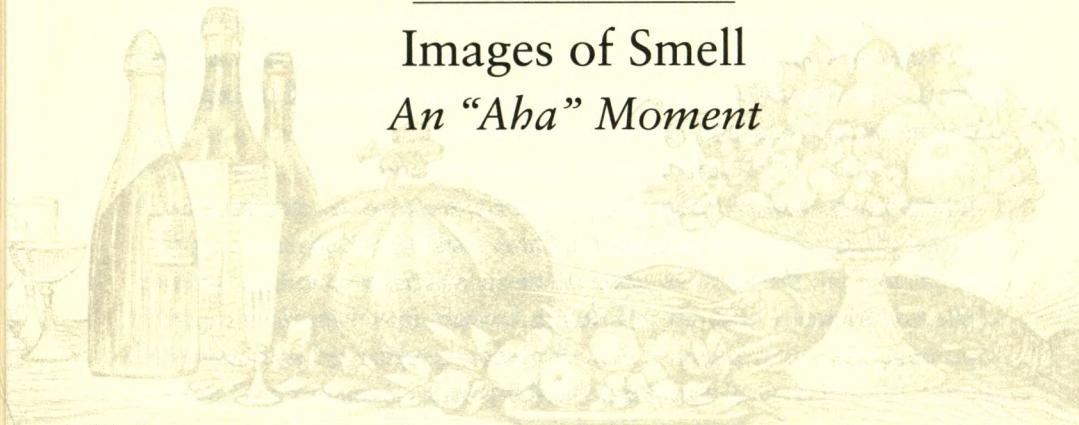


# CHAPTER SEVEN

## Images of Smell *An “Aha” Moment*



From the olfactory receptor cells, the pathway to smell perception in the brain passes through a series of regions: the olfactory bulb, the olfactory cortex, and the orbitofrontal olfactory cortex. The first processing steps take place in the olfactory bulb. Because of its critical role in forming the smell image that is the major component of flavor, we will take several chapters to explain how it works.

### The Olfactory Bulb

As its name implies, the olfactory bulb is shaped like an incandescent light bulb, sticking out in front of the frontal lobe of the brain. In comparison with the visual pathway, which starts in the retina and progresses through the thalamus to the visual cortex, it is as if the olfactory equivalents of all these structures are compressed into just the olfactory bulb. A big challenge is understanding all that goes on inside, and this requires getting familiar with the cells.

Figure 7.1 shows the olfactory pathway in a representative mammal such as the rat. When smell molecules bounce in and out of a receptor binding pocket in an olfactory receptor neuron (*orn*), all an individual cell “knows” is how much the features of the smell molecules have tickled its binding sites. Again, the greater the tickle, the more the cell responds by generating impulses. The code that it sends on to the olfactory bulb is therefore in the form of frequency of impulses in the olfactory nerves (*on*),

