Update on the Use of MRI and PET in Alzheimer’s Disease and Mild Cognitive Impairment

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ABSTRACT

Alzheimer’s disease (AD) is a progressive and eventually fatal condition of advancing age characterized by cognitive and behavioral changes that places a large burden on patients, their families, and society. Scientific understanding of the disease has advanced in the past few decades with important new information based on the imaging of structural and functional changes of the brain. Autopsy remains the only method of positive diagnosis, but a great deal of current research into clinical, imaging, biochemical and genetic biomarkers are making strong contributions to earlier detection with the possibility of treatment to slow disease progression. In order to help the medical community more effectively diagnose and treat patients with AD, advancements in imaging techniques, specifically magnetic resonance imaging (MRI) and positron emission tomography (PET), have been made over the last few years. It is hoped that results from the Alzheimer’s Association Neuroimaging Initiative, which specifically studies MRI and PET in patients with AD and mild cognitive impairment (MCI), will yield valuable insight to enhance this understanding. This article will provide updates on the guidelines for AD classification, the Alzheimer’s Disease Neuroimaging Initiative studies, and the use of PET and MRI as tools for the identification and tracking of patients with MCI and who are in the early stages of AD.
Introduction

Alzheimer’s disease (AD) is an insidious, incurable, ultimately fatal condition of advancing age caused by a pathophysiological process characterized by a decline in social and occupational functioning and progressively worsening impairment in memory, cognition, and behavior. This diagnosis is typically made by primary care physicians, referred neurologists, or psychiatrists as a result of clinical assessment based on reports by family and friends, physical examination, and cognitive assessment with a mental status screening and/or neurological testing.¹ Ancillary neuroimaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are used to rule out other possible diagnoses that present with symptoms comparable to dementia such as the presence of a possible brain tumor, evidence of stroke, head trauma, or fluid buildup in the brain.²

Clinical studies have shown links between cognitive and behavioral disease progression and identification of AD on autopsy through detecting neuritic plaques in affected areas of the neocortex.³ Pathological studies have demonstrated the association between accumulations of β amyloid and tau and neurodegeneration in patients with AD.⁴ While no effective treatment to slow the progression of AD has yet been identified, a great deal of research into underlying mechanisms and possible treatments is underway. Recent research utilizing neuroimaging technologies and the identification of biomarkers is providing ways to detect structural and chemical changes in patients’ brains who are in the very early stages of cognitive decline or who have probable AD. A focus has been placed on disease prevention for patients who are at high risk for and diagnosed with mild cognitive impairment (MCI).

Background Statistics

Alzheimer’s disease (AD) is the most common type of dementia and accounts for 60% to 80% of all cases.⁵ In 2011, it was estimated that 5.4 million people in the United States had been diagnosed with AD, which is projected to increase to 12 to 16 million people by 2050. In approximately 200,000 patients under the age of 65, a younger-onset type of AD has been reported.⁵ What is sometimes referred to as AD may instead be one of a constellation of dementia-related disorders, some of which include vascular dementia, dementia with Lewy bodies, mixed dementia, Parkinson’s disease, frontotemporal lobar degeneration, Creutzfeldt-Jakob disease, and normal pressure hydrocephalus, among many others.⁶

In the majority of patients, the onset of AD occurs later in life. Data from a study of AD prevalence show that in 2000, of the 4.5 million patients in the United States with AD, 7% were 65 to 74 years of age, 53% were 75 to 84 years of age, and 40% were age 85 years of age and older.⁷ In the United States, AD is a leading cause of death for patients more than 65 years of age with the number of deaths attributed to it on the rise. In 2007, it was noted as the seventh leading cause of death in the United States.⁸ In 2009, it moved up to the sixth leading cause of death, accounting for 3.2% of total deaths. Of those, 2.0% occurred in men and 4.5% occurred in women.⁹

The pathogenesis of AD is unknown, however, an increased risk of developing this disease has been associated with advanced age, female gender, current smoking status, family history of AD or other forms of dementia, carrying the apolipoprotein E (APOE) ε4 allele, few years of formal education, lower income, and lower occupational status. While a variety of therapies exist, at present, there is no cure.¹⁰,¹¹

