You Smell:
The Mysterious Science of Scent

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ABSTRACT

The sense of smell is a mystery—and the human sense of smell is a particularly inscrutable one. Only in the last 25 years have scientists identified the molecules in our noses responsible for detecting odors, and since then, the unexpected discovery of a new family of olfactory detection molecules has complicated the story. When the complexities of the human brain, human motivation, and human variation are added to the mix, the question of what smells do to and for us becomes even more perplexing—and intriguing.

Essayist and physician Lewis Thomas wrote that understanding the sense of smell "may not seem a profound enough problem to dominate all the life sciences, but it contains, piece by piece, all the mysteries." Scientists from all fields are coming together to solve these mysteries of olfaction, and their investigations are starting to reveal that the sense of smell can move us in ways that we aren't even always aware. While it's clear that scientists are far from closing the case on smell, it is also becoming increasingly obvious that the power of the human nose is nothing to sniff at.

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Imagine the worst smell you can think of. Maybe you smelled it when you first opened that bloated Tupperware you forgot in your desk a month ago. Maybe it was when you forgot to clean your pet's litter box. The smells may have made you gag, but in the mid-2000's a few of these nasty, nose-wrinkling odors helped launch Stephen Liberles' academic career.[1]

Back then, Liberles was a postdoctoral fellow in Linda Buck's lab. This was right around the time that Buck won the Nobel Prize in 2004 for her role in discovering the first family of odorant receptors—the molecules in our noses that are the front line in our sense of smell.[2]

Liberles was working on something different: trying to understand the functions of other molecules in the same family as those Buck and her collaborators had identified.[3] This family—with the unwieldy name G protein-coupled receptors or GPCRs[4]—included so-called orphan GPCRs, molecules whose roles were unknown.[5]

Things took a turn, though, when he started looking at orphan GPCRs in the mouse nose. His probes lit up the layers and folds of the mouse nasal cavity with red and green fluorescence.[6] When he slid the tissue under the microscope, Liberles realized the pattern of these molecules looked just like the pattern his boss had seen a decade earlier when she discovered the first—and, until then, thought to be the only—family of smell receptors. Now Liberles had stumbled upon an entirely new, and unknown, class of olfactory detectors. Which, in retrospect, he says, "I think came as a little bit of a surprise to the field."[7]

He looked deeper. The genetic sequences of these proteins led him to a group of molecules called TAARs—trace amine associated receptors. At the time, scientists' best guess about what these TAARs did was to detect nitrogen-containing molecules—neurotransmitters like serotonin. To figure out what else might get them activated, Liberles mutated kidney cells to express TAARs that would fluoresce when they found their molecular soul mates.[1] And then he started collecting mouse pee.

"It's known in the field that mouse pee is a rich source of pheromones," he says.[8] While mice have a specific pheromone detection organ called the vomeronasal organ, they can also use their regular noses to sniff out social signals from other mice.[9] Liberles thought the TAARs—expressed in the nose but not the vomeronasal organ[1]—might be how they do this. Plus, the mouse pee "was easy to collect," says Liberles.[10]

TAARs' chemical partners, he discovered, are odiferous nitrogen containing compounds called amines. There were three such compounds in mouse urine that triggered responses in the TAARs found in mouse noses.[1]

Present-day Liberles scrabbled around his shelves for a photocopied page of his old lab notebook. On the page, his younger self had written "I LOVE TAARS" in all capital letters. Images of the tell-tale nasal epithelium speckled with TAARs had been pasted in.

Liberles remembers the day he first saw those images through the microscope. "I talked to Linda that night on the phone and we were like 'Alright. A new family of receptors," Liberles says. He remembers Buck coming in the next day and looking through the microscope with him. Liberles admitted, after additional prodding that, "she was very excited."[11]

"It's so bizarre to come up with a whole new sub-system in a sensory system," says NYU professor Donald Wilson, researcher at the Nathan Kline Institute for Psychiatric Research,[12] and author of the book *Learning to Smell.*[13] "You don't make big discoveries like that very often. It would be like finding out that we have a new color in our visual system."[14] Leslie Vosshall, olfaction scientist at Rockefeller University, writes in an email, "The TAARs were a nice surprise."[15]

Discovering the TAARs presented another clue in an extremely complex case—the mystery of the sense of smell. Despite the incredible power of smells to drop us down rabbit holes of memory and transport us to other places and times, the machinery that detects and makes sense of this information remains poorly understood. As essayist and physician Lewis Thomas wrote in the mid-1980s, "I should think we might fairly gauge the future of biological science, centuries ahead, by estimating the time it will take to reach a complete, comprehensive understanding of odor."

We certainly aren't there yet. "It may not seem a profound enough problem to dominate all the life sciences," Thomas continued, "but it contains, piece by piece, all the mysteries."[16] Over the three and a half decades since Thomas wrote those words, scientists have reached into every corner of the sciences to piece together clues gathered from cells, flies, fish, rodents, and humans—and humans, of course, are the most complicated of them all. Molecular biology and genetic tools are making inroads into elucidating olfaction's basic biology, but the ephemerality of a scent makes the neural circuitry governing odor perception difficult to tease apart.

Our sense of the distance between ourselves and our animal relatives who rely on their noses to identify each other, choose mates, and avoid predators creates the mistaken impression that our noses are sensory organs to be sniffed at. But slowly, clues are emerging that reveal the human nose is more powerful than we imagine, even to the point that it can subtly govern our behavior below our conscious awareness. In the end, the truth is—for most of us, at least—that we smell. It's time to understand why and how.

The Mystery of the Invisible Sense

When light hits our eyes, it bends photoreceptor molecules in 91 million rods and 4.5 million cones to start the sequence of neural events with which we render the visual world.[17] In our ears, a chain of moving, mechanical parts transforms the rhythms of sound waves into electrical signals that our minds play as tones.[18,19] In our skin, capsules that deform when pressed tickle sensory nerve endings to communicate the sensation of touch.[20]

But taste and smell, our chemical senses, are different. They're the most intimate of the five. To use them, we actually draw tiny molecular samples of the source inside our bodies. Tasting is voluntary: we actively place food in our mouths in order to sense it. Smelling, however, is involuntary. We sample both good and bad odorants in our environment with each inhalation.

