Fragrant Flashbacks

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Memory and smell are intertwined; it's through memory that we learn to remember smells, and disorders that take away memory also take away the ability to distinguish scents. Some of this learning starts even before we are born, when fetuses learn about their mother's preferences through the amniotic fluid.

Flavor, like that described by Proust, is what happens when taste and smell come together. Technically, "taste" refers only to the senses that are associated with receptors on the tongue: sweet, sour, bitter, salty, and — some people argue — umami.

"What everybody calls 'smell' is when you sniff through your nostrils to get an odorant. That's technically 'orthonasal olfaction,' " says Linda Bartoshuk, a past president of APS and director of human research at the University of Florida Center for Smell and Taste. Volatile organic molecules come into your nose, where they meet receptors in the cells in the nose. From those receptors, the message travels to the brain. The other kind of olfaction, retronasal olfaction, works similarly. "You can illustrate this yourself with a jelly bean," says Bartoshuk. All you have to do is pinch your nose with your fingers, put the jelly bean in your mouth, and chew it up. It shouldn't taste like anything in particular — just sweet, and maybe a little bit sour. But, says Bartoshuk, when you "open your nose and swallow, that will be the first time you know what flavor the jellybean was." Air rushes up behind the palate, into the nose from the back, carrying the jelly bean's aromatic molecules along. Like smells coming from the front of the nose, those molecules meet the receptors and spread the news that the jelly bean in your mouth is popcorn or licorice or watermelon. The same is true for real food: "When you enjoy roast beef and lemon and rhubarb and chocolate, most of those are smells," Bartoshuk says.

Getting back to Proust's madeleines, Maria Larsson studies how smell evokes autobiographical memories at Stockholm University. She was trained in the study of memory, but became interested in smell when she realized that "there are a range of descriptions and stories from novelists like Marcel Proust and others." But, when she turned to the scientific literature, she says, "We found there was very little scientific evidence of this." So she set out to find out whether smells really do evoke emotional memories.

Other researchers have found that the formation of autobiographical memory peaks between the ages of 15 and 30. This trend makes sense, Larsson says; it's when people are going to college, getting married, and starting to establish themselves in the world. She modeled her work after that literature, exposing older adults to different smells and interviewing them about a memory evoked by the smell. "What we found was really amazing," she says. For visual and verbal cues, people's memories came from their teens and 20s, as expected. But for smells, the peak was around age 5. "It was really, totally clear that when they recollected a specific memory, that memory was localized to the childhood period," she says. The memories were also more emotional and more vivid than memories brought up by visual or verbal cues.

Just finding the smells to test people with was tricky, Larsson says. She quickly learned that she couldn't offer people smells like coffee, because they smell coffee all the time and it wouldn't evoke particular early memories. Instead, she settled on scents that are less common in daily life, such as lily of the valley, mulled wine, chlorine, cloves, and tar. For example, "Tar is an odor that is related to wood and to springtime," Larsson says. Even people who had smelled those scents in the intervening years didn't think of later memories. "They pick one of the first times when they experienced this event," she says. With other types of memories, memory researchers have found a phenomenon called *retroactive interference*, in which newer memories mingle with older memories and may change them. But this phenomenon doesn't seem to happen with memories that are called up by a smell. "When it comes to odors, this is like an imprint that really lasts and is not disturbed by later experiences," Larsson says. "Why this is, we don't know."

She speculates that this persistence of early memories could come from one of the functions of smell: to warn us away from things that are dangerous. If you eat something with a particular smell or flavor and immediately get sick, it would make sense to avoid that smell forever. Maybe it's important for the brain to quickly and permanently learn to associate a particular smell with a particular experience, she says. "Maybe it's a one-trial learning system and it's very important that you remember the first time." Or maybe smells are so important in early memories because the chemical senses of taste and smell are extremely active. After all, everything within reach goes into a baby's mouth or past its nose. "As we get older — maybe luckily so — we stop exploring the world by putting things into our mouths, and we end up being more visually and auditorily-driven animals," Larsson says.

Researchers like Larsson who study behavior have found a tight connection between smell, emotion, and memory. Those connections can also be seen in the brain, says Johan Lundstrom, an APS Fellow at the Monell Chemical Senses Center in Philadelphia. For every other sense, the message travels first to the brain stem and the thalamus before going out to the primary sensory areas. “Olfaction is completely differently wired,” Lundstrom says. First, odor molecules bind to receptors in the nose. Signals from the receptors travel up to the olfactory bulb, a Q-tip-like structure roughly above the eyes. From there, some signals go to the primary olfactory cortex and on to the higher-order parts of the brain. But there are also connections from the olfactory bulb directly to the amygdala, an area that is relevant to emotions and salience, and the hippocampus, which is involved in memory. That puts the receptors in the nose only one synapse away from emotion and memory.

Lundstrom suspects there is something special about how the brain learns about odors. It takes many trials to get people to associate some visual cue with negative feedback like an electric shock. “When we do this for odors, it takes just a few pairings — two or three, even one, for the system to react very strongly the next time you sense an odor,” Lundstrom says. Among other projects, he is working on understanding how classical conditioning works in odor — whether the brain acts differently when it’s learning to pair odors with negative stimuli.

