

Spatial Gradients of Perfusion and Myelin Density in White Matter Hyperintensities and Surrounding NAWM



F. Masserini, L. Lorenzini, M. Tranfa, L. Pieperhoff, P. Arunachalam, J.M. Hendriks, F. Heeman, M.M. Yaqub, A.A. Lammertsma, C. H. Sudre, H.J.M.M. Mutsaerts, A. M. Wink, H. Vrenken, L.E. Collij, L. Pantoni, F. Barkhof *on behalf of the AMYPAD Consortium*



Perilesional zone of alterations may extend up to 16 mm around WMHs. Tight perfusion–myelin coupling within 8 mm might mark a "hot" pre-damage core, while uncoupling and predominant hypoperfusion characterise the outer 8–16 mm band.

Introduction and aims

White matter hyperintensities (WMHs), a hallmark of cerebral small vessel disease (cSVD), are characterised by hypoperfusion, extracellular fluid accumulation, and loss of tissue integrity. The spatial interplay of perfusion and myelin alterations within WMHs and surrounding normal-appearing white matter (NAWM) remain poorly understood. We investigated perfusion and myelin density gradients around WMHs using quantitative PET.

Methods

Participants without dementia from the AMYPAD-PNHS cohort underwent dynamic amyloid PET and MRI (volumetric T1w and T2-FLAIR, *Table 1*). DynPET data were modelled with SRTM2 to derive R1 (perfusion proxy) and BP_{ND} (myelin-density proxy). WMHs were segmented with BaMoS, and NAWM Euclidean distance maps from nearest WMH voxels were discretised into 2-mm bands (Figure 1). Distance-dependent trajectories were modelled with generalised additive models (GAM); R1–BP_{ND} coupling over distance was characterised via a varying-coefficient GAM ($\partial \text{BPND} / \partial \text{R1}$ varying with distance) and sliding-window linear mixed-effects slopes (BPND ~ R1).

Table 1 – Main descriptives

Descriptives	Participants (n = 188)
Age	70 (SD 6)
Biological sex	54% F
MMSE	29.1 (SD 1.09)
WMH burden	4.1 mL (25-75 IQR 2.1-7.8)

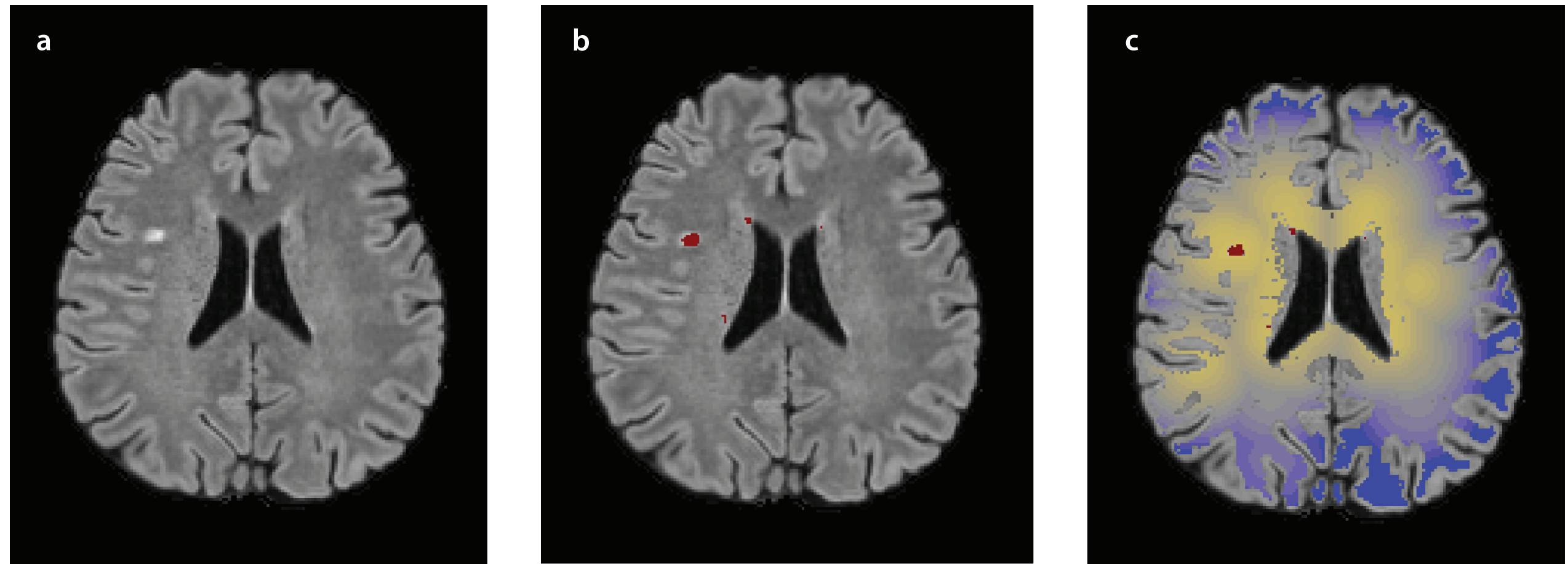


Figure 1 – Example of WMH segmentation and distance-based NAWM voxel binning. Starting from the original 3D FLAIR images, panel (a), we applied the BaMoS algorithm for WMH segmentation (panel b, red). NAWM voxels were then classified according to their distance from the nearest WMH voxel, discretised into 2 mm distance bins (panel c), ranging from the closest bins (yellow) to the most distant ones (blue); distance in the legend is reported in mm.

