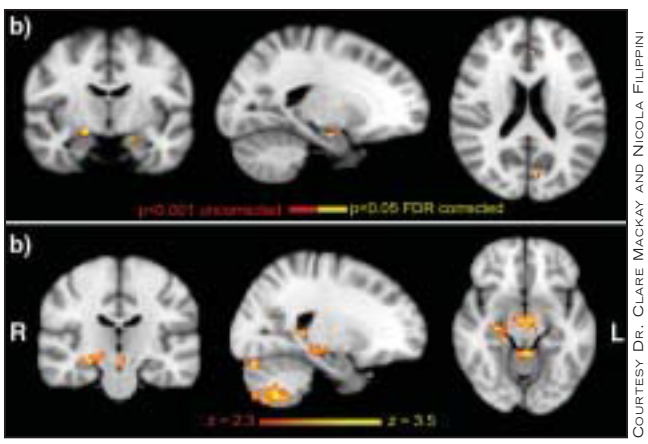
## NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

# APOE e4 Allele Activity Seen in Young Adult Brains

Young adult carriers of the apolipoprotein E e4 allele show differences in activation of brain regions that are known to display the first pathologic changes in Alzheimer's disease even before degenerative processes or cognitive impairments can be demonstrated, according to a functional MRI study.

Nicola Filippini of the University of Oxford (United Kingdom) and her colleagues found that a group of 18 healthy APOE e4 carriers aged 20-35 years had greater brain activation in regions that are temporally coactivated during quiet rest than did 18 matched control participants.




COURTESY DR. CLARE MACKAY AND NICOLA FILIPPINI

**APOE e4 carriers show greater activation than noncarriers in a resting state in the retrosplenial, medial-prefrontal, and mesial temporal lobe regions (top row) and during a memory task in the right hippocampus and cerebellum (bottom row). Yellow indicates the greatest activity.**

The carriers also had greater activation in regions that are involved in memory-related tasks, such as the hippocampus (Proc. Natl. Acad. Sci. U.S.A. 2009 April 8 [doi:10.1073/pnas.0811879106]).

Previous data have shown that resting glucose metabolism in young and middle-aged carriers is increased in brain regions known to be affected by Alzheimer's disease (AD) and that brain activation on memory tasks is greater in middle-aged and elderly APOE e4 carriers, compared with noncarriers.

However, the researchers noted that these studies "do not make clear at what age these influences initially manifest" and have not established the extent to which differences in structure, resting metabolism, and function interact.

Measurement of blood oxygen levels in networks of brain regions that coactivate when a person is at rest showed that carriers had significantly greater activity than did noncarriers in brain regions that are a part of a default mode network (DMN) that is affected by neurodegenerative processes. Within the DMN, the areas that showed greater activation in carriers included regions in the mesial temporal lobe (head of the hippocampus and amygdala) and in the medial-prefrontal and retrosplenial cortices.

"The difference between our results and the previous observations … may relate to hippocampal atrophy, normal aging, or factors related to disease progression … However, the increases in coactivation we observe suggest the function of those areas subject to the disease process in AD are modulated by the presence of the APOE e4 allele even in young adults."

During a blood oxygen level–dependent (BOLD) fMRI task that involved remembering novel versus familiar pictures, the authors found that carriers showed 20%-40% greater right hippocampal activation than did noncarriers. Carriers also had greater activation than noncarriers in certain regions (dentate nucleus, anterior midbrain, and lateral and cortical portions of the cerebellum) when they compared novel and familiar images. "We suggest that the genotypic contribution to the hippocampal activation manifests decades before potential neurodegenerative or age-related processes," the investigators wrote.

In both the resting state and during memory tasks, there were no brain regions where carriers had decreased coactivation or activation, compared with noncarriers. The investigators also could not find differences between the groups in total brain volume or in gray matter, white matter, cerebrospinal fluid, or hippocampal volume. The relationships the investigators found did not change appreciably when they included maps of gray matter and resting brain perfusion as covariates in their analysis of the memory tasks.

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"It is possible that [our] results reflect neuronal mechanisms to compensate for processes, such as reduced synaptic plasticity, neuronal growth, or altered long-term potentiation in people carrying the e4 allele," the authors concluded, noting that "longitudinal studies are required to determine whether increased coactivation within the DMN at rest, increased task-related BOLD signal, or both together are associated with a higher risk of developing later pathological changes."

***Dr. Caselli's comment:*** When does Alzheimer's disease begin? What is a sign of vulnerability and what is a sign of disease? These remain open questions of considerable interest, especially as interventional strategies become more seriously considered at younger ages and at earlier stages of disease because of the growing number of older-age and late-stage interventions that have been proven inefficacious.