The close connections to emotions and memory, rather than to the parts of the brain that put words on things, may help explain why humans are so bad at identifying smells. Studies have found that people can identify fewer than half of the odors of household items they use daily. But if you give them a list of a few possibilities, they can usually choose the right one. Or, if the odor is paired with a visual clue, it makes instant sense.

Just as we know a chair is a chair whether it’s red, blue, upholstered, plastic, in a living room, or in a dumpster, we know that coffee smells like coffee whether it’s from Starbucks, Dunkin’ Donuts, or a church coffeemaker. Coffee has hundreds of volatile molecules, each of which may have several components that activate receptors. These form part of the idea of coffee, but not the whole thing. “It looks as if those sort of feelings and contexts and memories can actually become tied into this object you call ‘coffee,’ ” says Donald Wilson, a neurobiologist at New York University. “That may be one reason why odors can be so evocative. You have these very strong other kinds of information that hit you at the same time you smell the odor.”

Research in animals is keeping pace with research in humans on how smell and memory work together, says Wilson, who works mostly with rodents. He has found that if you give a rat or mouse a drug to disrupt its memory, it gets worse at telling the difference between different odors.

This result could explain another connection between smell and memory. The sense of smell is often dull in people who have other cognitive impairments, like Alzheimer’s disease, Parkinson’s disease, schizophrenia, or Down syndrome. “If memory is critical for perception, then it starts to make sense,” Wilson says, that a decline in memory would mean a decline in smell, while other senses remain intact. Smell is a complex sense that requires people to learn and remember these “odor objects,” he says. As memory fails, those odor objects may also start to fall apart.

In fact, deficiencies in smell seem to appear years before other symptoms of Alzheimer’s disease. A sense of smell that’s not so sharp may be an early sign of brain damage. Of course, it could also be a sign of a cold. But if a smell test is combined with one or two other measures, such as a cognitive test or an imaging test, it may be possible to diagnose Alzheimer's disease much earlier than is currently possible. Wilson was a coauthor on a paper published in *Science* in which researchers gave the cancer drug bexarotene to mice that had a mouse version of Alzheimer's disease and found that it rapidly cleared plaques from the brain — and the mice regained their sense of smell.

Wilson is also working on learning how smell memories are formed. Scientists already know that sleep is vital for cementing some kinds of memories. For example, when a rat is learning to run through a maze, particular neurons in its brain fire at particular locations in the maze. Then, when it goes back to its cage, curls up, and falls asleep, those same neurons can be seen firing in the same order, in quick succession. Wilson and his colleagues are trying to find out if the same process happens with olfactory memories by stimulating receptors in a rat's nose and introducing a "smell" to a rat electronically. Initial results suggest that encouraging this replay in sleep helps rats learn smells better.

The process of learning about smells starts very early — even, research has shown, before babies are born. In the 1990s, APS Fellow Julie Mennella at the Monell Chemical Sciences Center suspected that smells made their way into amniotic fluid. She designed a study in which 10 pregnant women took either a garlic pill or a placebo 45 minutes before a routine amniocentesis. Samples of the women's amniotic fluid were presented in pairs to people who were asked to pick the one that smelled more like garlic. For most of the pairs, the volunteers were able to tell the difference. So the environment that a fetus inhabits is full of smells that filter through from the mother's diet. Smell seems to work the same way before birth that it does after birth. "Memories are formed from the experiences with flavors in amniotic fluid," Mennella says. That means a fetus is already learning about the foods it's likely to encounter in the outside world.

Benoist Schaal, a behavioral scientist at CNRS in France who also studies how babies respond to smells, tried an experiment with anise, the scent associated with licorice. In France, anise-flavored snacks are popular. Schaal and his colleagues worked with pregnant women who already habitually ate anise and had them eat more anise. As a control, they asked women who didn't eat anise to continue avoiding anise at the end of their pregnancies. If their mothers had eaten anise-flavored cookies before birth, "these babies had very clear appetitive responses to the odor of anise," Schaal says. In one test, the babies were offered the smell of anise and another odor. "When the head was placed between two pads, they turned their head toward the odor they had in the womb," he says.

When a mother eats, ultrasounds have shown that babies speed up their pseudorespiration, inhaling and exhaling more quickly. "We do not really know how they learn in the womb," Schaal says. "What we know is that the glucose in the brain is a promoter of memory." One possibility is that babies are learning to associate the aromas of their mother's food with the glucose that arrives at the same time.

And those associations last for a long time. About 10 years ago, around the same time Schaal was plying pregnant women with anise, Mennella did a study in which women drank either carrot juice or water during the last trimester of their pregnancy and the first two months of breastfeeding. Soon after each mother started feeding her baby cereal — but before the youngster had ever been offered carrots — the baby was offered cereal made with water and with carrot juice, in two different sessions. The babies who'd had prenatal exposure to carrot juice made fewer nasty faces while eating the carroty cereal and seemed to eat more, too. Mennella has done several studies that have shown that eating vegetables and fruit while breastfeeding makes babies more enthusiastic about them when they're weaned.

Now Mennella is working on experiments to figure out if there's some sensitive period when it's best to expose babies to a new food through breast milk. "We're trying to really get into the sensory world of the baby to look at the potency of these really early experiences and later behaviors, and also looking at the mother and her liking for these foods," she says. These experiences may last. A preference for green beans might be passed from mother to child and carry on into adulthood. Or, like Proust's narrator, the young children in Mennella's studies could one day find themselves tasting an unusual flavor and being transported back through their lives.