In addition, prior imaging studies did not demonstrate a right hemispheric abnormality as the basis for a cerebral pathology and the present pattern of hyperintense signal in the diffusion-weighted MRI sequences throughout the entire right hemisphere would not be seen in a patient with ischemic lesions. This is because the signal does not respect typical vascular distributions and also because the magnetic resonance angiography (not shown) did not reveal any signs of intracranial or extracranial stenosis or occlusions.

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*Disclosure:* Dr. DeGeorgia served on the Orsan Medical Inc. advisory board. Dr. Grommes reports no disclosures.



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## FACTORS ASSOCIATED WITH RESISTANCE TO DEMENTIA DESPITE HIGH ALZHEIMER DISEASE PATHOLOGY

**To the Editor:** Dr. Erten-Lyons et al.[1] report an important observation that raises new questions regarding the accuracy of Alzheimer disease (AD) diagnosis in 80+ elderly. Other studies have shown that brains of the elderly contain mixed pathology in the presence or absence of dementia.[2] It should be considered whether the label "AD" should continue to be assigned to elderly patients who experience cognitive decline.

Most people in their 80s and 90s have varying degrees of plaques and tangles, just as they may have varying degrees of cerebrovascular damage, Lewy body disease, or white matter changes.[2] The combination of these factors, and not any single factor, determines the degree of their mental frailty.[2] Thus, is it accurate to assume, or even imply, that they have developed a single "disease" that accounts for their cognitive decline? In clinical trials, some patients with "AD" may have large loads of plaques and tangles, whereas control subjects may have just as many plaques and tangles. Could an unjustified focus on "AD" partly account for the failure of all disease-modifying drugs for dementia?

Diagnostic criteria for late-onset AD should be updated. An alternative framework for thinking about cognitive decline is necessary—one that is broader and views plaques and tangles only as players among a team of culprits, and not necessarily as the captains. Plaques and tangles may have some role in cognitive deterioration in 80+ elderly, but it accompanies at least a dozen other interrelated genetic and environmental factors (e.g., chronic hypertension, diabetes, obesity, obstructive sleep apnea, and head trauma, as well as exposure to chronic stress or toxins such as lead and mercury). Therefore, we must stop overdiagnosing this population with AD. Perhaps a better and more respectful label would be mild, intermediate, and severe cognitive impairment (MCI, ICI, and SCI) "with mixed etiology."

A strong link between factors that determine the amount of brain substrate and mental agility strengthens the new field of research toward finding ways to improve cognitive fitness. For example, MRI studies in adult humans have shown that 6 months of exercise or 3 months of rigorous cognitive stimulation increases brain volume.[3,4] Do effects of these interventions last for years? Omega-3 fatty acids lower risk of cognitive decline with aging.[5] Do they affect brain volume? Answers to these questions can help baby boomers who are worried about "AD" make better decisions regarding methods to improve their brain health and longevity.

Isn't it time for us to shift viewing the world of cognition through an AD lens and toward examining factors that impact size of cortex and hippocampus?

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**Reply from the Authors:** We appreciate the comments by Dr. Fotuhi and colleagues who point out that while diverse neuropathology leads to dementia in older persons,[2] diverse amounts of the same kinds of neuropathology may be present in cognitively healthy older persons.[1] Thus, the effects of various neuropathologic changes, alone or in combination, on the clinical phenotype commonly referred to as "AD" is not entirely clear.

We agree with Dr. Fotuhi et al. that better understanding of factors that mediate which neuropathologic changes result in particular clinical syndromes will ultimately lead to interventions promoting healthy brain aging. In this quest, it will be important to identify genetic and environmental roles be-

cause, as we suggest, individuals may harbor similar amounts of pathology but without the same effects on the brain.

This phenomenon must be rooted in different life experiences or exposures as well as genetic endowments that modulate the relationship between pathology and clinical symptoms.

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## CORRECTION

**Normal and mutant *HTT* interact to affect clinical severity and progression in Huntington disease**

In the article "Normal and mutant *HTT* interact to affect clinical severity and progression in Huntington disease" by N.A. Aziz et al. (*Neurology*® 2009;73:1280–1285), the complete list of members of the EHDN Registry Study Group was omitted from the printed article. The listing is available as a data supplement to the article (on the *Neurology*® Web site at www.neurology.org). The authors regret the error.

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