each other with a relative line-of-sight velocity of 358 km s^{-1} – similar to the value proposed in the bullet-dwarf scenario. From the relative positions and line-of-sight velocities of DF2 and DF4, along with the estimated age of DF2, the authors traced DF2 and DF4 back in time and argued that the two might have originated from the same collision event, approximately eight billion years ago.

Using advanced image-analysis techniques on a catalogue of galaxies around the large galaxy NGC 1052 that was compiled last year[8], the authors found that multiple substructures near NGC 1052 (including DF2 and DF4) form a long trail, a feature suggestive of the collision-induced formation scenario. The authors point out that the trail is perpendicular to the structure associated with NGC 1052, which excludes the possibility that the trail is simply matter flowing in towards NGC 1052. Most of the substructures in the trail fall into the category of ultra-diffuse galaxies, such as DF2 and DF4.

Van Dokkum and colleagues' discovery invites intriguing discussions and follow-up observations. The proposed formation event for a trail of ultra-diffuse galaxies devoid of dark matter is based on relatively few observations. Stricter constraints will be needed to fully validate the formation picture of DF2 and DF4 – and of the other diffuse objects in the trail. For example, the 3D velocities, 3D positions, dark-matter fractions and stellar ages of these diffuse objects should match the predictions made by the simulations of colliding galaxies.

If verified, the bullet-dwarf scenario has the potential to provide a new constraint on estimates of how often dark matter interacts with ordinary matter and with itself. Such a constraint requires measurement of the dynamic properties of the diffuse objects in the trail, and, more importantly, of those of the two dwarf galaxies that triggered the collision. The scenario predicts that the remnants of these dwarf galaxies are dominated by dark matter and deprived of ordinary matter. Observing these remnants could verify this picture, but will be challenging, because they are expected to be gas-poor and very faint. Nevertheless, once acquired, such observations will provide crucial insight into the nature of dark matter – one of the most intriguing topics in modern physics and cosmology.

Eun-jin Shin and **Ji-hoon Kim** are in the Center for Theoretical Physics, Department of Physics and Astronomy, Seoul National University, Seoul 08826, South Korea.
e-mails: shinej816@snu.ac.kr; mornkr@snu.ac.kr

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Ageing

Young cerebrospinal fluid is a tonic for memory

Miriam Zawadzki & Maria K. Lehtinen

Infusion of cerebrospinal fluid from young mice into old mice restores memory recall in the aged animals by triggering production of the fatty myelin sheath that insulates neurons in the brain. **See p.509**

Age-related cognitive decline affects up to one-quarter of adults over the age of sixty[1]. A healthy diet and regular exercise can help to prevent this decline, but as yet there are no treatments to reverse it[2]. Progress in understanding how the brain changes during development and ageing has sparked tantalizing ideas for harnessing youthful factors to slow age-associated cognitive changes – or even to rejuvenate the ageing brain. On page 509, Iram *et al.*[3] bolster this line of thinking by tapping into the cerebrospinal fluid (CSF), which bathes the brain tissue and contains several protein growth factors necessary for normal brain development.

The authors infused CSF from young adult mice (10 weeks old) into the brains of aged mice (18 months old) over 7 days. This treatment improved the memory recall of the old animals in a fear-conditioning task, in which they learnt to associate a small electric shock with a tone and flashing light. Iram and colleagues then used RNA sequencing to determine how CSF treatment altered gene expression in the hippocampus – a key memory centre in the brain that is often the focus of studies of age-associated cognitive decline.

