A fragrance to remember

The intriguing link between smells and memories stored by the brain raises the possibility of using odours to improve recall and overcome trauma. **By Roxanne Khamsi**

A bite of a madeleine cake and a sip of tea is all it took to send Marcel Proust tumbling back into the childhood memory of Sunday mornings with his aunt. "No sooner had the warm liquid, and the crumbs with it, touched my palate, a shudder ran through my whole body, and I stopped, intent upon the extraordinary changes that were taking place," the French novelist wrote in 1913.

This experience of a smell sparking a vivid memory will be familiar to many people. As Proust said, "the smell and taste of things remain poised a long time, like souls, ready to remind us." But how smells cause us to time travel in our minds and evoke emotion is not just of literary interest – it's something that scientists are trying to decipher.

"Smell is very deeply ingrained in our emotional memory," says Eric Vermetten, a clinical psychiatrist and trauma researcher at Leiden University Medical Center in the Netherlands. For him and many other researchers, the architecture of the brain itself is a clue to how tightly connected odours are to memories. When we hear a sound, the signal is conveyed from our ears to the brainstem, then up to a part of the brain called the thalamus, before finally reaching the auditory cortex. But when it comes to sensing smells, the connection to the brain is less circuitous. Smell-sensing neurons in the nose extend directly to the olfactory bulb of the brain, from which they can be passed on to other brain regions – including areas involved in memory.

The sense of smell is specific, which helps to explain how our smell memories can be so precise. Humans have more than 400 types of olfactory receptor. This affords us a tremendous amount of olfactory detail, and our nervous system needs to categorize all of that smell input. In 2013, one group of scientists suggested that just as there are five senses of taste (sweet, salty, sour, bitter and umami), there are ten basic dimensions of smell, such as fruity, nutty, woody and citrus[1]. However, the researchers gave participants in their study only 144 scents to profile – a tiny fraction of the full spectrum of smells, which might have limited the number of odour dimensions that the volunteers picked up.

Knowing how our brains keep track of the smells we encounter has been a source of fascination for Sandeep Robert Datta, a neuroscientist at Harvard Medical School in Boston, Massachusetts. In the past two years, he and his colleagues have published two studies that show how short-term and long-term odour memories function in the brain.

In one experiment, published in the journal

Cell last December, they tried to understand how short-term neural memories of scents affected the sense of smell in mice[2]. It was previously thought that all olfactory sensory neurons had the same genetic inner workings, even though they have different odour receptors. But when the team exposed mice to odours and then looked at the gene-activity signatures of their odour receptor cells two hours later, they noticed that different olfactory sensory neurons had different patterns of gene activity. The key discovery was that exposure to odours would trigger smell-sensing cells to boost the activity of genes that attenuated their responses to those same odours. In other words, when neurons pick up a scent, they become less sensitive to it in the short term – "filtering out the expected to emphasize the new," as Datta puts it. Many people experience this as getting used to a smell in their environment and becoming temporarily unaware of it.

The second paper from Datta's group, published in *Nature*, addresses how smell memories are coded in the brain over the long term[3]. The group exposed mice to different smells while recording their responses to those scents in the olfactory cortex – the region of the brain where smell signals are often sent from the olfactory bulb. Initially, scents that were chemically similar were transmitted to nearby places in the olfactory cortex. But the researchers worked out that, over the long term, exposing mice to two dissimilar smells simultaneously could change where in the cortex the smell signals would map to. The researchers could get two radically different scents to map to a similar region of the cortex, which could explain why our unique personal smell memories can be a concoction of various odours – the smells of sunscreen and the ocean evoking a holiday, say, or the scent of bug spray mixed with smoke bringing to mind summer campfires. This also suggests that experience can shape the association of smell memories. "What is crazy, is as your experience changes, the actual relationships that are encoded in your brain move around," Datta says.

