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APOE-4 Genotype and Neurophysiological Vulnerability to Alzheimer's and Cognitive Aging

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Abstract

Many years before receiving a clinical diagnosis of Alzheimer's disease (AD), patients experience evidence of cognitive decline. Recent studies using a variety of brain imaging technologies have detected subtle changes in brain structure and function in normal adults with a genetic risk for AD; these brain changes have similar pathological features as AD, and some appear to be predictive of future cognitive decline. This review examines the most recent data on brain changes in genetic risk for AD and discusses the benefits and potential risks of detecting individuals at risk.

Keywords

neuroimaging; functional MRI (fMRI); dementia

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting between 5% and 10% of individuals in their sixties; the incidence increases to nearly 50% of those who reach their nineties (Small et al. 1997). Characterized first by memory loss, the disease is relentlessly progressive, culminating in sharp cognitive decline and complete incapacity. Because the brain but not the body is affected, patients can live for years while lacking the ability to recognize friends, family, and self, unable to communicate, eat independently, or maintain continence. Alzheimer's likewise has a devastating effect on families and caregivers (Schulz et al. 2008); up to 65% of caregivers suffer from depression (Papastavrou et al. 2007). Psychiatric symptoms, ranging from anxiety, agitation, and depression to psychosis, may occur in preclinical Alzheimer's mild cognitive impairment (MCI) at a rate of twice that of healthy controls (Geda et al. 2008). There is no cure for AD, and treatments are generally limited. A few pharmacotherapies may improve cognition for a relatively short duration, and although new treatments are under development, the most promising treatments aim to reduce or halt the rate of decline rather than reverse it. As these treatments are developed, there will be an increasing need to identify in the earliest possible stages the individuals fated to develop AD who will benefit most from intervention; preservation of cognitive status at the time of diagnosis offers little to patients or family.

Although a small percentage of patients have an inherited mutation that makes AD a likely outcome, most genetic risk for AD is only statistical. For instance, a single apolipoprotein E (APOE)-4 allele confers only a 20% risk of developing the disease, and there are likely numerous other AD risk genes with less certain outcomes. Thus, a goal in early detection research is to discover additional factors that may help to identify which individuals with a known genetic marker or a family history of AD will be more likely to develop the disease. Neuroimaging offers a promising approach to identifying those likely to develop AD. Patients with AD can be reliably discriminated from those with normal aging or with other dementias through a variety of different approaches, from structural magnetic resonance imaging (MRI) and functional MRI (fMRI) to molecular imaging of characteristic patterns of abnormal brain structure and function with positron emission tomography (PET). The challenge with such studies is in applying these techniques to predict outcome in those who have not yet developed the disease.

In this review, we detail the nature of the known genetic risks for AD and evaluate how well each of the primary imaging techniques—structural MRI, fMRI, and PET—has differentiated individuals with a genetic risk for Alzheimer's from those without this risk. We critically evaluate the evidence in support of a predictive value of each methodology. We also discuss the psychological impact of learning about one's AD risk status and some of the psychological and behavioral manifestations of early AD.

WHAT ARE THE KNOWN GENETIC RISKS OF ALZHEIMER'S?

We can summarize the genetic risks for AD as falling roughly into three categories: rare autosomal dominant inherited mutations typically occurring before age 65 (early-onset Alzheimer's), the APOE-4 genetic polymorphism that incurs an increased risk for late-onset Alzheimer's, and unknown genetic contributions associated with a family history of AD.

Of the known autosomal dominant conditions leading to Alzheimer's, the most common are the presenilin mutations PS1 and PS2 and the amyloid precursor protein gene APP. All of these genes have in common an abnormal mechanism for amyloid production resulting in a buildup of beta amyloid in the form of amyloid plaques, increases in amyloid oligomers and neurofibrillary tangles, the pathological hallmarks of AD. The PS-1 gene is found on chromosome 14, and mutations in this gene are associated with several different types of dementia, not just Alzheimer's. In fact, more than 130 mutations in the PS-1 gene have been identified in genetic studies (Signorini et al. 2004), with differences in dementia presentation varying with the site of mutation. For example, Dermaut et al. (2004) identified a PS1 mutation at codon 183 associated with Pick's disease, a dementia characterized by a very different cognitive and neurological profile including Parkinson-like symptoms and a waxing and waning presentation. Fronto-temporal dementia, characterized by personality change, disinhibition, and memory loss, has been identified in patients with PS-1 mutations in several different loci (Tang-Wai et al. 2002, Zekanowski et al. 2006). The PS2 gene on chromosome 1 is similar in action and presentation to PS1 except that the age of onset is more variable in PS2 mutations (Levy-Lahad et al. 1995, Sherrington et al. 1996) and among the autosomal dominant mutations is the most rare. The APP gene on chromosome 21 is similarly an autosomal dominant mutation causing AD in those who inherit it. It is typically related to abnormal cleavage of beta amyloid secretases and results in overproduction of beta amyloid. As in PS1, several APP mutation variants appear to result in somewhat different presentations, often with more vascular features (Basun et al. 2008). Together, these familial mutations account for only about 5% of the total cases of AD. However, for the most part they appear to share the primary pathological features of AD—amyloid plaques, increased intracellular tau proteins with neurofibrillary tangles—as well as the

cognitive symptoms, primarily a relentless progression of memory loss followed by profoundly impaired global cognition.

