

KEY TAKEAWAY Quantitative myelin mapping reveals early myelin loss along entorhinal-anchored olfactory–limbic circuits in MCI — linked to odor identification and cognition — positioning myelin volume fraction (MVF) as a rapid, clinically feasible complement to the A/T/N framework.

INTRODUCTION

- Olfactory dysfunction is among the earliest features of AD, often preceding memory loss by years and reflecting vulnerability of entorhinal cortex (EC)–anchored olfactory–limbic circuits.
- Growing evidence implicates early myelin breakdown as an active event in the AD cascade that interacts with amyloid-β and tau pathology.
- Late-myelinating association and entorhinal regions are selectively vulnerable to demyelination (“retrogenesis”), shaping network-level spread of pathology.
- We tested whether SyMRI-derived MVF detects early myelin alterations in MCI and relates to olfactory and cognitive performance.

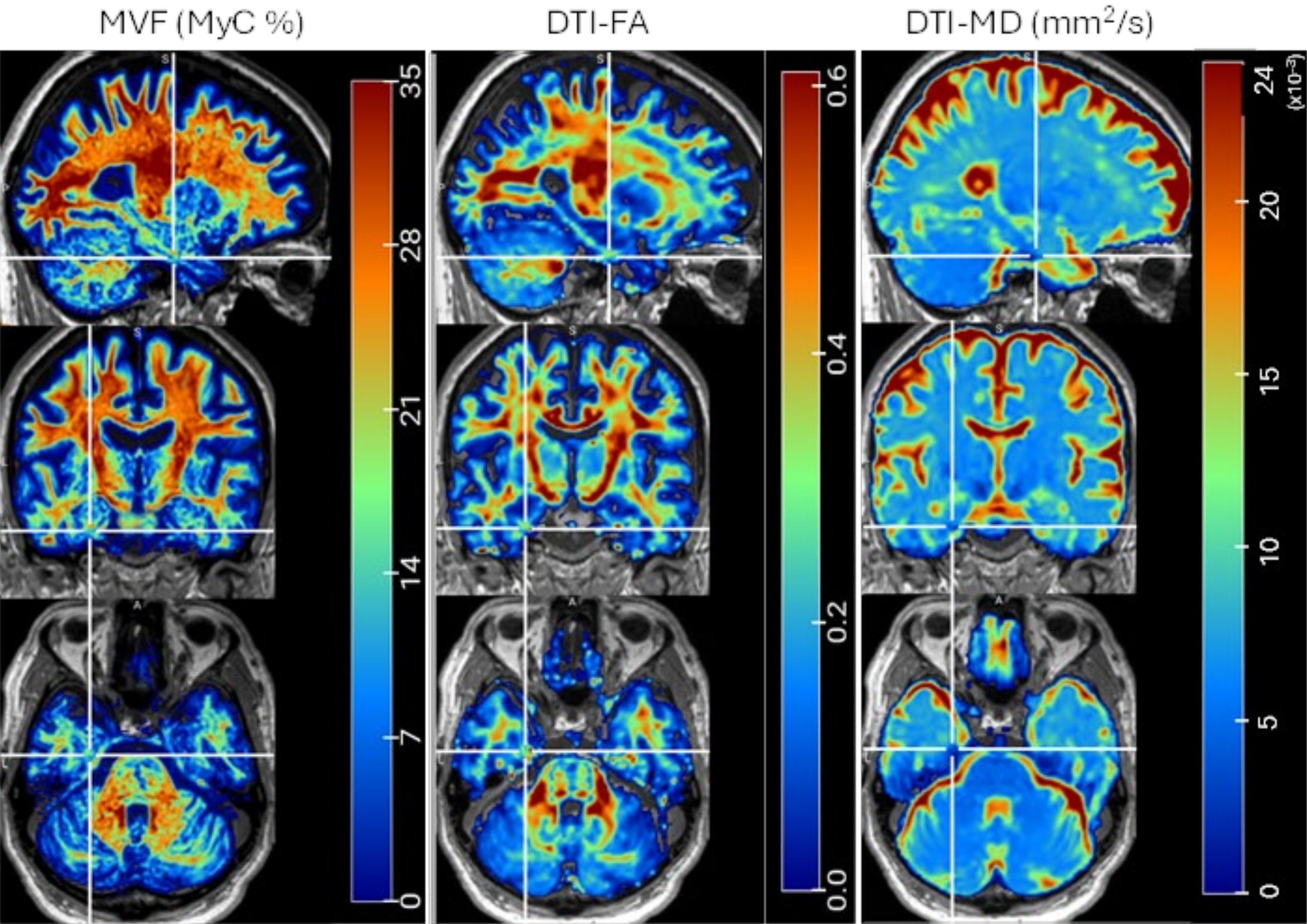


Fig 1.. A contrast-illustration of the MVF map in comparison to DTI-FA and MD maps .

