Vascular reserve in brain resilience: pipes or perfusion?

This scientific commentary refers to ‘Hippocampal vascular reserve associated with cognitive performance and hippocampal volume’, by Perosa et al. (doi: 10.1093/brain/awz383).

Cognitive performance decreases with ageing across every domain (O’Shea et al., 2016). Identification of the neural substrates underlying these changes has been one of the main achievements of brain MRI. For example, declining episodic memory performance with ageing has been attributed to hippocampal atrophy, whereas slowing of executive performance has consistently been related to progression of cerebral small vessel disease (CSVD) (Ter Telgte et al., 2018). However, MRI sometimes reveals striking differences in the severity of atrophy or burden of CSVD among individuals with similar cognitive performance, or even remarkably preserved cognitive performance despite the presence of a considerable degree of atrophy and/or CSVD. Recent studies have therefore shifted gears by focusing not only on the accumulation of damage over the lifespan, but also on brain resilience, which is the capacity of the brain to accommodate a certain degree of damage before clinical symptoms become apparent. This approach could lead to therapeutic interventions targeting mechanisms that support resilience, in place of often unsuccessful attempts to restore lost brain functions or structures. Brain resilience is a combination of the brain’s capacity to counteract the lifetime accumulation of damage and the compensatory mechanisms it can be used to mitigate the effects of this damage (Ter Telgte et al., 2018). Resilience may entail differences in brain structure (e.g. hippocampal or intracranial volume) or function (e.g. degree of functional connectivity). It can also reflect cognitive reserve, whereby experiences such as education protect against the effects of pathology by enabling use of different cognitive strategies or recruitment of alternative brain networks. In this issue of Brain, Perosa and co-workers propose that vascular reserve may be yet another marker of brain resilience (Perosa et al., 2019).

Peroe et al. hypothesized that a mixed vascular supply of the hippocampus—i.e. by both the posterior cerebral artery (PCA) and the anterior choroidal artery (AChA)—could help maintain better hippocampal structure and function than a single arterial supply (PCA only). To investigate this possibility, they classified in vivo hippocampal vascularization with high-resolution 7 T time-of-flight angiography in older adults (mean age 71 years; 44% female) with or without CSVD. Hippocampal volume was measured by high-resolution voxel-based morphometry (VBM) on 7 T structural MRI. CSVD was characterized using a 3 T MRI scan, prior to 7 T MRI, according to well-established criteria (Wardlaw et al., 2013). Neuropsychological tests, including those that evaluate cognitive domains related to hippocampal function, were administered to all patients. Perosa et al. found a mixed vascular supply of the hippocampus in 32 subjects and a single supply in 11. They demonstrated that participants with a mixed vascular supply (in at least one hemisphere) performed better than those with a single supply in several medial temporal lobe-related cognitive domains, including verbal memory, but also in other cognitive domains, like attention, language, and global cognition. Moreover, in patients with CSVD, the presence of a mixed vascular supply was associated with better verbal memory performance than a single supply. A mixed supply was also associated with greater anterior hippocampal grey matter volume on average across all subjects.

Peroe et al. used the term ‘vascular reserve’ to reflect their observation of a larger hippocampal volume in the presence of a mixed vascular supply. A smaller hippocampus is also one of the radiological hallmarks of Alzheimer’s disease and is related to amyloid pathology. With the intriguing observation of smaller hippocampi in patients with a single arterial supply, the question arises as to whether this

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type of supply makes the hippocampus more vulnerable to (progression of) amyloid pathology and attendant atrophy. Future research should investigate the complex interaction between amyloid pathology, CSVD and hippocampal atrophy.

There are some methodological issues that should be considered for a better understanding of the data. First, the study by Perosa et al. was cross-sectional, meaning that reverse causality may play a role, especially when it comes to hippocampal volume. A smaller hippocampus might simply need a smaller blood supply and therefore only one artery may be required, a possibility discussed by Perosa et al. themselves.

Second, previous studies have indicated a clear relation between the severity of CSVD and the extent of hippocampal atrophy, both in healthy elderly and in patients with Alzheimer’s disease (Fiford et al., 2017). It could thus be that those participants with a smaller hippocampus had a higher burden of CSVD. In subgroup analyses of participants with or without CSVD, Perosa et al. found no relation between type of vascular supply and hippocampal volume. However, a type II error cannot be ruled out, as the groups were small \((n = 20 \text{ and } n = 27)\).

Third, there is always the possibility of misclassification of mixed versus single supply if some of the uncal artery branches are below the detection threshold, even with high-resolution time-of-flight angiography \((0.28 \text{ mm isotropic voxel size})\), or if they are obscured by motion artefacts. This would result in underestimation of the number of patients with mixed supplied hippocampi. To quantify the degree of misclassification, post-mortem analysis of hippocampal vascularization patterns would be a useful gold standard. Furthermore, there are multiple ways of classifying variation in vascular supply. In another recent paper by the same research group, Spallazzi et al. classified hippocampal vascular supply according to PCA patterns (Spallazzi et al., 2019). In that study, they found that when the temporal cortical branches of the PCA emerge from a common trunk, the hippocampal head is usually supplied mainly by the AChA. Moreover, they also demonstrated that the AChA is frequently smaller and less branched towards the hippocampus, if the hippocampal artery arises directly from the PCA. Unfortunately, Spallazzi et al. did not investigate the impact of these PCA patterns and hippocampal vascularization patterns on hippocampal volume and cognition. In common with a mixed supply of the hippocampus via the PCA and AChA, different PCA patterns might also lead to altered hippocampal perfusion, correlating with changes in hippocampal volume and cognition.

Finally, misclassification of grey matter belonging to the hippocampus (as opposed to a neighbouring structure) could potentially also explain the lack of difference in grey matter volume in participants with or without CSVD. Perosa et al. used a T1-weighted sequence with 3D magnetization-prepared rapid gradient echo (3D-MPRAGE) with an isotropic voxel size \(1 \times 1 \times 1 \text{ mm}^3\), which cannot allow for a proper delineation of, for example, adjacent

Figure 1 Visualization of the absence (A) or presence (B) of hippocampal ‘vascular reserve’ with concomitant CSVD. Perosa et al. show that a mixed supplied hippocampus (via posterior cerebral artery and anterior choroidal artery) is an advantage relative to a single supply in terms of greater hippocampal volume and better neuropsychological performance, against a background of well-known MRI markers of CSVD including microbleeds, lacunes, white matter hyperintensities, and microinfarcts. ACA = anterior cerebral artery; AChA = anterior choroidal artery; EPVS = enlarged perivascular spaces; HA = hippocampal artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; WMH = white matter hyperintensities.
participants with or without CSVD. An increased hippocampal perfusion was found to be accompanied by poorer spatial memory, whereas cerebral perfusion can potentially be increased, for example through regular physical exercise (Haeger et al., 2019).

Taken together, Perosa and colleagues’ innovative work points towards an important role for vascular reserve as an integral part of brain resilience. Prospective studies are required to examine the impact of vascular reserve on brain resilience further, especially with respect to the mechanisms underlying age-related hippocampal functional and structural changes. These insights can then be used to tailor therapeutic interventions in patients with CSVD and its accompanying sequelae.

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Competing interests

The authors report no competing interests.

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