There are several striking advantages of studying patients with these mutations. Because the genetic status can be determined well in advance of clinical deterioration, these patients can be studied long before brain changes associated with normal aging occur. These age-related brain changes cannot be understated: Even in patients who never develop dementia or significant cognitive decline, there is a characteristic brain deterioration in normal aging that includes gray and white matter loss and ventricular enlargement (Ge et al. 2002) and is accompanied by memory decline. Since in most cases AD is of late onset, it is frequently difficult to determine which brain changes are specific to AD and which are part of the natural aging process. PS and APP family members can be studied early in life, well before these changes occur, and the goal in imaging studies of these patients is to identify neuroimaging signatures of AD independent of normal aging. The age of onset is also significantly reduced in the familial autosomal dominant cases, so it is possible to monitor the progression of brain changes in these individuals as they progress from health to disease. A major disadvantage, however, is that these cases are relatively rare, and it is rarer still to find identical mutations in different family cohorts. There is also the problem that the pathology, presentation, or course of the autosomal dominant mutations may not match sufficiently to the more typical, late-onset AD that comprises the large majority of cases. As discussed below, the imaging data to date suggest that the pathological presentations are similar in both types of AD.

It is also important to consider psychological factors in gene expression. Psychological distress in individuals with early-onset AD genotypes can influence the expression of the disease. Mejia et al. (2003) found that both depressive symptoms and a history of personal losses and other life stresses predicted a significantly earlier age of onset in PS and APP carriers. This might seem to discourage disclosure of AD risk status. Yet a recent study found that disclosure of genetic risk status had no effect on anxiety in the majority of carriers and approximately equally lowered or raised anxiety in the remaining carriers, whereas all noncarriers experienced relief and a decrease in anxiety (Molinuevo et al. 2005).

COMMON POLYMORPHISMS

Common polymorphisms are allelic variations found frequently in the population; these variations may incur a vulnerability to a disorder; that is, they may be overrepresented in the population having a particular trait or disease. Possession of the APOE-4 allele is the primary common polymorphism associated with AD. The APOE-4 allele sits on chromosome 19 and is apparently associated with amyloid and tau production. In numerous population based genetic studies the APOE-4 allele has consistently appeared as overrepresented in patients with AD. Furthermore, there is a dose-dependency of APOE-4, such that two APOE-4 alleles, the 4/4 genotype, confer a substantially greater risk for AD in comparison to those with only a single copy (3/4), who in turn are at greater risk than those without a 4 allele (3/3). A rare APOE-2 variant appears to be protective against AD (Corder et al. 1993). Although APOE-4 contributes nearly 50% of the genetic variance in AD, only 10% to 20% of the total variance is accountable by APOE-4. Other hypothesized risks include IQ, head trauma, and unknown environmental factors, but none has been demonstrated as causal of the pathology; these factors are likely to interact with genetic predisposition (Bird 2008).

OTHER GENETIC CONTRIBUTIONS

Family history is itself a risk factor for AD. Having one first-degree relative significantly increases the lifelong risk of AD over the general population (Roberts et al. 2005); for those

with two parents carrying an AD diagnosis, the risk increases to more than 40% in those over the age of 70 (Jayadev et al. 2008). A single gene, APOE-4, accounts for approximately 50% of this genetic variance. Other risk genes undoubtedly exist for AD, and several have been found in some linkage studies, such as ubiquilin-1 (Kamboh et al. 2006), Cystatin-C (Goddard et al. 2004), and IDE-4U (McQueen et al. 2007), but many of these reports have not held up to cross validation in independent samples (Bertram & Tanzi 2004, Wang et al. 2008).

Because APOE-4 is the most common and best-studied genetic marker of AD and the most reliably replicated common polymorphism, our discussion of neuroimaging and the prediction of decline in genetic risk for AD is limited to this polymorphism, although to the extent the early onset markers have been studied, the results tend to be consistent with APOE-4 findings.

NEUROIMAGING FINDINGS IN GENETIC RISK FOR ALZHEIMER'S

The gold standard, definitive diagnosis of AD comes from postmortem examination of the AD brain, where there are prominent amyloid plaques and neuritic tangles in association with a living history of dementia. Figure 1 shows these pathological hallmarks. Although in vivo imaging measures cannot provide a definitive diagnosis of AD, a growing body of research into these methods in accordance with neurocognitive evaluation and in many cases postmortem validation has generated a wealth of data supporting relatively specific, observable brain changes in patients proven to have AD. We focus on the three major categories of imaging approaches: structural MRI, fMRI, and PET.

STRUCTURAL MRI IN APOE-4

By the time of AD diagnosis, MRI scans show marked evidence for widespread neural loss, enlarged ventricles, demyelination, and cortical thinning, and these patterns are more severe among AD patients who also have APOE-4 (Juottonen et al. 1998). Figure 2 is an example of an MRI scan in a patient with recently diagnosed (mild) Alzheimer's in comparison with an age-matched control subject. In the hippocampal region, there is evidence for massive breakdown of structure, with the nearby ventricles expanding to fill the void. Striations through the white matter indicate loss of myelin, and concomitant signs of cerebral vascular small vessel disease, common in AD, are evident. This is the endpoint in a long process of brain deterioration, but studies with patients at genetic risk indicate that these changes occur well before disease onset. However, this deterioration begins in the hippocampus, and in particular in the entorhinal cortex. Patients diagnosed with MCI, often considered a pre-AD condition because a significant percentage will convert to AD within a few years, show similar though less marked hippocampal volume loss, which is exacerbated in those with APOE-4 (Farlow et al. 2004, Jack et al. 1999). An early study of cognitively normal older subjects found hippocampal volume loss in APOE-4 compared to APOE-3 carriers (Reiman et al. 1998).