The burden of Alzheimer’s dementia is high in terms of both suffering for patients and their families and the cost to society. The progressive nature of the disease can exist with comorbid conditions and leads to dependency on family time and resources. In terms of healthcare expenditure, long-term care, and hospice for patients with AD and other dementias, the cost is estimated to be $200 billion in 2012 and is projected to increase to $1.1 trillion by 2050.⁵

Diagnosis of Patients with AD

The first diagnosis of AD was made in 1901 by German psychiatrist, Alois Alzheimer, in a 51-year-old patient with short-term memory loss and behavior problems. Upon her death, Alzheimer sent her brain to a laboratory where the amyloid plaques and neurofibrillary tangles, which are typical of the disease, were identified.¹² As a result, today, the presence of these pathological criteria upon autopsy is needed to make a definitive diagnosis.

Society Guidelines

A number of guidelines are available for the clinical and pathological diagnosis of patients with AD. From the perspective of psychiatry, as defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), symptoms of patients with AD must include decline in memory and at least one of the following:

- Ability to generate coherent speech or understand spoken or written language.
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- Ability to recognize or identify objects, assuming intact sensory function.
- Ability to execute motor activities, assuming intact motor abilities and sensory function, and comprehension often required for the task.
- Ability to think abstractly, make sound judgments, and plan and carry out complex tasks.
- The decline in cognitive abilities must be severe enough to interfere with daily life.13

The DSM-IV-TR, a text revision of DSM-IV, subdivided AD into categories of, “With Early-Onset,” “With Late-Onset,” and “With and Without Behavioral Disturbance.”13

In 1984, clinical guidelines were published by the National Institute of Neurological Disorders and Stroke (NINDS) and the AD and Related Disorders Association (ADRA) that divided the disease into a mild/early-stage, a moderate/midstage, and a severe/late-stage.1 Clinical features of patients with AD include loss of short-term memory, difficulty with abstract thinking, and loss of judgment. Neuropsychiatric symptoms, once thought to occur only in patients with late-stage AD, are now acknowledged as part of early MCI, which may include depression, apathy, agitation, anxiety, insomnia, delusions, hallucinations, and aggression.14

In 2011, based on a review of clinical criteria and the incorporation of advancements in clinical understanding and technology that have taken place in the ensuing decades, the NINCDS/ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association) guidelines were updated. Once considered a process in which clinical symptoms were closely associated with neuropathology, and therefore, patients were either diagnosed or not diagnosed with dementia, the new guidelines are grounded on the understanding that the pathological presence of amyloid plaques can be found in the absence of clinical symptoms, necessitating a distinction between the pathological and clinical presentation of disease.15 Diagnosis continues to be based on clinical criteria as determined by reports from the patient’s family and friends, physical examination, cognitive assessment, and neurological testing. The 2011 Alzheimer’s Association/NINDS guidelines employ a classification scheme of probable Alzheimer’s dementia, possible Alzheimer’s dementia, or probable or possible Alzheimer’s dementia with evidence of the pathophysiologic process (on autopsy).15

Diagnostically, the updated Alzheimer’s Association/NINDS guidelines differentiate AD into 3 stages: preclinical AD; MCI due to AD; and dementia due to AD.1 Guidelines and recommendations for Alzheimer’s dementia and MCI stages have clinical utility; at this time, those diagnosed with preclinical stage are intended for research purposes only.15 Also included in the update is the recognition that memory impairment is not always the primary symptom. Other manifestations of the pathophysiologic process are posterior cortical atrophy and logopenic-primary progressive aphasia. Additionally, while earlier guidelines did not include diagnostic use of MRI, positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) assays, the update indicates that these may be coupled with clinical criteria for a more comprehensive assessment.16,17