Cells in the central nervous system called oligodendrocytes produce myelin, a fat- and protein-rich material that insulates neuronal fibres called axons. Myelination of axonal projections throughout the brain ensures that strong signal

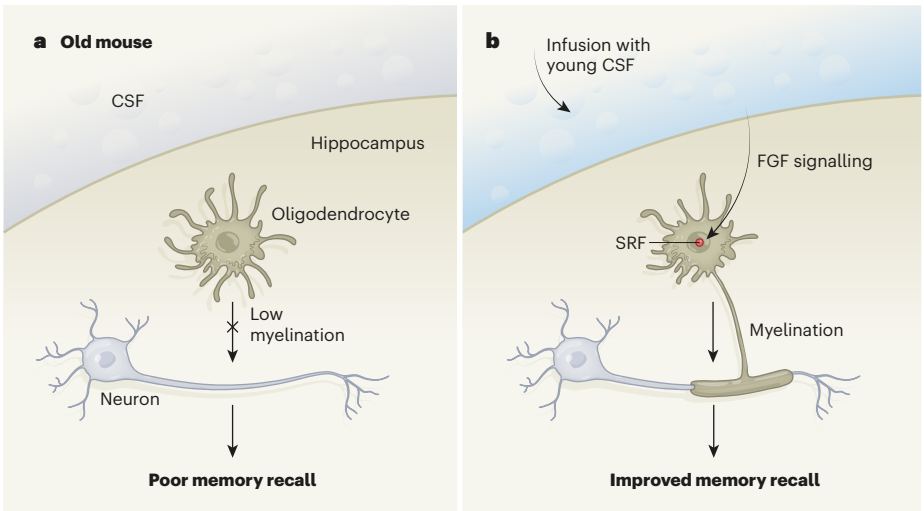

Figure 1 | Infusion of cerebrospinal fluid improves memory in old mice. The mouse hippocampus is located adjacent to the brain ventricles that contain cerebrospinal fluid (CSF). Hippocampal neurons can be insulated by a fatty sheath of myelin, which aids connectivity; long-term recall of negative stimuli in mice requires the generation of new myelin by cells called oligodendrocytes. **a**, In old mice, myelination by oligodendrocytes is impaired, and this is correlated with poor memory recall. **b**, Iram *et al.*[3] infused old mice with CSF from young mice; CSF is enriched in many health-promoting growth factors, probably including FGF17 (not shown). The authors show that CSF infusion triggers FGF signalling pathways. This activates a transcription factor called SRF, which promotes signalling pathways that lead to the proliferation and maturation of oligodendrocytes. These cells then produce myelin to support neuronal signalling, which leads to improved memory recall.

connections are maintained between neurons. Iram and colleagues found that genes that are typically expressed in oligodendrocytes were highly upregulated in old mice treated with CSF from young mice, compared with the animals' aged counterparts treated with artificial CSF.

Previous work has demonstrated that successful fear-conditioning in mice requires oligodendrocyte proliferation and myelin formation, and that disruption of this process impairs memory[4,5]. The authors therefore examined whether treatment with the young CSF affected the proliferation and maturation of oligodendrocyte precursor cells (OPCs). Indeed, they found that young CSF more than doubled the percentage of OPCs actively proliferating in the hippocampus of old animals. This cellular change was followed three weeks later by an increase in myelin production. The findings strongly suggest that young CSF improves the cognitive abilities of aged mice by modulating oligodendrocytes.

The authors took a deeper dive into the pathways activated by young CSF using an established line of rat OPCs grown in cell culture. Gene transcription involves the formation of chains of various nucleoside molecules to make RNA, so Iram *et al.* added a labelled nucleoside to the culture medium in which the OPCs were grown — this enabled the authors to isolate and sequence newly made RNA transcripts, which had incorporated the labelled nucleoside. The greatest increase in gene expression in response to young CSF treatment was in serum response factor (*Srf*), which encodes a transcription factor that initiates cell proliferation and differentiation. Six hours after young human CSF administration to the OPCs, *Srf* expression had returned to baseline levels, but downstream targets related to the cell cycle and proliferation were upregulated. The authors confirmed that these SRF signalling pathways were also activated in old mice after young CSF administration.