"Without breathing, you're dead. You can live without looking, and hearing, and whatever, but the moment you stop breathing, you're dead," says Norwegian smell artist Sissel Tolaas.[21] Humans take over 23,000 breaths in 24 hours —that's nearly 1000 breaths each hour, or around 16 inhalations a minute.[22] "Every breath you take, you inhale smell molecules," Tolaas added. "Even when you sleep, you smell."[21]

Unlike tastebuds, the cells responsible for detecting smells are neurons connected directly to our brains. The body of an olfactory sensory neuron sits in the nasal epithelium, a little less than one square inch of tissue located at the top rear of the nose. From there, it extends two axonal arms. One arm reaches through the skull and into the olfactory bulb of the brain, where it starts a cascade of chemical and electrical activity eventually leading to the perception of a smell, and the appropriate behavioral response to it.[23]

The other arm stretches from the neuron into the outside world where it wiggles little sensory fingers called cilia through a layer of mucus.[23] This is where the mystery of smell begins, with the puzzle of how olfactory sensory neurons detect smell molecules borne on the air. Attempts to solve it have resulted in a series of plausible but imperfect hypotheses that have jostled for dominance. "There were 20 different ideas," says Wilson, who has studied olfaction since the 1980s. In his early days, "We were really grasping at straws as to how the system works," he says.[24]

One overarching organizational theory scientists used to try and understand odor detection was the brutally named "puncture and penetration theory." Supporters of this theory believed that the cells in the nasal epithelium take the odorant molecules inside themselves, resulting in a series of electrochemical changes that incite neuronal signaling from the nose to the brain.[25]

Another was the vibrational theory. In the late 1930s, a British researcher proposed that like our eyes, which catch and interpret the vibrational frequencies of light, and like our ears, which pluck sound vibrations from the air, our noses could smell the vibrational frequencies of odorant molecules.[26] This theory gained some traction in the 1990s when biophysicist Luca Turin theorized that our noses detect the spectrum of vibrational frequencies of odorant molecules, accounting for the differences in odor between molecules that look, structurally, very similar.[27]

In 2004, perfume critic Chandler Burr wrote about the trials and travails of Turin's search for scientific validation in a book called *The Emperor of Scent*.[28] A review in the journal *Nature* damned both it and Turin with highly ambivalent praise: "While implausible, Turin's proposal is certainly a delightful potpourri of creativity, conjecture, extrapolation, and isolated observations. And it's brazen: a universal theory of smell based on one man's olfactory impressions," wrote reviewer (and author of another smell-related book)[29] Avery Gilbert.[30]

In the face of such controversy, Rockefeller University professor Leslie Vosshall and postdoctoral researcher Andreas Keller decided to put Turin's theory and olfactory impressions to the test.

"The vibration theory was getting a huge amount of press, and was not backed up by rigorous double-blind controlled studies," writes Vosshall in an email. "We felt strongly that the attention this theory got, and continues to get in the popular press, was polluting the whole idea of the scientific process. We should be evidence-based, not hype-based."[15]

One of the predictions that the two scientists sought to test was Turin's expectation that molecules with the same shape but different vibrational frequencies would have different scents. Vosshall and Keller compared acetophenone—a chemical with a "sweet, pungent, and strong medicinal odor" according to *Feneroli's Handbook of Flavor Ingredients*, used to create grape, cherry, and tobacco flavors[31]—to an analogue built with deuterium, "heavy" hydrogen. Those heavier components changed acetophenone's vibrational frequency without changing its chemical structure.

If Turin were right, the heavier molecule would smell different from the original. But when Vosshall and Keller wafted acetophenone and heavy acetophenone under the noses of their small group of human smell testers, the testers couldn't tell the two apart.[32]

"The vibration theory is a fringe theory ignored by the vast majority of scientists," Vosshall writes in an email. They have instead coalesced around an alternative: the shape theory of olfaction.[33] "All the evidence points to physical-chemical properties of odor molecules activating receptors," she says.[34] Metaphors for this theory often include a lock and a key, or puzzle pieces fitting together. The idea is that odorant receptors are shaped to conform around odorant molecules—when the odorant key fits into the odorant receptor lock, the neuron sends that information shooting to the brain. But for a long time, no one knew what the odorant receptor 'lock' might be, or looked like—let alone whether it could fit a key.

The Mystery of the Missing Lock

In 1988, during Linda Buck's postdoctoral fellowship with neuroscientist Richard Axel, Buck began delving into the sense of smell.[35]

She had originally trained as an immunologist, but changed her research trajectory after reading a study about odor molecules in 1985.[36] The authors of that paper were curious about how the nose detected a molecule in bell peppers' olfactory bouquet, so they attached a radioactive marker to the molecule so they could see it. They then washed the tagged odorant over cow and rat nasal epithelium, reporting that it stuck to the tissue and providing the first clue in the great mystery of how we detect smells.[37] Molecules on the surface of the nasal epithelium, not inside it, grabbed and held onto odorants. Were these smell receptors?

Buck wrote that faced with the complex puzzle of how one organ could detect at least thousands of stimuli, she was "hooked."[38] Back then, she cited an estimate that the human nose could perceive at least 10,000 individual odors—recently, Leslie Vosshall's lab published a peer-reviewed study in the high-impact journal *Science* calculating that humans can detect more than one trillion odors.[39,40,41*]

Buck started her investigation where earlier work left off. Previous studies had suggested that the G-protein coupled receptor molecules (the GPCRs) might be responsible for detecting smells in the nose.[36] GPCRs are proteins that stich in and out of cellular membranes seven times. When these protein receptors bind to something outside the cell, they change shape and send a message in the form of another protein on the inside of their host cell to start a domino effect of intracellular signaling.[4,42]

When Buck began to study these molecules, no one actually knew if GPCRs were to be found in the nasal epithelium.[36] To see for herself, Buck took advantage of a new technique invented a few years earlier by biochemist Kary Mullis. In 1983, Mullis took a nighttime drive through northern California and along the way dreamed up a process that can replicate a segment of DNA a billion-fold.[43] This multiplication process uses synthetic segments of DNA called primers that start the DNA polymerase enzyme zipping along a single strand of DNA to create its mate. Repeating the process over and over again increases tiny amounts of genetic code exponentially, to levels that can be analyzed. [44]

Usually, scientists use primers that are a unique match to the segment of DNA they're interested in, so that they don't accidentally multiply the wrong gene. But in this case, Buck wasn't sure if there was just one relevant molecule so she used an intentional bastardization of the technique—actually called degenerate PCR[45]—that uses non-specific primers to multiply many similar genes.[46,36] By casting her net wide, Buck had a better chance of detecting something that looked like a GPCR in the nasal epithelium.