Clinical Studies
As demonstrated in a review of 13 studies, the accuracy rate of clinical assessment of patients with existing AD gave values for sensitivity and specificity of 81% and 72%, respectively.18 To date, clinical assessment has not been able to determine which patients are at risk for developing dementia or which patients will do so in the future. Evidence suggests that diagnosing a patient with AD is often missed in the primary care setting. In 2006, a study was conducted that compared the detection of Alzheimer’s dementia through the use of a cognitive screening tool with detection by the patient’s primary care physician. Of the 371 participants, 231 met the criteria for a diagnosis of dementia or MCI. Of those, screening identified 84% as having MCI compared with the physician’s identification of only 41% of cognitively impaired subjects.19

In an earlier cross-sectional study, 930 patients who were 65 years of age and older in a large primary care practice were contacted for the study, and 303 agreed to participate. Of those, 95% had been with their primary care physician for 1 year or more. Twenty-six patients with dementia were diagnosed with the use of a cognitive screening instrument. Of these, 17 patients had documentation of dementia in their records.20

Because patients with mild symptoms are often overlooked, it is apparent that the need for better methods of screening and treating at-risk patients earlier in the course of disease is beneficial to overall outcomes. For example, some studies indicate that medications to treat patients with AD are most effective when given in initial stages. Earlier diagnosis allows researchers to seek causes and allows clinicians to provide suitable treatment, arrange for long-term care planning, and ensure patient safety.21 In order to treat patients as early as possible, early screening and diagnosis are also essential, specifically via PET and MRI imaging.

Neuroimaging in Patients with AD

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Neuroimaging provides numerous benefits in patients with AD in clinical and research settings. When used with cognitive and behavioral assessments, fluorodeoxyglucose (FDG)-PET and MRI have shown diagnostic validity and have been correlated with AD as diagnosed on autopsy. A major benefit of MRI and FDG-PET is that they show actual structural changes in the brain as opposed to cognitive/functional assessments, which record only the result of these changes (Figure 1). Neuroimaging also affords test/retest reliability; for example, the reliability of measuring hippocampal volume has an intraclass correlation coefficient of more than 0.95. Because AD progression is considered to be related to synapse loss and neurodegeneration, imaging can show a reduction in brain activity (as demonstrated by FDG-PET activity) and brain shrinkage (as detected by structural MRI).

Structural and functional imaging techniques have utility in patients with AD in both research and clinical applications. Imaging plays a role in the differential diagnosis of patients with AD, which must be distinguished from other chronic dementias such as vascular dementia or dementia with Lewy bodies. In patients with early stage AD, imaging studies may play a role in the cognitive decline that precedes it, especially when combined with information about the patient’s genetic risk factors. This is especially true for patients who would benefit from drug interventions that may delay the progress of the decline before neuronal damage develops. Additionally, imaging studies may be used in research to tease out underlying disease mechanisms, develop effective therapeutic agents, and follow response to treatment in later stages.

Since the 1990s, a body of literature has evolved about MCI, which primarily includes information about patients’ memory deficits prior to a decrease in functional ability. It has been found that of the 10% of patients age 65 or older with MCI, 15% of those developed AD each year. The 2011 NINCDS-ADRDA guidelines developed 2 sets of criteria for the development of MCI due to AD and described as the symptomatic predementia phase of the disease. The core clinical criteria can be used diagnostically by physicians without requiring access to or the need for supportive imaging studies or CSF analysis. The second set of criteria that incorporate the use of biomarkers (a cellular or molecular indicator) can also be used diagnostically in academic and clinical research settings and clinical trials. More work is needed to validate and standardize the use of biomarkers before they can be broadly applied in clinical settings.

