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.

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Microfluidics

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

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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

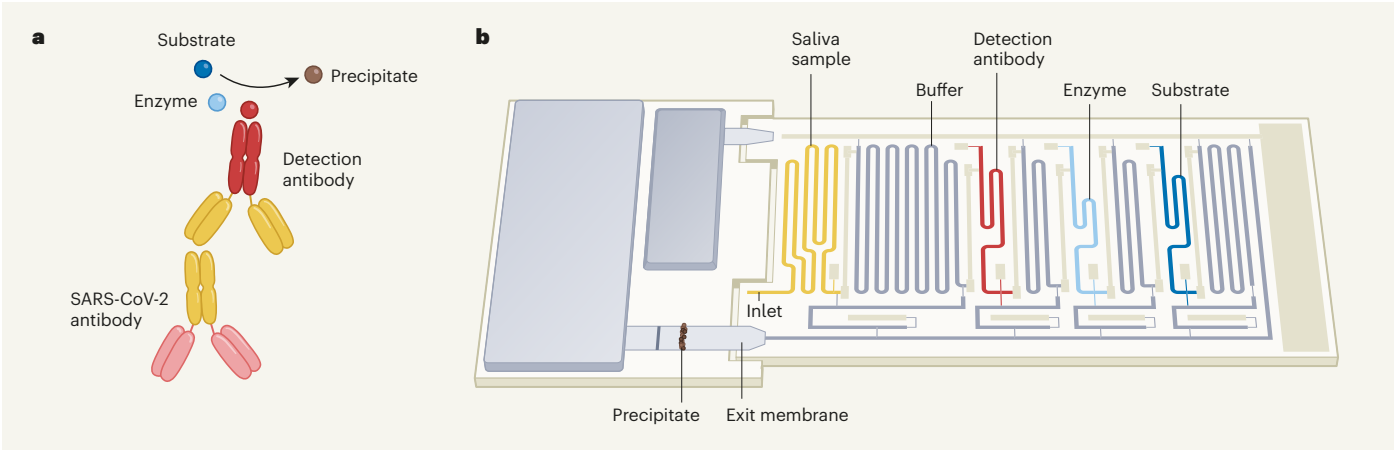

Figure 1 | A 'microfluidic chain reaction' on a chip. Yafia *et al.*[2] designed a microfluidic chip comprising networks of micrometre-scale channels that can be used to control the mixing of liquids containing reagents. The authors used this microfluidic chain reaction to automate an eight-step sequence in a common protocol for detecting SARS-CoV-2 antibodies in a human saliva sample. **a**, The protocol introduces detection antibodies that bind to the SARS-CoV-2 antibodies, and that are connected to an enzyme enabling detection. A substrate solution triggers the creation of a brown precipitate. **b**, The saliva sample flows into the chip through an inlet and remains in a channel until the chip is manually connected to an exit membrane containing a protein that binds to SARS-CoV-2 antibodies. All liquids in the chip are sequentially released into this membrane, starting with the sample, and a buffer solution is introduced between reactions. The brown precipitate can be seen by the naked eye on a detection band or quantified using a smartphone. (Adapted from Fig. 3 of ref. 2.)

devices also typically require multiple precision-fabrication processes, and this limits the scalability of manufacturing.

Attention is therefore moving towards testing prototypes of systems that are constructed using laser ablation and 2D- or 3D-printing technologies[5–7]. Yafia and colleagues used 3D printing to construct their lab-on-a-chip system. This offers a blueprint for building low-cost devices that require minimal fabrication skills and can incorporate functionalities such as fluidic flow.

The authors' device comprises networks of micrometre-scale channels and reservoirs that can be used to manipulate liquids containing reagents, and thereby to control biological reactions. The system facilitates a 'microfluidic chain reaction', using domino-like valves to enable controlled release of reagents from a series of reservoirs (Fig. 1). The opening of one reservoir occurs only when the one preceding it in the chain has been drained. In this way, Yafia *et al.* were able to control the propagation of a chemical chain reaction.

To do this, they made use of capillary action, a phenomenon that occurs when intermolecular adhesive forces at the interface between a solid and a liquid compete with cohesive forces in the fluid. Plants use this mechanism to draw water into their roots, and microfluidic platforms can use the same principle to control the flow of a fluid by modifying the effective 'wettability' of a channel surface. Yafia and colleagues designed a system in which the surface interaction of a fluid of interest can be controlled in 3D-printed channels. They achieved this through careful consideration of the material's surface properties and the channel geometry, allowing for complex flow control.

The key advantage of using capillary action is that it removes the need for bulky fluidic pumping systems. The authors analysed their microfluidic devices with a system analogous to an electric circuit. For instance, flow speed is comparable to electrical resistance, in that an increase in the flow resistance slows the migration of a fluid. If resistance increases beyond a threshold, the fluid can be immobilized within a channel structure.

One impressive aspect of the study is the development of configurations that can be used to manipulate the flow, controlling migration speed and halting and reinitiating flow. The device can also bring multiple flow streams together without introducing bubbles — the bane of any microfluidic system.

Perhaps more importantly, these configurations can be used to evacuate a fluid from a filled channel. This ability is a game-changer, because clearing complex microchannel networks of fluid is a far from trivial task. It is typically achieved using air to displace the fluid — an approach that often results in the formation of bubbles and stagnant areas that are difficult to clear. Yafia and colleagues' demonstration paves the way for precise control of the fluidic volumes used in reaction processes, making such microfluidic systems easy to use and minimizing waste of often-expensive reagents.

The team used its device on a saliva test for SARS-CoV-2 antibodies. The test could potentially be used to detect infection, to assess a patient's prognosis and to distinguish between vaccinated individuals and those who have acquired antibodies through infection. The result can be read out by eye or quantified using a smartphone equipped with a simple cardboard attachment designed to block ambient light. The authors also showed that the chip could be used to test the coagulation of blood plasma, and thus assess a person's risk of thrombosis.

Ultimately, Yafia and colleagues' study provides a robust solution to several long-standing 'chip in a lab' issues that have plagued microfluidic systems — and it does so in dramatic fashion. The authors' device has the potential to dethrone the current 'king' of portable diagnostics systems, the lateral flow test, because it is a more sophisticated platform that can produce quantitative — rather than purely qualitative — diagnostic results. Could this research be a key chapter in the story of how quantitative and clinically useful diagnostics come to be conducted at home? Only time will tell, but in light of the ubiquity of home diagnostics in the wake of the COVID-19 pandemic, it is an exciting step towards that goal.

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