## FORMING THE PICTURE OF SMELL

**Odor Molecules**  
activate olfactory receptors.

**Smell Image**  
of the molecules is  
formed by glomerular layer.

**Enhanced Smell Image**  
is formed by glomerular  
layer microcircuits.

**Contextual Smell Image**  
is formed by mitral and  
lateral inhibitory microcircuits.

**Content addressable memory**  
is formed by olfactory  
cortex microcircuits.

**Perception** is  
mediated by orbito-  
frontal cortex  
microcircuits.

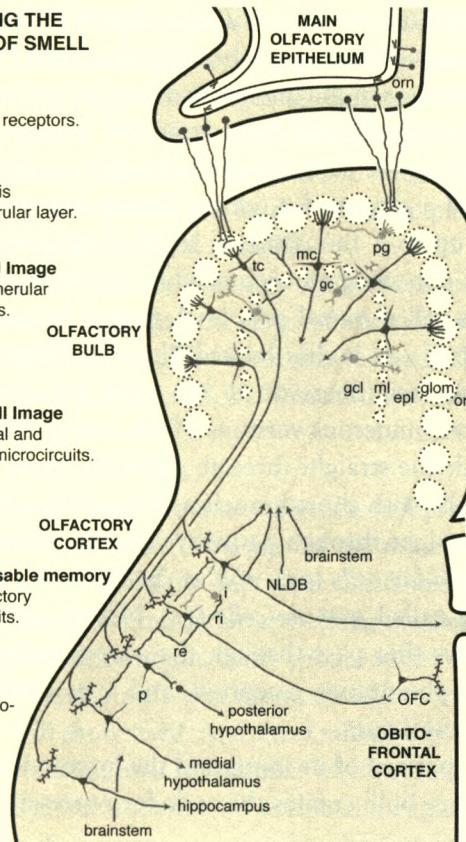


FIGURE 7.1 The smell pathway

On the left, the series of operations to process the smell input from reception in the nose to perception in the cerebral cortex. On the right, the successive stages of the smell pathway that carry out these operations. In the **olfactory epithelium**, the main type of cell is the olfactory receptor neuron (orn).

In the **olfactory bulb**, the main types of cells are the mitral cell (mc); tufted cell (tc); periglomerular cell (pg); and granule cell (gc). The cells lie in different layers: olfactory nerve (on); glomeruli (glom); external plexiform layer (epi); mitral cell body layer (ml); and granule cell layer (gcl). In the **olfactory cortex**, pyramidal cells receive input from the olfactory bulb and connect to interneurons. Central fibers extending out to modulate the olfactory bulb cells arise in the nucleus of the horizontal limb of the diagonal band (NLDB). The **orbitofrontal cortex** (OFC) is represented by a single pyramidal cell to conserve space.

which does not tell much about which smell it is. This means that the code for smell molecules, the code the brain reads, must lie in the differences between the responses in the different cells.

In the olfactory bulb, the fibers from the several thousand receptor cells, all containing the same type of olfactory receptor, converge on a single site, called a *glomerulus* (*glom*). Depending on the species of animal, there are up to a thousand or so of these sites, each receiving its unique input. Connecting to each module within the olfactory bulb are some large cells called *mitral cells* (*mc*), named so because early histologists thought their cell bodies looked like a bishop's cap, or mitre. The mitral cells send their fibers on to the olfactory cortex. Together with smaller and more numerous versions of the mitral cells called *tufted cells* (*tc*), they provide the straight-through pathway. There are also numerous interneurons, cells with short branches, that are involved with local processing of the straight-through pathways. At the glomerular level they are called *periglomerular cells* (*pg*), and at the level of mitral and tufted cell output they are called *granule cells* (*gc*). Not shown, for simplicity, are parallel pathways that pass through the accessory olfactory bulb, often associated with pheromone reception, and a modified glomerular complex for special odor cues.

Through the pattern of its input and the interactions between its neurons, the olfactory bulb creates the code for representing the stimulating molecules.

### How the Olfactory Bulb Represents Smells

The story starts at Cambridge University with Edgar Adrian, one of the great physiologists of the nervous system. After being a leader in the pioneering advances of the 1930s in the physiology of other sensory systems, he launched into a study of the olfactory system, the last major work of his career. He selected the brain of the hedgehog for his first study in 1943, showing electrical responses to natural odor stimuli. This was an era when biologists often chose species on the basis of behavioral considerations, whereas today there is an increasing focus on a few species available for genetic engineering. No one could doubt that the hedgehog burrowing through the ground lives primarily by its sense of smell!

One of Adrian's recordings became famous because its caption read: "Odor of decayed earthworm." The story goes that, in looking for a natural stimulus with which to test the hedgehog, Adrian found the shriveled remains of an earthworm in a dark and dank corner of his basement laboratory. By the time of these studies Adrian was a famous scientist with many administrative duties, yet he did all his experiments himself (and saved money by using natural stimuli).

