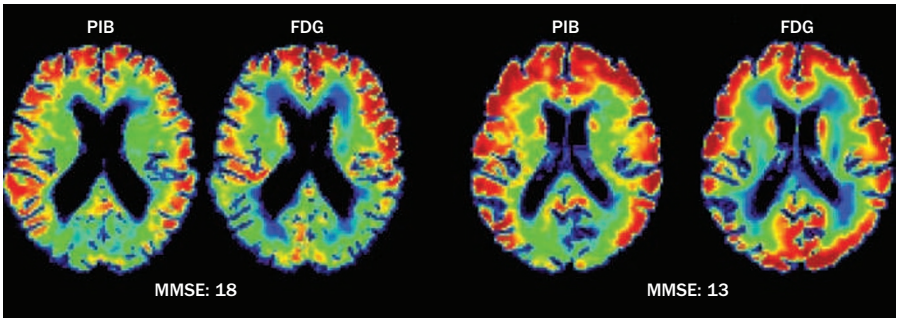
ALZHEIMER DISEASE

Amyloid-β plaques and glucose metabolism in early-onset AD

Severe cortical hypometabolism in young patients with Alzheimer disease (AD) is not explained by an increased amyloid-β (Aβ) plaque burden, according to a study by Gil Rabinovici and colleagues from the University of California, San Francisco. "Most people believed that the aggressive phenotype of early-onset AD was related to a higher burden of pathology. Our study suggests that patients who present with the disease at a young age not only produce plaques early in life, but also may show a selective vulnerability to the pathology present," explains Rabinovici.

Patients who present with AD at an early age (<65 years) often have a more-aggressive clinical presentation and shorter survival than patients who present with AD at a later age. Studies have also shown that individuals with early-onset AD have a different pattern of cognitive deficits and more-severe cortical atrophy, hypoperfusion and hypometabolism compared with patients with late-onset AD.

Rabinovici and colleagues enrolled 39 patients (aged 43–82 years) with AD into a PET study that used the radiolabeled tracers Pittsburgh compound B (PIB) and fluorodeoxyglucose (FDG) to measure Aβ plaques and glucose metabolism, respectively, in the brain. The researchers allocated patients to two groups—'early-onset' (age 55 ± 5.9 years) or 'late-onset' (age 72 ± 4.7 years)—and compared cognitive test performance, Aβ plaque burden and distribution, and glucose metabolism between the two groups. A group of 30 cognitively normal volunteers acted as controls.



Amyloid-β plaques (PIB), glucose metabolism (FDG) and cognitive impairment (Mini-Mental State Examination [MMSE] score) in patients with early-onset (left) or late-onset (right) Alzheimer disease. Image provided by Dr Gil Rabinovici.

The researchers found that all patients with AD had more fibrillar Aβ plaques in the frontal, parietal and lateral temporal cortices than did the control group. As the image above shows, however, Rabinovici's team observed no difference in plaque burden and distribution between early-onset and late-onset patients. By contrast, early-onset patients had significantly lower glucose metabolism in the precuneus, lateral temporoparietal and occipital cortices than late-onset patients, as seen in the accompanying image. The researchers suggest that young patients are thus more metabolically vulnerable to the effects of Aβ pathology.

"This is the first study to directly compare amyloid-β plaques *in vivo* in young versus older AD patients. The burden of amyloid was similar regardless of whether patients were young or old," explains Rabinovici, who is interested in studying the link between soluble Aβ species, which are the most neurotoxic, and age of onset of AD. He also plans to investigate why young patients with AD are more likely to present with atypical and highly focal neurodegenerative syndromes.

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Original article Rabinovici, G. D. *et al.* Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. *Brain* doi:10.1093/brain/awp326