Cortese A, Simone R, Sullivan R, Vandrovcova J, Tariq H, Yau WY, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet 2019; 51: 649–58.
Cortese A, Tozza S, Yau WY, Rossi S, Beecroft S, Jaunmuktane Z, et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RCF1 repeat expansion. Brain 2020; 143: 480–90.
Larsen PA, Hunnicutt KE, Larsen RJ, Yoder AD, Saunders AM. Warning SINEs: alu elements, evolution of the human brain, and the spectrum of neurological disease. Chromosome Res 2018; 26: 93–111.
Leigh RJ, Zee DS. The neurology of eye movements. 5th edn. Oxford; New York: Oxford University Press; 2015.
Migliaccio AA, Halmagyi GM, McGarvie LA, Cremer PD. Cerebellar ataxia with bilateral vestibulopathy: description of a syndrome and its characteristic clinical sign. Brain 2004; 127: 280–93.
Rafehi H, Szmulewicz DJ, Bennett MF, Sobreira NLM, Pope K, Smith KR, et al. Bioinformatics-based identification of expanded repeats: a non-reference intronic pentamer expansion in RFC1 causes CANVAS. Am J Hum Genet 2019; 105: 151–65.
Szmulewicz DJ, McLean CA, Rodriguez ML, Chancellor AM, Mossman S, Lamont D, et al. Dorsal root ganglionopathy is responsible for the sensory impairment in CANVAS. Neurology 2014; 82: 1410–5.

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).

Perosa *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.

Perosa *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

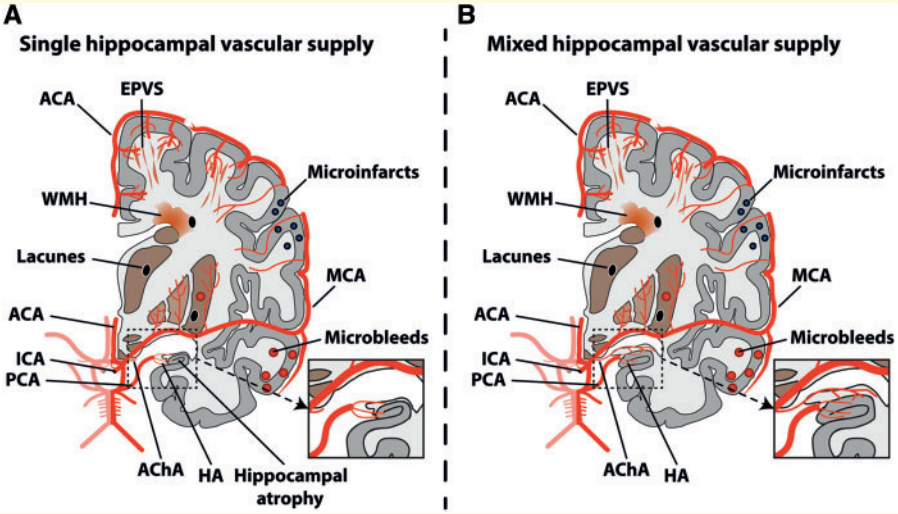

Figure 1 Visualization of the absence (A) or presence (B) of hippocampal 'vascular reserve' with concomitant CSVD. Perosa *et al.* show that a mixed supplied hippocampus (via posterior cerebral artery and anterior choroidal artery) is an advantage relative to a single supply in terms of greater hippocampal 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.

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 ($n = 20$ 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 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 T_1-weighted sequence with 3D magnetization-prepared rapid gradient echo (3D-MPRAGE) with an isotropic voxel size $1 \times 1 \times 1\,mm^3$, which cannot allow for a proper delineation of, for example, adjacent

grey matter structures such as the amygdala. An ultrahigh isotropic resolution of 250 μm could have overcome these methodological issues in 7 T MRI (Lüsebrink *et al.*, 2017), while also improving white and grey matter classification inside the hippocampus. To avoid potential segmentation errors, Perosa *et al.* inspected each segmented image visually to exclude artefacts and misclassification; they also used a sample homogeneity check to identify outliers. However, Perosa *et al.* performed VBM group analysis in only a subset of their participants (single supplied hippocampus: 11 subjects, five with and six without CSVD; mixed supplied hippocampi, 12 subjects, five with and seven without CSVD), possibly explaining the lack of significant difference in grey matter volume in participants with or without CSVD.

The findings by Perosa *et al.* are compatible with the view that cerebral vascularization is critical to the brain's performance and that, as well as providing the brain with a vascular reserve, the anatomy of cerebral vascularization may also create areas with a 'vascular vulnerability' to CSVD. For example, (confluent) periventricular white matter hyperintensities often develop in the large white matter regions located in the border zone of a mixed vascular supply, 'watershed areas', from the deep perforating and superficial cortical arteries.

Notably, variation in vascular supply does not necessarily translate into higher cerebral/hippocampal perfusion, at least this was not demonstrated in the current study. This may be important as ageing-related reduction in hippocampal cerebral blood flow was found to be accompanied by poorer spatial memory, whereas increased hippocampal perfusion was positively related to memory performance (Heo *et al.*, 2010). It would be interesting to test the hypothesis that lower hippocampal perfusion is related to cognitive impairment, and Perosa *et al.* would seem ideally placed to do so as they have the expertise and suitable techniques such as 7 T MRI. Another unanswered question is whether, as Perosa *et al.* suggest, such a two-pipe (mixed vascular supply) system leads to increased perfusion of the hippocampus, thereby increasing the vascular reserve and helping protect against hippocampal ischaemia leading to hippocampal atrophy and cognitive impairment. If confirmed, this could provide a stepping stone for future therapeutic opportunities, as 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.

References

Fiford CM, Manning EN, Bartlett JW, Cash DM, Malone IB, Ridgway GR, et al. White matter hyperintensities are associated with disproportionate progressive hippocampal atrophy. Hippocampus 2017; 27: 249–62.

Haeger A, Costa AS, Schulz JB, Reetz K. Cerebral changes improved by physical activity during cognitive decline: a systematic review on MRI studies. NeuroImage Clin 2019; 23: 101933.

Heo S, Prakash RS, Voss MW, Erickson KI, Ouyang C, Sutton BP, et al. Resting hippocampal blood flow, spatial memory and aging. Brain Res 2010; 1315: 119–27.

Lüsebrink F, Sciarra A, Mattern H, Yakupov R, Speck O. T1-weighted in vivo human whole brain MRI dataset with an ultrahigh isotropic resolution of 250 mum. Sci Data 2017; 4: 170032.

O'Shea A, Cohen RA, Porges EC, Nissim NR, Woods AJ. Cognitive aging and the hippocampus in older adults. Front Aging Neurosci 2016; 8: 298.

Perosa V, Priester A, Ziegler G, Cardenas-Blanco A, Dobisch L, Spallazzi M, et al. Hippocampal vascular reserve associated with cognitive performance and hippocampal volume. Brain 2020; 143: 622–34.

Spallazzi M, Dobisch L, Becke A, Berron D, Stucht D, Oeltze-Jafra S, et al. Hippocampal vascularization patterns: a high-resolution 7 Tesla time-of-flight magnetic resonance angiography study. NeuroImage Clin 2019; 21: 101609.

Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. Nat Rev Neurol 2018; 14: 387–98.

Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013; 12: 822–38.