Acknowledgement(s): This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115952. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. F. Masserini was partially supported by AIRALZH (AGYR2024 grant).

Results

R1 and BP_{ND} showed significant differences between WMH and NAWM and showed non-linear associations with distance from WMH boundary (p<0.001).

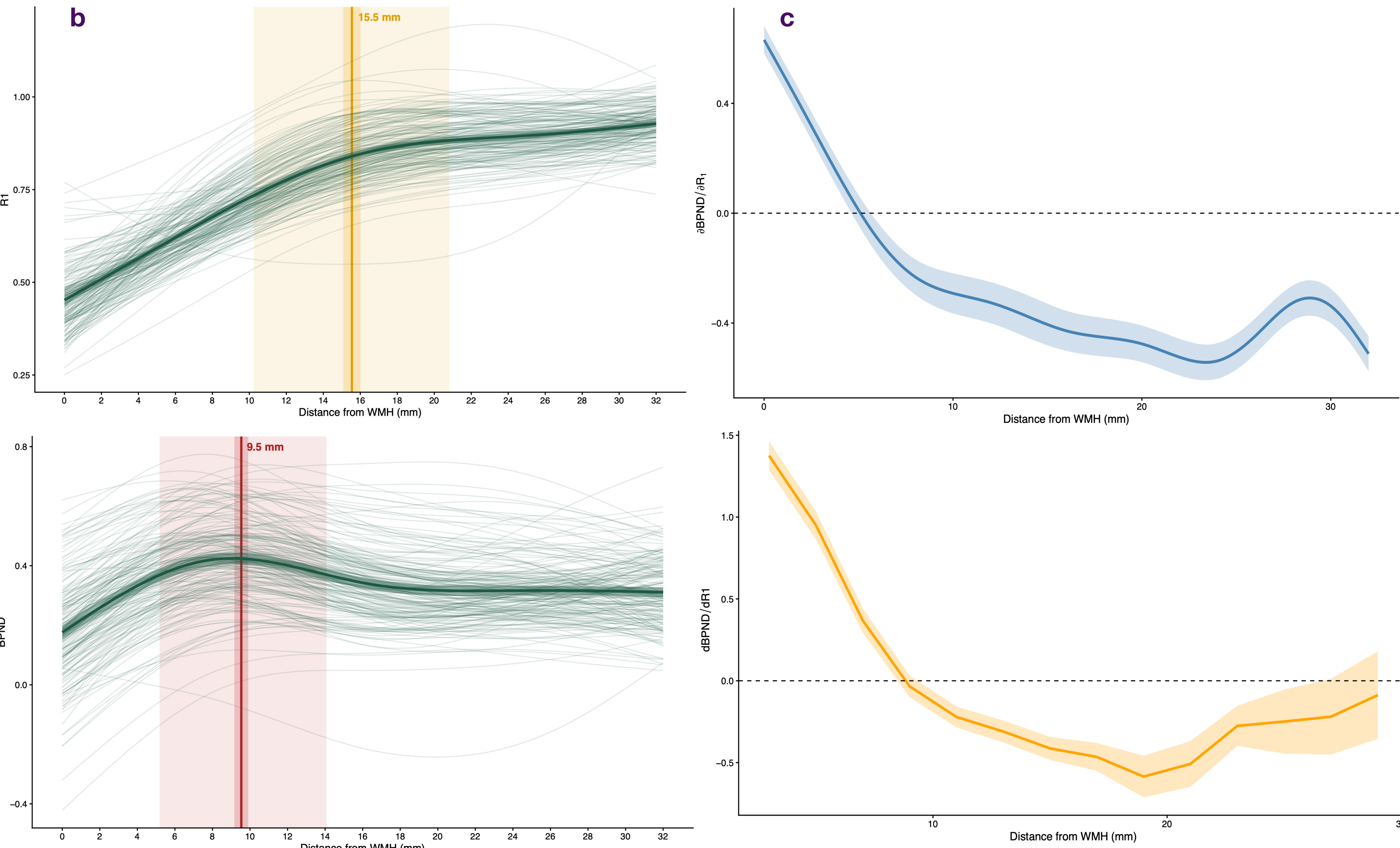
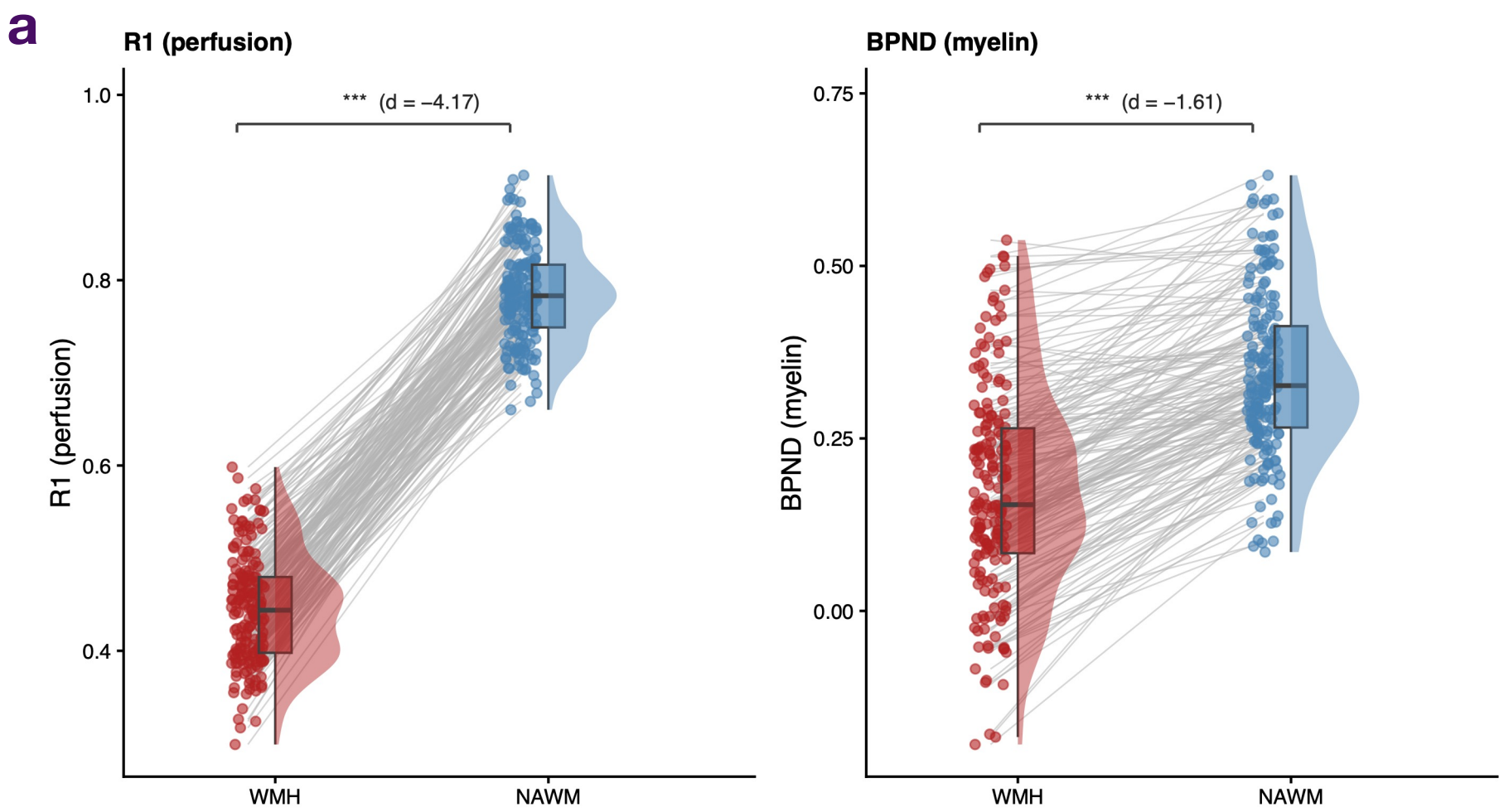


Figure 2 – Metric variation within the WMH core and surrounding perilesional NAWM, and between-metric correlation as a function of distance. (a) Pairwise difference between R1 and BPND values in lesional tissue (red) vs NAWM (blue). (b) Non-linear distance-dependent trajectories of R1 (above) and BPND (below), estimated using repeated-measures generalised additive models with subject-specific smooths with landmark estimation (maximum curvature and peak value). (c) Distance-resolved coupling between dynPET metrics, showing continuous variation of the association between metric values across the perilesional gradient and the linear association between the two metrics as a function of distance from WMH.



Conclusions

The perilesional area surrounding WMHs may extend up to ~16 mm from lesion border. Tight perfusion–myelin coupling within ~8 mm may mark a "hotter" pre-damage core, while uncoupling and predominant hypoperfusion characterise the outer 8–16 mm band. These distance-dependent profiles point to distinct processes in perilesional NAWM and a spatially defined, potentially reversible zone relevant to cSVD progression.

Contacts

e-mail:
f.masserini@amsterdamumc.nl

LinkedIn

Bluesky
(fmasserini)