The study of how smells influence memory in humans has long been a niche area of research. However, around a century after Proust wrote about his madeleine-and-tea-induced flashback, olfaction is beginning to attract more interest from researchers, who are starting to understand the mechanics of odour memory. "It's getting more popular," says Kei Igarashi, a neuroscientist at the University of California, Irvine.

By watching rodents navigate mazes guided by memories of odours, scientists are getting a sense of how neurons in the brain store this information. And there are also insights into the psychological elements of odour memories in humans. Smells can stir up cherished nostalgia, but there are also times when odours can cause anguish: researchers have shown that certain smells can trigger physiological stress in people with post-traumatic stress disorder (PTSD). Thanks to a flurry of research in the past decade, we might be on the cusp of understanding the lasting power of smells – and how odour memories might be used to boost and heal our brains.

Early recollections

Even before babies can see well, they have a robust sense of smell. An infant's ability to detect odours is so strong that newborns will prefer the scent of their mother's breast and clothes over those of other people[4]. One idea for why this preference develops so early is that human amniotic fluid seems to contain individualized chemical signatures that prime the developing fetus to be attracted to their parent. The memory and attachment to these smells in early life is so powerful that scientists have even explored ways to harness it therapeutically. In one experiment involving babies who were about to be vaccinated against hepatitis B (ref. 5), researchers exposed some babies to the smell of their mother's milk, whereas others were exposed to the scent of another woman's milk or to water. The infants who were exposed to the odour of their own mother's milk were less likely to show signs of pain or an elevated heart rate when receiving the immunization.

"Smell is very deeply ingrained in our emotional memory."

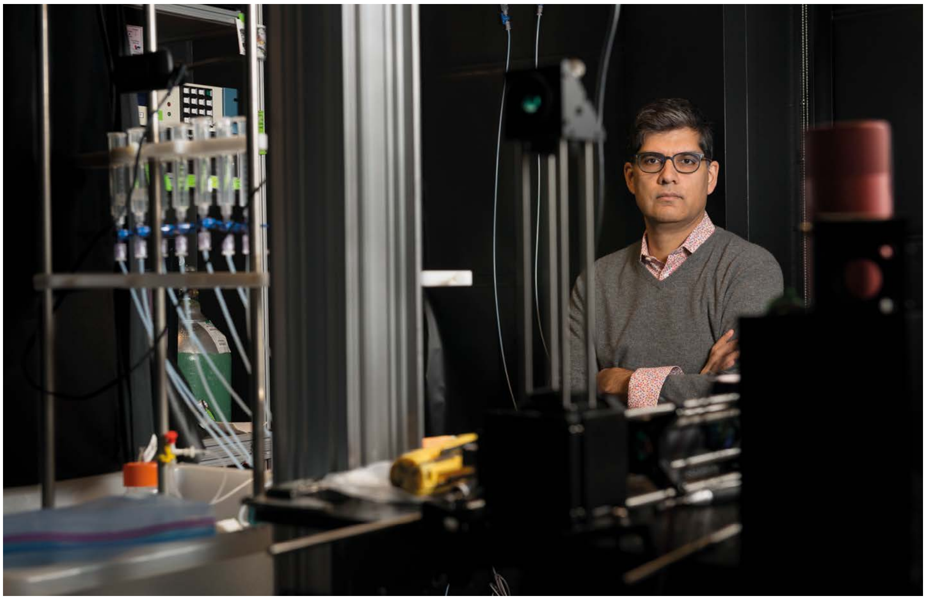
Even as adults, the tight connection between smell and memory persists. One brain-scan study[6] published in June last year found that when people are resting, the activity of their olfactory brain centres is in sync with that of another brain region called the hippocampus – which is deeply involved in memory. The activities of other sensory systems such as sight and touch were significantly less correlated with the hippocampus. The finding suggests that olfaction is more-continuously connected to certain memory processes in the brain than are those other senses.

