Review Article

Positron emission tomography and magnetic resonance imaging in the diagnosis and prediction of dementia

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Abstract

Background: The diagnosis of dementia, along with the prediction of who will develop dementia, has been assisted by the development of the brain imaging techniques of magnetic resonance imaging (MRI) and positron emission tomography (PET).

Methods: This paper reviews the brain imaging technologies of structural MRI and PET scanning as they have been applied to both the diagnosis of dementia and prediction of who will develop dementia.

Results: Diagnosis has long been enhanced by the use of structural imaging techniques like MRI to rule out non-degenerative causes of disease. More recently, PET imaging with the glucose metabolic tracer $^{18}$F-Fluorodeoxyglucose (FDG) may be useful in providing information on the cause of dementia during life, most specifically in differentiating Alzheimer's disease from frontotemporal lobar degeneration. In addition to diagnosis, potential therapeutic advances have increased interest in prediction of dementia. Both MR and FDG-PET have shown evidence of change in brain structure and metabolism in several models of individuals at-risk for dementia, including those with mild cognitive impairment and genetic risk factors.

Conclusions: While these studies have not yet advanced to the level of prospective individual-subject predictive ability, the pattern of data emerging suggests likely candidate approaches for such studies. The advent of newer techniques such as amyloid imaging with PET and functional MRI may ultimately have relevance for both diagnosis and prediction.

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1. Overview and clinical issues

The application of imaging to dementia diagnosis and prediction must be examined in the context of current clinical knowledge. In this regard, 2 major factors affect the scientific validity of such studies. With regard to the question of using imaging for diagnosis, we need to understand how well imaging results are substantiated by more than just a clinical diagnosis. Usually, such validation requires autopsy confirmation of a diagnosis. For prediction studies, the question is more complex but revolves around potential generalizability and applicability. Clearly, for an imaging prediction study to be eventually applicable to a population sample, the results must be generalizable outside the context in which it was done. In addition, clinical application will require both replication of a measure that might show true prediction (as opposed to retrospective analysis), as well as application on the level of single subjects.

These are indeed high standards that are difficult to meet. Although relatively few imaging studies of diagnostic application are supported by neuropathology, there are some, and many convincing studies have been reported that lack pathology. The prediction of AD in individuals is a more difficult problem that involves not only well-devised prospective imaging criteria, but longitudinal ascertainment and careful attention to a host of practical and ethical issues.
Considerable data exist to support the contention that this is an attainable goal. Issues of generalizability are applicable to both types of studies. Dementia diagnostic studies may suffer from enrollment of highly selected individuals such as those seen at academic medical centers who are likely to undergo autopsy and who may reflect either very unusual or very typical disease presentations. Prediction studies may enroll those with specific genetic risks that are uncommon in the population. Nevertheless, these approaches currently provide the best way of defining at-risk subjects or validating diagnoses.

Finally, diagnostic applications of imaging techniques must address the question of the utility of imaging in addition to clinical assessment. A recent practice parameter developed by the American Academy of Neurology reported sensitivity and specificity of the diagnosis of AD relative to pathology of 81% and 70%, respectively, when averaged over 13 studies [1]. An imaging modality should be shown to improve this performance to be clinically useful or to make contributions to the differentiation of specific dementias from one another.

2. Structural magnetic resonance imaging and diagnosis

There are a substantial number of studies that have reported on the use of structural magnetic resonance imaging (MRI) in differentiating patients with AD from both normal aging and other dementias during life. Many of these studies have used clinically defined (as opposed to pathologically validated) samples. Two general approaches have been reported—those that focus on either region of interest (ROI) volumes or visual ratings of medial temporal lobe structures, and voxel-based approaches that normalize images to standard coordinate systems and report on group differences in regional patterns of atrophy across the entire brain. For example, using voxel-based morphometry, a recent report examined a first group of subjects and found that parahippocampal gyral grey matter concentration was different between AD patients and controls; application of this region as a classifier in a second group showed overall accuracy of 87.8% [2]. The magnitude of these results is fairly typical of a host of studies that have used MRI to classify normal older people and those with AD, regardless of the exact methodology for selection of brain regions. Such studies, for example, have utilized rating schema of medial temporal lobe size [3] or quantitative measurement of hippocampal volume [4]. Results of these studies have shown sensitivities for the diagnosis of AD in the range of 80% to 90%, depending on the exact contrast group. Fewer studies have addressed the question of whether hippocampal atrophy can differentiate different dementias from one another, and these studies have generally utilized small groups of clinically defined patients. Some of these studies have shown no differences in hippocampal volumes among patients with AD and other dementias such as vascular dementia (VaD), and Parkinson’s disease [5]. Of course, pathologic overlap between these diagnoses makes clinical distinction very difficult. In frontotemporal lobar degeneration (FTLD), hippocampal atrophy may also be seen, although it is usually of lesser degree than that seen in AD [6], and it is accompanied by other signs of frontal and temporal atrophy. Citing a lack of prospective evidence, the American Academy of Neurology did not recommend routine use of volumetric or linear measurement of brain structure in the diagnosis of dementia [1].