With that degenerate approach, Buck didn't just find one GPCR. She found an entire family of them inside the noses of rats: "The multigene family we have identified consists of 100 to several hundred member genes," she wrote.[46] Based on their location, she concluded that they were likely the family of rodent odorant receptors. Buck and her advisor Richard Axel published their results in 1991.[46]

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[*] These findings, and her lab's calculations, were met with debate on both the free pre-print server bioRxiv and on Twitter. An updated version of the bioRxiv post is under review at a journal at the moment, writes the post's author, Caltech professor Markus Meister, in an email. "Part of the debate is about assumptions that we made and that we thought were uncontroversial, but now we find out that there are people who don't believe those assumptions," says Vosshall lab postdoc Andreas Keller, the corresponding author of the study. "That's a discussion that has to be had now," he says.

Seven years later, a team at Johns Hopkins University directly confirmed that inside the nose this family of molecules does in fact, detect odor molecules.[47] But with relatively few odorant/odorant receptor pairs identified, scientists couldn't figure out how odorant receptors worked together to take a molecularly complex smell and communicate it to the brain. Was there one receptor per odorant molecule? Many receptors? Many odorants per receptor, or did each particular smell have a pretty monogamous relationship with its receptor?

To find out, Linda Buck and her colleagues isolated individual olfactory neurons, put them on a thin glass coverslip, and coated them with a fluorescent dye that would indicate whether the neuron's receptor had met its matching odorant. [48]

By monitoring the fluorescence, they found that multiple odorants could stimulate a single odorant receptor. This would be comparable to a catcher able to catch projectiles of all shapes—baseballs, basketballs, baguettes—neatly in his mitt. Conversely, they also found that multiple receptors could recognize a single odorant, like a collection of catcher's mitts all with differently sized openings able to catch the same baseball-shaped projectile.[48]

With multiple receptors able to recognize a single odorant, and multiple odorants able to trigger the same receptor, how is the brain able to tell the scent of a rose from the scent of a rancid gym sock?

It helps to imagine the odorant receptors in our noses like the classic image of a group of blindfolded people trying to figure out an elephant by feel, where an odorant molecule is like the elephant.[49] Some receptors can detect the trunk. Some can detect the feet. Some might even be able to feel the entire elephant. Buck called this theory "combinatorial coding." Different combinations of odorant receptors (the blindfolded observers) work together to identify different parts of an odorant (the elephant)—creating a unique code. From such piecemeal information, the evidence suggests, our brains put together the pieces of odor molecules and olfactory mixtures into distinct perceptual smells.[48]

Buck and Axel's discovery of the family of odorant receptors seemed to find a key piece of the puzzle, and in 2004, they shared the Nobel Prize for their work on the olfactory system.[50] "The burst of research in smell really was enabled by the cloning of olfactory receptors," says MIT professor Gloria Choi—another former postdoc of Richard Axel who also continues to study the sense of smell.[51] Over the past several years, a few more clues have emerged that continue to clarify how the sense of smell works. In mammals, we now know that between 1–5% of the genes in the entire genome are genes for odorant receptors. There are around 1200 odorant receptors in a mouse's nose, and around 400 in our own.[52,53]

"By having these receptors, now you have an entry point into how smell is detected and how that smell is transformed and processed in the brain," Choi says.[51] When Buck and Axel uncovered a whole family of odorant receptors, it appeared to close one of the main cases in the mystery of smell: how the nose detects odors. "We thought all the receptors had been discovered," Liberles says.[3] But a few years later, Liberles, one of Buck's own academic progeny, revealed that there's more to the story than just that original set of odorant receptors.

The Mystery of the Connected Brain

In his office at Harvard Medical School, Liberles swiveled his head to check his computer every time his email dinged. He was waiting for an update about a paper his group had recently submitted for publication. Above him, his shelves were stacked with sheaves of paper and books, with chemistry and biology texts standing side by side. Trained as a chemist,[54] Liberles was an unlikely olfactory sleuth—much like former immunologist Linda Buck.

Liberles attributes his interest in smell directly to his chemistry training. He got up from his seat to retrieve a paper-covered workbook from his shelves. “Chemistry 27 Laboratory Manual Spring 1998” was written on the book’s paper cover dotted with chemical structures. He flipped to a page: “Lab 5: Esterification I, II, III.”

"I was teaching a synthetic chemistry lab on esters, and how you can add one methyl group on an ester, and it changes from apple to cherry or to banana,” he says. “So, you can get wildly different odor perceptions from very simple structural chemical changes,” he says. "I thought it was a really beautiful system for getting at behavior and perception.”[3]

This system’s beauty comes partially from its unique neuroanatomy. “You can go directly from the sensory input to neural centers that control the behavioral output, in only a few synapses,” says Liberles.[3]

In the visual system, there are four synapses,[55] or, junctions between the rods and cones in the eyes and the primary visual cortex responsible for detecting patterns, edges, and directionality in visual information.[56] That’s four stops from detecting light to the earliest stages of actually processing it, before the brain can even make sense of it. The signal must cross two of those synapses before visual information even leaves the eye.

Olfactory information takes a much shorter path through the brain.[57] The neurons sitting in the nasal epithelium send their axonal arms to converge in clumps called glomeruli in the olfactory bulb. From there, olfactory information can take a couple of different routes through the brain. One takes it straight to the amygdala, an almond shaped brain structure associated with emotion and motivation.[58] (Several studies debate the role of the amygdala in pairing a smell with its emotional valence and instead suggest that its role is more sensory than interpretive.)[59]

Another shoots it over to the entorhinal cortex, which is involved in memory formation[60] and which, in turn, connects to the memory epicenter of the brain, the hippocampus. A third sends the olfactory information to the piriform (also called olfactory) cortex.[61] All three regions—the amygdala, the entorhinal cortex, and the piriform cortex—then bounce that smell information and interpretations of it over to the frontal cortex, a higher-order brain region required for cognitive processes like decision making.[62]

So, there are two stops from the nose to emotion, two stops to memory, and three to decision making, compared to the four stops it takes visual information to get to the brain region in charge of decoding what it is you’re looking at. The nose gets straight to the important stuff.