Adrian next recorded from the olfactory bulb of the anesthetized rabbit. He put his electrodes in various parts of the olfactory bulb while stimulating with different odors. He found that the cells in different parts responded differently to different odors. We can do no better than quote from his paper of 1953:

So far then it looks as though Acetone molecules will produce an excitation coming mainly from the front part of the organ and from the particular groups of receptors in that area which have this specific sensitivity to it. A strong concentration may bring in other groups but, owing to the structure of the organ, there will always be critical regions where the concentration is only just strong enough to excite and here the specific effect will show itself. And there will also be critical times. At each inspiration the amount of material which enters the nose will increase progressively to a maximum and at the beginning and end of each inspiration the concentration is near the threshold value. The physical and chemical properties of the substance will therefore determine the time course of excitation. For instance, a large spike unit may have a specific sensitivity to Xylol. As the concentration of Xylol in the air is increased, other units will begin to come in during the later part of the discharge. With pyridine and eucalyptus the smaller spikes appear first and the large ones come later on. The result is that the photographic reproduction of the discharge has a characteristic shape for each substance, and this shape is reproduced with remarkable constancy each time the substance is presented to the nose.

The result is that the electrophysiologist, looking at a series of these records, could identify the particular smell that caused each one. We must not conclude that the brain identifies the smell by the same criteria but we can at least see how a great variety of smells might be distinguished without the need for very great variations in the receptors.

The basic concept that odors are encoded by spatial patterns and by their timing dates to this work of Adrian. Remarkably, he suggests how this differential encoding can come about "without need for very great variations in the receptors." As we have seen, very small differences in the molecular structure of the receptors accounts for their ability to respond differentially to specific features of the odor molecules. But Adrian knew the limitations of the knowledge he had at the time. His speculations were limited to the different shapes of multiunit recordings from assorted regions rather than being about actual mechanisms; he did not actually specify that these were "spatial patterns" in the olfactory bulb. He even cautioned against concluding that the brain recognizes smells in the way he could from looking at the different recordings from the different regions.

During my graduate work on the physiology of the olfactory bulb, I made the pilgrimage from Oxford to Cambridge to visit Adrian and discuss my experiments on the cells in the olfactory bulb and how they might relate to his studies. My adviser, Charles Phillips, cautioned me that Adrian was well known to be shy of visitors. Adrian courteously listened to my eager account of my work, but after a while he explained he was urgently needed elsewhere and began to make motions as if, literally, to run away. Our interview ended on the staircase of the old physiology building on Downing Street. My last question was what he thought was the most important problem to be solved in understanding the neural basis of olfaction. Over his shoulder came the reply: "Look to the glomeruli." With that, he disappeared. They were prophetic words.

### A New Method for Mapping Brain Activity

Following Adrian's studies, electrophysiological studies made little progress in characterizing further the responses produced by different smells in the olfactory bulb. The problem was that, in contrast to the situation in vision and somatosensation (touch), where the experimenter knows where to put the electrode in a particular part of the sensory field in order to record from cells responsive to the stimulus, in olfaction we didn't know where to look; we had no a priori knowledge to guide us about where a given odor might be mapped in the olfactory pathway. So although the pioneering studies of Vernon Mountcastle at Johns Hop-

kins University in the somatosensory cortex and David Hubel and Torsten Wiesel at Harvard Medical School in the visual cortex were our inspiration, their electrophysiological approach to characterizing the mapping of sensory responses in the brain could not be used effectively for revealing the central representation of smell.

The breakthrough came from a visit by Ed Evarts, of the National Institute of Neurological Disease and Stroke in Bethesda, Maryland, to our department at Yale in 1974. Evarts was a leading investigator of the motor cortex. During his visit, I explained our experiments on the olfactory bulb and how difficult it was to know where to look for responses to different odors. Evarts responded that we might be interested in a new method that Frank Sharp, a postdoctoral student in his laboratory, was working on. It was a method being developed in the nearby laboratory of a leading biochemist, Lou Sokoloff. Sokoloff had joined with a great pioneer in the biochemistry of the brain, Seymour Kety, and an outstanding young pharmacologist, Floyd Bloom, to develop a method for mapping activity in the brain based on where the brain uses its energy. The method was based on the fact that nerve cells are exquisitely dependent on oxygen and glucose for their immediate energy needs when they are active; this is why we faint if there is an interruption in blood flow to the brain. The energy is required not for the flow of charged ions across the cell membrane that underlies the impulses or synaptic potentials (electrical changes due to the flow of ions at synaptic connections between nerve cells), but for the membrane pumps that pump back the ions to restore the ionic equilibrium across the membrane.