Our lab examined the thickness of the cortical ribbon across the many subregions of the hippocampal complex—including the entorhinal cortex, subiculum, and the Ammon's Horn (CA) fields—in older, nondemented control subjects with and without the APOE-4 allele (Burggren et al. 2008). These subjects had normal memory for their age, and genetic groups were equivalent in their memory and cognitive abilities. Nonetheless, careful measurements of the cortical width revealed a specific decline among APOE-4 carriers in the entorhinal cortex, the region where amyloid plaques first appear in AD, as well as in subiculum, a primary projection site of hippocampal neurons. This study also showed that subregional thickness measures were more sensitive than were volumetric measures typically used in

MRI research. A recent large-scale MRI study that included genotyping found significant reductions in entorhinal cortex thickness among APOE-4 carriers who were children and adolescents (Shaw et al. 2007). This striking result suggests that reduced entorhinal cortex volume may represent a lifetime risk factor for AD rather than necessarily indicating evidence of early disease progression.

The predictive ability of structural MRI is limited by several factors, most notably a large baseline variance in hippocampal volume. Even when normalizing for head size, volumes can vary substantially across individuals, making a single, static measure of volume a poor predictive variable. Measurements of longitudinal change in MRI metrics have better support as outcome predictors. Thompson and colleagues identified a rate of change metric using cortical thickness and ventricular size over a two-year period, finding different rates of atrophy in AD compared to control subjects (Thompson et al. 2003, 2004). A large-scale study of MCI patients followed 300 subjects longitudinally with MRI (Rusinek et al. 2003); patients with the APOE-4 allele showed greater rates of atrophy over time than did those with APOE-3, but other variables including age and baseline cognition were equally associated with hippocampal loss. Jack et al. (2007) reported that in a smaller cohort of MCI patients, the rates of hippocampal volume loss were greater in APOE-4 patients and the change-rate metrics were superior to cross-sectional measures of hippocampal volume. However, similar rate of change metrics have not been studied in cognitively normal, genetically at-risk subjects. Overall, the existing studies do indicate that longitudinal change measures based on MRI, particularly of the ERC and hippocampus, are predictive of conversion to AD from MCI and are on average greater among APOE-4 carriers.

Although the MRI data, particularly those studies that carefully measure the hippocampus or the entorhinal cortex, show a difference between genetic risk groups, little evidence supports MRI as a predictor of future cognitive decline in normal APOE-4 carriers. Even in populations for whom further decline is likely (AD and MCI patients), studies to date have focused on finding differences at the group level; only one study has attempted to identify the probability of future decline based on MRI atrophy rate. Only one study to date has examined the ability of MRI to predict future decline in healthy elderly. Rusinek and colleagues (2003) found that the rate of hippocampal atrophy predicted future cognitive decline accurately in 89% of cases, with high sensitivity and specificity (91% and 85%, respectively), but found no predictive effect of genotype. However, the number of participants was small overall, particularly in the APOE-4 group (10 total). Furthermore, the age of recruitment (average 69.8) was sufficiently high that ascertainment may have been biased against recruiting APOE-4 subjects destined to decline. Because APOE-4 confers an earlier risk of developing AD, particularly in those with two APOE-4 alleles, a representative sample of APOE-4 subjects would likely contain more subjects with MCI and AD, subjects who could not have been recruited as healthy controls. Nonetheless, this study is very important in demonstrating the predictive potential of an MRI metric.

FUNCTIONAL MAGNETIC RESONANCE IMAGING IN APOE-4

Functional MRI measures local changes in MRI signal intensity that are associated with increases in blood flow during the performance of a cognitive task. Unlike many other imaging methods, fMRI typically requires active participation and engagement of the subject, which has limited its use in more severely demented patients. Prior work using activation imaging with either fMRI or H₂¹⁵O PET in patients with Alzheimer's has tended to show reduced activity, particularly in brain regions involved in higher-order cognition, with relative preservation of primary sensory regions (Grady et al. 1993). In genetically at-risk, healthy subjects, the pattern is quite different: During memory challenge, we reported increases in fMRI activity particularly in association cortex among APOE-4 carriers

(Bookheimer et al. 2000) (Figure 3). This finding has been replicated by several groups using an array of memory paradigms (Bondi et al. 2005, Dickerson et al. 2004, Han et al. 2006) and during verbal fluency (Smith et al. 2002), which is also impaired in AD, but not during tasks that are usually unaffected in mild AD (Burggren et al. 2002, Lind et al. 2006). This pattern of results has been hypothesized to represent a compensatory mechanism in which increased cognitive effort is required to achieve an equivalent level of performance (Bondi et al. 2005, Bookheimer et al. 2000). One study using a sample with unusually high family risk for AD (two first-degree relatives) found a similar compensatory main effect for family history but not for APOE status (Bassett et al. 2006), whereas Fleisher and colleagues found that the combined risk of family history and APOE-genotype produced an increase in fMRI activity compared to those without these risk factors (Fleisher et al. 2005).