Liberles speculated that there might be an evolutionary reason for an olfactory shortcut in the brain. “There's a looming hawk that's about to eat a mouse. And the mouse needs to know it’s above him, it needs to know its shape, and needs to know its size, to then figure out ‘oh, that’s a predator,’” says Liberles. With smell, the mental leap from detecting an odor to avoiding a predator is much shorter.[3]

Most behaviors become associated with smells through contextual pairings. Rachel Herz, a neuroscientist at Brown and author of the popular science book *The Scent of Desire* published in 2007, wrote that she finds the scent of skunk comforting, rather than repellant. On a beautiful car ride when she was a child, the wind wafted the smell of skunk into the car. Her mother exclaimed that she loved the smell, “And from that day on I loved the smell of skunk. I did not realize this was abnormal until a year or so later…” Herz wrote.[63]

Similarly, the smell of coffee and breakfast might draw someone greedily to the kitchen in the morning, but only because that person has learned to connect those odors with the pleasure of a meal. For veterans, the smell of diesel is a powerful reminder of combat to soldiers who fought in the Vietnam and Gulf wars.[64] Without repeated contextual pairing, there's nothing about the smell of coffee that would inspire pleasure or diesel that would necessarily make a person feel fear.

A canonical memory test in mice takes advantage of this phenomenon to test a mouse's ability to learn and remember. Scientists pair a context that includes a unique smell with something painful or unpleasant, like a foot shock. Eventually, the mouse's memory of the foot shock and the sensory details of the context, like its smell, become so intertwined that the context alone makes the mouse anxious.[65]

Gloria Choi, professor and olfaction researcher at MIT, studies those brain circuits that are responsible for coupling experiences to smells, and smells to behaviors. Even as a postdoc who, like Buck and Vosshall, worked with Richard Axel, Choi was curious about the connections within the brain that lead from smell to behavior. In her office, she describes this as a "black box" in the olfaction field.

"How do our brains learn how to associate a given stimulus with a different context, or a different meaning? And how do we store that information in our brain and also appropriately produce behaviors that are consistent with that memory?" she asks.[51]

The brain regions involved with associating smells and contexts, processing this information, and inducing the appropriate response have remained elusive because the types of studies necessary to uncover them are difficult. As most of us have experienced, it's hard to control a smell once it's on the loose. And it's especially challenging to control when, and how much, a mouse inhales.[66] So to hunt down the brain regions connecting smells to learned behaviors, Choi and her research team in the Axel lab reworked the olfactory system so they could directly activate neurons in the piriform (aka olfactory) cortex with light, instead of activating them by routing smell information through the olfactory bulb.

The technique of using light to trigger neuronal signaling—even in neurons completely unconnected to the visual system—is called optogenetics. Optogenetics uses viruses to infect cells inside of an animal or in a dish. The virus injects its modified genetic material into the cells, making them express light-activated channels in their membranes. When light shines on these cells, the channels open and turn on the neuron.[67]

In their experiment,[68] Choi and her co-authors targeted a laser into the brain, enabling them to shine a light on the piriform cortex and turn the neurons on at will which made the mouse think that it had smelled something. Mice learned to flee from these phantom smells when they were delivered with foot shocks, but were drawn to them when they were paired with water (for thirsty mice), or with the presence of a female (for lonely males).

Surprisingly, they were able to get fine enough optogenetic resolution that they could activate different regions of neurons in the piriform cortex to create two different 'smell' perceptions, which could be paired with different learned outcomes: smell one was paired with a foot shock on one side of the arena, and smell two was paired with safety. When Choi triggered smell one by shining light into the mouse's piriform cortex, the mouse took off running to the opposite side of the arena. When she triggered smell two, the mouse stayed put—revealing that even with phantom odors, mice have can have powerful learned behavioral responses to smells.

"All these stimuli produce behavior not as innate, but as a function of learning," says Choi. "Our lab is interested in that component."[51] Others, like Liberles, are more interested in how odors trigger innate behaviors in the absence of learning—which gives researchers insight into the broader question of how genes versus the environment shape behavior. Liberles thought he might know what was connecting odor to instinct, too: the commonality of his new family of olfactory GPCRs in creatures from fish to rodents to humans hinted that TAARs might play a role that differs from that of the classical odorant receptors.

The year after he and Buck published their discovery of a new family of odorant receptors in their 2006 *Nature* paper, Liberles got his career break: a move to Harvard Medical School as a professor of cell biology. "That discovery was what enabled me to move on from my postdoc to get the faculty position, and enabled me to have the opportunity to investigate other questions that I think are really fascinating as well," Liberles says.[8]

One such question was whether he could find other odorants that trigger TAAR signaling—and through them learn TAARs' purpose. Since the mouse pee had been such a rich source of TAAR-activating smell molecules the first go around, Liberles and his new lab took the next logical step: "We wanted to test various urines from animals of different ages, or physiological states, or species," he says.[8]

But where to get potentially fear-inducing pee? Liberles turned to the PredatorPee.com, the purveyor of fine urines from coyotes, bobcats, wolves and more. ("It's amazing what you can buy online," Liberles says.)[8] Even their attractively named 'Butterfly Lure' liquid that supposedly brings the winged creatures flocking to your garden is made of pee. For indoor use, there are PeeShots! (punctuation theirs). In addition to such readily available predator urines, Liberles also took a look at human urine—purchasing it from a clinical samples repository in New York.[69] (Liberles didn't take advantage of a cheaper and more ready supply of it "…for protocol reasons," he wrote in an email.)[70]

Just as they did in the first study, Liberles' team tested how kidney cells modified to express TAARs reacted to urine—from predators, this time.[71] The cells expressing TAAR4, specifically, went crazy when diluted bobcat and mountain lion pee—but not mouse, human, or rat pee—washed over them.

This meant that something specific in cat urine was triggering TAAR4. Now they had to find it. So Liberles' team, led by graduate student David Ferraro, filtered bobcat pee into fractions of differently sized molecules. "We reasoned that TAAR4 detected a specific chemical enriched in predator urine, and that this cue might function as a kairomone," wrote Ferraro and Liberles as rationale.[71] (Kairomones are inter-species olfactory signals.)