Sokoloff and his colleagues proposed to track this energy by using a slightly modified form of glucose, an isotope that lacks an oxygen on the number two carbon atom in the molecule; hence the name *2-deoxyglucose* (*2DG*). *2DG* is taken up like glucose by active cells but cannot be metabolized further. In large doses it therefore blocks metabolic activity, but if given in small doses (called *tracer amounts*) it shows where glucose is taken up without interfering significantly with it. The Sokoloff method involved injecting the substance into an experimental animal, stimulating in the desired way for 45 minutes, and processing the tissue by exposing slices of it to X-ray film to register where the radioactivity was located.

The early results with the method had demonstrated mapping of the visual cortex in the expected way, giving reassurance that the method

should give reliable results in mapping brain areas where the results could not be predicted. The significance of this work was far reaching for all of brain science, because development of the  $^{2}\text{DG}$  approach led to positron emission tomography (PET) in humans, opening the way to modern brain scans with PET and functional magnetic resonance imaging (fMRI), and their related methods.

### The "Aha" Moment

When Ed told us about this new method, it was still being tested physiologically by Frank. Ed cautioned us that one of the possible disadvantages of the method was that it seemed not to label impulse activity but rather mostly activity at the junctions (synapses) between neurons.

It was one of those moments that change one's life. I looked at my postdoctoral colleague, John Kauer, and we realized that this was just what we needed. The incoming fibers (axons) of the receptor cells terminate in the glomeruli at a distance from the mitral cell bodies where the impulse response arises. Electrophysiological recordings from the mitral cell body were therefore a long way from the glomeruli, but the  $^{2}\text{DG}$  uptake should be right in the glomeruli where the input from the receptor cells makes its connections to the cells in the olfactory bulb. The  $^{2}\text{DG}$  method should therefore be well suited to testing our hypothesis that odors produce spatial patterns of activation of the glomeruli. Evarts and Sharp kindly invited us to join them to test this hypothesis.

### The First Smell Patterns

I traveled in December 1974 to the National Institutes of Health to perform the initial experiments. For stimuli, remembering Adrian and the earthworm, I wanted to include something realistic, so Frank and I went to a local supermarket to buy some strong cheddar cheese. An advantage of the  $^{2}\text{DG}$  method is that it can be carried out in an animal that is awake, so we put it in a loose holder with its nose into an air stream. We did several controls (meaning with no odor) and several with cheese and with the chemical amyl acetate, which has a fruity banana odor. We

did the experiments on rats and rabbits, and, not too hopefully, I left Frank to do the work in preparing the slides.

Early in January, Frank called, elated. There were small dots on the films. Could they mean anything? I asked. Yes, he exclaimed; they were the clearest activity he had seen with the method. Are you sure? I persisted. Yes, he repeated; you should have seen Ed dancing around the laboratory when he saw the dots!

John and I soon returned together to do more experiments, which also gave more positive results. There were sites of increased density on the X-ray films, meaning increased nervous activity, over limited parts of the glomerular layer. So rapidly did the story emerge for us in 1975 that we had to delay our paper to let the paper by the Sokoloff group on the <sup>2</sup>DG method come out first. In our first report by Frank Sharp, John Kauer, and me, we wrote:

It appears that there may be a specific pattern of metabolically active sites within the bulb associated with odor stimulation by amyl acetate. This implies that a specific topographical pattern of neuronal activity might be associated with processing of this odor information. Preliminary results obtained with other odors (e.g., camphor, cheese) suggest that there may be differential spatial patterns associated with different odors or odor groups.