In contrast to structural MRI, few studies have used fMRI for prediction of cognitive decline in healthy, at-risk subjects. One study (Miller et al. 2008) evaluated the predictive value of increased hippocampal activation in an MCI population, finding that fMRI activation successfully predicted later cognitive decline even when controlling for other risk factors, such as APOE-status and age. Similarly, Dickerson et al. (2004) found that MCI patients had less activity in the hippocampus than did controls, but those who later declined in cognition had paradoxically increased regions of activity in parahippocampal cortex, consistent with a compensatory hypothesis. In healthy older controls with and without a genetic risk for AD, we found that the magnitude of fMRI hyperactivation correlated with decline in memory scores two years later in a relatively small sample of subjects (Bookheimer et al. 2000). Because fMRI is a new technique, it is not surprising to see few longitudinal studies published to date. Furthermore, fMRI is a complex technique, and the predictions about the expected pattern of fMRI results are not straightforward. First, there is no single “best” fMRI task to use, and published fMRI studies in AD and AD risk include passive memory encoding (Miller et al. 2008) and active associated encoding (Bookheimer et al. 2000, Sperling 2007, Sperling et al. 2003) as well as tasks that do not involve memory systems at all (Burggren et al. 2002, Lind et al. 2006). Each produces a unique pattern of activation, and only some would be expected to elicit an aberrant response in AD risk, depending on the brain regions typically engaged by the task and the assumptions of the compensatory hypothesis. A second major concern associated with the compensatory hypothesis is that the expected pattern of fMRI activity as cognition worsens takes a nonlinear trajectory: Compensation is thought to occur when the subject must work harder to achieve adequate performance. Hence, increased fMRI activity is predicted during memory challenge in healthier, at-risk subjects. However, when compensation fails (i.e., the patient is no longer able to perform the task, as in many patients with AD), the opposite result—a decrease in activation relative to controls—is predicted. This nonlinear response has been elegantly demonstrated by Sperling and colleagues (Sperling 2007, Sperling et al. 2003), who examined younger and older controls and AD patients, with all groups demonstrating a complex pattern of age- and cognition-related increases and decreases in fMRI activation. There are also technical concerns in interpreting fMRI results in the context of aging studies. Cortical atrophy may differ across groups, and most studies do not account for potential partial volume averaging. Another factor is performance: Increased task difficulty is associated with increased fMRI activation, especially in cortical association areas (Burggren et al. 2002, Kroger et al. 2002), so differences in behavioral performance of genetic risk groups present an important potential confound. Finally, the accuracy of a compensation hypothesis in APOE-4 hyperactivation has been recently challenged by reports testing the relationship between baseline-reduced perfusion and the blood-oxygen-level dependent (BOLD) response. Using an arterial spin label technique, which measures absolute cerebral blood flow (as opposed to the relative, indirect measurements offered by traditional BOLD fMRI), Bangen, Restom, and colleagues (Bangen et al. 2007, Restom et al. 2007) found decreased cerebral perfusion at rest and higher perfusion during activation in older adults.

These data indicate that cerebral metabolic rate may increase with age, suggesting that differences in the magnitude of BOLD activation may have a vascular rather than a strategic cause, in accord with the compensatory hypothesis.

POSITRON EMISSION TOMOGRAPHY IN APOE-4

PET is an imaging technique that measures the distribution of a radioactively labeled isotope that is injected into the bloodstream or in some cases is inhaled. The most common radioactive isotope used for ligand synthesis in PET is fluorine 18 or ^{18}F , which can be attached to a wide range of compounds metabolized in the brain. Most research into Alzheimer's and AD risk involves the compound fluorodeoxyglucose or ^{18}F FDG. This ligand is essentially a radioactive form of glucose, which travels through the bloodstream after it is injected and is taken up in the brain, where it is metabolized. Brain regions that are less metabolic, either because of neural loss or neural dysfunction, are easily visualized in PET images. In combination with structural MRI, one can identify local regions of interest and extract metabolic values, allowing for regional comparisons across groups or individuals; other approaches include voxel-based analyses in which scans are normalized into a common space and PET values are compared at each point in the brain, as is typically done in fMRI research or voxel-based morphometry in structural MRI. FDG PET studies in AD have consistently shown a characteristic pattern of hypometabolism that differentiates AD from other types of dementia, such as fronto-temporal dementia or Pick's disease (Foster et al. 2007, Jagust et al. 2007). In AD, the pattern is marked by an initial loss of metabolism in the parietal lobe and posterior cingulate cortex as well as in the temporal lobes; in time, the hypometabolism becomes widespread and involves much of the cerebral cortex, with relative sparing of primary sensory and motor regions. The PET hypometabolic profile is so robust that it exceeds a full clinical evaluation for dementia in reliability (Jagust et al. 2007).

Alzheimer's patients who have the APOE-4 allele present with a more dramatic metabolic profile in these characteristic brain regions than do AD patients without APOE-4, even when the level of cognitive impairment is comparable (Mielke et al. 1998, Mosconi et al. 2004). The spatial extent of hypometabolism is greater in APOE-4, extending into intraparietal cortex and frontal and temporal lobes (Drzezga et al. 2005). FDG PET shows similar metabolic patterns and accurately identifies preclinical MCI patients (Jagust et al. 2006).

Studies of cognitively normal older adults with a family history of AD (Reiman et al. 1996, Small et al. 1995) found that carriers of the APOE-4 allele displayed similar patterns of glucose hypometabolism as AD patients, though to a lesser extent. These metabolic changes are now thought to occur significantly before the average age of AD onset. Reiman and colleagues studied normal APOE-4 carriers in their twenties and thirties, who also showed the characteristic pattern of parietal, cingulate, and temporal hypometabolism (Reiman et al. 2005). Figure 4 presents an example of the characteristic PET patterns of metabolic changes in AD and APOE-4.

