Published in final edited form as:
Neuroimage. 2012 June ; 61(2): 505–516. doi:10.1016/j.neuroimage.2011.11.075.

BRAIN IMAGING IN THE STUDY OF ALZHEIMER'S DISEASE

Eric M. Reiman, M.D.[1] and **William J. Jagust, M.D.**[2]

[1]the Banner Alzheimer's Institute, the Department of Psychiatry, University of Arizona, the Neurogenomics Division, Translational Genomics Research Institute (TGen), and the Arizona Alzheimer's Consortium, Phoenix, AZ

[2]the Helen Wills Neuroscience Institute and School of Public Health, University of California, Berkeley, and Lawrence Berkeley National Laboratory, Berkeley, CA.

Abstract

Over the last 20 years, there has been extraordinary progress in brain imaging research and its application to the study of Alzheimer's disease (AD). Brain imaging researchers have contributed to the scientific understanding, early detection and tracking of AD. They have set the stage for imaging techniques to play growing roles in the clinical setting, the evaluation of disease-modifying treatments, and the identification of demonstrably effective prevention therapies. They have developed ground-breaking methods, including positron emission tomography (PET) ligands to measure fibrillar amyloid-β (Aβ) deposition, new magnetic resonance imaging (MRI) pulse sequences, and powerful image analysis techniques, to help in these endeavors. Additional work is needed to develop even more powerful imaging methods, to further clarify the relationship and time course of Aβ and other disease processes in the predisposition to AD, to establish the role of brain imaging methods in the clinical setting, and to provide the scientific means and regulatory approval pathway needed to evaluate the range of promising disease-modifying and prevention therapies as quickly as possible. Twenty years from now, AD may not yet be a distant memory, but the best is yet to come.

Keywords

Alzheimer's disease; dementia; mild cognitive impairment; MRI; PET; amyloid; diagnosis; prevention

Introduction

Alzheimer's disease (AD) is the most common cause of cognitive impairment in older people. When one considers the impact of AD on patients and families and the growing number of people living to older ages, there is a need to understand the progressive brain changes associated with the development of AD. There is also an urgent need to find treatments to slow down, stop, reduce the risk of, or completely prevent AD symptoms as soon as possible. Brain imaging techniques have had a profound impact on the scientific study of AD; they are expected to play growing roles in the clinical setting, and they are

Please address correspondence to Dr. Reiman at the Banner Alzheimer's Institute, 901 East Willetta Street, Phoenix, Arizona 85006; telephone: 602.239.6999; facsimile: 602.239.6253; eric.reiman@bannerhealth.com.

expected to play critical roles in the effort to find effective AD-modifying and prevention therapies.

In the last 20 years, there has been an explosion of interest in the development and use of brain imaging techniques for the scientific study, early detection, tracking, treatment and prevention of AD. This interest is reflected by the growing proportion of imaging researchers who attend and present their data at the major AD meetings, the development of imaging techniques to measure fibrillar amyloid-β deposition (a cardinal neuropathological feature of AD (Braak and Braak, 1991; Hardy and Selkoe, 2002)) in the living human brain (Klunk et al., 2004), the role that imaging studies have already played in the reconceptualization of AD (Sperling et al., 2011), the extraordinary opportunities researchers have to help in the scientific fight against this devastating disease, and the challenges the field continues to face along the way.

In this article, we review the best established brain imaging measurements for the detection and tracking of AD, and we note several other important imaging measurements, some of which have been less extensively applied or more recently developed. We then consider the how these imaging techniques have contributed to the scientific understanding of AD, their growing roles in the clinical setting, and their emerging roles in the evaluation of treatments to slow down the progression or prevent the onset of AD symptoms. Finally, we consider future research directions and offer a few recommendations. We are indebted to many investigators who have played pioneering roles in the development of brain imaging research, and we apologize in advance for our inability to cite all of the researchers and studies that have had a major impact on the field.

The Best Established Brain Imaging Measurements of AD

Researchers continue to develop a range of brain imaging measurements for the scientific study and clinical evaluation of AD. To date, the best established measurements for the detection and tracking of AD include structural magnetic resonance imaging (sMRI) measurements of regional and whole brain tissue shrinkage, fluorodeoxyglucose positron emission tomography (FDG PET) measurements of decline in the regional cerebral metabolic rate for glucose (CMRgl), and PET measurements of fibrillar amyloid-β (Aβ) burden. The information provided by these and other brain imaging measurements depends not only upon the imaging modality used, but the manner in which the data are acquired and analyzed.

Structural MRI has been the most extensively used brain imaging method in the study of AD. Clinically affected patients have significantly reduced hippocampal and entorhinal cortex volumes, gray matter, and cortical thickness, increased ventricular and sulcal volumes, reduced gray matter or cortical thickness in other cerebral regions, like the precuneus and posterior cingulate, parietal, and temporal cortex, and accelerated rates of decline in these and whole brain measurements over time (Dickerson et al., 2009; Jack, Jr. et al., 2009; Jack, Jr. et al., 2010) (Figure 1). Reductions in hippocampal and entorhinal cortex size appear to correspond to early memory decline and anticipate progression to more severe clinical stages, including mild cognitive impairment (MCI) and Alzheimer's dementia (de Leon et al., 1989; Dickerson et al., 2001; Jack et al., 2004; Jack, Jr. et al., 2005; Kaye et al., 1997). In a few studies, volumetric reductions and accelerated rates of brain tissue loss have been found in cognitively normal people who are at higher genetic risk for AD or who show subsequent evidence of cognitive decline—evidence that may depend in part on the sensitivity of the image analysis technique used (Alexander et al., 2002b; Chen et al., 2007; den Heijer et al., 2002; Espeseth et al., 2008; Jak et al., 2007; Wishart et al., 2006). In the clinical setting, structural MRI is often recommended to help rule out potentially reversible

brain abnormalities like tumors or subdural hematomas in patients with dementia and MCI, and it sometimes provides useful information about vascular pathology or the pattern of cortical atrophy. Researchers continue to clarify the extent to which it can be used alone or in combination with other measurements to predict subsequent cognitive decline in MCI patients, but it may not provide sufficient specificity to differentiate AD from other conditions(Knopman et al., 2001).