The idea that spatial patterns might play a role in olfactory processing is not new; it originated with Adrian and has been the subject of various subsequent studies. The present method recommends itself for direct analysis of this question.

We noted the advantages of the method: that it shows activity throughout the entire system (indeed, the entire brain) and does not interfere with the responses (as an electrode may do poking an active cell). In addition, it can be applied to an animal that is awake and behaving, and it can reveal activity in response to very weak stimuli. All these advantages applied as well to PET and the other methods of functional brain scans in humans.

To get an overview of the activity patterns and compare them with one another, in 1979 our lab, led by William Stewart and John Kauer, developed a pattern mapping procedure based on the fact that the olfactory

bulb is approximately like a sphere except for the part where it is attached to the brain. We adapted a “projection” used for world maps, with coordinates reflecting longitude and latitude. It is called the *Molweide projection*; you can look it up in any world atlas.

In neuroscience terminology, this produces what are called *flat maps*. Our results showed activity foci within the glomerular layer, characteristic for a given odor. Taken together, the foci are overlapping but different for different odors. We therefore advanced the hypothesis that the odor discrimination postulated by Adrian could be based on discrimination between glomerular spatial activity patterns. The 2DG results also showed that, at the lowest odor intensities (at threshold for human perception), only one or a few foci were present, each focus presumably representing one or a few glomeruli. When odor intensity increased, so did the extent of activated glomeruli. This suggested that the activity patterns could also encode odor intensity.

Given these promising results, it might be supposed that many other laboratories adopted the method to confirm and extend the idea of odor patterns. However, there were several obstacles. The isotope was expensive, which put the method beyond the budgets and resources of most laboratories. The method required tedious histological procedures. And it required the use of radioactivity, which most physiology or psychology laboratories are not set up to deal with.

In the first extension of the method, Leslie Skeen of Delaware worked with Sharp to obtain evidence for pheromone stimulation of the olfactory bulb in the primate. André Holley and his colleagues in Lyon, France, soon adopted the method and supported and extended our results. They pointed out that the different patterns with different odors meant that odor recognition might fall under the general category of “pattern recognition” in the visual system, an essential idea mentioned in the previous chapter, and which has become a central concept for the neural basis of smell perception.

#### Archives of Smell Images

The basic findings with the 2DG method have been greatly extended by Michael Leon and Brett Johnson at the University of California, Irvine.

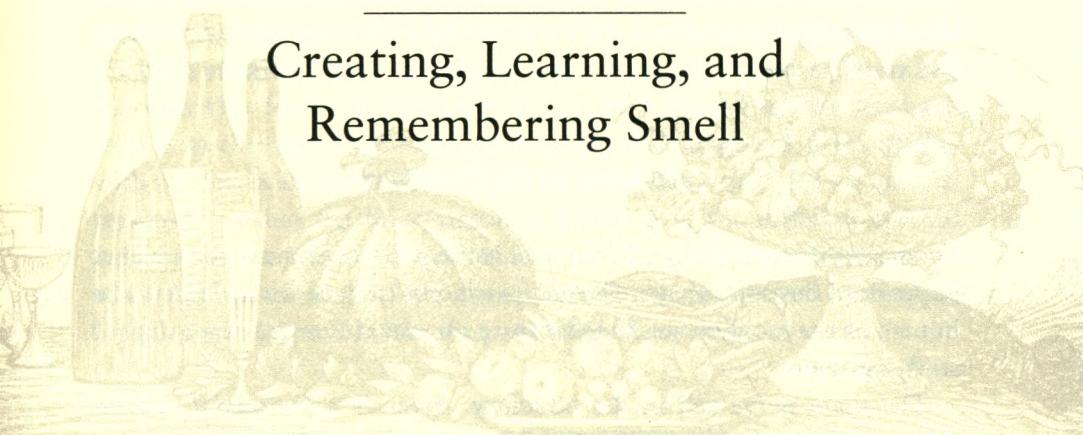
## IMAGES OF SMELL

(Their Web site contains an archive of more than 500 odor images. These and others can be accessed through SenseLab.)