The predictive value of FDG PET has been established in several studies. In a cohort of MCI patients, 40% of whom converted to AD over 16 months, Drzezga et al. (2005) used a combination of genetic risk and FDG PET to identify those most likely to develop AD. FDG was found to be strongly predictive of conversion, and notably the PET patterns appeared to differentiate MCI patients who did convert from those who did not. A similar study by Mosconi et al. (2004) evaluated the additive power of combining FDG with genotype in predictive conversion to AD. PET alone was a power predictor—84%—for AD conversion, but genotype plus FDG predicted conversion with 100% sensitivity and 90% specificity. To date, however, no studies have examined the predictive ability of PET in conjunction with APOE-4 status in healthy elderly or younger controls. Such studies would benefit from more

sensitive measures of cognitive change rather than conversion to AD, which is more reasonable in the MCI population with its high base rate of conversion. Because FDG PET has reliably demonstrated an ability to differentiate APOE-4 and -3 carriers in youth, it is likely that studies of older but cognitively intact at-risk subjects would similarly show promise in predicting cognitive decline.

Numerous other PET ligands have been studied in AD, and among the most promising are those that directly measure amyloid accumulation in the brain. Two major compounds are currently in use: Pittsburgh Compound B (PIB) and ^{18}F FDDNP. Both measure deposition of amyloid in the brain, but they appear to have different distribution patterns: FDDNP both amyloid and tau, and in AD is distributed predominantly in the medial temporal lobe as well as neocortex (Small et al. 2006a); PIB is concentrated in the cortex, particularly the frontal lobe but also in parietal, temporal, and occipital cortex (Klunk et al. 2004). In a recent comparison of the distribution patterns of PIB and FDDNP, Shin and colleagues (2008) found strong FDDNP signal in medial temporal cortex but no PIB binding, whereas both ligands showed significant binding in neocortical regions. This finding suggests that the medial temporal signal derives primarily from tangles rather than amyloid plaques. Medial temporal lobe distribution of FDDNP has been shown to differentiate AD from other dementias, and correlates both with aging and with memory impairment (Small et al. 2006a). Interestingly, a PIB study of AD patients with the PS-1 mutations showed a pattern of results different from that in sporadic AD, with concentration predominantly in the striatum (Klunk et al. 2007).

There is less work on these compounds in nondemented and at-risk patients. In MCI patients and in healthy aging, Pike et al. (2007) reported a significant negative correlation between PIB binding and composite memory scores, which suggests that in preclinical stages, increased amyloid is associated with poorer memory, though an early study with a small N found that PIB distribution was no different in younger versus older controls (Klunk et al. 2004). Using ^{18}F FDDNP, Small and colleagues (2006a) found that MCI patients scored between AD and control subjects with memory complaints, and ^{18}F FDDNP values correlated strongly with memory and cognitive performance on a range of neuropsychological measures. With respect to genetic risk and amyloid imaging, no studies have focused on combining these techniques to predict AD risk, but several studies have reported amyloid binding differences in APOE-4 carriers (Kemppainen et al. 2007, Pike et al. 2007). For instance, Pike and colleagues (2007) found that in a population of MCI patients, only 61% had a positive PIB signal; however, of those MCI patients who had a positive PIB signal, 80% were also carriers of APOE-4, whereas only 23% with a PIB-negative scan had APOE-4.

At this point, there is little data on longitudinal progression of amyloid PET signals and thus no solid data on its predictive power. One recent study followed a small cohort of control, MCI, and AD subjects and found that the AD subjects and the MCI subjects who progressed to AD had increased FDDNP signal at an average of 14 months follow-up, whereas those showing no progression had only minimal increases in DDNP binding. This finding suggests that this agent may serve as a good surrogate marker for disease progression (Small et al. 2006a). However, no studies to date have used amyloid imaging techniques in combination with genetic risk status to predict cognitive decline or conversion to Alzheimer's. No doubt this is due to the novelty of the technique, and it is likely we shall see such studies in the future.

SUMMARY OF NEUROIMAGING TECHNIQUES FOR ASSESSING ALZHEIMER'S DISEASE RISK: ARE THEY READY FOR CLINICAL PRACTICE?

Substantial evidence indicates that brain changes in individuals at genetic risk for developing AD begin many years—perhaps decades—before the onset of the disease. As discussed above, neuroimaging techniques, including structural MRI, fMRI, and several varieties of PET imaging, all show differences at the group level between APOE-4 carriers and noncarriers in the severity of brain changes in AD, MCI, healthy elderly, and (in some cases) younger controls. Power at the group level for predicting cognitive decline has been demonstrated by several of these techniques, particularly structural MRI of the hippocampus or entorhinal cortex, rate of change measures in resting glucose metabolism, rate of brain atrophy, and magnitude of fMRI activation increases. Only a few studies have attempted to characterize the sensitivity and specificity of these techniques, the metrics that are required to have relevance for an individual. Furthermore, no studies to date have attempted to combine data across methodologies to predict cognitive decline in conjunction with genetic risk status. For these reasons, we must question the value of identifying individuals with a genetic risk for AD through genetic screening or voluntary genetic testing. Based on the research to date, knowing one's APOE-4 status provides limited information in most cases about whether one will develop Alzheimer's. As discussed above, the odds of developing AD are increased by the presence of APOE-4 but are by no means definitive, and the majority of AD cases are APOE-4 negative. From the perspective of clinical practice, none of these techniques alone or in combination have achieved the level of reliability and scientific rigor to translate into guidelines for the psychologist or physician treating individuals who may be concerned about their future mental capacity. As a result, most physicians are unwilling to recommend APOE testing, and in the research environment APOE-status is rarely revealed to subjects. However, we would argue that genetic testing in the service of intervention research is of great importance.