FDG PET is currently the best characterized functional brain imaging method in the study of AD. Studies consistently find reduced CMRgl in the precuneus, in posterior cingulate, parietal, and temporal cortex in clinically affected patients, and in frontal cortex and whole brain as the illness becomes more severe (Alexander et al., 2002a; Chen et al., 2010; Choo et al., 2007; Drzezga et al., 2005b; Foster et al., 1983; Herholz et al., 2002; Hoffman et al., 2000; Langbaum et al., 2009; Li et al., 2008; Minoshima et al., 1997; Mosconi et al., 2009; Reiman et al., 1996). In a smaller number of studies, CMRgl reductions have also been reported in hippocampal and entorhinal cortex regions-of-interest (De Santi et al., 2001; Mosconi et al., 2004b; Mosconi et al., 2005). CMRgl reductions are correlated with clinical severity (Bokde et al., 2005; Choo et al., 2007; Haxby et al., 1990; Landau et al., 2011; Langbaum et al., 2009), and predict subsequent clinical decline and/or the neuropathological diagnosis of AD (Alexander et al., 2002a; Herholz et al., 1999; Hoffman et al., 2000; Jagust et al., 1988; Silverman et al., 2001). Characteristic CMRgl reductions have been demonstrated in the asymptomatic stages of AD (e.g., in people with one or two copies of the *apolipoprotein E (APOE) ε4* allele, the major AD susceptibility gene, in those at risk for autosomal dominant early-onset AD, and those with higher rates of subsequent cognitive decline) (Kennedy et al., 1995; Langbaum et al., 2010; Mosconi et al., 2006; Mosconi et al., 2008; Reiman et al., 1996; Reiman et al., 2001; Reiman et al., 2004; Reiman et al., 2005; Rimajova et al., 2008; Scholl et al., 2011; Small et al., 1995; Small et al., 2000; Villemagne et al., 2009) (Figure 2). In the clinical setting, FDG PET is sometimes used to help in the differential diagnosis between AD and frontotemporal lobar degeneration, and researchers continue to clarify the extent to which it can be used alone or in combination with other measurements to predict subsequent cognitive decline in MCI patients. FDG PET has the potential to help in the evaluation of AD-modifying treatments in the clinical and preclinical stages of AD, to further clarify the preclinical stages of AD and a person's risk for subsequent clinical decline, to help evaluate suggested AD risk factors, and to complement other imaging and fluid biomarker measurements in these endeavors, as noted further below (Reiman and Langbaum, 2009; Reiman et al., 2010; Reiman et al., 2011).

Fibrillar Aβ PET, introduced during the last decade, promises to have a profound impact on the scientific study of AD, the clinical evaluation of patients, and the evaluation of Aβ-modifying treatments. Several PET radioligands have now been shown to provide information about Aβ plaque deposition, a cardinal neuropathological feature of AD, in the living human brain. They include [11C]-labeled “Pittsburgh Compound B (PIB),”(Klunk et al., 2004; Mathis et al., 2002) which has had a major impact on the field and other investigational ligands, including several [F18] ligands that are being developed for the clinical setting due to their longer radioactive half-life and the ability to transport the tracer to different PET Centers from a regional radiopharmacy (Choi et al., 2009; Jureus et al., 2010; Nelissen et al., 2009; Rowe et al., 2008; Tolboom et al., 2009; Vandenberghe et al., 2010). Among other things, fibrillar Aβ PET studies have already confirmed the cortical distribution of fibrillar Aβ in clinically affected patients, with preferential deposition in precuneus, posterior cingulate, parietotemporal, and frontal regions and relative sparing in the hippocampus, and they have suggested that fibrillar Aβ levels are virtually saturated by the time patients have MCI (Doraiswamy et al., 2009; Forsberg et al., 2008; Grimmer et al., 2009; Jack, Jr. et al., 2008; Kemppainen et al., 2007; Klunk et al., 2004; Klunk et al., 2006; Morris et al., 2009; Resnick et al., 2010; Rowe et al., 2007; Rowe et al., 2010; Villemagne et

al., 2011; Wolk et al., 2009) (Figure 3). They have suggested significant fibrillar Aβ deposition in about 30% of cognitively normal adults over the age of 70, perhaps 10-15 years before clinical onset, and that the magnitude and spatial extent of fibrillar Aβ is associated with older age and the genetic risk for late-onset AD (Aizenstein et al., 2008; Mintun et al., 2006; Morris et al., 2010; Pike et al., 2007; Reiman et al., 2009; Rowe et al., 2010; Small et al., 2009; Villemagne et al., 2011). They have also suggested a slightly different pattern, with preferential deposition in the striatum in at least some cognitively normal people at genetic risk for early-onset AD (Klunk et al., 2007; Scholl et al., 2011; Villemagne et al., 2009). Initial studies have suggested a close association between PET measurements of fibrillar Aβ at the end of life and subsequent neuropathological measurements of fibrillar Aβ (Clark et al., 2011; Ikonomovic et al., 2008; Sojkova et al., 2011), and the first of these ligands (florbetapir F18) is now being considered for regulatory agency approval to help exclude the diagnosis of AD in patients with dementia or MCI (Clark et al., 2011). Although the technique might increase confidence in the diagnosis of AD, it cannot rule out the possibility that the syndrome is related to mixed pathology. While this technique does not provide direct information about other Aβ species (e.g., soluble oligomers, postulated to have a more toxic effects on neurons), it will now be possible to determine the extent to which cognitively normal people with significant fibrillar Aβ alone or in combination with other measurements predicts subsequent clinical decline, evaluate investigational Aβ-*clearing* (e.g., immunization) therapies in clinically affected patients, and evaluate the ability of even more investigational Aβ-modifying treatments to slow down the accumulation of fibrillar Aβ in presymptomatic AD (i.e., prevention) trials (Bateman et al., 2011; Reiman and Langbaum, 2009; Reiman et al., 2010; Reiman et al., 2011). Along the way, it will help to provide a key test of the amyloid hypothesis of AD, which suggests that certain amyloid species play a critical and relatively early role in the predisposition to this disease (Hardy and Selkoe, 2002).

Other Brain Imaging Measurements

The number of different brain imaging techniques that have been applied to the study of AD is too large to review in a single article. Here we touch on some of the more or less widely used approaches and try to summarize the major findings and applications, fully aware of the incomplete nature of this review.

Functional MRI (fMRI) and Functional Connectivity MRI (fcMRI)

MRI techniques that take advantage of the blood oxygen level dependent (BOLD) signal have been applied to both patients with AD and those at risk. These studies include approaches that utilize cognitive tasks to assess brain activation, and experiments performed during resting states that assess functional connectivity. A primary finding that has emerged is the dysfunction of the default mode network (DMN, see below for more information) in AD (Greicius et al., 2004). This network dysfunction is seen in individuals with PET evidence of Aβ accumulation but no overt symptoms (Hedden et al., 2009) and also predicts decline in patients with MCI (Petrella et al., 2011). fMRI studies that use cognitive paradigms to assess brain activation frequently reveal increased activation in those at risk for dementia (Bookheimer et al., 2000; Quiroz et al., 2010), which appears to decline with disease progression (O'Brien et al., 2010). The reliability of repeated measurements in some studies has suggested the use in clinical trials, although the issues of standardization, compensatory changes, and the ability to distinguish between biological factors and task performance need to be further addressed. Studies of brain activation and the resting state have been informative in application to fundamental questions of disease pathogenesis that are discussed in greater detail below.