Launched in October 2004, The Alzheimer’s Disease Neuroimaging Initiative (ADNI) began recruiting adults aged 50 to 99 years of age across the United States and Canada for a longitudinal multicenter (59 site) study of the early detection and tracking of patients with AD. The initial goal of these studies was to correlate and validate identifiers and biomarkers as predictors of a disease process that develops from normal aging, to MCI, to AD. Participants included 3 groups: older adults with AD (n = 200); adults with MCI (n = 200); and cognitively normal controls (n = 400). Data were collected using
A study by Jack et al.33 demonstrated the correlation between hippocampal atrophy and clinical decline. Subjects recruited from the Mayo Alzheimer’s Disease Patient Registry met criteria for MCI, probable Alzheimer’s dementia, or both along with normal controls.33 All subjects (n = 129) received 2 clinical assessments and MRI over a 2- to 4-year period. All subjects were imaged at baseline, followed up with at 3 years, and imaged on a 1.5T scanner using a standardized protocol. Intracranial volume measurements were derived from a T-1 weighted sagittal sequence with 5 mm continuous sections. Hippocampal volume measurements were derived from a T-1 weighted (3-dimensional [3D]) volumetric spoiled gradient recalled echo sequence with 124 contiguous partitions (field-of-view = 22 cm x 16.5 cm; flip angle = 45°; slice thickness = 1.6 mm; number of views = 192). Borders of the hippocampus were manually traced with a mouse-driven cursor for each slice from posterior to anterior, so that the entire hippocampus was included in the study measurements. The margin of the inner table of the skull was traced on contiguous images from the sagittal sequence to determine the intracranial volume. Imaging dates were masked, and the clinical information was blinded. Computations of the annualized percent change in hippocampal volume over the study period showed progressive volume loss of -3.5 ± 1.8 in the AD group; -3.0 ± 1.6 in the MCI group; and -1.9 ± 1.1 in the control group. Of the 58 controls, 10 (17%) declined to the MCI or probable AD categories. Of the 43 subjects in the MCI group, 18 (42%) declined to the probable AD category. Data showed that MRI studies can be used to determine the hippocampal volume decline of patients with probable AD, which can be useful in helping to diagnose and treat patients early in order to give them the best possible outcome.33

In another study, Killiany et al.34 used MRI to compare subjects with mild memory difficulty (n = 79) with normal controls (n = 24) as assessed by the Mini-Mental State Examination to predict progression to AD.34 All patients were volunteer subjects and were an average of 72 years of age. All patients received a baseline MRI and were followed-up with annually for 3 years. The MRI data were from regions of interest (ROIs), which were derived from 3D T-1 weighted gradient echo scans of the brain (repetition time = 35 msec; echo time 5 msec; field-of-view = 220; flip angle = 45°; slice thickness = 1.5 mm; matrix size = 256 x 256). One set of MRI measurements was manually drawn and one was defined by automated algorithm. ROIs included: the volume of the entorhinal cortex; the volume of the banks of the superior temporal sulcus; and the volume of the cingulate gyrus, subdivided into the rostral and caudal portions of the anterior cingulate and the posterior cingulate. A second set of ROIs consisted of 6 automated measurements of CSF spaces to view the integrity of the medial temporal lobe or assess generalized atrophy. APOE was also examined to see if it could predict which patients would convert from mild memory impairment to AD over time.34
At the 3-year end mark, 24% (19) of subjects who entered the study with mild memory impairment had progressed to meet the 1984 NINCDS/ADRDA criteria for probable dementia. Researchers described the use of baseline MRI measurements as showing the most significance in discriminating between patients with mild memory impairments who progress to a diagnosis of AD within 3 years, and those who do not progress to the same diagnosis as compared with normal controls. Most significantly, the accuracy of the discrimination between normal controls versus those with mild memory impairment who converted to a diagnosis of AD was 93% (sensitivity = 95%; specificity = 90%). MRI scans were also able to discriminate patients with mild AD from normal controls with 100% accuracy. MRI findings also confirmed the involvement of the entorhinal cortex and the banks of the superior temporal sulcus (both related to functions of memory) in patients with prodromal AD. Findings also confirmed the involvement of the caudal portion of the anterior cingulate in patients who have been diagnosed with early stage AD. All of these findings suggest that neuronal loss begins in the early stages of AD. Researchers speculated that the hierarchy in which brain changes occur in patients with early AD are likely those that are first affected in the disease process.34

**MRI in ADNI**

Alzheimer's Disease Neuroimaging Initiative-1 (2005-2010) generated data that has improved understanding of the correlations between the clinical manifestations of AD, imaging findings, and biomarkers. Major accomplishments include the development of standardized methods for MRI and PET image testing, CSF biomarkers and patterns, biomarkers’ rate of change in normal controls, patients with MCI, and patients with AD (Figure 3).35,36

Clinical findings in ADNI-1 over the course of the first 12 months showed 16% of MCI subjects progressed to AD and an additional 24% progressed in the second year.37 ADNI-GO, a 2-year extension of ADNI-1, enrolled 200 additional subjects and focused on memory loss in patients with early stage MCI. Finally, ADNI-2, which will run through 2017, builds on findings from ADNI-1 with the addition of new volunteers to help identify the earliest presymptomatic stages of AD.38 As a result of multiple studies, the use of MRI in testing patients with early AD has evolved and is important in the diagnosis and staging of each patient.

