

31 Relating the Activity of Sensory Neurons to Perception

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ABSTRACT One of the major goals of systems neuroscience is to understand how the activity of sensory neurons gives rise to our perceptual experience. When scientists first began recording from sensory neurons while subjects performed perceptual tasks, Parker and Newsome (1998) wrote a seminal paper laying out a rubric for how to establish that the electrical impulses on the end of the electrode were actually responsible for a specific percept. The intervening years have seen an explosion of interest in this question, technical developments that have paved the way for new types of answers, and theoretical advances that provide a context for the new experimental results. In this chapter we will update the rubric of Parker and Newsome to incorporate recent work and to pose questions whose answers will provide a new level of understanding in the coming years.

Since the fourth century BC, when Aristotle claimed that the heart was the seat of the mind and the soul, scientists and philosophers have been searching for a link between biology and our internal perception of the world around us. Modern neuroscience has long recognized that the physical source of our internal experience is the brain. Over the last few decades, neuroscientists have begun to amass a body of evidence linking the activity of groups of sensory neurons in specific brain areas with individual percepts.

Although the claim that our internal experience is due solely to the activity of neurons is no longer controversial, associating a specific group of neurons with a particular perceptual experience is challenging for both conceptual and experimental reasons. First, it is necessary to measure a subject's percept, which is a fuzzy, subjective experience, in a quantifiable way. This challenge has largely been met thanks to centuries of work by psychologists and psychophysicists who have designed clever tasks to measure subjects' perceptual abilities. Still, we are left relating neuronal activity to *performance* on a task, rather than *perception*.

Determining whether the activity of a particular group of neurons is in a position to underlie performance is even trickier. Many thousands of neurons across sensory cortex as well as in subcortical areas respond every time we see, hear, touch, smell, or taste a sensory stimulus. The neurons that respond to any stimulus vary tremendously in their functional and anatomical properties. The sensory information they encode may or may not be useful for the task at hand or sufficiently sensitive to explain the detail with which

a subject perceives a stimulus. Different cortical areas or other groupings of cells work as a network, so simply determining the effect of removing or activating a group of neurons might be either too crude or too subtle a manipulation to yield specific behavioral effects. To make matters worse, most neurons do more than simply provide sensory information, so dissociating their contributions to perception rather than a cognitive or motor process can be challenging. In general, establishing a link between neurons and task performance entails monitoring the activity of and manipulating specific (but often large) groups of neurons while a subject performs a task, which can be experimentally challenging.

In 1998, Parker and Newsome wrote an influential review summarizing the state of the field and providing a rubric for establishing a link between a group of candidate neurons and a specific percept (Parker & Newsome, 1998). Their rubric has become an invaluable framework for interpreting and combining the results of many studies. The nature and quantity of the experimental evidence linking sensory neurons to perception has exploded since that time, leading to many new insights. Out of technological necessity, earlier experiments typically monitored the activity of one neuron at a time and extrapolated their responses to the large groups of neurons thought to underlie any percept. The technology for activating or inactivating neurons was crude, akin to using a chain saw when a scalpel was called for. The techniques for analyzing data focused on these single neuron recordings or gross causal manipulations. In the intervening decade and a half, new experimental technology and techniques for analyzing data have revolutionized the field.

These developments have recently begun to bear fruit, and hard drives are being filled with data as quickly as engineers can increase their size. As the field adjusts to this wealth of new information, it is more important than ever to establish a conceptual framework for understanding the meaning of these new data. For those who spend their days in the lab or at the computer, such a framework will be the only way of recognizing when we have accomplished the goal. What evidence will convince us that we've found the biological basis for a percept?

Our goals in this chapter are fourfold. We aim to

1. provide an updated framework that is based largely on the rubric of Parker and Newsome but reflects new insights for linking groups of neurons to perception;
2. review the current state of the art for performing experiments and analyzing the results;
3. review the results of influential experiments using older technology and describe early experiments using the newest methods;
4. highlight current and future avenues of research aimed at understanding how neural activity gives rise to perception.

Although we will discuss evidence linking different sets of neurons with particular percepts from a variety of model systems and organisms, our goal is not to provide a comprehensive review of this field. We aim to explore the depth of knowledge necessary to present a compelling case that a particular set of neurons underlies a specific perception.

