Review

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Neuroimaging Genetic Risk for Alzheimer's Disease in Preclinical Individuals: From Candidate Genes to Polygenic Approaches

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ABSTRACT

Better characterization of the preclinical phase of Alzheimer's disease (AD) is needed to develop effective interventions. Neuropathologic changes in AD, including neuronal loss and the formation of proteinaceous deposits, can begin 20 years before the onset of clinical symptoms. As such, the emergence of cognitive impairment should not be the sole basis used to diagnose AD or to evaluate individuals for enrollment in clinical trials for preventive AD treatments. Instead, early preclinical biomarkers of disease and genetic risk should be used to determine the most likely prognosis and to enroll individuals in appropriate clinical trials. Neuroimaging-based biomarkers and genetic analysis together present a powerful system for classifying preclinical pathology in patients. Disease-modifying interventions are more likely to produce positive outcomes when administered early in the course of AD. This review examines the utility of the neuroimaging genetics field as it applies to AD and early detection during the preclinical phase. Neuroimaging studies focused on single genetic risk factors are summarized. Particular focus is on the recent increased interest in polygenic methods, and the benefits and disadvantages of these approaches are discussed. Challenges in the neuroimaging genetics field, including limitations of statistical power arising from small effect sizes and the overuse of cross-sectional designs, are also discussed. Despite the limitations, neuroimaging genetics has already begun to influence clinical trial design and is expected to play a major role in the prevention of AD.

Keywords: Alzheimer's disease, Clinical trials, Genetics, Neuroimaging, Polygenic risk score, Preclinical

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A long prodrome precedes the emergence of the clinical symptoms of Alzheimer's disease (AD) (1–3). Increasingly, the time between the first silent pathologic changes in the brain and the earliest stages of cognitive impairment is understood to be a critical window during which prevention and treatment strategies may be most effective (4). This preclinical phase of AD pathogenesis that occurs before clinical symptoms emerge is not well characterized. By definition, individuals with preclinical AD are unaware that they are affected by any neurologic pathology, and their deficits are not detectable with cognitive testing. Preclinical AD is distinct from mild cognitive impairment, which is characterized by subtle cognitive decline and sometimes can progress to a clinical diagnosis of AD (5,6). In the absence of detectable cognitive decline, investigators have access to a limited set of research tools to explore preclinical AD in humans. These tools include neuroimaging, genetic testing, and biochemical assays of the blood and cerebrospinal fluid. Neuroimaging genetics research is poised to play a critical role in improving the characterization of the earliest phases of AD pathophysiology. In this article, we discuss the important role of neuroimaging genetics in AD prevention and treatment with a particular focus on the preclinical phase of the disease. Specifically, we review findings resulting from candidate gene and polygenic approaches to neuroimaging genetics studies in AD. The goal of this review is to educate readers on the status of the field, including its many limitations, and to argue that neuroimaging genetics research using polygenic approaches will lead to better characterization of preclinical AD, which is necessary to achieve effective AD prevention.

NEUROIMAGING OF PRECLINICAL AD

A common approach for studying preclinical AD is to use a group at increased risk for AD as a potential preclinical cohort and compare them with a cohort of controls without the risk factor. Increased risk can be defined by the presence of a particular genetic risk variant, such as the apolipoprotein E ε4 (*APOEε4*) allele; a positive family history of AD; subjective memory impairment; and the presence of an early neuroimaging or cerebrospinal fluid biomarker. Well-validated neuroimaging-based biomarkers for AD in these types of cohorts include hippocampal volume loss or thinning, cortical thinning of key AD-related cortical regions, β-amyloid (Aβ) positivity measured by positron emission tomography (PET), and default mode network dysfunction measured by resting state functional magnetic resonance imaging (MRI) (7–16). There is evidence from patients with familial AD that these biomarkers

precede the emergence of clinical symptoms by at least 3–5 and up to 20 years (1). A thorough description of the literature supporting these biomarker data is outside our focus, and there are many excellent reviews available on these topics (17–21).

Clinical neuroimaging findings positive for biomarker changes, such as thinning of the hippocampus as measured with structural MRI, have been added to the updated AD diagnostic criteria (22). The acquisition of MRI-based biomarkers is minimally invasive, making these methods preferable to lumbar punctures. Both MRI and PET can and have been used in longitudinal studies and provide a quantitative measure of change over time that is not influenced by cognitive performance, which can be affected by sleep patterns, illness, stress, and other confounding factors. However, characteristics of imaging biomarkers are not yet sufficient for a preclinical AD diagnosis on the individual level; this is due to several factors, including the lack of extensive longitudinal data to map biomarker changes over time in an individual and the limitations in resolution and measurement of modern imaging techniques. Combining known biomarker trajectories with genetic risk stratification may increase prediction power, especially in clinical trial settings, giving greater relative importance to possible disease-related changes in individuals at the highest genetic risk for AD.