Diffusion tensor imaging (DTI)

DTI has been used to study both the integrity and connectivity of white matter in patients with dementia and those at risk. Reduction in white matter integrity, generally measured as decreases in anisotropy (due to reduction in the axonal restrictions on directional diffusion) is now a widely reported finding in patients with AD and preclinical syndromes. Both AD and MCI patients show decreased fractional anisotropy in a wide variety of brain regions including areas known to be affected by AD such as the hippocampus (Sexton et al.); many studies also note relationships between FA and dementia severity. Voxelwise approaches to the analysis of DTI data have also demonstrated regional similarities between patterns of loss of white matter integrity in AD and MCI patients(Medina et al., 2006). The measurement of diffusion changes in the hippocampus may also be predictive of conversion to dementia (Fellgiebel et al., 2006). Through the use of fiber-tracking, or tractography, specific neural tracts of interest such as the cingulate (Zhang et al., 2007) and uncinate fasciculi (Kiuchi et al., 2009) have been shown to be particularly susceptible to white matter changes. The specificity and clinical application of these techniques requires more study.

SPECT Perfusion

Single photon emission computed tomography (SPECT) is a technique that is quite similar to PET and its application to dementia using radiotracers that track cerebral perfusion has produced results that are largely similar to PET scanning of glucose metabolism in clinical diagnostic applications (Bonte et al., 1986; DeKosky et al., 1990; Holman et al., 1992; Miller et al., 1991). SPECT studies have been shown to predict decline in MCI (Johnson et al., 1998) and are related to autopsy findings (Bonte et al., 1997; Jagust et al., 2001). For many years the limited availability of PET resulted in substantial use of SPECT scanning, however the proliferation of PET scanners in conjunction with oncological applications in clinical settings has increased its availability and application to dementia care and research.

Magnetic Resonance Spectroscopy (MRS)

While MRS can acquire data from multiple different atomic nuclei, the largest application has been proton MRS to quantify metabolites such as choline, N-acetyl aspartate (NAA) and myo-inositol (mI) in the brain. These data are usually expressed as normalized values by relating the spectral peaks to those from Creatinine (Cr). Many studies of AD patients have revealed reductions in NAA/Cr that can be found early in the disease prior to frank loss of volume (Adalsteinsson et al., 2000; Schuff et al., 1997). These findings have been taken as evidence of neuronal loss based on the predominant localization of NAA in neurons. A number of studies have also reported increases in mI/Cr which has been interpreted as evidence of gliosis (Kantarci et al., 2004; Valenzuela and Sachdev, 2001).

Other Imaging Techniques

A host of other imaging techniques have proven useful for specific clinical applications or interesting from the perspective of probing the pathology of AD and other dementias. For instance, fluid attenuated inversion recovery (FLAIR) is an MRI pulse sequence that permits researchers to detect the cerebral white matter hyperintensities suggestive of vascular disease, which is commonly found in AD patients (Yoshita et al., 2006) and may contribute to their cognitive decline (Brickman et al., 2008), and which could be used to help characterize a potentially reversible adverse effect of Aβ-modifying immunotherapeutic and medication treatments, now called Amyloid Related Imaging Abnormalities (ARIA). Gradient-recalled echo (GRE) T2* MR images appear to be sensitive to hemosiderin deposits, and as such are capable of detecting microbleeds, which are highly prevalent in dementia samples (Goos et al., 2010) and are particularly related to cerebral amyloid angiopathy (Kimberly et al., 2009). Initial reports suggest that GRE and FLAIR imaging

may not only be helpful, but required by regulatory agencies to monitor Aβ-modifying immunotherapeutic and medication treatments.

While PET studies of AD have been largely focused on the assessment of rCMRgl decline and fibrillar Aβ deposition, a wide range of other tracers has been utilized. Studies of inflammation using the tracer PK11195, a ligand that binds to the peripheral benzodiazepine receptor that is expressed on activated microglia, have shown conflicting results, with evidence of both increases (Cagnin et al., 2001; Edison et al., 2008; Okello et al., 2009a) and lack of change in AD and MCI (Wiley et al., 2009); other PET tracers for inflammation that are under development may ultimately yield less ambiguous results. PET tracers have also been applied to dementia to study a wide range of neurotransmitter systems particularly the cholinergic system (Kuhl et al., 1999; Nordberg et al., 1997); these and others are the subject of recent reviews (Kadir and Nordberg, 2010; Nagren et al., 2010; Nordberg et al., 2010; Pappata et al., 2008). In general, neurotransmitter and neuroreceptor studies reveal reductions in a host of different pre- and post-synaptic elements in AD that in some cases are related to symptoms or other disease features. Researchers have suggested the potential of a PET radioligand for the detection of both fibrillar Aβ and tau pathology (Shoghi-Jadid et al., 2002); more recently, other researchers have proposed a PET radioligand with high affinity and selectivity for tau pathology (Fodero-Tavoletti et al., 2009); and researchers continue to explore PET radioligands for the assessment of tau and oligomeric Aβ species.

A growing number of brain imaging methods are available for the study of AD (and, as with the better established methods, they generate images that could be analyzed in a variety of ways). In general, the approaches reviewed here have not received widespread use in the clinic because either the processes being measured have no direct clinical implications or, in some cases because the techniques themselves have not been adequately standardized. These methods can also be expensive and technically demanding. This situation could change if effective therapy becomes available and these measures are shown to affect subject selection or monitoring of treatment.

Contributions to the Early Detection and Tracking of AD

As previously noted, researchers have used brain imaging techniques to detect and track brain changes associated with AD (Jack, Jr. et al., 2009). Several of the reported brain changes are correlated with clinical severity, progressive, predictive of subsequent clinical decline, and predictive of the neuropathological diagnosis of AD. Several of these changes are observed years before the onset of symptoms in persons at increased genetic risk for AD (e.g., *APOE ε4* carriers, early-onset AD-causing mutation carriers, and Down syndrome patients) and individuals who subsequently demonstrated accelerated cognitive decline or progression to the clinical stages of AD. Additional studies are needed to determine the extent to which these measurements, alone or in combination with other factors, predict subsequent rates of clinical decline.

Cross-sectional PET studies suggest the onset of significant fibrillar Aβ burden about 10-15 years before the clinical onset of AD—though longitudinal studies are needed to determine the extent to which Aβ burden predicts clinical decline over shorter and longer time frames — and that it may reach a virtual plateau by the time most patients have MCI. It has been suggested that fibrillar Aβ deposition is associated with non-progressive reductions in CSF $A\beta_{42}$ levels and that it anticipates downstream brain imaging and CSF changes (Fagan et al., 2006), including progressive MRI measurements of brain shrinkage, progressive PET measurements or rCMRgl decline, non-progressive elevations in CSF total tau and phospho-tau levels and, eventually, cognitive decline (Jack, Jr. et al., 2010; Sperling et al., 2011). Imaging studies have raised the possibility of even earlier brain changes, preceding Aβ

pathology, in the predisposition to AD (Buckner et al., 2005; Reiman et al., 2004; Shaw et al., 2007; Sheline et al., 2010; Vaishnavi et al., 2010; Vlassenko et al., 2010).