It is interesting to note that although hippocampal atrophy is associated frequently with the neurofibrillary pathology of AD postmortem [7,8], it is not specific and may be seen with other conditions such as hippocampal sclerosis and frontotemporal lobar degeneration [9]. Thus, although MRI of hippocampal volume is reasonably sensitive and specific in clinical studies comparing AD patients with controls, there are little data to show the relationship between MR findings and pathology and the utility of MR imaging in making a specific dementia diagnosis when added to a high-quality clinical evaluation.

3. Structural magnetic resonance imaging and prediction

Magnetic resonance imaging as a predictive method in the diagnosis of AD has been applied in a variety of settings, most notably in at-risk groups with either mild cognitive impairment (MCI) or genetic risks for AD. From the imaging perspective, studies have evaluated whole brain volume, hippocampal and entorhinal cortical volume, and longitudinal changes in these measures as predictors of AD. Whole brain volumes are, on average, smaller in AD than normal older people, and there is considerable evidence that the rate of whole brain atrophy occurs at twice the rate in AD, 1% per year as opposed to 0.5% per year in normal aging [10]. Measurement of longitudinal change has been applied to preclinical populations using a method, the brain boundary shift integral (BBSI), which essentially performs a volume subtraction of images taken at different time-points, showing areas of brain atrophy or volume expansion (the latter generally seen in the ventricles) [11]. Such studies show not only faster rates of atrophy in AD patients than controls, but regional predilection of atrophy for posterior cingulate and medial temporal cortex. Similar findings have been seen in groups of presymptomatic people destined to have AD by virtue of autosomal dominant genetic mutations [12]. In one study using a region of interest approach for measuring longitudinal change, the rate of brain volume loss over time and the rate of ventricular expansion over time were related to the degree of AD neuropathology [13]. Thus, there is evidence that repeated imaging can detect change before symptoms are present in brain regions that are biologically plausible sites of disease in groups of individuals at risk.
In addition to whole brain volume measures and exploratory voxel-based approaches, MRI is uniquely suited to the delineation of regions of interest in key brain structures known to be affected by early AD, such as hippocampus and entorhinal cortex (Figure 1). MRI volumetric measurements of hippocampus and entorhinal cortex have been applied to groups of subjects at risk for AD by virtue of having MCI. Initial studies found that MCI patients with smaller hippocampal volumes were at greater risk for developing AD than those with larger hippocampi [14] and have been followed by a host of studies showing both smaller volumes and faster atrophy rates over time in MCI patients who clinically decline [15,16]. Combining whole brain volume changes over time with cross-sectional hippocampal volume measurement may be more predictive than either measure alone, although even this approach may fail to yield predictive power for single subjects [17]. Similar findings have been reported showing that entorhinal cortex volume predicts conversion from MCI to AD [18]. Whether hippocampal volume or entorhinal cortical volume is a better predictor of decline remains a matter of controversy. Relatively few studies have compared imaging modalities with other methods of prediction such as cognitive testing [19], so that, as in the clinical diagnosis situation, multivariate use of different measures to predict disease needs to be studied. Thus, although structural brain imaging has potential as a predictor of AD in individuals with either genetic risk factors or MCI, the best MR technique for accomplishing this is still unclear, as is the question of how imaging and other biomarkers may be used in concert.