NEUROIMAGING AND AD CANDIDATE GENES

In 2000, the first study to combine neuroimaging and genetic risk for AD in healthy subjects found that carriers of the *APOEε4* allele had higher activation across several cortical regions during a memory task compared with noncarriers (Figure 1A) (23). This approach, examining a selected variant within a single gene and the association of that variant with brain structure and function, is a type of candidate gene study. Candidate gene studies in neuroimaging are common, but they are controversial because of difficulties in interpretation and replication of results (24). The now common practice of restricting candidates to genes for which a disease association has already been demonstrated has helped to make findings more robust. Still, a gene with a relatively large effect on disease incidence in a genome-wide association study (GWAS) is not necessarily related to neuroimaging phenotypes to the same degree. *APOE* is the most commonly studied candidate gene for AD. Because of the large proportion of the variance in AD heritability that is accounted for by *APOE*, investigators have been successful in identifying differences in many neuroimaging modalities based on *APOE* genotype (Figure 1) (17–19,21); for an updated review including recent findings, see Supplement 1.

In addition to *APOE*, other GWAS-identified AD risk genes have been studied using a candidate gene approach, including *CLU*, *PICALM*, *CR1*, *BIN1*, *ABCA7*, and *EPHA1*. Of these genes, the one that has received the most attention in the neuroimaging literature is *CLU*. First linked to AD by May *et al.* (25) in 1990, the coincident discovery of *CLU* in two independent GWAS in 2009 renewed interest in *CLU* and its role in AD (26,27). The association of rs11136000 to AD has been replicated several times (28–30).

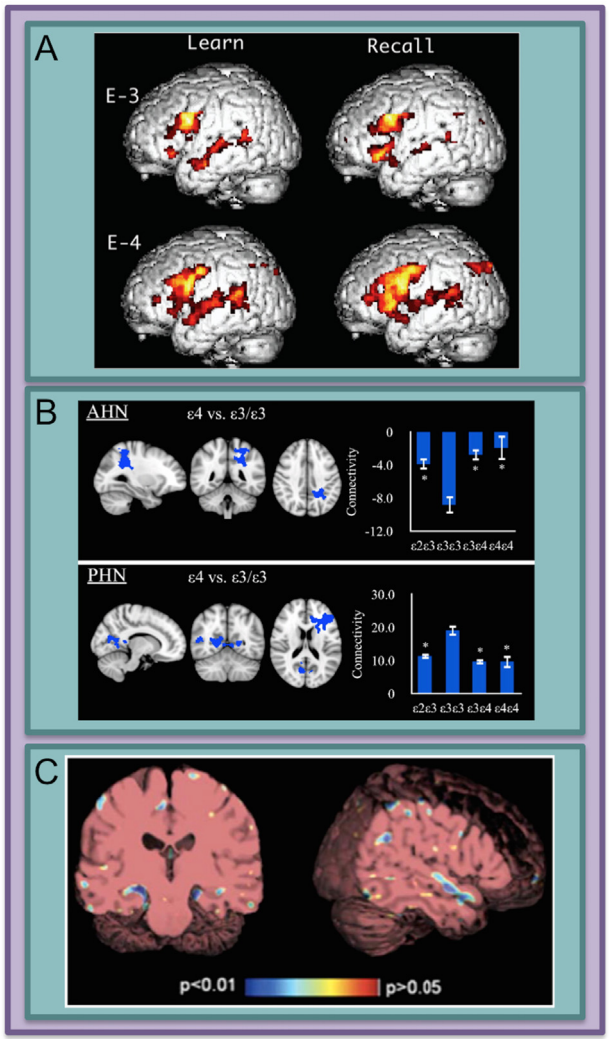

Figure 1. Differences between carriers and noncarriers of the *APOEε4* allele have been identified using structural and functional neuroimaging. The association between *APOEε4* and Alzheimer's disease risk has a moderate effect size, and this may increase the likelihood of observing differences in neuroimaging phenotypes, which are relatively gross measures of neural structure and function. **(A)** Carriers of the *APOEε4* risk allele show potentially compensatory cortical activity in language areas during the learning and recall phases of a word-based paired-associates task. **(B)** The anterior hippocampal network (AHN) and posterior hippocampal network (PHN) connectivity is modulated by *APOEε4* genotype. Bar graphs represent the network as a region of interest and denote average connectivity in each genotype group. **(C)** Structural magnetic resonance imaging shows that healthy older carriers of *APOEε4* have a greater atrophy rate over time in the hippocampus and superior temporal gyrus compared with noncarriers. [Reproduced with permission from Bookheimer *et al.* (23) (panel A), Trachtenberg *et al.* (78) (panel B), and Lu *et al.* (7) (panel C).]

Several functional imaging studies have reported an effect of a *CLU* genotype in task-based and resting functional MRI paradigms. One functional MRI experiment that tested for additive effects of *CLU* and *APOE* on blood oxygen level–dependent (BOLD) signal during an executive attention task found a negative correlation between genetic risk and the BOLD signal associated with executive attention in the medial