Contributions to the Scientific Understanding of AD

Brain imaging studies have produced insights that have had a profound effect on how we think about the disease. To some extent these findings have come from multimodality approaches that have merged studies of structure, function, and biochemistry, especially those conducted in individuals who have minimal or no symptoms. Here we note some of the key findings in this area.

Brain Networks and the Deposition of Fibrillar Aβ

The observation that task induced brain activations are accompanied by clusters of regions that are consistently deactivated has lead to the notion that there is a resting state of the brain, commonly referred to as the default mode network (DMN) (Raichle et al., 2001). Subsequent work has shown that this network anatomically overlaps with both Aβ deposition and the pattern of MRI regional atrophy and PET-FDG hypometabolism (Buckner et al., 2005) (Figure 4). These nodes of the DMN parallel the location of many cortical hubs (Buckner et al., 2009), indicating that they serve as major foci of cortical connections and as key components of multiple networks. As noted, the DMN is disrupted in AD (Greicius et al., 2004) and in resting state connectivity studies in normal older people with asymptomatic fibrillar Aβ deposition (Hedden et al., 2009; Sheline et al., 2010); there is also some evidence that subcomponents of this network show increased connectivity that could represent shifting of the topography of the network perhaps as a compensatory process (Mormino et al., 2011). Failure to deactivate the same regions has been reported in aging and in early stage AD (Lustig et al., 2003), and most recently has been associated with fibrillar Aβ deposition in asymptomatic normal older people performing a memory encoding task (Sperling et al., 2009). The degeneration of this network in AD is paralleled by findings in other disorders in which patterns of neurodegeneration follow the patterns of neural connectivity in a number of different networks, suggesting that intrinsic functional and structural connectivity somehow mediates the regional progression of disorders as disparate as AD, frontotemporal lobar degeneration, and progressive supranuclear palsy (Seeley et al., 2009).

The DMN is also interesting in another respect; it overlaps with both Aβ deposition and with brain regions that preferentially utilize aerobic glycolysis (Vaishnavi et al., 2010; Vlassenko et al., 2010). This aerobic glycolysis could reflect several different aspects of this brain network including the requirement for rapid production of ATP necessary for glutamate cycling (as aerobic glycolysis generates ATP more quickly than oxidative phosphorylation) or factors associated with neural plasticity including the role of glycolysis in fueling the receptor turnover at the post-synaptic density and activity in biosynthesis through the pentose-phosphate shunt. Why brain regions that preferentially utilize this form of energy metabolism should overlap with both cortical hubs and Aβ deposition is a subject requiring further investigation, but it suggests a relationship between neural metabolism and neuroplasticity and the etiopathogenesis of AD.

In addition to failure to adequately deactivate the DMN, a number of studies have pointed to increased brain activation as a feature of early and pre-symptomatic stages of AD (Bookheimer et al., 2000; Celone et al., 2006; Dickerson et al., 2004; Quiroz et al., 2010). These increases in “task positive” networks (as opposed to brain networks that deactivate during tasks such as the DMN) have been interpreted as attempts at compensation although this remains to be conclusively demonstrated. Alternative explanations include dedifferentiation of cortical function, and aberrant excitation, a finding that has also been

seen in vivo in animal models of AD (Palop et al., 2007). In addition, it is possible that lifelong patterns of increased brain activity might themselves predispose to the deposition of β-amyloid(Jagust and Mormino, 2011).

Testing the Amyloid Hypothesis—The combined use of multiple imaging modalities has also resulted in new formulations of the sequence of pathological events in AD as proposed in a recent review (Jack, Jr. et al., 2010). By studying groups of individuals with a variety of imaging techniques at different stages of the disease, a picture of the progression of AD is emerging. For example, it has long been known that older individuals can show pronounced deposition of Aβ in the form of neuritic plaques without having evidence of cognitive impairment (Bennett et al., 2006; Tomlinson et al., 1968). PET amyloid imaging has confirmed the finding of substantial Aβ in normal older people, particularly as related to Apolipoprotein E genotype (Morris et al., 2010; Reiman et al., 2009), and it has permitted the simultaneous examination of cognition in great detail. While there remains some debate, most studies show that cognitive function is normal or only mildly affected in older individuals with brain Aβ who are classified as cognitively normal (Aizenstein et al., 2008; Rentz et al., 2010; Villemagne et al., 2011). While such data establish that very early brain abnormalities include Aβ deposits, they cannot definitely rule out the involvement of other pathological processes in the cascade of events leading to cognitive decline and dementia. Indeed, several other studies have noted that Aβ in normal people is accompanied by subtle evidence of brain atrophy that may be even more important than Aβ itself in leading to cognitive decline (Chetelat et al., 2010; Dickerson et al., 2009; Jack, Jr. et al., 2009; Mormino et al., 2009). These findings are echoed by some data from patients with dementia, in whom characteristics of Aβ deposition bear little relationship to clinical syndromes, while functional changes (both in glucose metabolism and brain activation) are more strongly associated with cognitive deficits (Nelissen et al., 2007; Rabinovici et al., 2008). Furthermore, progression from normal cognition through MCI and AD appears to be associated with very slow increases in Aβ accumulation but more rapid atrophy (Chetelat et al., 2010; Jack, Jr. et al., 2009; Villemagne et al., 2011). Accumulating evidence suggests that PET evidence of Aβ deposition is associated with longitudinal cognitive decline in normals (Resnick et al., 2010; Storandt et al., 2009) and conversion to dementia in those with MCI (Forsberg et al., 2008; Okello et al., 2009b; Wolk et al., 2009).

How can we reconcile seemingly contradictory findings wherein Aβ shows minimal relationships to cognitive symptoms but is associated with subsequent decline and dementia? The likely explanation is that there is a long preclinical period during with Aβ produces relatively few clinically observable findings, but is subtly altering both brain structure and function. We can begin to see evidence of Aβ, structural, and functional changes in normal aging. While Aβ appears to increase the probability of subsequent decline, it is not clear to what extent this decline is also predicted by the degree of structural and functional change. As dementia supervenes, structural and functional changes bear a stronger relationship to symptoms, suggesting that Aβ could serve as an initiating event after which “downstream” changes may become uncoupled from amyloid pathology. This has important implications for the early initiation of anti-amyloid therapy, and the potential importance of non-amyloid targets for individuals later in the disease course.

Still, other questions remain: For instance, why do researchers detect some of the earliest fibrillar Aβ deposition in frontal cortex in those at risk for AD (Mintun et al., 2006) (and in the striatum in some of the individuals at risk for autosomal dominant early-onset of AD (Klunk et al., 2007)), while they are unable to detect the declines in executive function (or the extrapyramidal symptoms) until later in the disease? That dissociation may give researchers clues about the differentially harmful or protective effects of Aβ species on neuronal function. Why have some researchers been able to show brain changes in young

adults at genetic risk for AD before any evidence of fibrillar or solube Aβ accumulation (Reiman et al., 2004)? They information may give researchers information about the earliest synpaptic or peri-synaptic changes associated with the predisposition to AD, many decades before the progressive biological and cognitive changes observed in the later stages of the disease.? Will presymptomatic treatments shown to slow or even reverse the accumulation of fibrillar Aβ deposition also be associated with a clinical benefit? That might be the best test of the amyloid hypothesis yet—better than a test of the same treatment in clinically affected patients, when there is a concern that those treatments may be too late to exert their most profound benefit.

