliminary assessment of [¹⁸F]3F4AP PET for Imaging Demyelination in Alzheimer's Disease



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RATIONALE

In addition to amyloid- β (A β) plaques and tau tangles, **Alzheimer's disease** may involve **myelin/white-matter alterations** and **perfusion changes** that could influence clinical expression and progression. [¹⁸F]3F4AP targets **voltage-dependent potassium ion channels**, which become increasingly exposed following myelin loss, providing an indirect PET marker of demyelination. We performed a **pilot study** investigating [¹⁸F]3F4AP for quantifying **myelin-related** signal and comparing that to **tau, A β , and perfusion surrogates** as well as **MRI-based myelin** measures.

OBJECTIVES

- Characterize regional [¹⁸F]3F4AP PET signal across **cognitively normal (CN)**, **mild cognitive impairment (MCI)**, and **Alzheimer's disease (AD)** participants
- Evaluate associations between [¹⁸F]3F4AP PET and **multimodal biomarkers** of tau, amyloid, perfusion, and myelin content
- Assess the potential of [¹⁸F]3F4AP PET to probe **myelin-related alterations in AD**

METHODS

❖ Participants and Data Acquisition

Four aging adult participants underwent dynamic [¹⁸F]3F4AP PET (myelin integrity/demyelination) and dynamic [¹⁸F]MK6240 PET (tau pathology) on the NeuroEXPLORER (NX) scanner. Three of those participants also underwent [¹¹C]PiB PET (A β pathology). MRI included T₁-weighted MEMPRAGE, T₂-FLAIR, and **myelin water fraction (MWF)** imaging.

Diagnosis	N	Sex (M/F)	Age (y)	Weight (kg)	[¹⁸ F]3F4AP (MBq)	[¹⁸ F]MK6240 (MBq)	[¹¹ C]PiB (MBq)
CN	2	2/0	73.9 ± 6.9	97.6 ± 26.4	356 ± 26	166 ± 15	329 ± 72
MCI	1	1/0	74.0	99.5	330	181	492
AD	1	0/1	62.15	52	178	161	—
Total	4	3/1	71.0 ± 7.1	85.4 ± 27.0	305 ± 87	168 ± 12	384 ± 106

❖ Image Processing

- Structural MRI (T₁-weighted MEMPRAGE) processed using FreeSurfer for cortical and subcortical segmentation
- PET images reconstructed and motion-corrected
- MRI and PET images co-registered
- FreeSurfer-defined ROIs transferred to PET space for regional analyses
- T₂-FLAIR and MWF images co-registered to T₁ MRI

