Multimodal imaging in Alzheimer's disease: validity and usefulness for early detection

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Alzheimer's disease is a progressive neurodegenerative disease that typically manifests clinically as an isolated amnestic deficit that progresses to a characteristic dementia syndrome. Advances in neuroimaging research have enabled mapping of diverse molecular, functional, and structural aspects of Alzheimer's disease pathology in ever increasing temporal and regional detail. Accumulating evidence suggests that distinct types of imaging abnormalities related to Alzheimer's disease follow a consistent trajectory during pathogenesis of the disease, and that the first changes can be detected years before the disease manifests clinically. These findings have fuelled clinical interest in the use of specific imaging markers for Alzheimer's disease to predict future development of dementia in patients who are at risk. The potential clinical usefulness of single or multimodal imaging markers is being investigated in selected patient samples from clinical expert centres, but additional research is needed before these promising imaging markers can be successfully translated from research into clinical practice in routine care.

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Introduction

According to research diagnostic criteria—such as those of the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association)—and recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, early clinical stages of Alzheimer's disease include patients with mild Alzheimer's disease dementia and those with prodromal disease (patients without dementia who have episodic memory impairment or mild cognitive impairment and positive imaging or neurochemical biomarkers of Alzheimer's disease).[1,2] Mild cognitive impairment is itself a complex clinical entity with many subcategories (appendix p 1). Although originally designed for research purposes, these research diagnostic criteria for prodromal and early dementia stages of Alzheimer's disease have already begun to affect clinical practice.[1,2] Patients with mild cognitive impairment who consult a specialised memory clinic are already informed about a probable underlying Alzheimer's disease pathology and the development of short-term dementia if diagnostic tests show the presence of both an amyloid β biomarker and a biomarker of neuronal injury.[2] In our view, this practice necessitates careful individual counselling of patients with mild cognitive impairment at a memory clinic before any further diagnostic procedures are done. The Alzheimer's Association goes beyond the use of such markers in specialised care by stating: "Core clinical diagnostic criteria spelled out in the guidelines for Alzheimer's dementia and [mild cognitive impairment] due to Alzheimer's can be used now in general practice."[3] In this Personal View, we respond to these developments by critically summarising evidence for the use of imaging as a diagnostic or prognostic biomarker in both the research and care settings. Potential prognostic use of CSF markers for Alzheimer's disease is reviewed elsewhere.[4,5]

A diagnostic biomarker should demonstrate the presence of pathological mechanisms of Alzheimer's disease in the presence of clinical symptoms of dementia, whereas the purpose of a prognostic biomarker is to predict cognitive decline and dementia in prodromal stages of the disease, especially amnestic mild cognitive impairment. Development of a valid imaging biomarker is a multistep process that begins with methodological studies and progresses through to studies with selected samples, including single-centre and multicentre settings, and then to studies in a clinical-care setting. Evidence is already available on the usefulness of single or multimodal imaging biomarkers in highly selected samples of individuals with prodromal stages of Alzheimer's disease, as discussed in the subsequent section. The final proof, however, will be the usefulness of imaging biomarkers to support a diagnosis of Alzheimer's disease in unselected patients from routine care, and their potential to provide outcome improvements that are cost effective and clinically relevant in clinical-care systems. We therefore explore whether the use of novel imaging biomarkers for the detection of dementia and prodromal stages of Alzheimer's disease, including prediction of short-term to mid-term conversion to dementia within 1–2 years, in well-defined research settings can be translated in the foreseeable future into a useful approach for the improvement of the care of patients and their families.

Imaging markers of Alzheimer's disease in the research setting

The most widely used imaging modalities for the assessment of brain changes related to Alzheimer's disease in the research setting are PET-based amyloid markers, which detect molecular pathology specific to Alzheimer's disease, and markers of neuronal injury, including measures from structural MRI, fluorodeoxyglucose (FDG) PET, and diffusion-tensor imaging (DTI). Markers of neuronal injury are more robustly associated with clinical symptoms as quantified by

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psychometric tests compared with amyloid markers, but are only indirectly linked to the underlying molecular pathological changes.[6] Functional MRI techniques detect pathological or compensatory changes of functional network organisation that might take place even before changes in local injury markers become evident.[7]

Studies in selected samples of patients have shown that imaging abnormalities specific to Alzheimer's disease, such as cortical amyloid deposition,[8] grey matter atrophy,[9] hypometabolism,[10] and structural[11] and functional[7] cortical disconnection, can reliably be used to differentiate mild to moderate dementia stages both from normal ageing and from other neurodegenerative dementias. Imaging assessments of the pathological state of an individual's brain might be able to predict the risk of future development of Alzheimer's disease dementia in a person with mild cognitive impairment. The suitability of imaging markers to predict conversion from mild cognitive impairment to Alzheimer's dementia is being explored in clinically highly selected patients, although the usefulness of these imaging markers in routine care will be an important topic of future research.