BEHAVIORAL AND NEUROCOGNITIVE DEFICITS IN APOE e4

In comparison with APOE e4 heterozygotes or noncarriers, cognitively intact e4 homozygous carriers have profoundly more deficits in episodic recall tasks (Nilsson et al. 2006), higher rates of cognitive domain decline before the diagnosis of MCI or AD (Caselli et al. 2004, 2007), and show age-related memory decline earlier in life (Caselli et al. 1999).

PSYCHOLOGICAL DISTRESS AND ALZHEIMER'S DISEASE EXPRESSION

We discussed above how the AD risk genes are expressed in imaging studies of brain structure and function. Ample evidence now demonstrates that psychological factors contribute to every aspect of AD risk and outcome, including early manifestations, factors leading to exacerbation of AD, and even brain pathology.

Apathy and depression are frequent concomitants of dementia. Recent data suggest that these features directly relate to amyloid expression. In plasma, increased A β 40 and decreased A β 42 is associated with increased Alzheimer's risk. Sun et al. (2008) studied plasma A β in a large cohort of homebound elderly subjects and found that those with depression had a higher A β 40:42 ratio and greater memory impairments, suggesting a prodromal or preclinical AD state. A large longitudinal study in Canada found that behavioral disturbances, including depression and changes in mood or personality, were more common in older adults with memory impairment than in those without cognitive deficits (Stepaniuk et al. 2008), and in a seven-year longitudinal study, Bidzan et al. (2008a) reported that most manifestations of behavioral and psychological disturbance related to an

increased risk of developing AD. Indeed, early-life symptoms of neuroticism, based on the Neuroticism, Extraversion, Openness Five-Factor Inventory, predicted an earlier age of onset of AD among female but not among male patients with AD (Archer et al. 2008). The psychological impact of distress on AD is also found in AD pathology. A large postmortem study in which depression was determined retrospectively, based on records, indicated that depression was associated with increased numbers of neuritic plaques and neurofibrillary tangles, an association that remained even when controlling for such factors as age, gender, and education, which also contribute to AD pathology (Rapp et al. 2008). Thus, significant psychological distress, including depression and anxiety, may reflect early manifestations of AD and may contribute to the brain deterioration found in AD risk.

Some evidence indicates that genetic polymorphisms relating to psychiatric but not dementing disorders may affect the presentation and severity of AD. The CHRNA7 gene, a nicotinic receptor gene linked to risk for schizophrenia, was also associated with more psychotic symptoms among patients with AD (Carson et al. 2008). Several serotonin 2A receptor polymorphisms have been implicated in psychosis in AD, including the HTR2A gene, which is linked with both depression and psychosis in AD. A gene affecting 5HT2A receptors T102C, the C variant, was associated with delusions and hallucinations in AD (Pritchard et al. 2008); the COMT H allele and serotonin transporter 5-HTTLPR short allele were similarly found to be associated with psychotic symptoms in AD and appeared to act synergistically (Borroni et al. 2006). The neuro-protective gene BDNF A allele carriers were more frequent in AD patients with depression (Borroni et al. 2008). Many similar reports exist in the literature, and overall it is clear that other genetic vulnerabilities can become manifest in patients with AD, generating significant psychiatric problems in patients without prior psychiatric diagnoses.

TREATMENT AND DRUG DISCOVERY: A CASE FOR RISK ASSESSMENT

Intervention studies in AD patients typically suffer from small effect sizes and modest clinical improvement (Rockwood et al. 2007); in more severe AD, the best outcome may be in delayed need for additional services such as nursing homes (Beusterien et al. 2004). By the time of diagnoses, the brain changes in AD are widespread, representing profound neural loss. Furthermore, most new targets for treatment are aimed at slowing decline rather than improving clinical status. To perpetuate the status quo for patients in a profoundly impaired state is not a reasonable goal of intervention. Recently, more studies have focused on conversion rate in patients with MCI (e.g., Karas et al. 2008), a state in which treatments may be more beneficial. Such approaches usually necessitate that the control group members get a placebo and the studies require that a significant number of patients develop AD before the efficacy of an intervention can be effectively tested. Furthermore, substantial cognitive decline and loss of function occur even in MCI, and interventions may have small effects and minimal benefits for preserving quality of life. An alternative approach is to use genetic risk data to identify individuals most likely to have or to develop brain changes that can be detected with neuroimaging, using rate of decline rather than conversion to AD as a dependent measure. This approach has several advantages. First, we believe that interventions are most effective when sufficient neural tissue survives and responds to the interventions. Second, the approach is more humane, leaving open the possibility of identifying effective interventions without waiting for the sample to develop Alzheimer's. Several recent studies are examining the efficacy of interventions in normal aging, assessing genetic risk and using neuroimaging and cognitive testing as endpoints (Carlsson et al. 2008, Schuit et al. 2001, Small et al. 2006b).