CSF contains a rich cocktail of signalling molecules and growth factors, many of which could induce the SRF signalling pathways seen in the OPCs. Iram *et al.* identified candidate factors capable of inducing *Srf* expression in published protein databases from large-scale studies of CSF. Fibroblast growth factor 17 (FGF17) emerged as a compelling candidate. The authors showed that the protein is robustly expressed in mouse neurons, exhibits decreased expression in aged mice, and induces OPC proliferation in cultured rat OPCs.

FGF17 infusion into old CSF partially recapitulated the effects of the young CSF, both *in vitro* in OPCs and *in vivo*, improving the memory recall of aged mice (Fig. 1). Finally, the authors demonstrated that the blockade of FGF17 in cultured OPCs treated with young CSF was sufficient to inhibit OPC proliferation, and that treatment of young mice with FGF17 blockers impaired cognition. The researchers' experiments strongly suggest that FGF17 is a CSF-borne factor crucial for cognition, and demonstrate that its effects are probably mediated by oligodendrocytes and myelination in the hippocampus.

Iram and colleagues' finding adds FGF17 to a growing list of factors that affect neuronal development and cognition and that are known to change with ageing[6,7]. There has been particular interest in CSF and its signalling factors during brain development, when neuronal progenitors depend on these signals to proliferate and build the cerebral cortex[8,9]. The CSF also has roles in adult mice, for instance in influencing neuron production in the brain's subventricular zone[10]. Previous work has often found that beneficial CSF factors originate in the choroid plexus — a sheet of tissue located in each ventricle of the brain that secretes CSF and forms a major barrier between the brain and the rest of the body. Unexpectedly, Iram and colleagues found that FGF17 in the CSF isn't sourced by the choroid plexus, but, instead, by youthful neurons themselves, providing evidence that neuron-based signals are delivered by the CSF — a provocative hypothesis about protein and fluid distribution throughout the brain. How FGF17 is distributed in the CSF and delivered to target cells in the hippocampus presents a new direction of research.

Iram and colleagues have broken ground in the field of brain health and ageing by discovering that young CSF contains a factor that aids memory recall in older mice through oligodendrocyte maturation and myelination in the hippocampus. Not only does the study imply that FGF17 has potential as a therapeutic target, but it also suggests that routes of drug administration that allow therapeutics to directly access the CSF could be beneficial in treating dementia. Any such treatments will be hugely helpful in supporting our ageing population.

Miriam Zawadzki and **Maria K. Lehtinen** are in the Department of Pathology, Boston Children's Hospital, Boston, Massachusetts 02115, USA.
e-mails: miriam.zawadzki@childrens.harvard.edu; maria.lehtinen@childrens.harvard.edu

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Microfluidics

A lab-on-a-chip that takes the chip out of the lab

Mazher Iqbal Mohammed

A microfluidic system achieves miniaturization without the need for extra equipment, bringing chip-based devices closer to mainstream commercial reality, with a framework that could be widely applied to diagnostics. **See p.464**

Lab-on-a-chip systems aim to encapsulate the capabilities of a laboratory in a single miniaturized device for use in medical diagnostics, biomedical tissue engineering and environmental sampling[1]. But such systems typically require bulky ancillary equipment, such as fluidic pumps, microscopes and high-voltage power supplies, earning them the tongue-in-cheek name 'chip in a lab'. On page 464, Yafia *et al.*[2] report a lab-on-a-chip system that can be easily 3D printed and requires only a smartphone, which is used as a photodetector. Together, the device and phone can test human saliva for a range of biological targets, including the coronavirus SARS-CoV-2.

The first lab-on-a-chip system was built in the 1970s. It was a gas chromatographic analyser, a device that separates compounds through vaporization, and was made from silicon, using fabrication techniques that were developed in the microelectronics industry[3]. However, although such techniques offer impressive precision, there are many logistical issues associated with the use of microfabrication methods to build lab-on-a-chip systems[4]. In particular, the devices produced by such methods are often made of polydimethylsiloxane (better known as PDMS), which is permeable to water, creating problems such as fluid leaching and evaporation. Components of lab-on-a-chip