Radiology

Disruption of White Matter Connectivity Precedes Development of Dementia in Alzheimer Disease

Linda K. McEvoy, PhD

Linda K. McEvoy, PhD, is a professor at the Herbert Wertheim School of Public Health and Human Longevity Science and in the Department of Radiology, School of Medicine, at the University of California San Diego. Her research focuses on improved understanding of cognitive changes in healthy and pathologic aging; clinical, behavioral, and genetic risk factors for cognitive decline and dementia; and prognostic markers for early detection of Alzheimer disease.

Pathologic evidence of Alzheimer disease (AD) begins to accumulate decades prior to the onset of dementia. The ability to image changes in the brain during this clinically silent disease period is important for understanding the brain changes that lead to cognitive dysfunction and for developing prognostic markers for dementia. There are two main forms of AD: sporadic, or late-onset AD, and familial, or autosomal dominant AD. Sporadic AD, which accounts for more than 95% of cases, arises from complex genetic and environmental influences. In sporadic AD, dementia rarely occurs prior to age 60 years, and it becomes increasingly more prevalent with advancing age. In autosomal dominant AD, individuals who inherit an AD-related mutation in the presenilin 1, presenilin 2, or amyloid precursor protein genes will develop dementia at approximately the same age as their affected parent, typically in their 50s. Thus, autosomal dominant AD has also been referred to as early-onset AD. Because the preclinical period of AD can be precisely defined in individuals with one of these mutations, autosomal dominant AD allows for studies of brain changes in the preclinical period leading to dementia. An additional advantage of the autosomal dominant AD model for studying brain changes related to AD is that the preclinical phase occurs when individuals are relatively young, allowing for the identification of disease-related changes in the absence of changes related to aging.

In this issue of *Radiology*, Prescott and colleagues (1) analyzed T1-weighted and diffusion-weighted MRI data along with PET amyloid imaging data from cognitively healthy participants of the Dominantly Inherited Alzheimer Network (DIAN), an international study of individuals from families with autosomal dominant AD (2). Prescott et al (1) examined imaging measures among 30 asymptomatic AD mutation carriers and 38 noncarriers from the same families and who had an average age below 40 years. Mutation carriers and noncarriers showed no difference in memory performance or in performance on the Mini-Mental State Examination.

The authors examined structural connectivity in three distributed cortical networks: the default mode network, frontoparietal control network, and ventral attention network. They calculated a global efficiency metric for each network based on the average fractional anisotropy of fibers connecting cortical regions within these networks, as determined with diffusion tensor imaging. They also measured cortical amyloid burden, one of the key hallmark pathologic indicators of AD, with use of the global summary standardized uptake value ratio (SUVr) from PET using radiotracer Pittsburgh compound B, or PiB.

As expected, mutation carriers showed elevated amyloid pathology relative to noncarriers. They also showed reduced global efficiency (reflecting reduced fractional anisotropy) in the frontoparietal control network after adjustment for age, sex, education, apolipoprotein E4 allele status, white matter volume, Mini-Mental State Examination score, and years to expected dementia onset. Among mutation carriers, the global efficiency value of the frontoparietal network systematically varied according to estimated years to symptom onset, being lower among those closer to the age of expected dementia onset. Although this reduced network efficiency occurred in the context of elevated amyloid pathology, the efficiency of this network was not correlated with the extent of amyloid abnormalities present in the brain. This suggests that some mechanism beyond amyloid is responsible for changes in white matter that precede cognitive decline.

It is unclear why network efficiency was affected only in the frontoparietal control network and not in the default mode network. Although spatial distribution of amyloid abnormalities was not evaluated by Prescott and colleagues, cortical areas within both of these networks have shown accumulation of amyloid abnormalities in the preclinical phase of the disease in prior studies (3). Indeed, an earlier report from the DIAN cohort showed amyloid abnormalities in asymptomatic mutation carriers in these areas, with greater accumulation at an earlier age in cortical areas comprising the default mode network (4). This further supports the likelihood that some mechanisms other than amyloid pathology underlie the white matter changes observed by Prescott and colleagues.

From the Herbert Wertheim School of Public Health and Human Longevity Science, Department of Radiology, School of Medicine, University of California San Diego, 9500 Gilman Dr, MC 0841, La Jolla, CA 92093. Received August 16, 2021; revision requested August 20; revision received August 23; accepted August 26. **Address correspondence to** the author (e-mail: *lkmcevoy@ucsd.edu*).

Conflicts of interest are listed at the end of this article.

See also the article by Prescott et al in this issue.

The study lacked measures of other AD-related pathologic indicators, which could inform on the potential mechanisms underlying white matter changes observed therein. For example, tau pathology, the other key pathologic hallmark of AD, could contribute to reductions in white matter fractional anisotropy. However, a prior report from the DIAN cohort indicates that tau pathology is not elevated in the asymptomatic disease phase (5). Another possible mechanism that may underlie white matter microstructural damage is reactive astrocyte activity, which can be assessed with blood-based measures of glial fibrillary acidic protein (GFAP) (6). The level of GFAP, a cytoskeletal component of activated astrocytes, increases in response to injury, including accumulation of amyloid and tau abnormalities (7). Serum GFAP levels are elevated in the preclinical phase of AD and add to the prognostic value of amyloid pathology for predicting dementia (8). It would be of interest to know whether elevated serum GFAP is associated with reduced network efficiency in the DIAN cohort and whether efficiency values correlate with GFAP levels.

Other acknowledged limitations of this study include its cross-sectional design and small sample size. Longitudinal studies are needed to confirm that frontoparietal network efficiency is reduced over time in individuals in the period leading to the development of cognitive impairment. The results also need to be replicated in cohort studies of sporadic AD to confirm that changes detected in autosomal dominant AD are reflective of the disease course in the far more common sporadic form of the disease.

Although this is a small, exploratory study, the results contribute to the growing literature on changes in brain white matter microstructure that occur during the long, clinically silent phase of AD. The lack of correlation between global amyloid levels and global efficiency in the frontoparietal control network among mutation carriers leaves unanswered questions about the mechanisms responsible for white matter microstructural damage. Future research on this cohort examining prognostic markers of other pathologic features of AD may prove informative. With further study, network efficiency metrics based on diffusion imaging measures may themselves prove useful as markers of brain changes in the preclinical phase of AD. Prognostic markers of early brain changes could be helpful in determining the efficacy of measures designed to prevent neurodegeneration, which would enable the preservation of cognitive function in individuals at risk for AD.

Disclosures of Conflicts of Interest: L.K.M. disclosed grant received by institution from the National Institutes of Health.

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