Redefining MRI:
From Image to Insight

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Hiding in Plain Sight: Uncovering Hidden Signals in Structural MRI for More Sensitive and Specific Study of Alzheimer's Disease Neuropathology

David H. Salat

Massachusetts General Hospital, Harvard Medical School, USA

Artificial intelligence and machine learning approaches in medical imaging are often judged by the sophistication of the model: the algorithm used, the architecture selected, and the magnitude of performance improvement achieved. However, in Alzheimer's disease and related dementias, a central source of untapped progress may lie upstream of the model itself: the way structural MRI data are represented. Conventional structural MRI analyses typically reduce the image to a limited set of morphometric features, including cortical thickness, regional brain volume, and total white matter hyperintensity burden. These measures are clinically and biologically meaningful, but they capture only a fraction of the information contained in routinely acquired structural images. Additional disease-relevant signals are hiding in plain sight within standard MRI data and extracting these signals may substantially improve the sensitivity and specificity of imaging-based studies of Alzheimer's disease neuropathology.

Two examples illustrate this opportunity. First, cortical signal properties, including gray-white matter contrast, gray-to-white matter signal ratio, and multiscale structural mapping, may provide information about tissue integrity that is not captured by atrophy-based measures alone. These features may reflect alterations in cortical and subcortical tissue composition, intracortical and juxtacortical myelin, tissue-boundary integrity, water content, gliosis, inflammation, or other microstructural processes relevant to Alzheimer's disease. Importantly, emerging work suggests that these signal-derived measures may relate to molecular markers of Alzheimer's disease, including amyloid and tau burden, and may detect disease-relevant abnormalities even when conventional cortical thickness or hippocampal volume measures show limited sensitivity.

Second, white matter lesion features provide a parallel example in which conventional summary measures may obscure biologically important heterogeneity. White matter hyperintensity volume is widely used, but lesions are not interchangeable units of injury. Their intensity, texture, spatial distribution, size, contrast, and subtype may distinguish different vascular, degenerative, aging-related, and mixed pathophysiological processes. Characterizing lesion quality and lesion heterogeneity may therefore provide more clinically specific information than lesion burden alone and may improve models of cognitive decline, disease progression, and resilience.

These examples support a broader principle for AI in medical imaging: model performance depends not only on the algorithm, but also on the biological adequacy of the features provided to that algorithm. More complex models cannot reliably recover information that has been discarded during feature extraction. For Alzheimer's disease research, an optimized structural MRI pipeline should therefore combine traditional morphometry with signal-based measures, multiscale tissue features, and lesion phenotyping. This approach may improve sensitivity by detecting subtle tissue alterations before overt atrophy and may improve specificity by separating distinct biological sources of MRI abnormality.

The presentation concludes with practical design principles for future imaging-AI studies: compare conventional and expanded feature sets directly, test incremental value beyond standard morphometry, harmonize signal-derived measures across scanners and protocols, validate against molecular biomarkers, and prioritize interpretable feature representations that map onto plausible neuropathological mechanisms. Thus, in Alzheimer's disease neuroimaging the next major advance may come not only from better models, but from better representations of the structural MRI image itself.

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