They performed a series of chemical tests, and eventually identified the relevant molecule as a chemical called 2-phenylethylamine. Ferraro and Liberles were curious—how common is 2-phenylethylamine? Is it restricted to bobcats, or is it a pan-carnivore molecular signal? To find out, Ferraro, Liberles and their team tested 123 samples obtained from 38 different kinds of mammals at local zoos and (again) from PredatorPee.com.[71]

"The veterinarians at the zoo loved it," Liberles says. "They collected it fresh, and froze it immediately—so that you wouldn't have bacterial contamination, for example—and then sent it in the mail. And every day, it was like Christmas with a new urine arriving." Like Christmas, but more pungent. "I encouraged people who worked with TAAR ligands to work in the fume hood," Liberles says. "Some of these are not the most pleasant of odors."[8]

They discovered that 18 of the 19 carnivores they tested had high levels of 2-phenylethylamine in their urine, supporting their hypothesis that this molecule served as a pan-predator warning signal to prey animals. At that point, they had found that predator pee triggers TAAR4 in cell culture and on neurons, they found the specific molecule in predator pee responsible for binding TAAR4, and they found that many predators had this molecule in their urine.[71] But what did this mean, they asked, for a living, breathing, smelling animal?

Liberles' collaborators ran a few tests. In the first, they put a rat in a square arena and dribbled water, lion urine, coyote urine, or 2-phenylethylamine in a corner. Rats did not like the corners of the arena with the predator pee or the 2-phenylethylamine one bit, and avoided them. Mice acted the same way. When the 2-phenylethylamine was removed from the lion urine, the rodents didn't mind it as much.[71]

These behaviors made the research team think that the TAAR system might be connecting to innate behavior pathways. When a mouse smells a predator like a cat for the first time, the mouse knows to avoid it regardless of whether the mouse was born in a house with cats, or in the sterilized cat-free lab environment. Similarly, a 2013 paper found that fish that have never before smelled the odor of decaying flesh freak out when they smell cadaverine and putrescine—key components in olfactory bouquet of decaying cadavers—and that one TAAR responds specifically to cadaverine.[72] This means that these predator and death avoidance behaviors are hard-wired, not learned, innate behaviors.

Liberles thinks that the ability of TAARs—in this case, TAAR4—to trigger such strong, innate predator avoidance in rodents is a way of cutting short the already abbreviated pathway between a smell and behavior. "With the olfactory system, especially with innate behaviors, a specific chemical is enough to be a trigger," Liberles says. "The olfactory system has so many different receptors that it can afford to tune a few to particularly salient chemicals like predator odors,"—like with speed dial, just in your nose.[3] Having a few key danger sensing odor molecules that are ready and able to induce predator avoidance behaviors at the whiff of a scent further shortcuts the route that smell takes through the brain.

It makes sense, but this conclusion troubled Liberles. There are more innate behaviors than just predator and dead body avoidance; finding a mate is just as crucial for evolutionary fitness as not being eaten. So theoretically, if there were TAAR-binding odorants that mice found repellant, which keeps them away from predators, then there should also be alluring odorants recognized by TAARs that trigger…other behavior.

"So in 2011 we had this model that several of the TAAR ligands were aversive, and this created a little bit of a conundrum because TAAR5 was detecting mouse urine—male mouse urine—and mouse urine is a very attractive odor to mice," Liberles says.[8]

In his very first paper about TAARs, Liberles found that mouse TAAR5 recognizes a molecule called trimethylamine (TMA), a molecule mainly found in male mouse pee. To humans, TMA smells terrible, like rotten fish. Two scientists who wrote a *Current Biology* dispatch on the subject compared the smell to "a public urinal at the Oktoberfest."[73] Humans who secrete excess TMA because of a hereditary condition unsympathetically called fish odor syndrome or trimethylaminuria are often ostracized because—through no fault of their own—other people find their body odor repellant.[74] Rats are the same: they don't like the smell of TMA at all.[75]

But mice, Liberles found, love it, a response that requires TAAR5.[75] The effect of TMA to draw mice of the opposite sexes together via its interaction with TAAR5 constitutes an innate behavior, this time of a more friendly variety than that elicited by the cat urine.

The discovery of the TAARs and their connection to such hardwired behaviors provides hard biological evidence for the fundamentality of odors to actions, but it also leaves more questions open than closed. For Liberles, exploring TAARs is an exciting way to get at his real question: what connects sensation to behavior? Looking ahead, Liberles thinks that the future of olfaction research is in connecting odors to receptors to behaviors. He uses the example of the disparate effects that stimulating TAAR4 (run away!) versus TAAR5 (oh hey there) have on mice.

"TAAR4 is mediating aversion and TAAR5 is mediating attraction, in the mouse, so how do TAAR4 and TAAR5 activate different behaviors? Are they coupling to different neural circuits in a predetermined way, and if so what are the differences between those circuits?" he asked.[8] "How do you get these divergent types of behavioral responses from particular chemicals? That, I think, is where the field is moving," he says.[3] Leslie Vosshall adds in an email that, "Every time the field says there are no more families of odorant receptors, someone finds one. So I think it's possible we are not done yet."[15]

We may be coming closer to understanding the neural circuitry that we share with other animals, but what a mouse or fly finds intoxicating does little to educate us about the forces that shape our own perceptions. What do smells do to, and for, us?

The Mystery of the Silent Conversation

Through our noses, we continually engage in a silent conversation with the world around us. Rodent studies have revealed enticing details about this olfactory back and forth.

But what we really want to know is how our noses guide our actions, with or without our conscious permission. Only human studies can tease apart how smells consciously and subconsciously govern our thoughts and behaviors, but making the leap to human olfaction is difficult for several reasons, not least the sheer complexity of the human brain.

The problem, in essence, is that our sense of smell moves us in ways we can't always detect. While experiments in rodents clarified the pieces of basic olfactory biology that are conserved between mice and humans, studies untangling the links between smell and human behavior will necessarily be more complicated, and the interpretation of their results will be murkier.

First, though, we need to take our fifth sense seriously. The first issue to be addressed is the misconception that decoding the sense smell might not be even worth doing. After all, humans don't even smell particularly well—right?

