

- 1 Lockhart, S. N., Roach, A. E., Luck, S. J., Geng, J., Beckett, L., Carmichael, O. et al. (2014). White matter hyperintensities are associated with visual search behavior independent of generalized slowing in aging. *Neuropsychologia*, 52, 93-101.  
Notes: A fundamental controversy is whether cognitive decline with advancing age can be entirely explained by decreased processing speed, or whether specific neural changes can elicit cognitive decline, independent of slowing. These hypotheses are anchored by studies of healthy older individuals where age is presumed the sole influence. Unfortunately, advancing age is also associated with asymptomatic brain white matter injury. We hypothesized that differences in white matter injury extent, manifest by MRI white matter hyperintensities (WMH), mediate differences in visual attentional control in healthy aging, beyond processing speed differences. We tested young and cognitively healthy older adults on search tasks indexing speed and attentional control. Increasing age was associated with generally slowed performance. WMH were also associated with slowed search times independent of processing speed differences. Consistent with evidence attributing reduced network connectivity to WMH, these results conclusively demonstrate that clinically silent white matter injury contributes to slower search performance indicative of compromised cognitive control, independent of generalized slowing of processing speed
- 2 Chao, L. L., DeCarli, C., Kriger, S., Truran, D., Zhang, Y., Laxamana, J. et al. (2013). Associations between white matter hyperintensities and beta amyloid on integrity of projection, association, and limbic fiber tracts measured with diffusion tensor MRI. *PLoS ONE*, 8, e65175.  
Notes: The goal of this study was to assess the relationship between Abeta deposition and white matter pathology (i.e., white matter hyperintensities, WMH) on microstructural integrity of the white matter. Fifty-seven participants (mean age: 78+/-7 years) from an ongoing multi-site research program who spanned the spectrum of normal to mild cognitive impairment (Clinical dementia rating 0-0.5) and low to high risk factors for arteriosclerosis and WMH pathology (defined as WMH volume >0.5% total intracranial volume) were assessed with positron emission tomography (PET) with Pittsburgh compound B (PiB) and magnetic resonance and diffusion tensor imaging (DTI). Multivariate analysis of covariance were used to investigate the relationship between Abeta deposition and WMH pathology on fractional anisotropy (FA) from 9 tracts of interest (i.e., corona radiata, internal capsule, cingulum, parahippocampal white matter, corpus callosum, superior longitudinal, superior and inferior front-occipital fasciculi, and fornix). WMH pathology was associated with reduced FA in projection (i.e., internal capsule and corona radiata) and association (i.e., superior longitudinal, superior and inferior fronto-occipital fasciculi) fiber tracts. Abeta deposition (i.e., PiB positivity) was associated with reduced FA in the fornix and splenium of the corpus callosum. There were interactions between PiB and WMH pathology in the internal capsule and parahippocampal white matter, where Abeta deposition reduced FA more among subjects with WMH pathology than those without. However, accounting for apoE epsilon4 genotype rendered these interactions insignificant. Although this finding suggests that apoE4 may increase amyloid deposition, both in the parenchyma (resulting in PiB positivity) and in blood vessels (resulting in amyloid angiopathy and WMH pathology), and that these two factors together may be associated with compromised white matter microstructural integrity in multiple brain regions, additional studies with a longitudinal design will be necessary to resolve this issue
- 3 DeCarli, C., Mungas, D., Harvey, D., Reed, B., Weiner, M., Chui, H. et al. (2004). Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. *Neurology*, 63, 220-227.  
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BACKGROUND: Mild cognitive impairment (MCI) is widely viewed as the transition phase between normal aging and Alzheimer disease (AD). Given that MCI can also result from cerebrovascular disease (CVD), the authors used clinical, MRI, and cognitive measures of AD and CVD to test the hypothesis that CVD increases the likelihood of progression from MCI to

dementia within 3 years. OBJECTIVE: To examine the impact of CVD on progression of MCI to dementia. METHODS: Fifty-two consecutive patients with MCI (71% men) including many with symptomatic CVD were longitudinally evaluated for 3.1 +/- 1.3 years. MCI was defined as a Clinical Dementia Rating Scale (CDR) score of 0.5. Dementia was defined as progression to a CDR score of > or =1.0. RESULTS: Forty-four percent of the MCI patients had MRI infarcts, 50% of which were symptomatic. Thirty-three percent of patients progressed to dementia, and 37.8% of these had MRI infarcts. Clinically probable or possible AD was diagnosed in approximately 82% of converters. Of the clinical and MRI measures, only hippocampal volume was associated with increased risk to progression (hazard ratio [HR] = 0.31 [95% CI 0.1 to 0.92], p = 0.03). When neuropsychological measures were included in the analysis, memory (HR = 0.90 [95% CI 0.84 to 0.96], p = 0.002) and executive function (HR = 0.96 [95% CI 0.92 to 1.0], p = 0.045) were associated with increased risk of dementia progression, whereas APOE genotype, cerebrovascular risk factors, clinical stroke, presence or absence of lacunes, and extent of white matter hyperintensities did not predict progression. CONCLUSION: Within a heterogeneous group of MCI patients, including many with clinically significant CVD, baseline memory and executive performance significantly predicted likelihood to develop dementia

- 4 DeCarli, C. (2003). The role of cerebrovascular disease in dementia. *Neurologist*, 9, 123-136. Notes: Department of Neurology, University of California at Davis, Sacramento, USA. cdecarli@ucdavis.edu

BACKGROUND: Improvements in health care over the last 50 years have lengthened average life expectancy significantly, resulting in considerable growth of the population over 65 years of age. With increased age, however, comes an increased risk for Alzheimer's disease (AD), and the prevalence of AD is predicted to reach epidemic proportions by the later half of the 21st century. The prevalence of cerebrovascular disease also increases with age, and recent evidence suggests that cerebrovascular risk factors such as hypertension and hypercholesterolemia also increase an individual's risk for AD, suggesting a potential interaction between these two very common disorders. The potential impact of cerebrovascular disease on general cognitive health is not yet well understood, but is now being actively explored and clarified. REVIEW SUMMARY: Cerebrovascular disease may manifest itself in many ways, and this review begins by discussing the possible spectrum of brain injury associated with common cerebrovascular risk factors. The prominent role of brain imaging to detect clinically silent cerebrovascular disease is recognized and reviewed. The neuropsychological consequences of cerebrovascular disease across the cognitive spectrum is also reviewed, including potential mechanisms by which cerebrovascular disease may interact with AD to increase the expression or hasten the progression of dementia. CONCLUSIONS: Cerebrovascular risk factors, common to the elderly, lead to pernicious brain injury and subtle cognitive impairment that most probably places the individual at greater lifetime risk for dementia. The cause of dementia among individuals with cerebrovascular disease, however, remains AD. Recognition of the potential role of cerebrovascular disease as an independent risk factor for AD offers the possibility of primary prevention through treatment of well-recognized risk factors and deserves further study. In the meantime, clinicians presented with an individual suffering from a slowly progressive dementia and findings of clinically silent cerebrovascular brain injury should recognize the potential role of cerebrovascular disease in the dementia process but not ignore the likely overwhelming effects of AD and treat appropriately