Relating brain function and structure to behavior

Numerous studies have helped to clarify how brain function and structure are related to behavior. PET studies have shown that the pattern and magnitude of glucose hypometabolism is related to pattern and magnitude of cognitive decline (Foster et al., 1983; Haxby et al., 1985; Landau et al., 2011). MRI studies have shown relationships between patterns of regional atrophy and the pattern of behavioral impairment (e.g., helping to define the relationship between regional atrophy and impaired language domains in patients with primary progressive aphasia (Rogalski et al., 2011). Effects of glucose metabolism and brain atrophy may be disarticulated through careful analysis of precise behavioral correlations. In one study, for example, posterior cingulate hypometabolism was related to deficits in memory retrieval, whereas hippocampal atrophy was related to deficits in both memory encoding and retrieval (Chetelat et al., 2003b).

Emerging Roles in the Clinical Setting

Guidelines for the use of imaging in the clinical evaluation of patients with dementia and pre-dementia syndromes such as MCI are actively being modified. Existing American Academy of Neurology practice parameters for the diagnosis of AD recommend CT or MR imaging only to rule out treatable structural pathology (Knopman et al., 2001) while MCI practice parameters do not address imaging at all (Petersen et al., 2001). These guidelines are 10 years old and outmoded not only because of the development of new imaging modalities, but also because the approach to AD has shifted from a diagnosis largely made by exclusion of other conditions to a diagnosis guided by specific historical, cognitive and, most recently, biomarker findings. This new approach has been reinforced by numerous studies in the clinical arena showing how PET imaging can contribute to the differentiation of AD and other conditions such as fronto-temporal Lobar degeneration (Foster et al., 2007) and how imaging findings may be related to pathology (Gosche et al., 2002).

It is in fact the availability of and increasing amounts of data concerning biomarkers in general that is shifting the thinking about diagnosis to include laboratory assessments that have value in supporting a diagnosis of AD. For instance the “Dubois criteria” propose the use of medial temporal atrophy, temporoparietal hypometabolism, and amyloid imaging (as well as CSF Aβ and tau measurements) as supportive features for a diagnosis of AD in the context of the core diagnostic feature of slowly progressive episodic memory loss (Dubois et al., 2007; Dubois et al., 2010). Notably, these criteria require neither pervasive cognitive loss nor functional impairment, thus including individuals in pre-dementia syndromes in the category of AD. While these criteria have not been widely applied, they have been influential in shifting the thinking about AD diagnosis to involve greater use of biomarkers. This approach has eventuated in a new series of diagnostic criteria developed by the National Institute on Aging and the Alzheimer's Association that cover AD, MCI, and even an asymptomatic, biomarker positive stage referred to as preclinical AD (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). Imaging figures prominently in all 3 diagnostic schemas, largely based upon the amyloid hypothesis and the conceptualization of the

pathological sequence of events reviewed above. In these criteria, biomarkers are classified as indicative of Aβ deposition (CSF or PET) or neuronal injury (CSF tau, MRI atrophy, or PET hypometabolism). For both AD and MCI, the presence of both Aβ and neuronal injury confers the highest biomarker evidence of AD, presence of one an intermediate level, conflicting biomarker evidence is considered uninformative, and negative biomarker results lower the likelihood of AD. These criteria thus bring imaging clearly into the diagnostic assessment, largely in the role of supporting a diagnosis of AD. They also raise the possibility of determining which cognitively normal older adults and MCI patients have evidence of the AD pathophysiological process. Conversely, amyloid PET and MRI measurements provide a new opportunity to study the biological and cognitive changes associated with normal aging in the absence of measurable AD or cerebovascular pathology.

The future use of imaging in the clinical evaluation of dementia and MCI is likely related in part to the availability of effective medication treatments. At the present time there is evidence to suggest that amyloid PET imaging can predict decline in both MCI patients and normal older people. There is of course also evidence that FDG-PET and MRI are predictive of decline (Chetelat et al., 2003a; Jack et al., 1999). There are few studies that use multivariate approaches to predict decline in MCI patients but it is possible that markers of neural dysfunction such as FDG-PET and MR atrophy are better indicators of more progressed individuals and, as such, might be more effective than Aβ measures at predicting imminent decline (Chen et al., 2011; Landau et al., 2010). While studies that compare different imaging approaches in prediction will be important from a scientific perspective, the clinical significance of prediction may be more helpful when the information can be related to a clinically effective medication treatment. However, the likely infusion of amyloid PET into the clinical arena through the application of longer-lived F-18 labeled PET tracers (Clark et al., 2011; Rowe et al., 2008; Vandenberghe et al., 2010) could have a major impact on clinical care if effective therapies become available.

We wish to suggest two considerations, as a complement to the inevitable discussion of costs and benefits. First, public policy makers will need to factor in the non-medication treatment issues that have the greatest impact on the welfare of patients and families at this time. For instance, it is possible that amyloid PET findings could help mobilize physicians and families to address the range of distressing non-medication issues (e.g., decisions about driving and retirement, proactive financial, medicolegal, and resource planning) and reduce the family's sense of uncertainty about the underlying diagnosis. Second, a negative fibrillar Aβ PET scan (suggesting that the diagnosis of AD is unlikely) may be more informative than a positive PET scan (since one cannot exclude other contributors to AD, including some of the mixed pathology frequently seen at autopsy). Clinicians, payers and policy makers will have challenging questions to address, starting in the near future.

Emerging Roles in the Evaluation of AD-Modifying Treatments

There is great interest in the role that brain imaging techniques could play in the evaluation of investigational AD-modifying treatments, a major effort to develop the best imaging techniques for this purpose, and an increasing use of MRI, FDG PET and fibrillar amyloid PET in clinical trials. Among other things, imaging techniques have the potential to a) reduce the number of clinically affected AD patients and time needed to evaluate investigational AD-modifying treatments; b) select patients with dementia or MCI based on their estimated likelihood of clinical progression or response to certain treatments; c) differentiate patient subgroups in their response to treatment, helping to minimize attrition in drug development; d) help clarify a treatment's amyloid-modifying and other AD-modifying effects; e) monitor the safety of amyloid-modifying treatments (i.e., evidence of potentially reversible vasogenic edema and microinfarcts using GRE and FLAIR MRI pulse

sequences); and f) as noted below, to help evaluate the range of promising presymptomatic AD treatments as quickly as possible (Reiman and Langbaum, 2009; Reiman et al., 2010; Reiman et al., 2011).