Not so, says Pamela Dalton, a professor at Monell Chemical Senses and expert in human olfaction. "I wish people knew much more that the human nose is more sensitive than most people think it is," Dalton says. "Even though we are certainly not as good as rodents or dogs, simply because we don't have as many receptors in our nose, we are still pretty darn sensitive."[76] Science journalist Carl Zimmer has written that if there were two Olympic swimming pools and someone squeezed into one of them just a few drops of the molecule that gives natural gas its rotten egg odor, we could sniff out the more pungent pool. That's how sensitive our noses are.[77]

One researcher designed an experiment that dramatizes this. Noam Sobel, now at the Weizmann Institute of Science,[78] wanted to gauge how well people smell (and whether they need both nostrils). So he and his research team asked nearly three dozen 18–26 year olds[79,80]—including students at the University of California, Berkeley—to track chocolate extract through a field on the Northern California campus using just their noses.[81] The study participants—clad in elbow-pads, kneepads, gloves, and blindfolds—navigated on all fours.[79] Considering that most humans don't typically follow their noses in the literal sense, they did pretty well. And they got even better with practice, revealing that human noses at baseline are better than we give them credit for, and become even more so with experience.[79]

The second myth to debunk is the idea that smell isn't all that important. Smell is the invisible, silent, and untouchable sense—which makes it difficult to appreciate, and even harder to study. "People do not ordinarily doubt the enormous importance of hearing and vision in their lives, but it is not uncommon for people to differ in talking about the importance of their sense of smell," wrote the authors of a study published in the journal *Chemical Senses* in the late 1990s.[82] The researchers found that 50% of people would prefer to lose their sense of smell than to go deaf in only one ear, or have their left small toe cut off. Another survey of 7000 people reported that 53% of 16–22 year olds and 48% of 23–30 year olds would sacrifice their senses of smell to keep their phones or laptops.[83]

It's "nice to have, not a need to have," says Sara, a social media manager engaged to Adam.[84] She may just be being kind—she is sitting next to Adam, and Adam can't smell a thing.

Adam says that he learned that his nose doesn't work during his freshman year of college. As he walked a date from dinner back to her dormitory one autumn evening, he remembers her asking whether he could smell the odor of burning leaves. Adam smelled nothing, and brushed it off, "No I never smell anything," he said, "I have a terrible sense of smell." But she insisted, "'No, no you have to smell them,'" Adam remembers her saying, until he finally relented and agreed to a smell challenge.

Years later, he doesn't remember the specifics—he vaguely recalls that she may have wafted candles, nail polish remover, or perfume at him. But Adam detected none of the scents, slowly realizing that maybe he didn't just have a terrible sense of smell—he might have none at all. He says an appointment with an Ear, Nose, and Throat doctor confirmed his date's diagnosis: Adam had congenital anosmia, meaning he had never smelled anything in his life.

Although he and Sara joke that maybe his absent olfaction is the reason for his inattentiveness, there are real-world consequences for his inability to smell "We could literally be walking into a fiery building, and if he was looking at something else, he wouldn't notice," Sara says. She's only half joking as the two sit together on their sofa. Proegler calls her his "life alert" because of the times she's saved him from eating spoiled food. Asked if he knows why he can't smell, Adam says no. "I went and did all the scans and everything, and they didn't find anything," he says. "But no, I don't know."[84]

Adam's inattentiveness to his own missing sense may seem to contradict the idea that smell is important, but in fact his situation highlights the subtlety, nuance, and individuality of the ways in which olfaction contributes to human experience.

People who once had a sense of smell, and lost it, are acutely aware of this. "It's a weird affliction," wrote one anosmic patient in a case series conducted by researchers at NYU. "We don't need seeing-eye dogs or sign language to interact with our environment…We can do virtually everything we could before we lost our sense of smell, except enjoy the immensely important aspects of human life that most people take for granted."[85] That would include tasting food, for example, since smell accounts for 80% of the perception of flavor.[86] "It was extremely depressing to have no sense of smell at all. You realize that rooms have smells, water has a taste, etc.," wrote another patient in the series. These patients described food as like sawdust, cardboard, and paper with glue. To them, coffee and tea both tasted like hot water, and were indistinguishable.[85]

But while the underestimated sensitivity of our sense of smell and its contribution to the sense of taste brings its importance into better focus, major challenges remain in actually carrying out the studies necessary to understand the human sense of smell. Humans are far more complex than mice, especially compared to mice that have been inbred and raised in a sterile and consistent lab environment that suppresses any diversity. Human beings differ in nearly every way from one another at the outset of almost any study. And one can’t simply manipulate an adult human’s genes or make a person’s neurons fire at will.

Still, said Jess Porter, one of Noam Sobel’s former graduate students, speaking to Josie Glausiusz at *Discover*, “We can exploit the fact that we can communicate with people and ask them to do really bizarre things exactly how we want them to do it.”[80] Like tracking chocolate extract by its smell through a field in northern California.

“If you want to study cognition, then I think humans are the right animals to study. And if you design your experiments carefully, then you can get good and reliable results," says Anat Arzi, a recent graduate of Noam Sobel’s lab at the Weizmann Institute in Israel.[87] “Not only can you record the neuroactivity, or physiology in response to odors, but you can actually tell what the person is thinking about the odor."

Andreas Keller, a postdoc in Leslie Vosshall’s lab who made the switch to human olfaction after studying flies, says that that is the *only* advantage to studying humans. “You can find out which things smell similar to fruit flies and so on, but what quality the smell has, the conscious experience of it, is inaccessible whereas in humans, it's accessible,” he says. Making the switch from an experimental system that you can manipulate, though, has not been easy. “It is a little weird, all the things that are obvious and easy to do are suddenly impossible. And when I talked to my lab members who study fruit flies, they always have higher standards to show something. And I just say that's not possible, or not legal, to do.”[88]

Even with that gift of conversation, drawing conclusions about the nature of human olfaction is fraught with challenges because people are not all the same—but Keller thinks interpersonal differences are where the interesting results lie. At the genetic level, nearly one-third of odorant receptor alleles differ from person to person,[89] and Keller found that this can make the same molecule smell completely different to three unrelated people. One person might think that a testosterone derivative found in body secretions smells like sweaty urine, another may find it redolent of sweet flowers, and a third might not even notice a smell.[90]

“I say, let's study the variability between the individuals,” says Keller. “Let's find out why that is, and then let's find out, based on that, how smell works in an individual. I think it's a great opportunity, those differences. You can learn a lot about how smell works, it's just you can't make any broad, species-wide statements. But who needs that?”[88]

In addition to genetic differences, context accounts for another large chunk of the inter-personal variation in smell perception. Dalton has been finding that the context in which she puffs the smell of feces at study participants changes how intense they find the odor. “If they're looking at an image of fluffy white sheep in a pasture—which could smell of fecal matter—they rate that odor as much less irritating or annoying. Much less intense as when they're looking at the image of a human porta-potty,” Dalton says. Similarly, Dalton said that body odor smells are rated much more negatively and more intensely when they’re paired with images of a homeless person, rather than with a professional athlete dripping with sweat. She called this project her “fun pilot work.”[76]

The variety—and complexity—of human olfactory experience makes it difficult to isolate just one single component of the sense to examine at a time. Our genetics, an odor’s context, our memories of a smell, and even how sick we are of a food can all affect our perceptions. But even if human beings can’t be reduced down to a simple stimulus and its triggered response, still, some scientists are exploring how the sense of smell shapes human behavior.