❖ Quantification

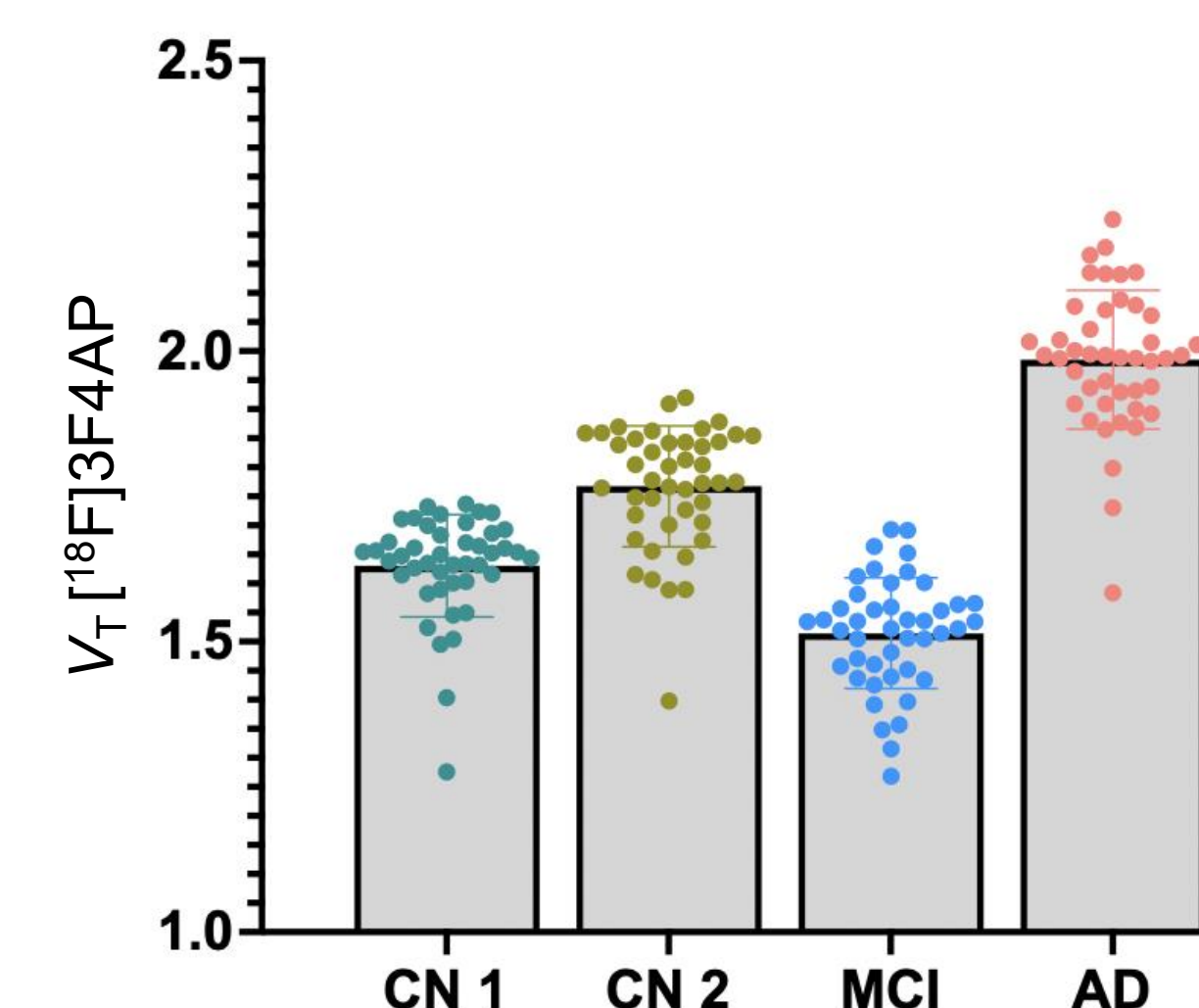
Biomarker	Outcome Measure	Quantification Method
[¹⁸ F]3F4AP	V _T	Logan graphical analysis with arterial input function
[¹⁸ F]MK6240	DVR	Logan graphical analysis (cerebellar cortex gray matter as reference region)
[¹¹ C]PiB	DVR	Logan graphical analysis (cerebellar cortex gray matter as reference region)
Perfusion	R_1 $K_{1\text{target}}/K_{1\text{reference}}$	SRTM2 (first 5 min of the scan) 1T2k1v (first 5 min of the scan)
MRI Myelin	MWF	Regional MRI-derived myelin water fraction

❖ Statistics

- Regional analyses performed across FreeSurfer-defined ROIs
- Group-level trends across participants explored descriptively
- ROI-wise associations between [¹⁸F]3F4AP V_T and other PET/MRI measures assessed using Spearman rank correlations
- Statistical significance set at $p < 0.05$, with results interpreted as exploratory due to the pilot sample size