For instance, volumetric MRI and FDG PET measurements appear to be better than clinical measurements in their statistical power to track the progression of AD in probable AD and MCI patients and in their estimated statistical power to evaluate AD-modifying treatment effects when used as endpoints in clinical trials (Alexander et al., 2002a; Beckett et al., 2010; Chen et al., 2010; Chen et al., 2011; Fox et al., 2000). Brain imaging and other biomarker measurements have been suggested to help to distinguish those MCI patients most likely to show subsequent clinical progression over the next 12-18 months, providing an enrichment strategy by which to reduce sample size and treatment duration in MCI trials (Chételat et al., 2005a; Chételat et al., 2005b; Drzezga et al., 2005a; Jack, Jr. et al., 2005; Mosconi et al., 2004a). PET or CSF measurements of amyloid burden have been suggested to help distinguish which symptomatic patients have amyloid pathology (Clark et al., 2011), offering the change to identify those candidates who may be most likely to respond to an amyloid-modifying treatment. PET may be too late to assess the ability of an amyloid-modifying treatment to slow down the further fibrillar Aβ accumulation in symptomatic patients, by which time fibrillar Aβ deposition may have reached a plateau (Klunk et al., 2006), but it may be able to detect the extent to which certain (e.g., immunization) treatments actually reverse fibrillar Aβ pathology. Indeed, PiB PET was recently used in a clinical trial to demonstrate greater clearance of amyloid plaques in AD dementia patients treated with an Aβ immunotherapy than those treated with placebo (Rinne et al., 2010). Brain imaging and other biomarker measurements are critically needed to rapidly evaluate disease-modifying treatments in the earliest symptomatic and presymptomatic stages of AD, when investigational treatments may be most likely to exert their most profound effects.

Established in 2004, the United States-based AD Neuroimaging Initiative (ADNI) is primarily intended to help inform the design and performance of multi-center clinical trials of investigational AD-modifying treatments using brain imaging, other biomarker, and clinical measurements in probable AD, MCI and cognitively normal older adults (Mueller et al., 2005), and it has inspired similar initiatives in Europe, Australia, and Japan. It has developed and implemented protocols for the acquisition of MRI, FDG PET, and certain fibrillar Aβ PET measurements, real-time quality-assurance and quality-control procedures and centralized image processing procedures to optimize the quality and comparability of data acquired on different MRI and PET systems. It has demonstrated the feasibility of collecting CSF samples in a high proportion of study participants. It has provided a publicly available resource of data and biological samples for the research community, providing an opportunity to compare new data analysis techniques and biological fluid assays to other measurements in the detection and tracking of AD. Most importantly, it has provided a means to directly compare the different kinds of measurements and different image-analysis techniques in terms of their ability to track the progression of AD, estimate sample sizes needed to detect AD-modifying treatment effects, and the effects of different biomarker enrichment strategies on these estimates.

While brain imaging and other AD biomarker measurements offer great promise in the evaluation of AD-modifying treatments, several uncertainties remain when it comes to the information they will provide in clinical trials. There is a need to embed the most promising biomarkers in clinical trials, determine the extent to which AD-modifying treatments budge the biomarkers, clarify and address potentially confounding effects of the treatment on the biomarkers (e.g., a treatment's effects on brain volume or regional CMRgl unrelated to disease progression), and determine the extent to which the treatment's biomarker effects predict a clinical benefit. While brain imaging and other biomarkers can provide information

that may help in the development of promising treatments, regulatory agencies are unlikely to provide an accelerated approval pathway for an AD-modifying treatment based solely on a biomarker (i.e., surrogate) endpoint until there is evidence from clinical trials themselves that a treatment's biomarker effects are reasonably likely to predict a clinical benefit (Reiman and Langbaum, 2009; Reiman et al., 2010; Reiman et al., 2011).

Emerging Roles in the Evaluation of Presymptomatic AD Treatments

When one considers the growing number of clinically affected AD patients, the healthy lifestyle interventions suggested but not proven to reduce the risk of AD symptoms (Haag et al., 2009; Lautenschlager et al., 2008; Peila et al., 2006; Scarmeas et al., 2009; Szekely et al., 2008; Wang et al., 2002; Willis et al., 2006; Zandi et al., 2004), and the possibility that investigational AD treatments may need to be started before the onset of symptoms to have their most profound benefit, there is a need to evaluate these range of “presymptomatic AD treatments” in the most rapid and rigorous way. It currently takes too many healthy volunteers and too many years to evaluate presymptomatic AD treatments in prevention trials using clinical endpoints. There is a growing interest in the role that brain imaging and other biomarker measurements could play in the rapid evaluation of promising presymptomatic AD treatments. Thus, researchers have provided brain imaging evidence of AD progression in cognitively normal late-middle-aged *APOE ε4* carriers and the estimated sample sizes needed to evaluate promising presymptomatic AD treatments in two-year proof-of-concept prevention trials.

Meantime, several groups have proposed the evaluation of investigational Aβ-modifying treatments in prevention trials. For instance, researchers from the Alzheimer's Prevention Initiative have proposed a trial using brain imaging, CSF biomarker and cognitive endpoints in cognitively normal people who, based on their age and genetic background, are at the highest imminent risk of early- or late-onset AD symptoms and to provide the evidence needed to show that the treatment's biomarker effects are reasonably likely to predict a clinical benefit so that these biomarkers may receive regulatory agency qualification for use in AD prevention trials (Reiman et al., 2010; Reiman et al., 2011). It is also intended to provide a better test of the amyloid hypothesis than trials in symptomatic patients, when the treatment may be too little too late to have the most profound effect. Researchers from the Dominantly Inherited Alzheimer's Network (DIAN) have proposed proof-of-concept prevention in early-onset AD causing mutation carriers, and to use other biomarker data to help provide the pharmacodynamic data needed to inform these studies (Bateman et al., 2011). Researchers from the AD Cooperative Study have proposed a prevention trial in cognitively normal people with PET evidence of significant fibrillar Aβ burden. These and other trials are needed to not only provide information about the effects of promising presymptomatic treatments on measurements on AD pathophysiology, but to help find the best biomarkers for use in other prevention trials and to help qualify the most suitable biomarkers for use as reasonably likely surrogate endpoints in prevention trials. In this way, AD biomarkers, alone or in combination (e.g., PET fibrillar Aβ measurements along with volumetric MRI, FDG PET or other downstream measures of disease more closely related to clinical outcome), could provide both the scientific means and accelerated regulatory approval pathway to galvanize the evaluation of promising presymptomatic treatments.