Quantifying a percept

Perception is an inherently subjective experience. We can easily quantify aspects of a physical stimulus, such as the speed of a moving object, the chemicals that give rise to an odor, or the pitch of a musical note. But the subjective experience of seeing your puppy sprint by you, smelling your mother's homemade chocolate chip cookies, or hearing the crescendo in a Beethoven symphony is not something that is readily accessible to experimentalists.

In everyday life, we try to understand the perceptual experiences of others by asking them what something looks, smells, or sounds like. Such *perceptual reports*, however, are an ineffective way of linking neuronal activity to perception for two reasons:

1. Perceptual reports are notoriously unreliable. Although it is beyond the scope of this chapter, there is abundant experimental evidence that people's reports of what they perceive (or do not perceive) are very different from what quantitative tests reveal are the limits of their perceptual capabilities. This has consequences far beyond neuroscience, including the validity of eyewitness testimony in the courtroom.
2. Most experimental methods for recording or manipulating the activity of neurons are invasive, so they cannot be used in humans except in rare cases when a patient is undergoing brain surgery for another reason. Therefore, the vast majority of data concerning the neuronal basis of perception comes from animal studies, in which the subjects cannot verbally describe their experiences.

To link neuronal activity with perception, we therefore rely on the field of *psychophysics* to quantify the relationship between physical stimuli and a subject's perceptual abilities.

Psychophysical experiments can be carefully designed to minimize the ambiguity inherent in perceptual reports, often in ways that can be generalized from human subjects to nonhuman subjects. Rather than asking a subject how fast something went, for example, one could probe their ability to judge speed by asking them which of two stimuli is moving faster. This experimental design removes the ambiguity associated with the subject's internal speed calibration, because it forces the subject to evaluate one stimulus with respect to another stimulus. The subject's response on a single trial could be compared to the activity of the candidate neurons at that moment (e.g., could a subject's mistake be predicted from the activity of that group of neurons?). The subject's performance on the task could also be compared to that group of neurons (e.g., how well could a hypothetical subject do if all the information they had to go on came from the activity of that group of neurons?).

The experiments described in the rest of this chapter attempt to determine whether the responses of a group of candidate neurons are necessary and sufficient to explain performance on perceptual tasks. Therefore, if the title of this chapter were to describe the status rather than the goal of this field, it would be called the more cumbersome "relating the activity of sensory neurons to performance on perceptual tasks."

Quantifying performance

Measuring a subject's overall performance on a task is therefore critical for assessing perception. Simple measures like total percent correct are affected by factors other than the subject (such as the difficulty of the task). Psychophysicists usually measure a *psychometric curve*, which is a plot of performance (either percent correct or percent of choices in favor of a particular decision) as a function of a measure of the sensory stimulus. For example, in a speed-discrimination task, the psychometric curve might plot percent correct as a function of the difference in speed between the two stimuli (figure 31.1A). Psychometric curves usually have a sigmoidal (or "S") shape and can be characterized by two parameters: their slope (the steepness of the linear part of the curve), and the *threshold* (corresponding to the left-right position of the curve on the graph; dashed line in figure 31.1A). Because experimental manipulations do not often change the slope (for review, see Parker & Newsome, 1998), performance is often quantified as the threshold. The threshold is in units of the physical stimulus rather than in units of performance or perception. It is defined slightly differently in different studies, but it is always the value of the stimulus that is necessary to achieve a certain level of performance. For example, in a speed-discrimination task, the threshold might be the speed difference that a subject can discriminate with 82% accuracy.