The question of whether there are any innate olfactory triggers of human behaviors is up for debate. “There are people who say that there are no innate smells,” Liberles said, although humans express

TAARs as well. “I haven't met very many people who like the smell of rotting flesh, or rotting food. But I think that the definitive experiment hasn't been done.”[3]

In an attempt to perform such a definitive experiment,[91] professor Denise Chen—then at Rice University, now at Baylor School of Medicine[92]—and her graduate student Wen Zhou[93] turned to man sweat. Zhou and Chen had a group of men purge themselves of scents, fragrances, and smelly foods like asparagus for two days, and then subjected them to either a scary movie or a slapstick comedy while she collected their sweat in armpit pads. (They used men as sweat donors because men usually have larger body-odor producing apocrine glands than women do).[91]

Chen and Zhou then cut up the sweat soaked armpit pads into little pieces, pasted them under the noses of a group of female volunteers, and had the women evaluate a series of faces for fearful or happy facial expressions. As the facial expressions became more ambiguous, the women with the fear-sweat under their noses became more likely to score the expressions as fearful than the women with the sweat-free control pads under their noses were. The happy sweat didn’t influence the women’s perceptions one way or the other, which the authors speculated might be because happiness doesn’t communicate information as urgently relevant for survival as fear does. They added, however, that they thought the proclivity to attribute fearful emotions to ambiguous faces when paired with fear sweat was a learned behavior: “Through learning, certain chemosensory input became associated with fearful visual information and acquired emotional value, and the ability to form such associations may have increased fitness.”[91]

While this study suggests that sweat might play a role as a social signal among humans, the investigators identified no specific chemical signal or cocktail of signals, their control was a pad with no sweat rather than neutral sweat, and they used only one kind of task to assess whether body odor can communicate emotion. It generates interesting theories about sweat as an odor-driven emotional cue, but few clear-cut answers.

Four years later a group from the Netherlands led by social and behavioral psychologist Gun Semin,[94] however, found additional evidence that aligned with Chen’s findings using a slightly different approach. After having a group of men do an odor-purge for two days, they collected sweat from men watching *The Shining* (the fear sweat condition) and men watching *Jackass* (this, apparently, was supposed to evoke feelings of disgust). They used clean sweat pads as a control.[95]

Instead of measuring how women scored ambiguous facial expressions while smelling the sweat pads, they measured the women’s actual facial expressions by monitoring facial muscle movements when the scent of scared versus disgusted man sweat wafted towards them. They scored widened eyes as fearful expressions, and curled lips as disgusted expressions. They found that women sniffing the fear sweat widened their eyes more, and women sniffing the disgusted sweat curled their lips more—unconsciously mimicking canonical fear or disgust facial expressions.[95]

Gun Semin’s team—who also tracked sniff volume and how women performed on visual attention tasks when smelling the different odors—called this transmission of embodied emotions via smell “emotional contagion.” They wrote that these results went against the “commonly accepted assumption that human communication runs exclusively via language or visual channels.”[95]

Another, subsequent study from this group again used similar methods to interrogate whether smelling happy sweat could also subconsciously tweak a woman’s tweak facial expressions—the results of their small 35 person double-blind study hint that the answer is yes.[96] Both of these investigations draw on Denise Chen’s research as rationale,[95,96] dramatizing the need for a large body of evidence that weighs in on the question of human olfaction. Individual studies contribute interesting clues—together, they can begin to form a stronger basis for hypotheses.

One problem with smell as a means of communication is that many cultures frown on overtly sniffing strangers. This made Noam Sobel's team speculate that there may be other, more covert ways to take another person's olfactory measure. Take handshakes, for instance. It's well known that handshakes are great ways to communicate germs between individuals—why not smells?[97]

To test their idea that handshakes might be able to transfer odor signals from one person to another, Sobel's team had ten study participants shake a gloved hand with a bare hand and analyzed the molecules that transferred between the two. Ten out of the ten people managed to transfer odor signals—also used by dogs, rats, and insects—from their bare hands, to the gloves.[97]

So how do these potential signaling molecules get from the hands, to the nose? Apparently, people sniff their hands a lot without even realizing it. Sobel and colleagues covertly filmed 175 study participants before and after they met a planted experimenter, who shook their hands (but 22 of them were eliminated for using their phones). At baseline, about half of the study subjects used their hands to touch their faces. This coincided with results from another experiment that showed increased nasal airflow when people raised their fingers to their faces—suggesting that they truly were sniffing their own fingers when their fingers were near their noses. After shaking hands with a planted 'greeter' of the same sex, participants increased touching their faces, especially around their noses, with the hand they used to shake. If the greeter was the opposite sex, however, study subjects did more sniffing of their non-shaking hand.[97]

When Sobel's team had the greeters wear odor-spritzers around their wrists containing either an odorant thought to be a male social signal or an odorant thought to be a female social signal, the study participants reduced how much they sniffed their shaking hand compared to when the greeters were wearing no scent, or just a regular perfume. This complicates the hypothesis that handshakes are sending chemical social signals.[97]

Semin, the senior author of the studies that assessed the effects of sweat on facial expressions, called this paper a "carefully packaged set of studies" in a commentary he co-authored and published alongside the study in the same issue of the open-access journal *eLife*. "The elegance of introducing a new perspective, as Sobel, Frumin and co-workers have done in this study, is that it not only opens our eyes to a previously ignored phenomenon, but also stimulates new research questions," he and his co-author wrote.[98] These results demonstrate that the sense of smell is a potential conduit for information flowing from both our environment and other people and, it shapes our behaviors in ways we have no conscious knowledge of. Yet it remains phenomenally under-characterized.

