

Does HIV age your brain?

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Since the introduction of highly active antiretroviral therapy in 1996, the epidemiologic profile of HIV-associated neurocognitive disorder (HAND) has shifted drastically. Although HIV-associated dementia has nearly disappeared from clinical practice, presymptomatic and milder variants of HAND affect up to 50% of patients on chronic antiretroviral therapy.^{1,2} Furthermore, the predominant phenotype has evolved from a subcortical dementia to a mixed cortical-subcortical cognitive syndrome affecting attention, executive, and memory systems, as well as slowing processing speed.² Yet, subtler forms of HAND often remain undetected. One Swedish HIV study found that only 27% of their patient cohort complained of cognitive dysfunction, but 67% actually demonstrated objective deficits on cognitive testing.³

Of interest, the clinical impairments observed with HAND are similar to those observed with aging and vascular disease. Furthermore, aging itself is an independent risk factor for HIV-associated dementia.² The possibility of overlapping pathophysiology has been raised, with a suggestion of a similar CSF biochemical profile. Patients infected with HIV (HIV+) carry increased levels of phosphorylated tau protein and other age-related markers, comparable to marker levels in healthy subjects who are 15 to 20 years older.⁴ An aging HIV+ cohort, the majority living with subclinical or mild impairment for years, raises new challenges for clinicians and researchers alike.

In this issue of *Neurology*®, Thomas et al.⁵ compare resting-state functional connectivity MRI (rs-fcMRI) changes in patients who are HIV+ with those of older normal subjects. In rs-fcMRI, patients are asked to lie quietly in the MRI scanner while spontaneous fluctuations in blood oxygen level dependent (BOLD) activity are recorded. The strength of correlated BOLD activity between distant brain regions is analyzed, and is a measure of functional connectivity. rs-fcMRI measures activity between sets of brain regions defining specific resting-state networks, and can also measure relationships between networks.⁶ The investigators found decreased correlations within and between several

networks in patients with HIV compared with controls. In a separate analysis, the investigators assessed the independent effect of aging on resting-state networks. They discovered that networks affected in patients who are HIV+ resemble those affected in normal aging (default mode and salience networks). The authors further proposed that an aging HIV population may experience an accelerated cognitive decline.⁵

The study has several strengths, including large subject cohorts, inclusion of “control” networks that do not change with HIV or aging, well-established rs-fcMRI processing techniques, and a quality-control algorithm to exclude participants based on poor data or excessive movement. The investigators controlled for the substantial confounders of highly active antiretroviral therapy and substance use. Perhaps the greatest strength of the article is that the authors move beyond simply reporting rs-fcMRI abnormalities in HIV as has been done for so many other diseases.⁶ By comparing changes seen in HIV with normal aging, the investigators test the hypothesis that group changes seen on fcMRI would overlap.

However, there are several methodologic limitations to consider when interpreting the presented results. First, although subjects with extreme movement were excluded in the analysis, the amount of movement was not directly compared between groups. Movement can greatly affect rs-fcMRI, particularly the strength of long-range correlations.⁷ If HIV+ or older patients move more than their counterparts, network strength may be artifactually decreased. Second, global signal regression, a preprocessing technique that removes spontaneous BOLD fluctuations common to the whole brain, has been useful to clean up rs-fcMRI data, but is affected by caffeine consumption, drowsiness, and respiratory patterns. When comparing 2 groups after global signal regression, it is helpful to ensure that similar variance is being removed from each group.⁸ Next, the authors acknowledge that sex and education differ between the HIV+ and HIV− groups. The latter may be a potential confounder given the known relationship between educational level and cognitive reserve.^{9,10} Moreover, the

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authors failed to find a relationship between fcMRI measures and neuropsychiatric tests or viral load, thereby challenging the hypothesis that altered fcMRI is directly related to the cognitive deficits, rather than an epiphenomenon. Finally, the strength of association found between alterations in HIV and normal aging rs-fMRI is modest at best. Of a total of 15 intra- or internetwork comparisons, 2 showed significant changes that were similar in both HIV and normal aging (default mode and salience networks), 3 showed significant changes in one group but not the other, and the remainder were nonsignificant.

Despite these limitations, the article proposes an intriguing network-level explanation for some of the similar cognitive features seen between HIV+ persons and normal aging: decreased executive ability, attention, memory, and processing speed.¹¹ Their overarching hypothesis, that comparable profiles of cognitive dysfunction may be associated with similar disturbances in resting-state networks, can be tested across other neurodegenerative entities.

Given the high prevalence of preclinical and clinical impairment, there is a need for sensitive imaging methods to characterize cognitive deficits and to advance our pathophysiologic understanding of HAND. fcMRI is an attractive tool because it can reveal group differences within and between networks. For practical purposes, fcMRI is independent of task performance and requires less patient cooperation. However, although the fcMRI data are easily obtained, the technique is limited by difficult processing and postprocessing requirements and its sensitivity to a number of physiologic artifacts (e.g., movement, breathing, and caffeine intake). Altogether, these analytic considerations make the separation of signal from noise extremely challenging.

Nevertheless, research interest in describing the neural basis of these resting-state networks and their modification in disease has proliferated. Indeed, descriptions of rs-fcMRI abnormalities in almost all neurologic disease states have been published.⁶ Our understanding of what these changes mean, let alone their potential for use in clinical diagnostics, remains in its infancy.

AUTHOR CONTRIBUTIONS

Anli Liu and Daniel Z. Press: drafting/revising the manuscript.

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