Rodent studies are also giving us clues to the pull that smell memories can exert. Female mice, for example, will keep returning to the place where they smelt urine pheromones of potential mates for at least a couple of weeks[7]. And there's even a suggestion that smell memories can be passed down through generations. Mice whose grandfathers were exposed to a scent similar to cherry blossom in conjunction with an electric shock are more anxious around that smell than are their control counterparts[8], for example. The scientists who conducted the study suggested that this learnt fear might be passed to future generations through chemical markers on DNA sequences known as epigenetic modifications.

In addition to amassing data underscoring that smell and memory are linked in the brain, scientists have sought to understand what is happening at the neuronal level when odour memories form. Earlier this year, Cindy Poo, a neuroscientist at the Champalimaud Foundation in Lisbon, and her colleagues reported the results of an experiment in which rats were trained to follow four distinct smells – citrus, grass, banana or vinegar – to specific locations in a maze to receive a reward[9]. They found that as the rats learnt to remember certain smells and their association with specific locations, there was activity in the hippocampus and a lesser-known brain region just beneath it called the entorhinal cortex. But, surprisingly, they also found that some neurons in the piriform cortex – thought to be involved in odour recognition – were doing double-duty: the neurons responded to both specific smells and locations. "They're telling you what odour you're smelling and also telling you where you are," Poo says. "It basically shows that our sense of smell is very intimately connected with our spatial memory at the level of individual neurons in the brain."

Igarashi also conducted a rodent experiment, published in 2014, to gain insight into how smell and memory are coded together in the brain. He and his colleagues designed a challenge for rats in which the animals were trained to navigate a maze using scent. One odour would indicate that the animal would need to turn right to find food, whereas another odour indicated the animal had to turn left. After three weeks of training, the rodents were choosing the correct direction on the basis of the odours more than 85% of the time[10]. Igarashi and his colleagues looked at brain recordings from the animals and noticed that as the rats learnt to respond to the scent cues, cells in three brain regions – the entorhinal cortex, the lateral entorhinal cortex and the hippocampus – would emit electrical signals in sync.

Igarashi wanted to know more about what kind of molecular changes were aiding memory consolidation at the cellular level. So he and his colleagues designed a follow-up study[11] in which they looked at the brain activity of mice that were trained to associate various smells with either sugar water or bitter water.



Sandeep Robert Datta studies how odour memories function in the brain.

ANNA OLIVELLA

The group trained the animals using a range of scents, including fruity odours and other non-food-related odours, such as pine.

When the mice were learning to associate odour with the sugar water, the cells in their entorhinal cortex were releasing dopamine. This proved to be a key molecule in consolidating the association. When the scientists blocked that dopamine release it impaired the animals' learning – they would not remember to lick for the sweet reward following exposure to the associated scent.

The work could have implications for Alzheimer's disease, because the entorhinal cortex is among the first brain regions to show deterioration in people with the condition, and olfactory dysfunction is thought to sometimes be an early sign of cognitive decline.

The odorous past

Often, smell memories are associated with positive recollections of the past, but smells can also trigger traumatic memories. Vermetten recalls that when he was living in Connecticut years ago, he provided psychiatric help for a Vietnam War veteran who was affected by the smells of the Asian-food restaurant that he lived above. The fragrance of the food brought the man back to his time in Vietnam. "He couldn't sleep at night," Vermetten says. "It bothered him, and he couldn't put it aside."

To better understand the role of smell in the surfacing of traumatic memories, Vermetten recruited 16 Vietnam War combat veterans, half of whom had PTSD and half of whom did not[12]. He and his team then exposed the veterans to three smells: the scent of diesel, which was tightly associated with traumatic experiences during the veterans' time fighting in the war; the pleasant smell of vanilla; and the stinky odour of hydrogen sulfide, which, although unpleasant, had no specific association with war. The scientists measured the brain activity of the participants, using a method called positron emission tomography, and noticed that the smell of diesel caused a rise in blood flow to a brain region associated with fear, known as the amygdala, in the veterans with PTSD but had less effect in the others. The former group also rated the diesel smell as more distressing than did the latter group.