Table 1	HC	MCI	P
	n=24	n=22	
Gender (M/F)	(4/20)	(12/10)	0.0124
AGE(year)	64.38±7.42	71.27±8.70	<0.01
Educational	17.33±2.18	16.75±2.89	0.4475
MOCA	26.88±1.51	22.50±2.96	<0.0001
CVLT-3 List A Trial 1	6.21±2.06	4.23±1.72	<0.001
CVLT-3 List A Trial 2	9.67±2.08	6.55±2.04	<0.0001
CVLT-3 List A Trial 3	11.83±2.22	7.41±2.97	<0.0001
CVLT-3 List A Trial 5	12.67±2.16	8.64±3.06	<0.0001
CVLT-3 List B	5.79±2.26	4.27±1.42	<0.05
CVLT-3 List A Short-Delay Free Recall	11.67±2.84	5.00±4.12	<0.0001
RCFT Delayed	17.25±7.26	7.91±6.55	<0.001
RCFT Recognition	20.21±2.13	17.64±3.06	<0.01
RCFT Immediate	20.21±2.13	17.64±3.06	<0.01
Olfactory ID	16.88±2.23	14.73±4.24	0.07

Table 1. Demographic & cognitive characteristics of the cohort (group differences age-adjusted, ANCOVA).

METHODS

- Participants: 46 older adults (55–85 y) — 22 MCI, 24 healthy controls (HC).
- 3T MRI: T1-MPRAGE, multi-shell DTI, and quantitative SyMRI MVF mapping via a rapid ~5–6 min 3D-QALAS acquisition.
- Behavior: odor identification (OLFACT-20, 4AFC); cognition (MoCA, CVLT, RCFT).
- A priori olfactory–limbic gray- and white-matter ROIs from EC-seeded resting-state connectivity + literature.
- Age-adjusted ANCOVA (HC vs MCI) for MVF and DTI-RD; voxel-wise and ROI regressions of MVF with odor ID and MoCA.
- MCI vs HC classification: five-fold cross-validated GLM on PCA-reduced ROI features.