The MRI Core of the ADNI-1 (a specific analysis of MRI results within the study) focused on structural MRI studies of the brain.38 The selected sequence was obtained using magnetization-prepared gradient echo, a 3D T1-weighted imaging sequence repeated back-to-back in the ADNI-1 study to ensure one good quality scan and allow for signal averaging. Also, a dual-fast spin-echo sequence was administered to detect vascular disease and overall pathology. A 1.5T protocol examination was administered to all participants ranging from baseline to 36 months depending on clinical diagnosis. Some significant findings from the application of MRI in ADNI-1 include:

- MRI had better longitudinal power to detect change than clinical evaluations or FDG-PET methods.
- Different groups showed different rates of MRI atrophy; these rates correlated with clinical measures of cognitive decline.
- Patients who are APOE e4 carriers and who are at a greater genetic risk for AD showed greater rates of change on MRI than patients who were not carriers of APOE e4.
• Structural brain alterations were associated with lower CSF Aβ$_{42}$ and higher CSF tau concentrations. Lower CSF Aβ$_{42}$ and higher CFS tau concentrations were associated with higher rates of regional brain atrophy in all clinical groups.

• A better prediction for risk of progression from MCI to AD was found with MRI than with CSF tau or Aβ$_{42}$.

Of note, results showed that baseline MRI is superior to either FDG-PET or CSF biomarkers as a predictor of cognitive change (Figure 4).^{38,39}

**PET in AD Studies**

For decades, the search for methods to distinguish patients with AD from patients with signs of normal aging has continued; the goal was to be able to intervene early in the disease process before a severe loss of synapses and neurons occurred. It was known that for patients with AD, impairment of cerebral glucose metabolism could be found in neocortical association areas of the brain. Measurements of local cerebral glucose metabolism by PET and FDG became routinely accepted.^{40}

Positron emission tomography has become an important tool in being able to depict significant alterations in the brain metabolism of patients with AD. Reductions in glucose metabolism in the posterior cingulate gyrus, the parietal and temporal cortices, and (in later stages of disease) in the prefrontal cortex and other regions of the brain are found in patients with probable and confirmed AD.^{41} Reductions in FDG have been shown to correlate with the patient's dementia severity. Therefore, these findings in at-risk patients can be used to predict the clinical decline in the early stages of AD and confirm the clinical diagnosis.^{32}

In a study of the predictive value of PET in the evaluation of patients with dementia, 284 patients with symptoms of cognitive decline or behavioral change were recruited.^{42} One group underwent evaluation for dementia at the University of California, Los Angeles (UCLA); the patients were evaluated with PET and followed-up with for at least 2 years (n = 146). A second group from 8 various international academic medical centers was initially evaluated with PET; later, diagnosis was confirmed by histopathology (n = 138). In the first group, PET was used to measure cerebral uptake of intravenously administered FDG with emission scanning 40 minutes after contrast administration. The canthomeatal plane of each patient's head was set parallel to the plane of the ring of detectors to obtain emission images. A calculated attenuation correction algorithm was used to reconstruct the images, which were displayed in axial and coronal orientations as contiguous planes of brain tissue. Patients were followed an average of 3.2 years after PET. In addition to data from UCLA medical records, data were obtained by questionnaires completed by the patients' physicians, which included information about the patients' functional, behavioral, and cognitive status.^{42}