Beginning in the 1990s, a number of new methods have been introduced for analyzing the activity patterns in the olfactory bulb. Many of them are summarized in an article by Fuqiang Xu, Charles Greer, and me published in 2000. (An archive for fMRI patterns can be found on the SenseLab Web site.) Just perusing Leon's or the SenseLab sites gives you the essential impression of how endlessly variable these spatial patterns are, reflecting the endless variety of smell molecules. The brain uses these patterns to create our smell perceptions.

## CHAPTER ELEVEN

# Creating, Learning, and Remembering Smell



In all mammals, the output fibers from the olfactory bulb gather in a bundle called the *lateral olfactory tract*, which connects to the next stage, the olfactory cortex. The tract is relatively short in most animals, but very long in humans, an inch or so (up to 30 mm), in order to reach from the olfactory bulbs, sitting in front over the nasal cavity, to the olfactory cortex on the underside of the brain. The length reflects the expansion of the brain as the neocortex grew in size during mammalian and especially primate evolution. As in the case of the olfactory nerves, all our sensations of smell depend on this connection.

The olfactory cortex is little noticed when the many higher cognitive functions of the cerebral cortex are discussed. What is the olfactory cortex for? Why is it that the coordinated, multidimensional smell image from the olfactory bulb cannot be sent straight to the highest cortical level—the neocortex—to serve as the basis of perception?

Modern research reveals the olfactory cortex to have remarkable properties that make it an essential player in the human brain flavor system. Most significantly, it represents the transition from the steps of extracting features in the smell stimulus to the steps of creating the perceptual qualities of smell. It is where the external features of the outside world meet the internal features of our perceptual world.

If you are able to smell something, it is because of the olfactory cortex. Similarly, if you sense the flavor of something, it is because of the olfactory cortex. Understanding how the olfactory cortex functions has to be an important subject in neurogastronomy.

Out of the extracted odor image of the stimulus in the olfactory bulb the olfactory cortex creates the basis for the human perception of a unified smell perception, what is called an *odor object*. How does it do it?

### Introducing the CEO of the Cortex

To answer this question, we look inside the olfactory cortex to see what happens to the odor image. These experiments can't be carried out in the human or the monkey, so the laboratory rat and mouse are necessary for studying them.

The main nerve cell in the olfactory cortex is a *pyramidal cell*. As shown in figure 7.1, its cell body is shaped like a small pyramid, giving rise to a large "apical" dendrite that ascends to the surface and several "basal" dendrites from the base of the pyramid. There must be something very useful in this arrangement of dendrites, because the pyramidal cell is the main kind of cell in all types of cerebral cortex. One could call it the CEO, the Chief Executive Officer, of the cortex. It is worth knowing something about this kind of cell. Your mind depends on it for normal thinking, and it is the target for degeneration in Alzheimer's disease. You can say that your mind is what the pyramidal cell does.

To pursue our analogy, this CEO has two possible actions, which it exerts through branches of its axon. One is to send impulses to excite its co-workers, the interneurons. As in the olfactory bulb, and in fact as in most parts of the brain, the interneurons feed back inhibition onto an excited pyramidal cell, controlling its output, and onto neighboring pyramidal cells, to sharpen contrast. So far this seems similar to the way a mitral cell is organized.

However, there is a big difference that accounts for much of what goes on in all areas of the cortex. The axon collaterals also feed back excitation onto an excited pyramidal cell and its neighbors. These re-excitatory feedback collaterals in the olfactory cortex were discovered in 1973 by Lewis Haberly, using physiological recordings when he was a graduate student in my laboratory at Yale. They were also independently revealed, using anatomical methods, by Joseph Price at Washington University in St. Louis.