Neuropathologic studies have occasionally found young APOE e4 carriers harbor some AD-like pathology (Exp. Neurol. 1998;153:152-5; Am. J. Pathol. 2000;157:2093-9), and afluorodeoxyglucose–positron emission tomography study showed reduced cerebral glucose metabolism in regions that topographically overlapped Alzheimer's disease–affected regions in young adults (Proc. Natl. Acad. Sci. U.S.A. 2004;101: 284-9). Dr. David A. Snowdon and his colleagues reported psycholinguistic differences in 20-year-old women that correlated with AD and neuropathologic disease burden 60 years later (Ann. Intern. Med. 2003;139:450-4). Dr. Lawrence J. Whalley and his associates found that school age performances on psychometric tests were predictive of dementia in old age (Neurology 2000;55: 1455-9), though later this was explained by increased vascular dementia rather than AD (Neurology 2008;71:1051-6). But my colleagues and I found no correlation between APOE genotype and intellectual achievement as measured by educational and occupational outcomes (J. Am. Geriatr. Soc. 2002;50:49-54).

Collectively these studies seem to suggest that individuals at genetic risk or otherwise "marked" for future dementia have some manifestation in early life of either minor or no functional consequence, but it remains unclear whether this is actual disease or developmental vulnerability. The work of Dr. George Bartzokis has shown that myelination of the human brain continues well into the adult years and is affected by APOE genotype, perhaps providing one possible example of vulnerability manifesting in at-risk individuals (Neurobiol. Aging 2004;25:5-18).

Might the exaggerated hippocampal activation found in the study conducted by Ms. Filippini and her colleagues be another example of a developmental susceptibility factor for medial temporal vulnerability to neurodegeneration and AD? Certainly this is possible. For now, we must content ourselves with the idea that AD is the part of the iceberg that surfaces in later adulthood, and that what is submerged beneath the surface may be a larger base that has developmental origins. Primary prevention will need to start before neurodegeneration supersedes development. When that time point passes remains unknown, but there is a good chance it is earlier than we think. ■

*Clinical perspective by* DR. CASELLI, *chair of neurology at the Mayo Clinic, Scottsdale, Ariz., and professor of neurology at the Mayo Medical School, Rochester, Minn.*

*Research report by Jeff Evans, clinical news editor.*

# Late-Life Statin Use Doesn't Block Alzheimer's or Dementia

BY HEIDI SPLETE

Statins have no impact on the development of dementia or Alzheimer's disease, according to a Cochrane Review of two randomized, controlled trials involving more than 26,000 adults.

Previous studies in animal models have shown that lowering cholesterol slows pathologic signs of Alzheimer's disease (AD), and data from clinical studies in older adults who took statins for vascular disease have suggested that statin users had a reduced risk of developing AD. But the clinical studies in humans were not randomized trials, said Dr. Bernadette McGuinness of Queen's University Belfast, Northern Ireland.

In this review, Dr. McGuinness and her colleagues examined data from two large, randomized controlled trials that included 26,340 adults aged 40-82 years (Cochrane Database Syst. Rev. 2009 April 15; doi: 10.1002/14651858.cd007514).

The Medical Research Council/British Heart Foundation Heart Protection Study (HPS) conducted in 2002 was a randomized, placebo-controlled trial of the effect of a daily dose of 40 mg simvastatin vs. placebo on the development of vascular disease in 20,536 high-risk adults, including 5,806 adults aged 70 years and older.

Cognitive decline was assessed via a questionnaire completed in person at the clinic or by phone. No significant differences appeared between the treatment and placebo groups in the overall percentages of patients who met criteria for cognitive impairment at the start of the study (23.7% vs. 24.2%). And 31 individuals in each group developed dementia during a 5-year follow-up period (Lancet 2002;360:7-22).

In another 2002 study, the Prospective Study of Pravastatin in the Elderly at Risk (known as the PROSPER trial), 5,804 adults aged 70-82 years were randomized to receive a daily dose of 40 mg pravastatin or a placebo. All the study participants had risk factors for vascular disease or a history of vascular disease. The cognitive function of the participants was assessed using neuropsychologic tests and the Mini-Mental State Examination. During a 3-year follow-up period, pravastatin had no significant impact on cognitive function (Lancet 2002;360:1623-30).

"The two trials identified were large scale and included patients at high risk of vascular disease," noted the researchers, who had no relevant conflicts of interest to disclose. "The fact that they had similar findings was reassuring." ■