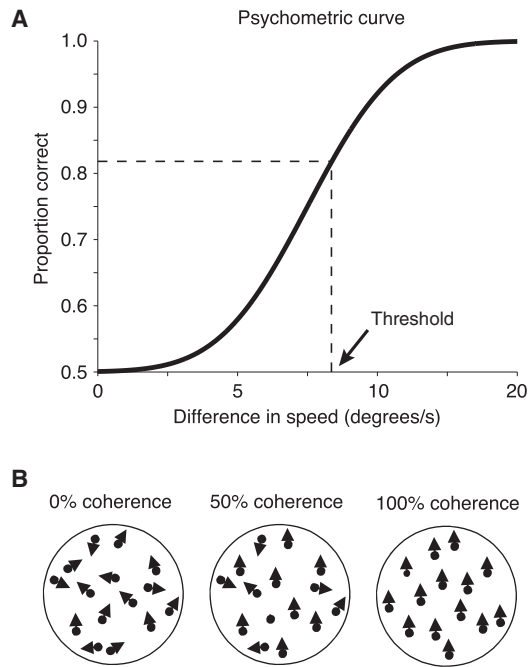


FIGURE 31.1 (A) Psychometric curves plot performance as a function of a measure of the stimulus. The dashed line represents the psychometric threshold, which is the stimulus value at which the subject can achieve a certain level of performance. In this example, the relevant stimulus parameter for the behavioral task is stimulus speed, but in principle it can be any one-dimensional analog parameter of the stimulus. (B) The stimuli in the motion-direction discrimination task as typically used by Newsome and colleagues.

COMMON PERCEPTUAL TASKS There are a multitude of psychophysical tasks designed to measure different aspects of perception. For use in comparing neurons to perception, each has a unique set of strengths and limitations. These are important to keep in mind when assessing the quality of the evidence that the results of each experiment bring to the hypothesis that a certain set of neurons is responsible for a specific percept. Much of this psychophysical work is discussed in detail elsewhere in this volume.

Two types of psychophysical tasks have been used most commonly to relate neuronal activity to perception: detection tasks and discrimination tasks.

Detection tasks In detection tasks, subjects are asked to signal that they perceive the onset or a change in a sensory stimulus. Chapter 25 (by Fred Rieke) of this volume described a classical detection task in which human observers were asked to detect weak flashes of light in a very dark room. Impressively, this task showed that humans can detect single photons of light under some conditions.

Strengths:

- Detection tasks are typically the easiest psychophysical tasks to train animals to do. Nearly all psychophysical tasks with nonprimate subjects use detection tasks for this reason.

- Because the onset of the stimulus can come at an uncertain time, subjects must remain focused on the stimulus (or expected stimulus location) for a long period of time. This is useful for physiology experiments because it gives a longer period for obtaining accurate measurements of neuronal responses.

Limitations:

- The psychophysical threshold depends on the subject's internal *criterion*, or willingness to make certain types of errors. In the light-detection task, some subjects might be willing to falsely report seeing a flash if they are unsure, while others will only report seeing the flash if they are absolutely certain. Therefore, most studies focus only on changes in threshold from experimental manipulations rather than absolute threshold values.

- It can be difficult to dissociate changes in performance or neuronal responses that are due to sensory factors from those caused by changes in the subject's cognitive state. For example, changes in alertness might increase the responses of neurons all over sensory cortex and also improve performance on psychophysical tasks (simply because increased alertness improves performance on most things). Therefore, one might observe a misleading correlation between performance and the responses of neurons, simply because both are modulated by the subject's alertness.

Discrimination tasks Discrimination tasks require the observer to choose between two or more options. A motion-direction discrimination task (figure 31.1B) was used to establish what is currently the best link between perception and sensory neurons. Newsome and his colleagues (Britten, Newsome, Shadlen, Celebrini, & Movshon, 1996; Britten, Shadlen, Newsome, & Movshon, 1992; Newsome & Paré, 1988; Salzman, Britten, & Newsome, 1990; Shadlen, Britten, Newsome, & Movshon, 1996) performed a series of experiments linking the responses of direction-selective neurons in the middle temporal area (MT) and performance on the task in figure 31.1B. In these studies, rhesus monkeys viewed a dynamic random dot display in which a percentage of the dots moved coherently in one of two opposite directions (up or down in figure 31.1B), while the rest of the dots moved randomly. The monkeys were required to indicate which of the two directions contained the coherent motion. When a large percentage of dots moved coherently, this task proved to be very easy. At low coherence, the random dots provided a masking stimulus, making the discrimination difficult.

There are two types of discrimination tasks. Some, like the direction-discrimination task (figure 31.1B), require subjects to observe a stimulus and choose between two or more options. When there are two options, these are called two-alternative forced-choice tasks (the "forced" is because the subject must pick an option rather than indicating "I don't

know”). The forced choice can often reveal perceptual abilities unknown to the subject. In the direction-discrimination task, human subjects often perform better than would be expected by chance even when they report seeing no coherent motion.