RESULTS

❖ [¹⁸F]3F4AP regional V_T across participants

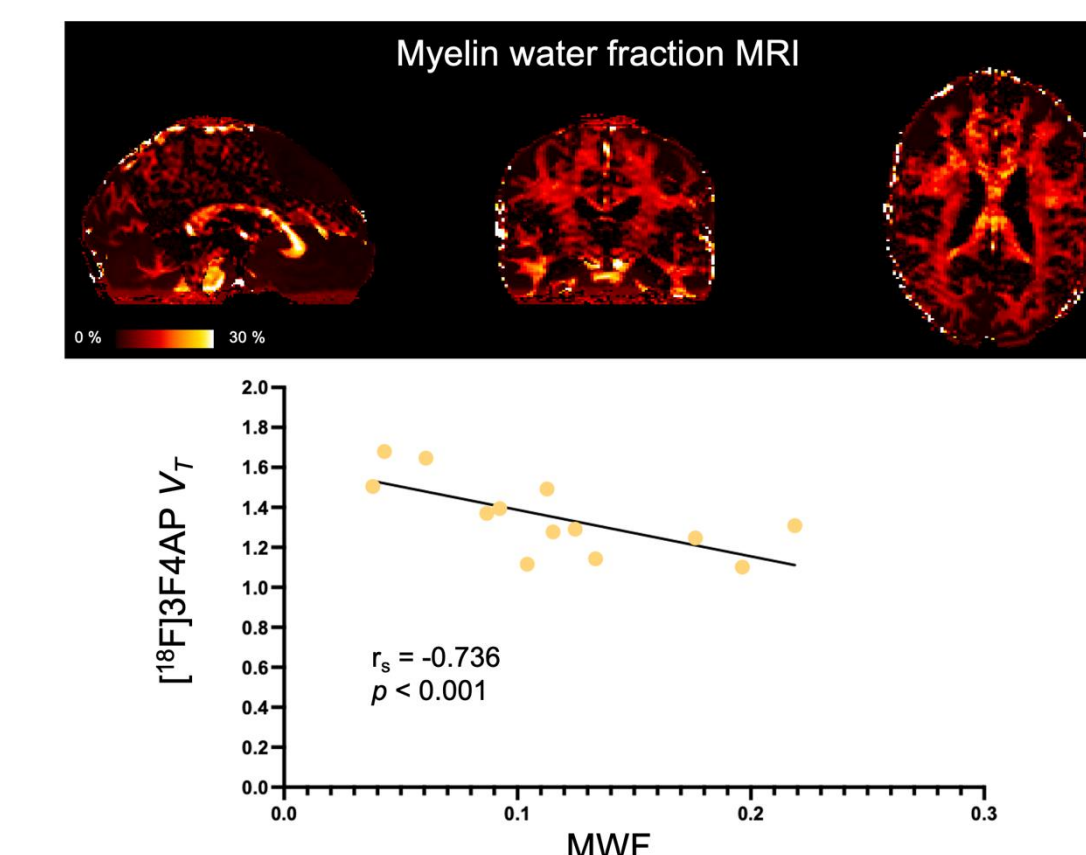


Regional [¹⁸F]3F4AP V_T across **50 FreeSurfer-defined brain regions**. Bars represent mean ± SD and dots represent individual region values. **Higher V_T was observed in AD participant** compared with CN and MCI participants, consistent with **increased myelin-related signal alterations**.

❖ ROI-wise associations between [¹⁸F]3F4AP, [¹⁸F]MK6240, [¹¹C]PiB

Subject	Main significant findings
CN1	Strong spatial coupling between [¹⁸ F]MK6240 and [¹¹ C]PiB in AD cortical regions ($r_s = 0.83$, $p < 0.001$). White matter showed positive associations among [¹⁸F]MK6240, [¹¹C]PiB and [¹⁸F]3F4AP ($r_s = 0.71$ - 0.91 , $p \leq 0.047$), suggesting similar regional distributions across tracers.
CN2	Strong positive whole-brain [¹⁸ F]MK6240-[¹¹ C]PiB coupling ($r_s = 0.57$, $p < 0.001$). White matter demonstrated strong associations between [¹⁸F]3F4AP and both [¹⁸F]MK6240 ($r_s = 0.76$, $p = 0.028$) and [¹¹ C]PiB ($r_s = 0.88$, $p = 0.004$).
MCI	Positive whole-brain association between [¹⁸F]MK6240 and [¹⁸F]3F4AP ($r_s = 0.45$, $p < 0.001$), but inverse association between [¹¹C]PiB and [¹⁸F]3F4AP ($r_s = -0.40$, $p = 0.002$). White matter showed particularly strong coupling among all tracers. Control-normalized abnormalities in [¹¹C]PiB and [¹⁸F]3F4AP were spatially correlated ($r_s = 0.50$, $p < 0.001$).
AD	Positive association between [¹⁸ F]MK6240 and [¹⁸ F]3F4AP across the whole brain ($r_s = 0.38$, $p = 0.003$), white matter ($r_s = 0.79$, $p = 0.021$), and subcortical regions ($r_s = 0.89$, $p = 0.007$), indicating strong spatial concordance between tau burden and [¹⁸F]3F4AP signal .

❖ ROI-wise associations between [¹⁸F]3F4AP and MWF



Myelin water fraction (MWF) was extracted from **white matter-rich** FreeSurfer brain regions. [¹⁸F]3F4AP V_T showed a **strong inverse association with MWF**, supporting the interpretation that **higher PET signal reflects reduced myelin integrity**.

CONCLUSIONS

[¹⁸F]3F4AP PET demonstrated **higher regional V_T in AD** participant and showed a **strong inverse relationship with MRI-derived MWF**, supporting its sensitivity to myelin-related alterations. While [¹⁸F]3F4AP was not associated with perfusion measures, exploratory associations with tau and amyloid suggest that myelin-related changes may interact with multiple pathological processes across the AD spectrum.

REFERENCES

Guehl et al., 2022; Tiss et al., 2025; Ramos et al., 2025; Guehl et al., 2023; Brugarolas et al., 2022; Mackay et al., 2016