COSTS AND BENEFITS OF EARLY IDENTIFICATION

The psychological impact of predicting AD on the basis of DNA must be evaluated when discussing the utility of assessing APOE genotype. The presence of the APOE-4 allelic variant does not ensure the likelihood of disease development, unlike genetic tests for some Mendelian conditions in which the presence of a particular genotype invariably leads to the disease (e.g., Huntington's disease and PS mutation in early-onset AD). In the case of diseases such as breast cancer, colorectal cancer, and ovarian cancer, genetic risk prediction not only can help identify individuals at increased disease risk, but also can unnecessarily increase fear and anxiety. With similar logic, the absence of the high-risk allele does not ensure evasion of the disease. Most studies that examined diseases of unknown susceptibility reported negative effects on carriers, but these were short lived (Heshka et al. 2008).

Heshka and colleagues recently published a review on the impact of knowing APOE status from behavioral, psychological, and perceived-risk perspectives (Heshka et al. 2008). Of the 30 studies included, only 2 investigated AD risk (Roberts et al. 2005, Romero et al. 2005). The remaining studies examined the impact of genetic risk disclosure in hereditary breast and ovarian cancer as well as colorectal cancer. Roberts and colleagues' (2005) study reported that APOE e4 carriers were more likely than were noncarriers to engage in activities believed to lower their risk for AD after disclosure of test results (adding vitamin E to their diet, changing their diet, or increasing exercise). This study also reported no increase in depression or anxiety symptoms, with both e4 carriers and noncarriers reporting the same or lower levels of anxiety about AD following risk disclosure. Romero and colleagues (2005) also reported that subjects at higher risk for AD did not report more depression or worry following genetic disclosure, and low-risk subjects felt relieved, although the study did exclude emotionally unstable subjects.

Recent clinical tests explored the question of subjects' response to APOE disclosure by divulging to a control group the lifetime risk estimates of AD based on gender and family history; the intervention group received both lifetime risk estimate and APOE genotype (Chao et al. 2008, Roberts et al. 2005). One year after disclosure, APOE-4-positive volunteers had nearly three times the likelihood of engaging in AD-specific health behavior changes, specifically, changing their medications or vitamins (Chao et al. 2008). The most common change was the addition of a vitamin E supplement. The addition of an e4-positive test result, however, did not significantly raise subjects' perception of their risk in comparison to those with knowledge of lifetime risk alone. Those subjects who received e4-negative test results perceived their risk as being lower (Marteau et al. 2005). Receiving an e4-positive test result did not appear to significantly raise subjects' perception of AD risk, but an e4-negative result did lower subjects' perception of risk for the disease. Also, subjects with an e4-positive result were almost six times more likely to alter their long-term care insurance than were those who did not receive genotyping information (Zick et al. 2005). The groups with the highest reported interest in genetic knowledge were women, college-educated persons, and persons under age 60 (Roberts et al. 2005).

All of these studies underscore the importance of appropriate education and genetic counseling to enable participants to best evaluate how to handle knowledge of their APOE status. Participants were told there are no proven preventative measures for AD, and therapies currently under investigation were described although none of the therapies were recommended. These findings suggest that subjects experience the same or a lower level of anxiety for AD following disclosure of genetic risk information (Roberts et al. 2005). Overall, genetic risk testing does not appear to change perceived risk, has no significant impact on psychological outcome, and has little effect on behavior. Although few genetic

risk disclosure studies have been published for AD, we suggest that knowledge among carriers would not have significant negative psychological effects and therefore is worth pursuing to improve educational strategies. Without a guarantee of disease progression or aversion, what value, then, does knowledge of the APOE genotype hold? Rather than finding a “cure” for AD, most currently available therapies as well as those in development will stave off or slow progression of the disease. Without the ability to reverse neuronal damage, the earlier these therapies are initiated, the more effective they will be at slowing the disease. Recently, Holmes and colleagues (2008) reported results from a six-year phase-I clinical trial for immunization against amyloid- β_{42} as treatment for AD. As expected, the immunized group has lower cortical A β loads; the most extensive A β removal was in patients with the biggest antibody response. Surprisingly, however, statistically significant evidence was not found for improvement in cognitive function or survival. Several patients who had near-complete plaque removal at autopsy had clinically deteriorated to severe dementia. The concern, based on these results, is that anti-amyloid therapies will be ineffectual (St George-Hyslop & Morris 2008) and that secondary effects of the A β accumulation remain even in the absence of amyloid.

Currently available drugs, which are moderately effective overall but in some cases can provide substantial improvement, include the cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the glutamatergic agent memantine. These neurotransmitter-based approaches will most likely be the mainstay of treatment for AD in the foreseeable future. One other notable new drug is dimebon, which began as a nonselective antihistamine but was withdrawn as more selective agents became available (Burns & Jacoby 2008). The drug's actions seem to cover all bases, with weak cholinesterase, weak glutamatergic, and weak neuroprotective activity (Doody et al. 2008). Improvements were seen after 26 months across all domains (cognition, activities of daily living, psychiatric symptoms, and global assessment).

In addition to new pharmaceutical agents, reports suggest the potential efficacy of over-the-counter drugs, vitamin treatment, and both mental and physical exercise in preventing AD symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to be protective in animal models of AD (Casolini et al. 2002) and to decrease amyloid accumulation (Thomas et al. 2001); some early clinical trials (Rogers et al. 1993) and epidemiological studies (McGeer & McGeer 2007) have shown a reduced incidence of AD in regular NSAID users with chronic conditions including arthritis or other pain conditions. A recent large-scale clinical trial showed no benefit and possible harm of the NSAIDS naproxen or celecoxib (Martin et al. 2008). One large-scale retrospective study suggested that NSAID use had more protective benefits to APOE-4 carriers and individuals who began NSAID use before the age of 65 (Hayden et al. 2007). Other naturopathics have shown modest or mixed results, including curcumin, vitamin E, folate, and ginkgo biloba, to name a few (for a comprehensive review, see Burns et al. 2006, Zhang et al. 2006). Several studies indicate there is a protective value in aerobic exercise (Deeny et al. 2008, Kramer & Erickson 2007) and mental activity (Fratiglioni et al. 2004, Valenzuela 2008), and these effects may be enhanced in APOE-4 carriers (Deeny et al. 2008). These treatments all have the benefit of being widely available and of minimal risk.