In the second type of discrimination task, two-interval forced-choice tasks, subjects are required to indicate in which of two time intervals a stimulus (or a stimulus with a certain property) occurred. An example of this type of task was used by Romo and colleagues (Romo, Hernández, Zainos, & Salinas, 1998) to determine the role of somatosensory areas in the perception of vibrating tactile stimuli. Two stimuli were presented in sequence and monkeys were required to indicate which of the two vibrated at a higher frequency.

Strengths:

- Thresholds are immune to differences in criterion because a bias in favor of one option (e.g., “up” answers in the motion-direction discrimination task) can be measured by comparing performance on trials when the dots actually moved up versus down.
- While cognitive factors like alertness still improve performance and modulate neuronal responses, they do so equally for all trial types. Therefore, increases in arousal will affect “up” and “down” trials equally.

Limitations:

- For nonhuman subjects, discrimination tasks are often more difficult to train than detection tasks.
- Decisions are often made quickly, limiting the time available to record neuronal responses. If subjects are forced to observe a stimulus for a long period of time before making a decision, they may not use all of the available sensory information, making it difficult to determine when the decision actually occurred.

Linking sensory neurons to perception

We will devote the rest of the chapter to establishing a series of questions (based heavily on the rubric of Parker & Newsome, 1998) that must be answered to demonstrate that a candidate group of neurons underlies performance on a particular perceptual task. The earliest attempts to characterize sensory neurons focused on describing the general properties they encode. On average, neurons in early sensory areas are selective for simple features like the orientation of a line, the pitch of a note, or which of a rodent’s whiskers has moved. In higher cortical areas, cells are tuned for more complex features like object identity. Building on this knowledge, one can make a somewhat educated guess about which neurons seem like good candidates to underlie the perception of a particular feature. The goal of the rest of this

chapter is to pose a series of experimentally tractable questions that test this hypothesis.

By far, the best-established connection between sensory neurons and perception is the one studied by Newsome and colleagues (figure 31.1B) between direction-selective neurons in the middle temporal visual area (MT) and performance in a motion-direction discrimination task. To our knowledge, this is the only connection between sensory neurons and perception for which all of the questions below can be answered in the affirmative. In each section, we will describe the evidence linking MT with motion perception and also provide recent examples showing how these concepts have been applied to other systems or tested using new experimental techniques.

Do the responses of the candidate neurons encode detailed enough sensory information to support the percept? The most basic requirement for the neural underpinnings of a percept is that the candidate neurons carry enough sensory information to explain performance on a perceptual task. For example, if, as a group, MT neurons could only discriminate strong upward from downward motion with 75% accuracy but the monkey can get 90% of the trials correct, then the monkey must be incorporating motion information from somewhere else.

Britten and colleagues (1992) quantified the amount of information about motion direction encoded by single neurons in MT using a metric that could be directly compared to the monkey’s performance. They first measured each neuron’s direction tuning curve (figure 31.2A) and determined the neuron’s preferred direction (the direction of motion that elicits the highest response from the neuron; up, in this example). They then measured neuronal responses while the monkey discriminated motion in the preferred direction (up) from the opposite direction (down) using the direction-discrimination task in figure 31.1B.

For each stimulus strength (e.g., 12% coherence motion), they computed the accuracy with which an ideal observer could discriminate the two motion directions (e.g., up from down) based only on the responses of the one neuron on the end of the electrode. (The ideal observer’s performance is equal to the area under the receiver operating characteristic curve corresponding to the responses to upward and downward motion; Green & Swets, 1966.) Using the ideal observer’s performance for each stimulus strength, they constructed a *neurometric curve* that could be directly compared to the monkey’s *psychometric curve* (figure 31.2B). The corresponding neurometric and psychometric thresholds from each curve (as in figure 31.1A) allowed them to compare the amount of motion information encoded by the neuron to the amount that the monkey used to perform the task.