The validity of an imaging biomarker can be assessed with two principal criteria: first, its pathological validity—ie, whether or not the biomarker measures the pathological changes expected; and second, its clinical validity—ie, the accuracy with which the biomarker can actually predict an individual's clinical outcome. Standards of reporting diagnostic or prognostic accuracy need to be further developed because most researchers do not use methods of cross-validation to assess the precision of variables of accuracy, as recommended in the statistical learning literature.[12]

The next sections will cover the most widely used imaging techniques with respect to their pathological validity and value for predicting conversion to Alzheimer's disease dementia in patients with mild cognitive impairment, including advanced techniques that are close to implementation in large multicentre diagnostic studies, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI),[13] AddNeuroMed,[14] the European multicentre PET study,[15] and several treatment trials (eg, NCT01953601, NCT01767311, and NCT01677572). We do not discuss other promising imaging technologies, such as tau-based PET,[16] because these techniques are undergoing dynamic development but are not yet ready to use in large multicentre trials.

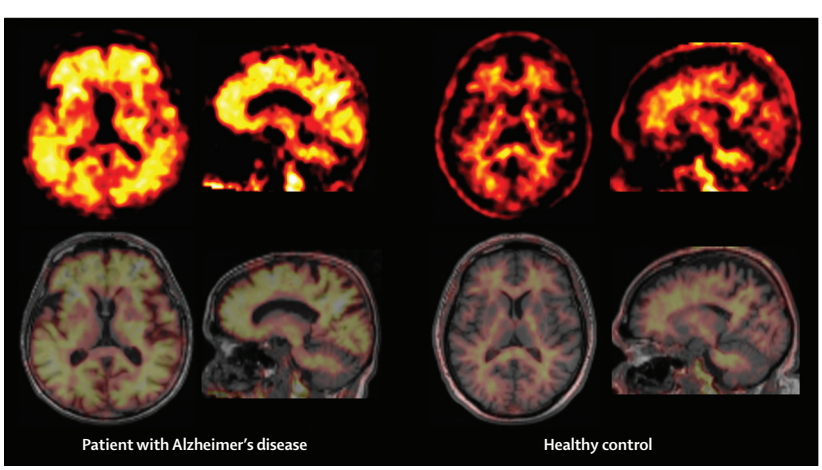

Figure 1: **Cortical amyloid accumulation on ^{18}F-florbetaben PET**
Representative amyloid PET images of a patient with Alzheimer's disease and a healthy control obtained with the ^{18}F-labelled tracer florbetaben. Non-specific white matter binding, as seen in the healthy control, spreads to the neocortical grey matter in the patient with Alzheimer's disease as a sign of cortical amyloid β load.

Amyloid imaging

Visual analysis of amyloid PET data provides binary information on the presence or absence of amyloid load in the brain (figure 1).[17] Whether or not quantitative approaches will have added value compared with qualitative visual analysis is not clear. Quantitative approaches would be beneficial if, for example, high amyloid levels (beyond a certain threshold of positivity) or some regional patterns of amyloid load predicted faster cognitive decline.[18,19] In multicentre settings, the reliability of amyloid PET binary reads across different sites was high.[20] Additionally, the centiloid project aims to unify the quantitative outcome variables for direct comparisons between different amyloid PET tracers.[21]

^{11}C-labelled Pittsburgh compound B (PIB) and ^{18}F-labelled amyloid PET tracers bind with high affinity to the β sheet structure of fibrillar amyloid. These compounds specifically bind to amyloid aggregates and not to other pathological proteins associated with neurodegenerative disorders, such as tau or α synuclein.[22]

A pooled analysis of published neuropathological validation studies of PIB PET, including a total of 15 autopsy cases with dementia (n=10) or normal cognition (n=5) at the time of death,[23–29] shows a pooled sensitivity of 73% and pooled specificity of 100% of binary reads of PIB PET scans in relation to the histopathological presence or absence of amyloid. Three studies[30–32] reported correlation coefficients for the association between regional PIB PET uptake in vivo and quantitative measures of regional amyloid plaque load at autopsy, yielding a pooled correlation coefficient of r=0·88 (SD 0·04). ^{18}F-labelled amyloid PET tracers (florbetapir, florbetaben, and flutemetamol) had a pooled sensitivity as high as 92% and a pooled specificity of 95% for detection of amyloid aggregates across a total of 252 cases in the medical literature, including a wide range of cognitive performance from cognitively normal to dementia at time of death.[33–38] These studies included patients who were terminally ill (with or without dementia), in whom in-vivo PET imaging was compared with post-mortem histopathological changes, and patients with hydrocephalus scheduled for shunt surgery, in whom in-vivo PET imaging was compared with ex-vivo histopathological changes from a biopsy specimen. Association analyses between tracer uptake and histopathological changes showed a mean correlation coefficient across studies[17,36] of r=0·69 (SD