Vermetten has advocated for scientists to look at how certain smells might be able to calm or 'reset' people who are in treatment for trauma. For example, when someone is recounting a traumatic war memory, he says, they can be given coffee grounds to sniff, which can help to bring them back to the present moment.

An evolving research area

The study of smell and recollections of the past continue to offer insights. Coincidentally, it was in 1973, around the time that the war in which Vermetten's veterans were fighting was ending, that the study of lasting smell memories intensified. Interest in the ties between olfaction and memory grew after a study published that year[13] demonstrated that participants who sniffed certain odours in a laboratory were able to identify those same odours when they encountered them again three months later. Further research showed that people exposed to smells and pictures had a better recall of the odours than of the images several months later.

More-recent studies have tried to harness the power of smell to help people recall information. In one 2019 study, volunteers were shown pictures – some of which were paired with unpleasant odours. When participants were tested on their recall 24 hours later, they were able to recall the images that were shown in tandem with the scent better than those shown without a smell[14]. And it's not just stinky odours that boost memory: a study published the following year showed that smelling the scent of rose while learning, and at night before a test, boosted participants' performance in exams[15].

Working out why smells and memory evolved to be so intertwined is of interest to researchers. Poo wonders if there could have been an evolutionary advantage to leveraging scent memories. She speculates that our ancestors might have oriented themselves and their migration by discerning the wafting smells of places such as the desert or the coastline. "Theoretically, for our human ancestors who were navigating across different landscapes, this would be a kind of long-distance way to navigate, whereas visual and auditory [senses] are very local," she says.

Although the reasons smell and memory have evolved to be connected are difficult to pin down, the flurry of data about how they interact on a neuronal level is heartening to scientists in the field. Thanks to faster and more-refined genetic sequencing approaches and brain-imagining technologies, studies are yielding new insights. "I'm a long-time olfaction researcher and I think we're going through a little bit of a renaissance in terms of the tools that we have available to understand the sense of smell," Datta says. With these tools in the hands of scientists, we might finally get more answers to why smells of the past linger in our brains long after the first whiff has wafted away.

Roxanne Khamsi is a science journalist in Montreal, Canada.

1. Castro, J. B., Ramanathan, A. & Chennubhotla, C. S. *PLoS ONE* **8**, e73289 (2013).
2. Tsukahara, T. *et al. Cell* **184**, 6326–6343 (2021).
3. Pashkovski, S. L. *et al. Nature* **583**, 253–258 (2020).
4. Vaglio, S. *Commun. Integr. Biol.* **2**, 279–281 (2009).
5. Rad, Z. A., Aziznejadroshan, P., Amiri, A. S., Ahangar, H. G. & Valizadehchari, Z. *BMC Pediatr*. **21**, 61 (2021).
6. Zhou, G. *et al. Prog. Neurobiol.* **201**, 102027 (2021).
7. Roberts, S. A., Davidson, A. J., McLean, L., Beynon, R. J. & Hurst, J. L. *Science* **338**, 1462–1465 (2012).
8. Dias, B. G. & Ressler, K. J. *Nature Neurosci.* **17**, 89–96 (2014).
9. Poo, C., Agarwal, G., Bonacchi, N. & Mainen, Z. *Nature* **601**, 595–599 (2022).
10. Igarashi, K. M., Lu, L., Colgin, L. L., Moser, M.-B. & Moser, E. I. *Nature* **510**, 143–147 (2014).
11. Lee, J. Y. *et al. Nature* **598**, 321–326 (2021).
12. Vermetten, E., Schmahl, C., Southwick, S. M. & Bremner, J. D. *Psychopharmacol. Bull.* **40**, 8–30 (2007).
13. Engen, T. & Ross, B. M. *J. Exp. Psychol.* **100**, 221–227 (1973).
14. Cohen, A. O. *et al. Learn. Mem.* **26**, 272–279 (2019).
15. Neumann, F., Oberhauser, V. & Kornmeier, J. *Sci. Rep.* **10**, 1227 (2020).