4. [18F]Fluorodeoxyglucose–Positron Emission Tomography imaging in diagnosis

[18F]Fluorodeoxyglucose–Positron Emission Tomography (FDG-PET) imaging has been applied to the study of dementia for more than 2 decades, yet, there is a surprising paucity of validated prospective longitudinal data on its diagnostic accuracy. The finding of temporal and parietal hypometabolism, with additional metabolic lesions in posterior cingulate cortex, has been a widely reported finding in AD and, in many studies, has good sensitivity and specificity for differentiating AD from normal older individuals [20–22]. With regard to clinical–pathologic validation, it is instructive to compare the clinical diagnosis of AD with the imaging diagnosis of AD. Figure 2 shows the sensitivity and specificity of 2 community-based clinical–pathologic studies comparing the clinical diagnosis of AD with a pathologic diagnosis [23,24], along with an average report of 13 studies judged to reflect class I or II evidence reviewed in the American Academy of Neurology dementia practice parameters [1]. These studies show sensitivity in the 75% to 80% range and specificity in the 55% to 70% range. In contrast, 2 imaging pathologic studies show that FDG-PET, clinically interpreted as “positive” or “negative” for AD-like patterns, had comparable or better performance relative to pathology. Whereas one of these studies was relatively small [25], the other was a large multicenter study with 138 subjects [26]. Although it is tempting to conclude that imaging is equal or superior to clinical diagnosis, it is important to bear in mind that the samples from the cohorts are likely not comparable. Furthermore, the question of how much these imaging techniques actually add to a clinical diagnosis is not addressed by these studies. One report using single photon emission tomography (SPECT) compared clinical diagnosis with and without imaging and found that imaging added a small but significant improvement in accuracy (on the order of 8% to 10%) to clinical diagnosis compared with pathology [27].

A related question is whether FDG-PET may have clinical utility in specific situations. Several studies, including one with autopsy confirmation of the diagnosis, have suggested that FDG-PET can differentiate AD from dementia with Lewy bodies (DLB), which is characterized by reduced glucose metabolism in the occipital cortex (both primary visual and visual association cortex) compared with AD.

Fig. 1. Coronal MR images of a normal older subject (left) and a patient with Alzheimer’s disease (right). Hippocampus (H) and entorhinal cortex (EC) are labeled on the normal subject and show severe atrophy in the AD patient.

Fig. 2. Graph of the sensitivity and specificity of 3 reports comparing the clinical diagnosis of dementia (3 leftmost bars, [24,23,1]) with pathology, and the imaging diagnosis of dementia (2 rightmost bars, [25,26]) with pathology.
[28–30]. Probably the area in which FDG-PET studies have received the greatest clinical use is in the differentiation of FTLD from AD. Reductions of glucose metabolism in frontal and anterior temporal lobes may contrast sharply with the more posterior temporal and parietal hypometabolism seen in AD (Figure 3). A number of clinical imaging series show the ability of PET to differentiate AD and FTLD by this pattern [31,32]. These findings, and general consensus that FDG-PET has something to add to this difficult clinical differential diagnosis, have prompted the US Center for Medicare Services to approve the use of FDG-PET in the differentiation of these 2 disorders when a state of the art evaluation has been inconclusive. This represents the first approved use of an imaging technique in making a positive diagnosis of dementia etiology.

5. FDG-PET and prediction

As is the case with MR, models for dementia prediction have utilized individuals with MCI, genetic risks, and normal older people, to study the utility of FDG-PET in prediction. Some of the initial findings in this regard were reports that asymptomatic middle-aged individuals who were homozygous for the Apolipoprotein E4 genotype showed metabolic reductions in the same brain regions that are reported in AD patients [33]. These findings have now been extended to the detection of similar metabolic abnormalities in young people who are asymptomatic and heterozygous for this allele [34]. Other studies reported similar findings in asymptomatic individuals with autosomal dominant mutations in the amyloid precursor protein and presenilin 1 genes [35]. Thus, genetic models show metabolic findings in groups of patients in preclinical situations.

With regard to MCI, similar findings have also been reported. A number of studies have now shown that individuals with MCI show metabolic reductions in the usual candidate brain regions. Groups of individuals with MCI who decline have been found to differ from those who do not decline in glucose metabolism in temporal and parietal cortex [36,37]. In general, these have been retrospective studies that have reported group, as opposed to individual level differences.

Finally, data are beginning to emerge concerning the ability of PET to predict decline or change in status in normal older people. In one such study of 48 normal older individuals, those who subsequently converted to MCI or AD (12 subjects converted over 3 years) showed lower metabolic rates in entorhinal cortex than those who did not [38]. With suitable clinical samples and imaging techniques, FDG-PET thus appears capable of prediction of decline in normal older individuals.