In summary, a variety of treatment options is available, none of which is curative and all of which are expected to have differentially effective results according to individual subjects. It is likely that we will never see a curative treatment for the disease once symptoms have begun, which makes it even more critical to effectively identify early in the course of the disease those subjects in greatest need of intervention.

Despite the relative paucity of curative treatments in AD, both behavioral and pharmacological treatments can effectively address many of the behavioral and psychiatric problems that often accompany the disease. Behavioral symptoms such as aggression are among the most difficult aspects of AD care and are those most likely to result in nursing home placement (Gilley et al. 2004). Patients with higher levels of aggression appear to have a more rapid and serious progression of their illness (Bidzan et al. 2008b). Treatment with Aricept targeted at AD patients with significant behavioral and psychological problems was found to significantly reduce these symptoms in one open trial (Barak et al. 2001). In addition, a review of the existing studies of rivastigmine, an acetylcholinesterase and butyrylcholinesterase inhibitor, found significant benefits on behavioral disturbances in AD supported by randomized control trials (Grossberg 2005), as did memantine (Wilcock et al. 2008) and galantamine (Herrmann et al. 2005) in meta-analyses. Atypical antipsychotics were also effective in reducing anger, aggression, and psychotic symptoms in AD patients without affecting cognition (Sultzer et al. 2008).

Behavioral treatments for the psychological and behavioral problems associated with AD have received less attention, but evidence from small case-controlled studies and open treatment protocols suggest efficacy for many symptoms. One recent randomized controlled trial combined behavior therapy and exercise in AD patients. Findings among treated patients included significant improvements in depression for those with depressive symptoms and a lower rate of institutionalization due to behavioral problems (Teri et al. 2003). In a smaller clinical trial of individualized, personalized daily recreation therapy, patients with AD showed significant reductions in several behavioral domains, including agitation and apathy (Fitzsimmons & Buettner 2002). In a study that focused on depression in dementia patients and compared two different behavioral treatments, one designed to promote positive thoughts and another aimed at effective caregiver training, both treatments were found efficacious compared to wait-list controls in reducing depressive symptoms. More systematized cognitive-behavioral strategies have not been studied in randomized controlled trials, but a small two-case study of cognitive behavior therapy in patients with both anxiety and dementia showed significant anxiety reduction following a treatment program that was modified for applicability to AD patients and caregivers (Kraus et al. 2008). In summary, many of the psychological difficulties that often accompany AD, from anxiety to psychosis, can be effectively treated with existing therapies, from purely behavioral approaches to psychotropic medications. It is important to note, however, that some of the best remedies for behavioral disturbances in AD came from studies using medications that treat Alzheimer's, notably the cholinesterase inhibitors, though more typical psychotropic drugs are also beneficial.

CONCLUSIONS

In the discussion above, we argue that although ample and increasing evidence exists for early brain changes in genetic risk for AD, only modest evidence to date supports a predictive value of imaging techniques, and more longitudinal studies are clearly needed before early detection with imaging is practical or economical. The best-validated tools at this time for predicting future cognitive decline and AD are structural MRI measurements of the hippocampus and resting metabolism measures from FDG-PET, although promising new results from receptor-imaging and amyloid-imaging PET as well as fMRI are likely to develop as viable tools in time. Rate-of-change metrics in all modalities are clearly superior to single time points. From a practical view, these metrics are more difficult to obtain and are more expensive, and because of the cost they will likely never be used as screening tools in the population. Limiting such evaluations to those at highest risk—those with both a family history and the APOE-4 allele—will limit unnecessary exams but will not benefit the majority of individuals who do not have identifiable risk factors. Nevertheless, ongoing

research into early imaging markers of genetic predisposition to AD will ultimately improve our ability to identify those at-risk individuals most likely to develop dementias. As new treatments are developed and validated as effective, and as other genetic markers for AD are discovered, genetic testing for AD risk may be a viable option for many individuals who have witnessed the profound loss of mental capacity in their relatives and are eager to try preventative interventions.

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Figure 1.
Stained brain section showing amyloid plaques (*lower left corner*) and neurofibrillary tangles (*upper right corner*). (Figure from Bird 2008.)

Figure 2.

Magnetic resonance imaging scans of a normal older control (*left*), an older control with apolipoprotein E (APOE)-4 (*center*), and a patient with Alzheimer's disease (*right*). The scans demonstrate the marked brain atrophy of Alzheimer's disease and the similar but less severe pathology in APOE-4.

Figure 3. Functional magnetic resonance imaging (fMRI) activation in healthy older controls with and without the apolipoprotein E (APOE)-4 allele during encoding and retrieval of word pairs. APOE-4 patients show an increase in the magnitude of fMRI activation in brain regions associated with task performance. (Figure from Bookheimer et al. 2000.)

Figure 4. Fluorodeoxyglucose positron emission tomography in apolipoprotein E (APOE)-3 (left) and APOE-4 (*center*) controls, and Alzheimer's disease (AD) (right). (Figure from Small et al. 2000.)