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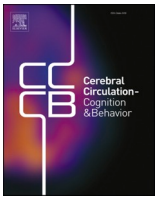

Functional and structural brain connectivity: Are they reproducible in cerebral small vessel disease?

Cerebral small vessel disease (SVD) is important due to its association with numerous outcomes relevant to function and quality of life as we age, including mood, mobility, stroke, dementia, and death [1,2]. SVD is very common among older adults: white matter hyperintensities (WMH), an MRI manifestation of SVD, are seen in 65-96% of participants in study populations with mean ages 60-74 years [3]. WMH volume progression rates range from 4-37%/year in older adults [4]. However, WMH are not present only in older adults—they are detected across a wide age range from young adulthood upward [4].

Given that SVD is typically detected by neuroimaging and often occurs in the absence of symptoms, this indicates a long latent period in the pathophysiology of the disease. This provides a wide potential time window for interventions designed to prevent progression to clinically overt symptoms. Disappointingly, few treatments have been demonstrated to be effective for this purpose in randomized controlled trials, with the exception of intensive blood pressure control among those with hypertension which has been shown to reduce WMH progression and reduce risk of Mild Cognitive Impairment (MCI) and a composite outcome of MCI or dementia [5,6]. Thus, there is a need for additional treatments for SVD. Furthermore, there is a need to better understand both the pathophysiology of SVD and who is at high risk of SVD to prioritize them for interventions. Meeting each of these needs requires longitudinal studies with repeated measures and thus valid, reproducible biomarkers to measure changes in cerebrovascular health over time and with treatment.

In this issue of Cerebral Circulation - Cognition and Behavior, Tozer and colleagues report on testing the reproducibility of network-specific structural and functional connectivity in participants with SVD as compared with age-matched controls [7]. Brain connectivity is expected to decline with declining cognition and with greater neuropathology. Although there have been studies on reproducibility of functional [8,9] and structural brain connectivity [10] measures, the reproducibility studies on participants with SVD are limited. This study gives important insights into the reproducibility of network-specific brain connectivity in older adults with SVD.

The authors found that across multiple brain networks, structural connectivity demonstrated good reproducibility for both SVD patients and controls. Regarding functional connectivity, reproducibility was good across multiple networks for controls, but not among the SVD patients. Overall, structural connectivity measures appeared more reproducible than functional connectivity measures, and the reproducibility of the functional connectivity did not appear to depend on average connectivity nor on the reproducibility of the structural connectivity.

Deriving reliable and reproducible brain connectivity-based biomarkers has been difficult. One reason is that with brain connectivity studies there is no standard method of data acquisition or analysis [11,12]. There are several methods for calculating both the functional connectivity (ROI [13] or seed-based [14] methods and data-driven methods [15]) and for calculating structural connectivity based on diffusion imaging (streamline tractography and probabilistic tractography [12]). Tozer, et al. collected multi-echo resting-state fMRI data and processed and analyzed the data using SPM and the CONN toolbox [13] for calculating functional connectivity, and they collected single b-value diffusion data and used streamline tractography for calculating structural connectivity [16]. Thus, one thing to keep in mind is that the reproducibility results they report are valid only for a data set acquired and processed with similar methods. Given this limitation, the results discussed here will be useful in developing biomarkers for functional and structural brain connectivity.

A key contribution of this work is its provision of preliminary evidence of reproducibility of network-specific connectivity rather than global metrics of brain connectivity. For example, the authors found that the control limbic, salience, somatomotor, and visual networks all had structural connectivity with intraclass correlation coefficients (ICCs) $\geq$0.82, indicating good to excellent reproducibility, and the control default mode network (DMN) and frontoparietal network (FPN) had structural connectivity ICCs around 0.65, indicating moderate reproducibility. They also found that DMN had the greatest reproducibility for functional connectivity in both SVD and control participants. It should be kept in mind that differences in reproducibility by network were not tested statistically. Thus, this work provides good candidate network-specific reproducibility differences to test in future, larger studies. This is important, because while global functional connectivity reproducibility is poor in SVD participants [16], if functional connectivity reproducibility is better in a specific network, it may be a more attractive candidate biomarker.

The findings that the SVD patients may have greater variability in their network-specific functional connectivity than the controls allow for the intriguing possibility that this variability could prove to be a biomarker of the disease. The authors did not statistically test differences in functional connectivity between SVD patients and controls, and it should be noted that the 95% confidence intervals for the ICCs in these two groups overlapped. Thus, whether Tozer and colleagues' results represent true differences between SVD patients and controls needs to be evaluated in future studies with larger sample sizes well-powered to detect such an effect. Nevertheless, recent biology of aging research has pointed to increasing variability in biomarkers as complex body systems

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deteriorate with aging and preceding critical transitions which often presage collapse [17]. Longitudinal study designs would be required to demonstrate increasing network functional connectivity variability in SVD patients over time.

Another key limitation of this study is that in this small study sample (N=25), women were underrepresented, and racial and ethnic diversity was limited. These limitations to generalizability should be addressed in future studies especially given that women, as compared to age-matched men, and some ethnoracial groups are likelier than others to have WMH and experience WMH progression [4].

While there are ongoing efforts to develop biomarkers for SVD and for vascular contributions to cognitive impairment and dementia (VCID) more broadly including the MarkVCID [18,19] and HARNESS [20] consortia, this paper makes a meaningful contribution to the literature by adding to the evidence regarding structural connectivity in SVD and providing preliminary evidence regarding functional connectivity as a potential biomarker in SVD. Studies that are larger, longitudinal, and include more diverse and representative samples will be needed to definitively test the utility of network connectivity as an SVD biomarker.

Declaration of Competing Interest

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