6. New techniques

The field of imaging is rapidly advancing, and at least 3 different areas hold promise for new approaches that may produce rapid advancement. First is the use of functional MRI (fMRI) to detect physiologic changes in individuals who may be at risk for dementia. Although problems related to subject motion are currently limiting for dementia subjects, studies of aging, MCI, and those with genetic risks have suggested that physiologic changes may be present early in the disease. For example, MCI subjects have been shown to have increased hippocampal activation while performing episodic memory tasks, and the degree of this activation is related to the subsequent risk of decline [39]. This technology is still young, and disparate results have been found, including reports of decreased activation in at-risk individuals [40] and differences in activation in widely different cortical regions [41]. Many different experimental variables make studies difficult to compare. Yet, it is plausible that functional changes with cognitive processing occur early, perhaps well before structural or “resting” metabolic abnormalities supervene. Limitations characteristic of new technologies include difficulties in standardizing methods for data acquisition and analysis. Limitations characteristic of new technologies include difficulties in standardizing methods for data acquisition and analysis, but it is likely that maturation of this field will lead to clearer conclusions.

Another major advance has been the advent of methods to image brain amyloid. At least 3 different tracers have been applied to human imaging [42–44] with PET, and approaches for SPECT and MRI imaging are under development. Initial results have shown increased tracer uptake in AD compared with controls, as would be expected of a tracer binding to amyloid. Applications to both diagnosis and prediction are readily apparent. One concern that has been raised is the danger of circular reasoning in which amyloid deposition is equated with the diagnosis of AD. This problem is amply clear in the study of normal aging. Based on data available from autopsy series, it is highly likely that a substantial proportion of cognitively normal
older individuals will show amyloid accumulation in the brain as many normal older people can meet pathological criteria for AD [45]. However, normal cognition, even in the presence of amyloid, is not consistent with a diagnosis of AD. Such individuals are, of course, of great interest for many reasons, including their likelihood of progression. Diagnosis, however, might best be limited to situations in which AD is being differentiated from a nonamyloid dementia such as FTLD. In this case, differentiating a tauopathy from an amyloid disease may offer great potential, as shown in Figure 4.

Finally, a major area of advance is not in imaging at all but in the application of imaging to large and longitudinally evaluated cohorts. One such example is the Alzheimer’s disease Neuroimaging Initiative (ADNI), a multicenter study that will enroll 800 subjects throughout North America and follow them longitudinally with MR and PET in addition to clinical and biomarker measurements [46]. This study will not only assist in standardization of imaging procedures, but will also acquire longitudinal data that may provide insight into prediction of change over time, because normal and MCI subjects are a major component of the study. In addition, we are now entering a phase in which many cohort studies that began to include imaging years ago are coming to maturity. Such studies, with baseline or repeated imaging measures and high-quality clinical outcome data, could provide a wealth of information on the use of imaging in prediction of decline in normal people.

7. Future studies

With regard to the imaging modalities reviewed in this report, the achievements and remaining challenges are amply clear. Studies using the newer techniques of fMRI and amyloid imaging, hopefully in large cohorts with prospective follow-up, will undoubtedly provide important insights into prediction of dementia. As far as our current knowledge, although both MR and PET may provide diagnostically useful information, this information is limited. Future studies of imaging as a diagnostic technique need not only pathologic validation but comparison to existing modalities including standard clinical examinations. Future studies of imaging as diagnostic techniques should try to ascertain the added value of imaging over high-quality clinical diagnosis.

There is also great promise for the use of these techniques in clinical prediction. The limitations that remain are the reliance on retrospective methods and group analyses. The pragmatic and ethical questions involved in the prediction of the trajectory of individual subjects are complex. Yet, the motivation for such prediction is the potential availability of effective disease-modifying treatment. If such treatment is to be applied on an individual basis, disease markers that have predictive power in a prospective fashion for single subjects need to be devised. The existing data suggest that there are obvious candidates for such imaging markers, but the prospective studies are difficult and remain to be performed.

Nevertheless, it is amply clear what brain regions should be targeted in prospective trials. With the abundance of retrospective data indicating temporal, parietal, and posterior cingulate hypometabolism on FDG-PET, and medial temporal atrophy on MRI as predictors of decline, we need to establish reference values to serve as “cutoffs” in prospective trials. These values could be tested on individual subjects to ascertain their utility in prediction of decline or conversion to dementia. Such approaches will likely involve larger-scale collaborations in which, perhaps, regional values for metabolism or hippocampal volume from one laboratory sample are applied prospectively to another. A powerful potential group for such an approach will include individuals recruited as part of the Alzheimer’s Disease Neuroimaging Initiative. Opportunities for testing hypotheses concerning clinical, biomarker, and imaging features that may predict decline are abundant in this project.

References


