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INTEGRATED MULTIMODAL IMAGING IN NEURODEGENERATIVE DISEASE

Murray Grossman

Department of Neurology and Penn Frontotemporal Degeneration Center, University of
Pennsylvania

In an era of disease-modifying treatments for neurodegenerative diseases, biomarkers play a crucial role for *in vivo* identification of patients with appropriate histopathologic targets. Multimodal neuroimaging can make an essential contribution to this process. In a comprehensive review, Teipel and his co-authors (REF) outline the varieties of available imaging for patients with Alzheimer's disease, and consider the clinical utility associated with each of these techniques. The authors provide authoritative reviews of functional and structural imaging. This includes positron emission tomography (PET) radioligands sensitive to amyloid as well as PET glucose metabolic studies, and structural MRI studies of gray matter atrophy, diffusion tensor imaging, and resting state fMRI techniques. The authors argue that these modalities can be used individually and serially to assist in the differential diagnosis of Alzheimer's disease.

Consider some examples of the utility of multimodal imaging. One important goal is the early diagnosis of Alzheimer's disease. Here, disease-modifying treatment may achieve the objective of preventing or significantly delaying the onset of clinical Alzheimer's disease^{1–3}. Presymptomatic diagnosis of Alzheimer's disease and other neurodegenerative conditions can be achieved with reasonable sensitivity and specificity using multimodal imaging. This involves minimizing false positives and avoiding false negatives through the use of structural MRI or functional PET-glucose imaging followed by PET-amyloid radioligand imaging.

Another important goal is to expand treatment trial eligibility to all with Alzheimer's disease pathology. The diagnosis of atypical variants with high sensitivity and specificity remains a significant challenge in the differential diagnosis of Alzheimer's disease. Patients with less common syndromes such as posterior cortical atrophy, the logopenic variant of primary progressive aphasia, and corticobasal syndrome are important to recognize because phenotypically similar patients have non-Alzheimer's pathology⁴. Notably, these individuals may never develop episodic memory difficulty despite histopathologic evidence indicating only Alzheimer's disease pathology, and they are routinely excluded from disease-modifying treatment trials. Indeed, Alzheimer's disease represents one of many neurodegenerative conditions associated with these phenotypes. Differential diagnosis

within this large, heterogeneous family of disorders would significantly benefit from multimodal imaging.

In the spectrum of dementia with Lewy bodies and Parkinson's disease dementia, Alzheimer's disease pathology is present in about 60% of cases⁵. PET amyloid imaging may be able to identify increased amyloid, but there is the risk of a false-positive result particularly in an older population. Indeed, while the clinical diagnosis of typical Alzheimer's disease may appear to be clinically straightforward, disease-modifying treatments ultimately must encompass the heterogeneous pathologies found in Alzheimer's disease, including amyloid, tau, TDP-43 and synuclein, and an individualized approach to disease-modifying treatments in the future will require multimodal imaging.

However, true multimodal imaging – the integration of multiple imaging modalities into a single connectome – can make even more powerful contributions^{6, 7}. Alzheimer's disease and other neurodegenerative conditions are progressive in nature, for example, yet we know little about mechanisms of progressive disease in humans. Multimodal imaging can contribute critically to improving our understanding of mechanisms of disease progression and the development of novel treatment targets. Several competing theories of disease progression are emerging, such as cell-to-cell prion-like spread of fibrils^{8, 9}, or selective vulnerability of specific neuronal populations due to high metabolic demand^{10, 11}. Most previous work has examined staging in neurodegenerative disease by quantifying the regional anatomic distribution of histopathologic burden¹². While this is crucial for hypothesis generation, the discovery of the mechanism underlying disease progression in humans can best be achieved *in vivo* with connectomic imaging, that is, the integration of multiple, longitudinal imaging modalities to reveal the manner in which large scale neural networks progressively degrade over time. The anatomic distribution of longitudinal imaging changes, and the imaging modalities integrated to reveal these changes, will play an essential role in this process. Moreover, the outcome of these imaging studies will play an important role in monitoring responses to disease-modifying treatment interventions. Finally, advanced bioinformatics approaches can also reveal highly informative relationships between imaging and other biomarker modalities. For example, imaging can be related to molecular biomarkers to determine the impact of genetics on brain structure and function^{13, 14}.

In sum, true multimodal imaging through the integration of multiple imaging modalities into a single connectome represents an important advance in human studies of neurodegenerative disease. While animal models of neurodegenerative disease and postmortem human studies constitute important methods for hypothesis generation, *in vivo* assessments of Alzheimer's disease and other neurodegenerative conditions now can be pursued during life with advanced multimodal imaging. The review by Teipel and his colleagues summarizes important advances in neuroimaging that can be brought to bear in achieving these ends.

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