RESULTS

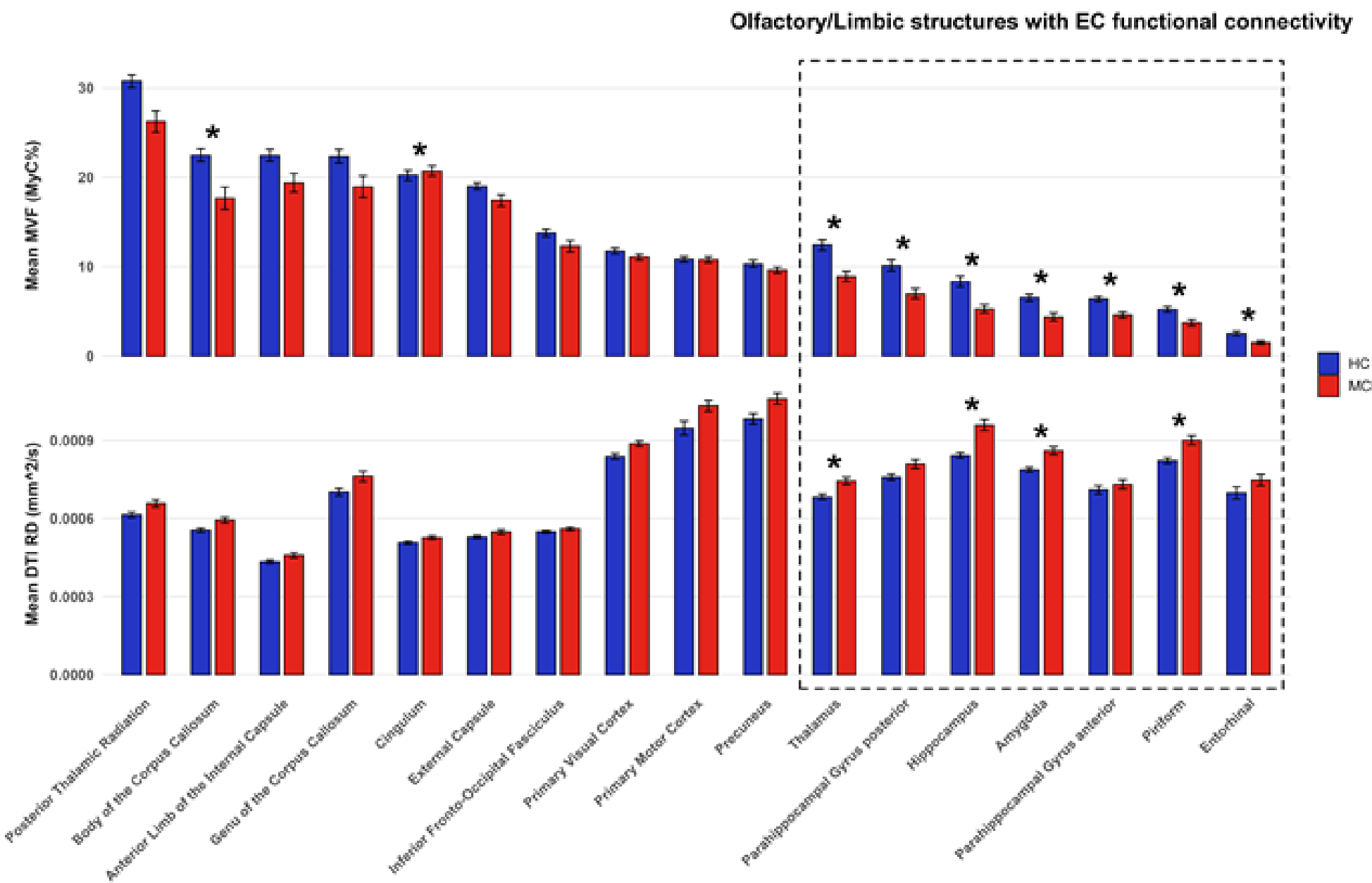


Fig 2. Mean MVF (a) and DTI-RD (b) by ROI for HC (blue) vs MCI (orange), ranked by MVF. Asterisks mark significant age-adjusted group differences (p<0.05). Dashed box = olfactory–limbic structures with EC functional connectivity.