The study documented a progressive course of AD in 59% (86/146) of cases in the first group; within this group, PET correctly predicted a progressive course with a sensitivity of 91% (78/86; 95% CI, 85%-97%), and a nonprogressive course with a specificity of 75% (45/60; 95% CI, 64%-86%). In the second group, autopsies were performed an average of 2.9 years after PET. Questionnaires sent to all sites for completion included information about general history as well as medications and severity of dementia symptoms at the time of PET, CT/MRI findings if available, date of autopsy, pathology-based diagnosis, and notation of any brain abnormalities. In this group, AD was identified in 70% (97/138) of histopathologically examined cases. The presence or absence of AD was correctly identified by PET in 88% of these cases with a sensitivity of 94% (91/97; 95% CI, 89%-99%) and a specificity of 73% (30/41; 95% CI, 60%-87%).^{42}

The predictive value of PET was obtained by pooling data from both study groups. Brain PET findings indicated a progressively dementing process in 210 patients. Of these, 191 (91%) were documented through longitudinal follow-up or histopathologic identification to have progressive disease. In comparison, of 74 patients with negative PET scans for a progressive disease process, only 15 (20%) subsequently showed evidence of progressive disease. The study authors concluded that the use of PET permits sensitive identification of future decline in patients with AD.^{42}
PET in ADNI

In the ADNI-1 PET Core, the initial goal was to show the benefits of FDG-PET over clinical assessment as an outcome measure for tracking drug effects in trials of patients with AD. Early in the course of the study, it was found that in patients with AD positive findings of Aβ plaque depositions were detected with PET and found in CSF. In fact, clinical and pathological evidence suggests that Aβ deposits in plaques may predate symptoms of AD by several years. Therefore, in PET imaging of the Aβ protein in fibrillar aggregated forms became increasingly important as a study method. As a result, the PET Core of the ADNI enrolled an additional 103 subjects in an add-on project that used tracer PIB. The role of PET evolved from a way of tracking outcome measures to being part of subject selection, particularly in the identification of patients with very mild AD, given the understanding that effective treatment will require early intervention.

At the beginning of the project, coordination of PET scanning parameters was accomplished across all study sites. During the second year, PET scans of ADNI subjects were acquired and approximately half of the subjects underwent FDG-PET imaging, yielding 404 baseline scans and subsequent scans at 6 months, 12 months, 18 months (MCI subjects only), 24 months, and 36 months (MCI subjects and controls only). Approximately, one-fourth of subjects enrolled in ADNI also received PIB scans for amyloid deposition.

Positron emission tomography-FDG data were analyzed using 3 approaches at different laboratories: 5 regions of interest derived from patients with AD and MCI studies (right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus); 3D stereotactic surface projections using an analysis program; and, a voxel-wise approach using statistical parametric mapping. A fourth laboratory analyzed PIB data.

Findings related to the original goal of imaging a biomarker as an indicator of disease progression show that low glucose at baseline predicted patients’ decline on the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog); longitudinal decline in glucose metabolism correlated with longitudinal decline in the ADAS-Cog. Because multiple biomarkers were tracked in ADNI subjects, comparisons between PIB-PET, FDG-PET, and CSF biomarkers (Aβ and tau) yielded interesting results. While there was agreement between different Aβ measures, non-Aβ measures provided better indications of disease status. For example, there was high agreement between PIB and CSF Aβ but less agreement between PIB and the other biomarkers. There was a high correlation between FDG-PET and the Mini-Mental Status Examination, but this did not hold true for PIB and CSF Aβ.

Voxel-based analysis using the brain-mapping algorithm SPM5 mapped between-group differences in regional/whole brain measures of the cerebral metabolic rate for glucose (CMRgl) across the study groups. Subjects with AD and MCI had lower CMRgl levels compared with normal controls in the posterior cingulate, precuneus, parietotemporal, and frontal cortex, bilaterally. In addition, significant 12-month CMRgl declines in the posterior cingulate, medial and lateral parietal, medial and lateral temporal, and frontal and occipital cortex bilaterally were seen in the AD and MCI groups compared with normal controls (Figure 5). These declines were consistent with clinical measures of decline.