Feeding back excitation onto an already excited cell seems like a recipe for runaway excitation, but in fact it is a fundamental element in not only the olfactory cortex but in all types of cerebral cortex. In normal function this feedback excitation is counterbalanced by the feedback inhibition through inhibitory interneurons. We suggested that together with the feedback inhibition this forms a “basic circuit” for all cortical regions, and that the basic circuit is modified in the different cortical regions for the specific functions in each. This basic circuit is similar to the “canonical circuit” for the cerebral cortex, suggested by Rodney Douglas and Kevan Martin, then at Oxford University.

### The Olfactory Cortex Creates a “Content Addressable Memory”

The fibers in the lateral olfactory tract carrying the odor image pass along the surface of the olfactory cortex and send many branches to the underlying layer, where they transfer their activity by means of synapses onto the most distal apical branches of pyramidal cells (see figure 7.1). There is thus a radical difference from the way input comes into the olfactory bulb, where receptor cells with the same response sensitivities—that is, the same “molecular receptive range”—converge onto one glomerular module. The mitral cells, the output of which still reflects the glomerular module to which they are connected, thus distribute their output across the olfactory cortex to many pyramidal cells. In this way, the information is changed from a mosaic image to a distributed representation of that image.

What is the nature of this distributed image? An answer was suggested by Haberly. After finishing his dissertation, he took postdoctoral training with Price in St. Louis, bringing together the two people who had put the re-excitatory collaterals on the map. Starting with the evidence for the smell patterns being sent to the olfactory cortex from the olfactory bulb, Haberly began to study the literature that was emerging on pattern recognition devices. He compared the anatomical and functional organization of the olfactory cortex that he knew so well with other parts of the brain doing similar kinds of pattern recognition.

In 1985, Haberly wrote a classic paper on the olfactory cortex in which he suggested that the “olfactory cortex serves as a content-addressable

memory for association of odor stimuli with memory traces of previous odor stimuli." He noted the properties necessary for the cortex to function in this manner: a large number of integrative units (pyramidal neurons and synapses) relative to the number of memory traces; a highly distributed, converging-diverging, input (from the olfactory bulb fibers); and positive feedback (the re-excitatory axon collaterals) via highly distributed interconnections between units. All these properties are found in the basic olfactory cortical microcircuit. Not surprisingly, this basic microcircuit is similar to that in the hippocampus, which is well known for its role in long-term memory (chapter 21).

The final property necessary for a cortex to mediate learning and memory consists of the synapses that are reinforced by coincident action of presynaptic and postsynaptic activity. This is the so-called Hebb rule, named after the psychologist Donald Hebb, who in 1949 suggested that this coincident action would build memory into brain circuits. This too is a property of the synapses in both olfactory and hippocampal cortices.

Haberly was particularly intrigued by a comparison of the recognition of odor images with recognition of faces in the visual system. He noted that processing of the highly distributed and complex patterns of activity in the olfactory cortex is different from the initial feature extraction known to be carried out in the primary visual cortex, resembling more closely the discrimination of complex visual patterns such as faces carried out by higher-order visual association areas. We have already seen the usefulness of a comparison with the visual system. As discussed in chapter 8, there is thus an analogy between recognition of the complex patterns laid down by odors in the olfactory cortex and recognition of the complex patterns of faces in visual association areas. By studying the microcircuits, we can now see that in both cases, the extensive horizontal connections through re-excitatory collaterals are essential for the storage and recognition mechanisms.

### Olfactory Cortex Matches Inputs to Memory

This has been a fertile hypothesis for the field of smell. An elegant summary of the experiments supporting it is contained in *Learning to Smell: Olfactory Perception from Neurobiology to Behavior* by Donald Wilson

of New York University and Richard Stevenson of McQuarrie University in Sydney, Australia. The main point is that, whereas the representation of smells in the olfactory bulb is driven by stimulus properties, the representation in the olfactory cortex is memory based. Wilson and Stevenson identify several defining characteristics of how this works, which may be summarized as follows:

1. The olfactory cortex responds especially to *changes* in its input signals from the olfactory bulb; it adapts (reduces its responses) to continued stimulation with the same smells. This, in fact, was the reason that first attempts using functional imaging in the human failed to identify responses to smell in the olfactory cortex. Noam Sobel and his colleagues realized that the responses were adapting out, and used changing smells to reveal the olfactory cortex activity.