Future Directions and a Few Recommendations

There has been has great progress in the scientific discovery of AD, the discovery of promising disease-modifying and presymptomatic treatments, and the development of brain imaging and biomarker techniques to help advance the scientific understanding, detection,

tracking, treatment and prevention of AD. But more work remains to be done. A few recommendations:

1. Continue to develop the brain imaging measurements needed to assess relevant biological processes, including but not limited to brain imaging and fluid biomarker measurements to assess other, potentially more toxic (e.g., oligomeric) Aβ species and neurofibrillary pathology.
2. Continue to develop, test and compare new image analysis algorithms, including voxel-based algorithms that can capitalize on the wealth of data available in complementary data sets from the same person, and those that can summarize the pattern of measurements or time-dependent changes in a single measurement.
3. Further characterize the extent to which brain imaging measurements, alone but especially in combination, predict subsequent clinical decline. These imaging biomarkers must also be compared with inexpensive potentially cost-effective measures such as brief cognitive evaluations and fluid biomarkers.
4. Further characterize the relationship and time course of biomarker and cognitive changes associated with the preclinical and increasingly severe clinical stages of AD—include those changes that may precede the earliest evidence of Aβ accumulation.
5. Further development and leverage animal imaging resources in the scientific study of AD and the preclinical evaluation of promising AD-modifying treatments.
6. Work with researchers from other disciplines (e.g., genomics, proteomics, and the basic neurosciences) to leverage each others' resources in a more effective way.
7. Embed the range of promising biomarker measurements (including volumetric MRI, FDG PET, fibrillar Aβ PET, CSF assays) and store the biological fluid samples in clinical trials of disease-modifying treatments and presymptomatic AD treatments, providing the evidence needed to inform the use of biomarkers in the evaluation of these treatments and to qualify the relevant biomarkers for use as endpoints in pivotal trials.
8. Develop, test, and apply PET tracers that can better characterize other neuropathological features of AD, such as those for the assessment of tau pathology (Fodero-Tavoletti et al., 2009), neuroinflammation, and other potentially neurotoxic (e.g., oligomeric) Aβ species.
9. Provide the federal funding and financial incentives needed to evaluate the range of promising presymptomatic treatments in prevention trials. It is time to advance AD prevention research, and imaging techniques are needed to help evaluate the range of promising treatments in the most rapid and rigorous way.

There is no guarantee that any of the treatments now in clinical and preclinical development will work. But the brain imaging research community is well positioned to help evaluate these treatments, extend them to the presymptomatic stages of AD when they might have their most profound effect, and improve the clinical management of AD as better treatments become available. A sense of urgency among all of the stakeholders is needed to address the problem of AD as quickly as possible.

Acknowledgments

The authors received relevant support from National Institute on Aging grants R01 AG031581, R01 AG034570, P30 AG19610, U01 AG024904 and RC AG036535. They thank Dr. Jessica Langbaum for her assistance in the editing of this article.

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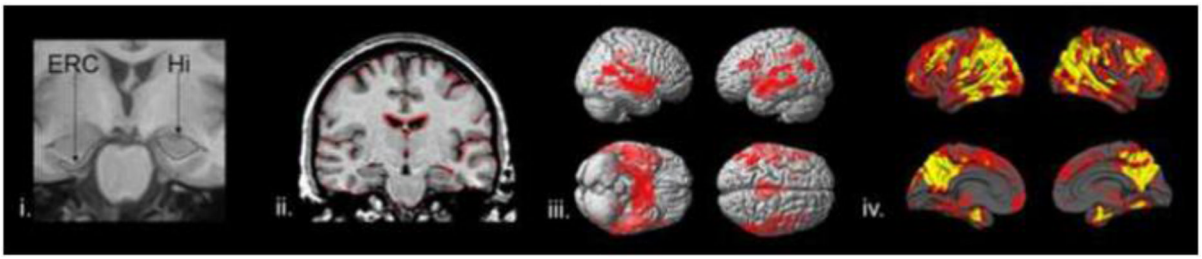

Figure 1.

Volumetric MRI in the the detection and tracking of AD, including **(i)** accelerated rates of atrophy in the hippocampus (Hi) and entorhinal cortex (ERC) regions-of-interest (Mike Weiner, with permission); **(ii)** accelerated rates of whole brain atrophy using sequential MRIs, as shown in red in a symptomatic AD patient (Nick Fox, with permission); **(iii)** regional gray matter loss, as shown in this statistical brain map comparing symptomatic AD patients and controls. Reprinted from (Baron et al., 2001), Copyright © 2001 with permission from Elsevier. All rights reserved; and **(iv)** regional thinning in cerebral cortex, as shown in this statistical brain map comparing symptomatic AD patients and controls. Reprinted with permission from (Du et al., 2007), Copyright © 2007 Oxford University Press. All rights reserved. This figure was reproduced with permission from (Reiman and Langbaum, 2009), Copyright © 2009 Oxford University Press. All rights reserved.

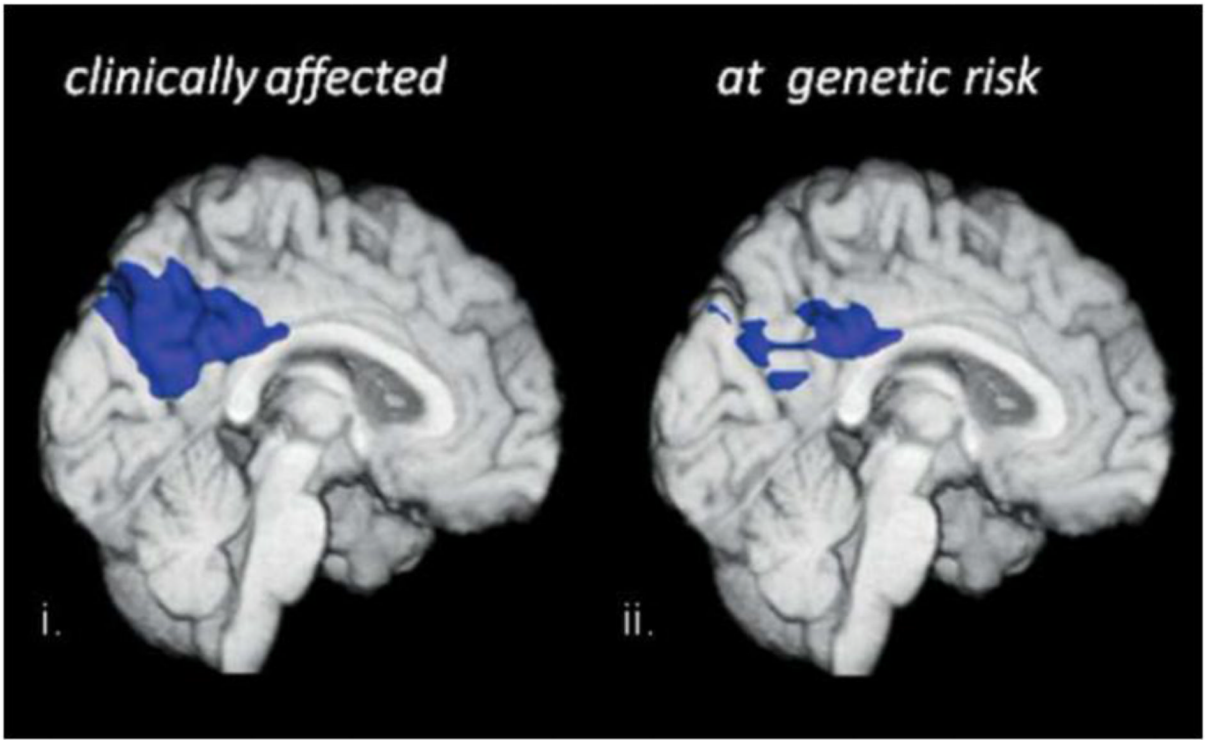

Figure 2.
FDG PET in people who are clinically affected by or at increased genetic risk of AD. Characteristic CMRgl reductions (compared to normal controls) are displayed on the medial surface of a brain MRI in clinically affected AD patients and in cognitively normal young adult with one copy of the *APOE ε4* allele, the major AD susceptibility gene. Adapted with permission from (Reiman et al., 1996), Copyright © 1996 Massachusetts Medical Society, all rights reserved, and (Reiman et al., 2004), Copyright © 2004 National Academy of Sciences, USA. All rights reserved.