Alzheimer’s Disease Neuroimaging Initiative researchers further examined the relationship between the topographic extent of glucose hypometabolism and AD diagnosis using software for biomedical and neurological image analysis. In patients with MCI who progressed to AD after 1 year, the extent of hypometabolism at baseline was found to be greater than in patients with MCI who maintained their clinical classification of MCI.
patients with MCI who maintained a clinical classification of MCI. Patients who progressed to AD at 6 months showed a greater extent of hypometabolism than those who converted later. In a study conducted to classify patients with AD and MCI using FDG-PET as a means of predicting the progression from MCI to AD, Gray et al used FDG-PET data, along with the corresponding 1.5T MRIs of 287 patients from the ADNI database, including healthy controls (n = 69), patients with MCI (n = 147), and patients with AD (n = 71). The study successfully discriminated patients with AD from healthy control subjects with an 82% accuracy. Discrimination between patients with MCI and healthy controls achieved 70% accuracy; an accuracy of 68% was achieved between AD and MCI subjects. The MCI group was further segmented into stable MCI and progressive MCI subgroups. However, the accuracy rate distinguishing these MCI groups was only 56%. Gray et al concluded that while FDG-PET is primarily used in clinical workups for patients with dementia, it may also serve as a method of diagnosis for patients with MCI that is comparable to the use of MRI and CSF biomarkers.  

ADNI-GO and ADNI-2  
The goal of the 2-year ADNI-GO study is to scan and analyze the brains of patients with MCI at the earliest stages. In 2010, 200 enrollees were added to the study, allowing ADNI-GO to expand to the length of ADNI-1. This allowed for further investigation of the timing and sequence of neurological events leading to the development of MCI and AD. It also allowed for the development of improved clinical and imaging biomarker methods for early detection and monitoring of disease progression in the new subjects as well as in those with late MCI and controls from ADNI-1. An added feature of this study is the use of amyloid imaging florbetapir F-18 on all ADNI subjects, which allows comparison of biomarkers (eg, amyloid compared with FDG-PET and MRI; amyloid compared with CSF). Alzheimer's Disease Neuroimaging Initiative-2 was designed to continue to develop and evaluate biomarkers for patients with AD as well as earlier stages of disease progression. Along with 450 to 500 cognitively normal and late-stage MCI subjects from ADNI-1 and 200 early MCI subjects from ADNI-GO, ADNI-2 is actively enrolling 550 new participants though the end of 2013. In the PET Core of ADNI-2, subjects will be studied with amyloid imaging with florbetapir F-18 along with FDG-PET, MRI, and CSF biomarkers, to define different stages of AD. The MRI Core will continue to follow existing subjects with serial MRI studies using the ADNI-1-1.5T protocol. Newly enrolled subjects will be scanned using 3 types of sequences: 3D T-1 weighted volume, fluid attenuated inversion recovery, and a long T2-gradient-recalled echo. The focus on subjects with early MCI in ADNI-2 may potentially identify people who are at-risk for AD early enough for preventive therapy. Screening will take place at baseline, 3 months, and within 2 weeks of 6 months and annual visits. Building on findings from ADNI-1, the ADNI-2 will use imaging techniques to evaluate:  
  - Rate of volume change of the whole brain and hippocampus  
  - Rates of change of each biochemical biomarker  
  - Rates of change of glucose metabolism (FDG-PET)  
  - The extent of amyloid deposition as measured by florbetapir F-18  
  - Correlations between clinical, imaging, genetic, and biochemical biomarkers across the spectrum of AD.  

Conclusions  
Numerous clinical trials are underway that are utilizing imaging techniques to diagnose patients with early MCI, monitor progression, and aid in therapeutic discoveries to slow disease progression. ADNI-1, ADNI-GO, and ADNI-2 comprise the only longitudinal observational clinical/imaging/biomarker study for AD that is being performed in the United States. Data from the studies are available to scientists globally through the study's Web site. To date, MRI and FDG-PET have been shown to have great value in tracking progression across the AD spectrum. Some of the findings are already being used in phase III trials. Other findings will contribute to new areas of research for early identification, prevention, and slowing of the progression of patients with AD.  

References  

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Very hard to follow... A lot of useful info, if you can get through it.

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