2. This system *learns*. The basic cortical circuit has the ability to improve its performance with repeated exposure to different smells. The *recurrent excitation* strengthens the cells activated by input from the olfactory bulb. The *lateral inhibition* enhances the contrast between activated and less activated cells. Finally, the *synaptic strengths* change so that the system can store these changes as a memory and match them to the input.

3. These changes with learning enable the system to improve its ability to *match* an input pattern to a stored pattern, so that finer discrimination between more similar smell molecules can occur.

4. These changes also enable the system to improve its *signal-to-noise ratio*, so that detection and discrimination of a particular smell can be enhanced against a background of many smells.

5. The olfactory cortex microcircuit functions to take an input reflecting many diverse stimuli and construct out of it a *coherent odor object*. This is an analogy with how the visual system takes an input of different shapes and sizes and constructs a “visual object.” An important aspect of such an object is that seeing only a small part of it still enables the system to “fill in” the missing parts. This is a feature of all sensory experience. As we have noted, we catch a glimpse of a distant figure, a few notes of a melody, a whiff of a smell, and can instantly “fill in” the rest. This especially applies to perceiving a face or just a part of a face, as discussed in chapter 8. It also means that the system “degrades gracefully” if damaged.

6. The odor object is in a form that can be *combined* with other sensory inputs to produce the sensation of flavor. This occurs at the final level in the smell pathway, the orbitofrontal cortex.

### Where Does Conscious Smell Perception Arise?

Given these impressive properties of the olfactory cortex, a key question is whether conscious perception of smell arises there. I have asked many behavioral psychologists this question, but apparently the crucial experiment of interfering with the next stage has never been done, at least not in primates. (For evidence from trauma to that level in humans, see chapter 25.)

The argument in favor of conscious perception arising in the olfactory cortex is that, although many call this the primary olfactory cortex, it is not really equivalent to the primary cortex in other sensory systems, where that term is reserved for the receiving area in the neocortex. The olfactory cortex, as Haberly suggested, is more equivalent to a higher-association area in other sensory systems, even though it is not yet at the neocortical level.

The argument against conscious perception arising in the olfactory cortex is that the smell information has not yet passed through the thalamus or reached the level of the neocortex, which is necessary for all other sensory systems.

So we need to go to the next level—the orbitofrontal area of the neocortex—for possible answers to where conscious smell arises.

### Detecting Essential Amino Acids

In addition to the role of the olfactory cortex in smell perception, another function began to emerge some two decades ago with the evidence that it contains an area sensitive to amino acids in the diet. Of the 20 amino acids required for building proteins, 10 are essential; if one of them is missing from the diet, an animal's health begins to fail and it will die if the deficit is uncorrected. Rats will cease feeding within 30 minutes if their chow lacks just one of these. What is the mechanism?

A series of studies over the past 20 years has shown that the sensor is in the brain and, surprisingly, has narrowed it to the olfactory cortex. Evidence from Dorothy Gietzen at the University of California, Davis, and her colleagues Shuzhen Hao and Tracy Anthony published in 2007 indicates that the pyramidal cells contain a molecular mechanism that senses the lack of an essential amino acid by its inability to "charge" its appropriate transfer ribonucleic acid (tRNA) molecule with that amino acid. How this is communicated to the cell membrane to change the cell's activity, and what is the pathway for communicating this message to the rest of the brain, is still under study. One can speculate that the exquisite balance between excitation and inhibition in this region enables the cells to be sensitive detectors of slight changes in the presence of the amino acid. This is an unexpected hidden function of the mammalian olfactory system, one that is apparently present in humans. It may be crucial to the nutrition of people in conditions of poverty and starvation around the world. It may also be a critical element in the need for vegetarian diets to include foods with all the essential amino acids. The relation to flavor is only indirect, but it presumably means that for an omnivore such as ourselves vegetable flavors must be learned in order to supply the needed amino acids.