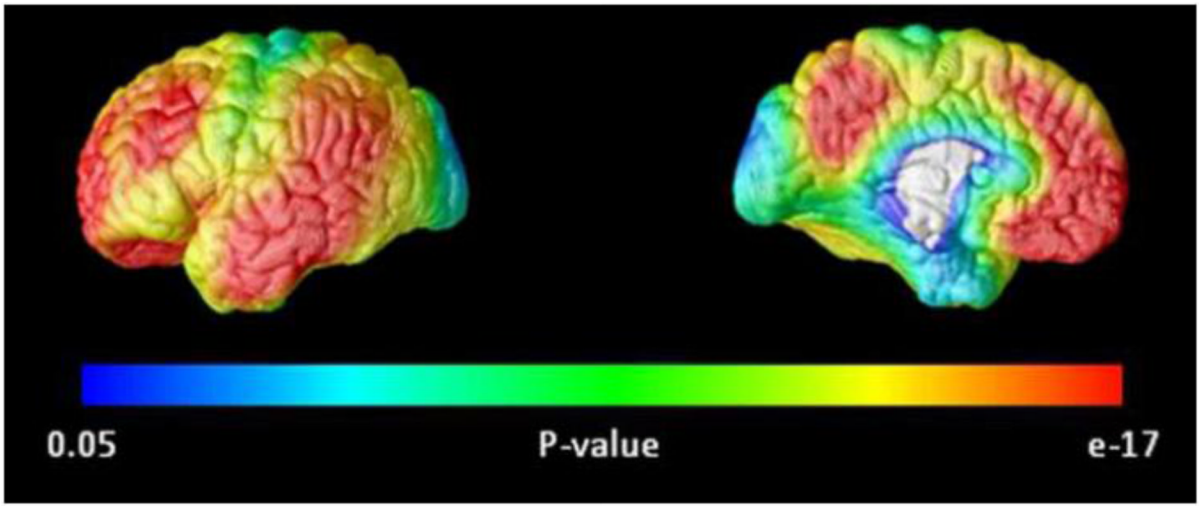

Figure 3.
Fibrillar amyloid imaging in the study of AD. Increases in Pittsburgh Compound-B PET measurements of fibrillar amyloid-β in symptomatic AD patients. Adapted with permission from (Reiman et al., 2009; Reiman et al., 2010), Copyright © 2009 National Academy of Sciences, USA. All rights reserved.

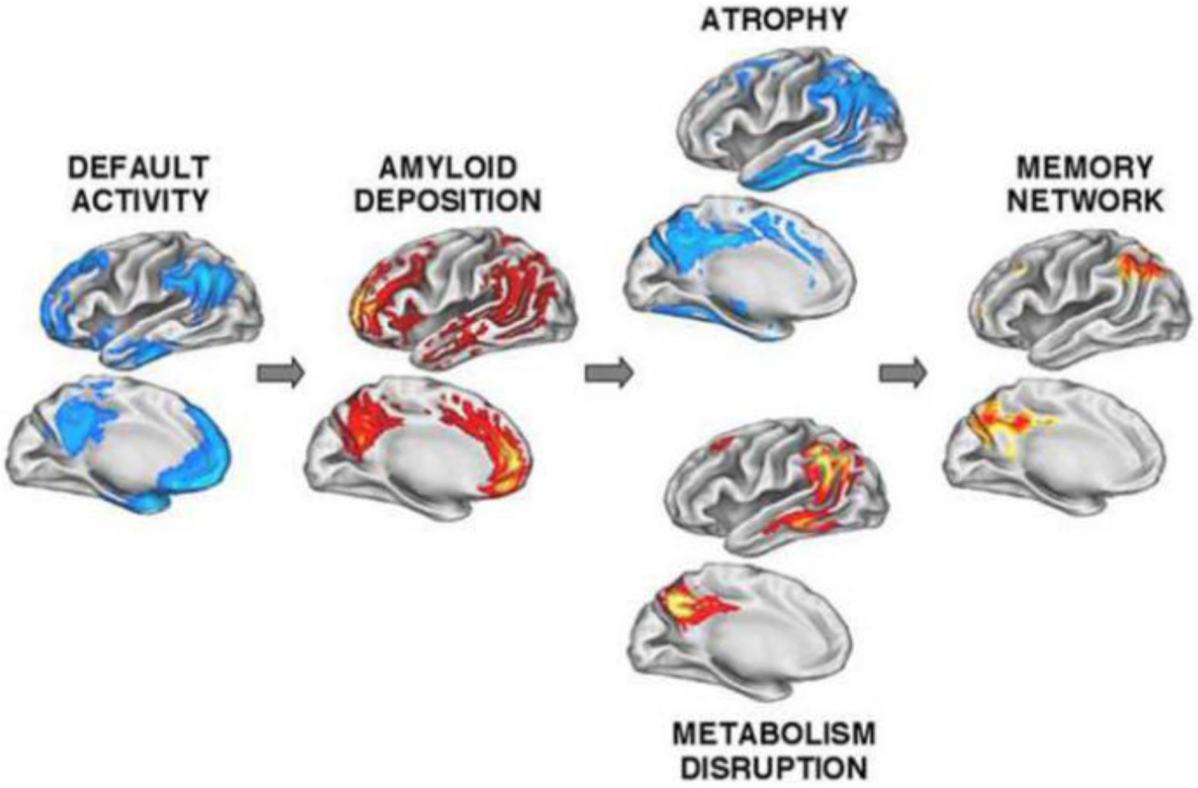

Figure 4.
Spatial relationships (and postulated causal connections) among the brain regions implicated in i and ii) the Default Mode Network and successful episodic memory retrieval in young adults, iii) the regions preferentially associated with fibrillar amyloid-β deposition, and iv and v) the regions preferentially associated with atrophy and CMRgl decline. Reprinted with permission from (Buckner et al., 2005), Copyright © 2005 Society for Neuroscience. All rights reserved.