VIEWPOINT

Vascular Plasticity and Cognition During Normal Aging and Dementia

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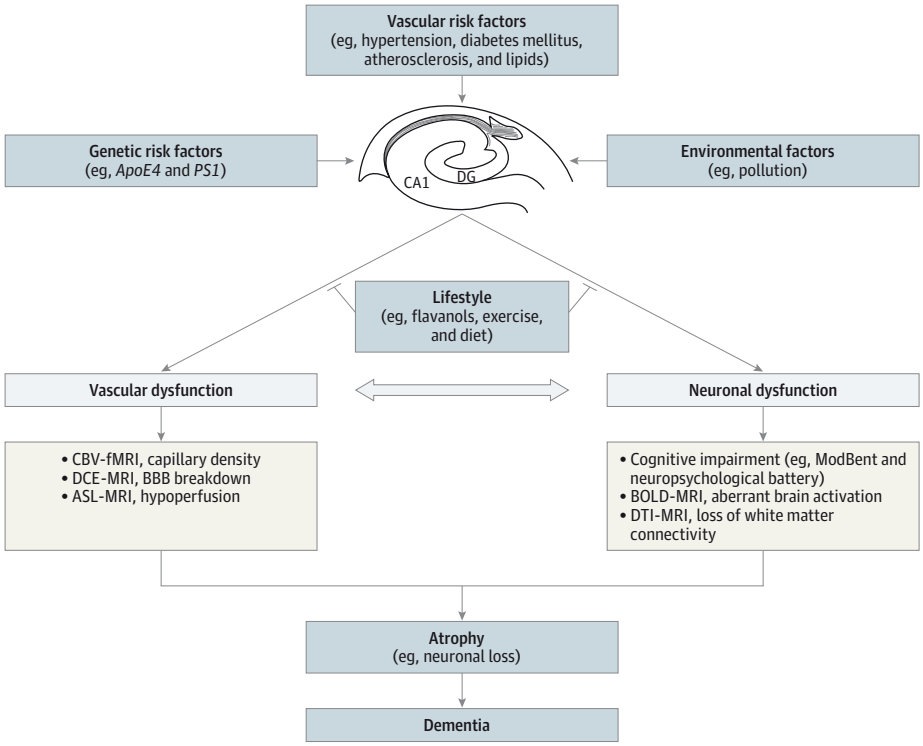
Functional neurovascular changes reflecting alterations in brain function and cognition and/or originating primarily from abnormalities localized to the cerebrovascular system have been described in many neurological disorders and during normal brain aging. However, the relationship between vascular and neuronal dysfunction, and how they relate to each other and contribute to cognitive impairment and dementia due to Alzheimer disease (AD), vascular cognitive impairment and dementia (VCID), and/or other neurological disorders, still remains controversial.[1,2] An obvious place to look for neurovascular and cognitive changes is in the hippocampus, a region involved with learning and memory that is particularly susceptible to changes in oxygen and blood supply and is damaged early in AD.

Using a variety of magnetic resonance imaging (MRI) techniques,[3,4] including cerebral blood volume (CBV)–functional MRI (fMRI) with gadolinium contrast,[5] it was found that hypometabolism coupled with diminished CBV in the hippocampus is associated with cognitive impairment in elderly individuals and early stages of AD. Using an advanced protocol and postprocessing analysis of the CBV-fMRI maps in the hippocampus, a study interrogated whether functional changes in the dentate gyrus drive hippocampus-specific cognitive dysfunction in cognitively normal older adults who were enrolled in a randomized trial with cocoa flavanols, an ingredient in cocoa, red wine, berries, and dark chocolate.[6] Interestingly, this study showed that high flavanol dietary intake increases the CBV in the dentate gyrus and enhances performance on a modified version of the Benton Visual Retention Test that is dependent on pattern separation in the hippocampus, specifically localized to the dentate gyrus.[6]

Figure. Modern Neuroimaging Techniques and Insights Into the Vascular and Neural Plasticity of the Hippocampus in Aging and Disease



Imaging vascular and neuronal functions in the living human brain in the hippocampus during normal aging, mild cognitive impairment, dementia due to Alzheimer disease (AD) and related disorders, and vascular cognitive impairment and dementia. Lifestyle can modify the effects of genetic, vascular, and environmental risk factors, which can impact vascular health and neuronal function. *ApoE4* indicates apolipoprotein E4 allele; ASL, arterial spin labeling; BBB, blood-brain barrier; BOLD, blood oxygen level–dependent; CA1, cornu ammonis 1; CBV, cerebral blood volume; DCE, dynamic contrast enhanced; DG, dentate gyrus; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; ModBent, modified Benton Visual Retention Test; MRI, magnetic resonance imaging; and *PS1*, presenilin 1.

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These findings raise a possibility that during normal aging, the human hippocampus retains significant vasculoplastic reserve that is likely mediated via enhanced angiogenesis and/or new blood vessel formation. However, the question persists whether changes in basal blood flow, blood-brain barrier permeability, and/or brain activation that all can be studied by imaging neurovascular function in the living human brain with different techniques, such as arterial spin labeling–MRI, dynamic contrast-enhanced–MRI,[7] and/or blood oxygen level–dependent fMRI, respectively, can also play a role in the observed adaptive cognition responses during normal aging (**Figure**). Additionally, major genetic risk factors, such as apolipoprotein E4 allele for late-onset AD or presenilin 1 gene mutations for familial AD, as well as environmental factors and vascular risk factors, might also affect formation of these adaptive responses. These questions warrant future investigations. Some other interesting and timely questions are when and whether cortical or subcortical brain regions or white matter connections become involved to cause cognitive impairment and/or accelerate progressive cognitive decline and hippocampal atrophy associated with dementia, which all can be studied in the living human brain by diffusion tensor imaging–MRI (Figure).

As CBV-fMRI is a neurovascular-dependent outcome measure of hippocampal function in the absence of brain activation, it is worth noting that increasingly recognized alterations in the neurovascular functions in many neurological disorders associated with cognitive impairment[1,2] might potentially influence presently used fMRI measurements. It would be interesting to know, for example, how the CBV-fMRI findings relate to changes in blood-brain barrier integrity that have been reported in AD and VCID[1,2] and during normal aging in the hippocampus that worsen with mild cognitive impairment, as suggested by another study.[7] Use of the dynamic contrast-enhanced–MRI approach to determine regional blood-brain barrier integrity[7] and the effects of lifestyle modifiers—such as flavanols, exercise, and/or the role of vascular risk factors and their treatment during cognitively normal aging and aging associated with mild cognitive impairment, AD, and/or VCID—may help us better understand the emerging role of the cerebral vascular system in maintaining overall cognitive health.

Future studies using multiple imaging biomarkers to access neurovascular function in relation to cognition and brain function (Figure) and combining imaging biomarkers with analysis of molecular cerebrospinal fluid biomarkers of the cell-specific injury within the neurovascular unit are needed. These would help to establish whether vascular dysfunction can precede neuronal dysfunction and cognitive impairment during normal aging, dementia due to AD and related disorders, or VCID and ultimately how these changes are influenced by lifestyle, genetics, and environment.

ARTICLE INFORMATION

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