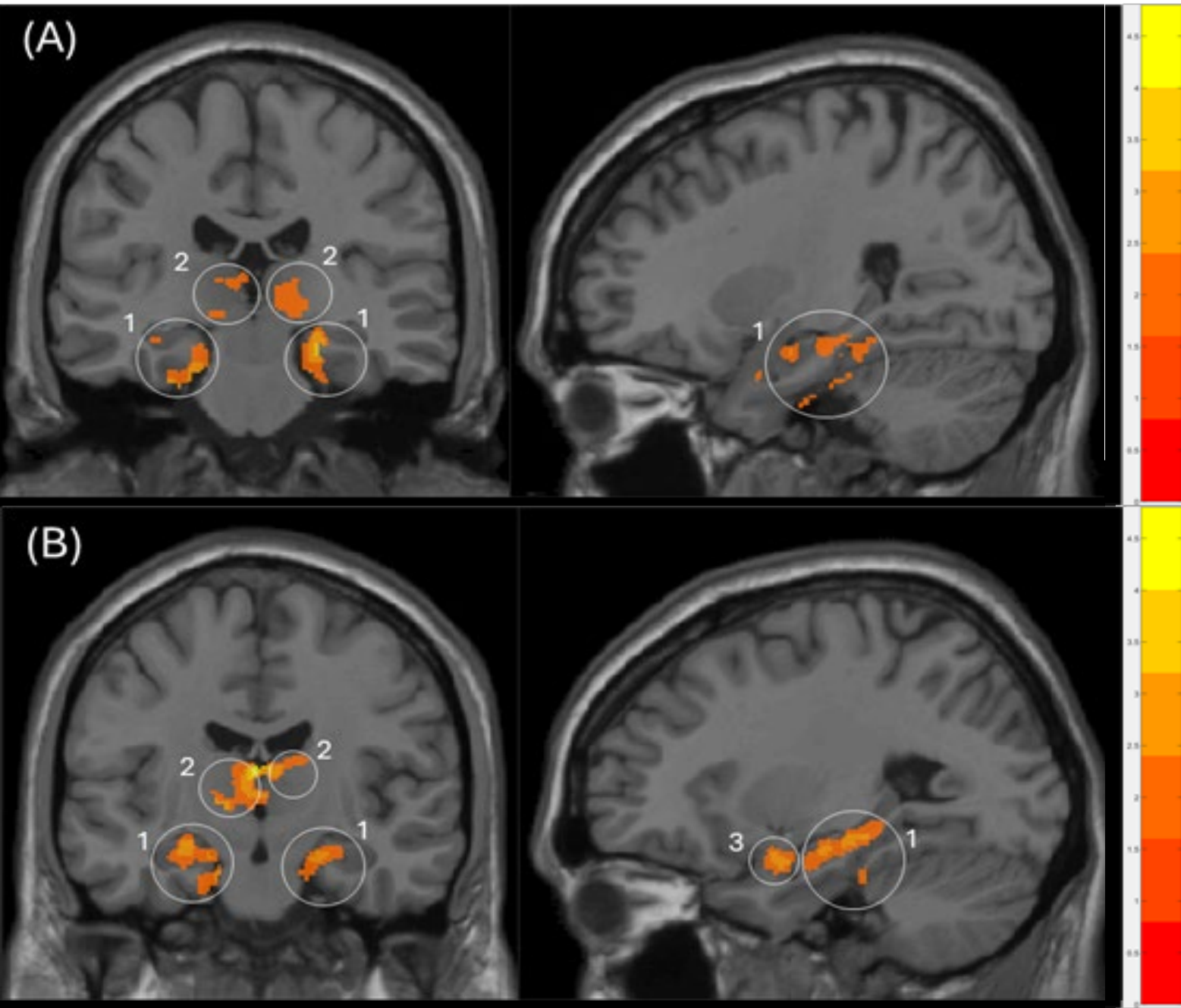


Fig 3. Voxel-wise correlations (age and sex-adjusted). MVF with (a) odor identification and (b) MoCA (p<0.05, uncorrected). White circles highlight effects within olfactory–limbic structures: hippocampal and parahippocampal regions (1), thalamus (2), and amygdala (3).

Table 2	MVF	MD	RD
Gray & White matter ROIs			
# of PCs	PC1–PC8	PC1–PC8	PC1–PC8
PC only AUC	0.828	0.737	0.706
PC + OdorID AUC	0.837	0.722	0.689
White matter ROIs			
# of PCs	PC1	PC1–PC6	PC1–PC3
PC only AUC	0.723	0.561	0.672
PC + OdorID AUC	0.72	0.625	0.676
Grey matter ROIs			
# of PCs	PC1–PC3	PC1–PC4	PC1–PC4
PC only AUC	0.795	0.794	0.797
PC + OdorID AUC	0.792	0.79	0.792

Table 2. Five-fold cross-validated AUCs for MCI vs HC from PCA-reduced MVF / DTI features.

CONCLUSIONS

- SyMRI-derived MVF is a rapid, clinically feasible myelin marker that captures early olfactory–limbic myelin loss at the MCI stage.
- Myelin integrity links to sensory–cognitive function, supporting demyelination as a complementary mechanism within the A/T/N framework.
- Odor identification adds incremental classification value, highlighting olfactory testing as a noninvasive early biomarker.
- Future work: longitudinal validation of MVF for MCI→AD progression, integration of tau, and larger, diverse cohorts.

KEY FINDINGS

- Lower MVF in MCI across olfactory–limbic gray matter (piriform cortex, hippocampus, parahippocampal gyrus, amygdala, thalamus) and white-matter tracts (cingulum, body of corpus callosum), with convergent RD increases (Fig 2).
- Higher MVF correlated with better odor identification and MoCA in hippocampal, parahippocampal, and thalamic regions (Fig 3 a–b).

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