Whether our unconscious responses to odors in our environments—like sniffing our hands, wrinkling our lips, or widening our eyes—are innate is another question. Olfaction researcher Pamela Dalton acknowledges that the sense of smell can unconsciously trigger behaviors, but thinks that it will be difficult to determine whether these are innate behaviors like those triggered by the TAARs in mice—or whether they're learned ones. "The olfactory system is formed at the end of the second trimester. So everything the woman wears or eats that partitions into the amniotic fluid is fueling the fetus's olfactory system. So, they're not born a tabula rasa."[76]

Nevertheless, Dalton adds, "A great deal of odor perception goes on below the conscious level, so it doesn't require someone to necessarily be aware of what they're smelling or even to recognize and say 'oh there's an odor there,' but those molecules can have an effect."[76]

Those effects can be felt even when the smeller is fully unconscious. In the fall of 2014, Anat Arzi, then a graduate student in Noam Sobel's lab, examined how smells detected during sleep might coax smokers to stop smoking. [99] Arzi and her co-authors extracted cigarette odor from smoked cigarette filters, and had 66 adult smokers evaluate the convincingness of the extracted cigarette odor. (During the course of the study, Arzi says that the price of cigarettes went up in Israel and the undergraduates she would have recruited began rolling their own cigarettes, which have a different odor from the store bought ones—so she had to be careful to recruit only those who smoked manufactured cigarettes).[100] They also had to rank the unpleasantness of several canned odors.[99]

The subjects then spent either a day or a night in the sleep lab having cigarette odor wafted at them. If they were in the experimental condition, that odor would be paired with ammonium sulfide or commercially available rotting fish smell—neither, to almost everyone, smell particularly good. When the noxious odor and the cigarette smell were delivered together during sleep, the smokers reported smoking fewer cigarettes the following week, with the greatest reduction the day after the sleep conditioning. When the noxious and cigarette odors were delivered separately or during the daytime, the self-reported reduction was not as large. [99]

We smell with every inhalation, even while sleeping—and at least in this case, odors encountered while asleep influenced waking behavior even more powerfully than those encountered while fully conscious. Arzi says that she was surprised by how powerful the aversive conditioning was during sleep compared to when the subjects were awake. “There was no change after the conditioning during wake and this was surprising, I thought there would be some kind of change, even if it's not so large," she says.[100]

While smells typically won’t wake a slumbering human, “the information is getting in and your brain is able to use it in one way or another,” says Don Wilson,[101] who has also studied how the sleeping brain processes olfactory information and memories.

A commentary about this study compared these techniques to transforming “odors into Trojan horses, sneaking into the sleeping brain and creating associations between cigarettes and noxious smells,” but called for more longitudinal studies to see whether using odors to train away bad behavior while sleeping can actually create sustainable changes. [102]

The writers also cautioned that the subjects all expressed a desire to stop smoking—which therefore makes it difficult to apply these findings to situations where desires are more complicated.[102] Science writer Mo Costandi added in *The Guardian* that self reports of smoking habits may not actually reflect reality, and suggested that future studies may want to find another way to track changes in behavior.[103] Arzi agrees, and says that if she were to do this again, she would correlate the self-reports with a nicotine biomarker she could measure in blood and urine.[100]

Studies of smells as triggers of complex human behavior and as conduits for human emotions are still in their early stages, but smells are well known—if underappreciated—indicators of hygiene, health, and disease. In fact, foul smells and illness are so intertwined that at one time bad smells were thought to actually cause illness. The odor of a wound can tell doctors whether it’s festering or not, and several diseases give the sufferer a unique aroma; yellow fever, for instance, causes the sufferer to smell putrid and diabetes can give people breath that smells like nail polish remover. That nausea you feel when sniffing a container of spoiled milk, or that shudder of revulsion that left you queasy when you smelled a food that had once made you vomit protects you from a second bout of food poisoning. Our sense of smell helps keep us safe—and yet we still know so little about it.

“That's what gives it that potential,” says Keller. “It's simple, but hasn't been worked at yet. It has a lot of potential to discover some basic principles of perception."[88]

The Mystery of the Science of Smell

Of all the barriers to greater understanding of the human experience of olfaction, perhaps the most insidious is language, the tool with which we express and organize knowledge. "It's almost like we have a neurological deficit for naming smells," Jay Gottfried, a neuroscientist at Northwestern University, told Greg Miller at *Wired*.[104] While we are able to provide distinct visual adjectives for visual stimuli, smells are typically described in relation to their source – which can bias how we perceive them.

Olfactory artist Sissel Tolaas's response to this linguistic gap was to develop her own smell language, using nonsense words to name smells in order to un-link olfactory cues from the biasing names of their sources.[105] Instead, she uses words like 'haqse' to describe the odor of citrus fruits, and 'casca,' to describe the rather unique odor of sweat mixed with car metal. Though interesting, this thought exercise hasn't caught on with the olfaction research community, or the public.

With our olfactory speech impediment and persistent removal of smells from our environments with fragrances and deodorizers, it's easy to forget that humans are smelling—and smelly—beings, much like our rodent cousins. But our relegation of olfaction to a sense that is used only covertly, and with embarrassment, to assess the world around us is a product of culture, not biology. When Lewis Thomas wrote thirty years ago that we could gauge the future of biology by estimating how long it would take to have a comprehensive explanation for olfaction, he may have hoped we'd be further along by now.

But Thomas's underlying message holds true. The sheer number of notes in the complex bouquet of olfaction requires that the many subspecialties of the life sciences work together towards a common goal. Buck was an immunologist before she started studying olfaction. Liberles a chemist. Geneticists, chemical biologists, neuroscientists and psychologists all have tools to bring to bear on the central question of how smells influence our thoughts and actions. Over the last three decades these researchers and their colleagues have developed a molecular framework for understanding the early steps of odorant detection, and created the tools to begin assessing the links between sensory input and behavioral output.

There are still myriad open questions. In fact, every question is still open. How molecular shape confers odor quality remains unclear, and shape theory continues to be an imperfect explanation for how olfactory receptors detect odorants. Less than a decade ago, Stephen Liberles discovered an entirely new class of odorant receptors after researchers in the field had thought they'd closed the case of the mystery of smell detection—and there may yet be more families of smell receptors hiding in the folds of nasal epithelium. We still don't know precisely how the fluidly overlapping influence of the mind's experiences, biases, and associations shape the brain's detection of scents, or what's under the black box that continues to obscure the intricacies of olfactory circuits.

The reward of the research that will address those mysteries will accomplish more than just satisfying our curiosity about how the pieces of the olfactory puzzle fit together. They will reveal fundamental insights into human experience and human nature. Even as our interactions with the world become increasingly sophisticated and we continue to try and distinguish ourselves from those animals who overtly communicate through their noses, invisible stimuli still manage to find their way inside of us to interact directly with our brains, shaping how we sense and behave in the world around us. We aren't fooling anyone—we smell.

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