Britten and colleagues (1992) found that MT neurons are shockingly sensitive. On average, the neurometric and

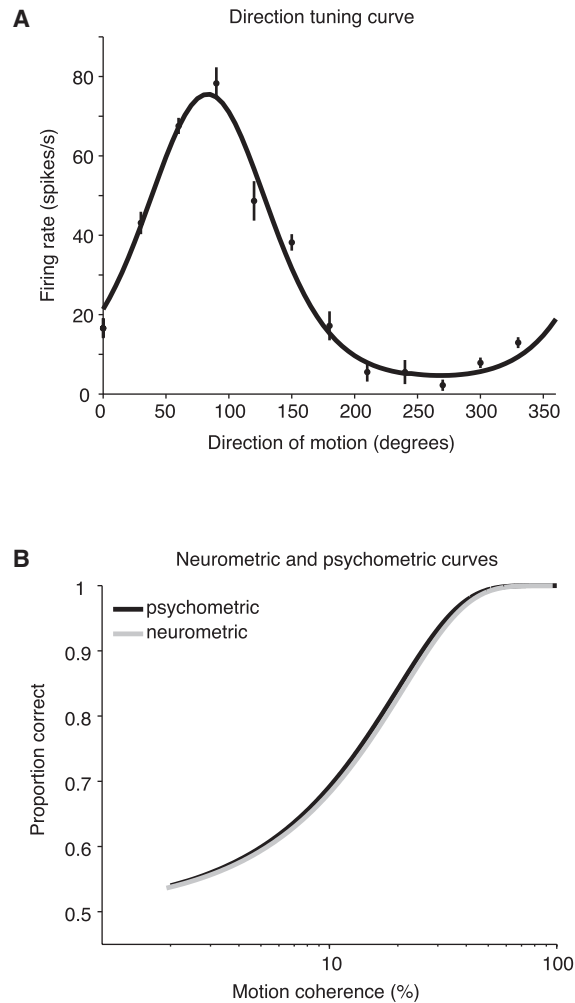


FIGURE 31.2 (A) Motion-direction tuning curve of an example MT neuron (Ruff and Cohen, unpublished data). (B) A schematic neurometric curve. The neurometric curve reflects how well an ideal observer could do a task based on the responses of a single neuron. In MT, neurometric and psychometric curves for the direction-discrimination task are similar (based on the results of Britten et al., 1992).

psychometric thresholds were identical, meaning that the monkey behaved as if he based his decisions on a single MT neuron. Later studies suggested that some details of the original experiment tilted the results in favor of the neuron, but that the observation that MT neurons are exquisitely sensitive was true: the monkeys' behavior suggested that they used only as much motion information as was carried by two or three MT neurons (Cohen & Newsome, 2009). This begs the question, why would the monkey ignore the other 100,000 MT neurons or the motion-selective neurons in other cortical areas?

We will discuss a resolution to this question in the next section, but the answer is not that MT neurons are markedly more sensitive than neurons in other areas or that the direction-discrimination task is unusually well suited to the

responses of sensory neurons. Similar experiments in a variety of species and cortical areas found that individual sensory neurons are extremely sensitive to the stimulus information they encode. For example, Prince and colleagues (Prince, Pointon, Cumming, & Parker, 2000) trained monkeys to judge the depth (or perceived distance) of ambiguous visual stimuli. They found that single neurons as early as primary visual cortex carry enough depth information to account for the monkey's performance. In rats trained to discriminate the frequency of stimuli vibrating against their whiskers, individual trigeminal ganglion neurons are similarly sensitive to vibration frequency (Gerdjikov, Bergner, Stüttgen, Waiblinger, & Schwarz, 2010).

There is no reason that single neurons alone need to be sensitive enough to account for a subject's psychophysical performance. After all, the brain contains lots of neurons! For a group of candidate neurons to underlie perception, however, they must together encode sufficient information to explain performance on psychophysical tasks. The results highlighted here show that this is not usually the most difficult requirement to fulfill in linking sensory neurons with perception.

Can the responses of the candidate neurons be used to predict the subject's choices? The idea that a group of neurons is responsible for what a subject perceives makes a strong prediction about what the subject will *do* with the sensory information encoded by those neurons. Neural responses are noisy. Say you regularly meet a friend for lunch, and you're in the habit of looking far down the street to see if she's coming. Each time you see your friend walking toward you (even if she is wearing the exact same thing and in the exact same spot), your visual neurons will respond slightly differently. If a group of neurons is responsible for your perception of your friend, the noise in their responses should affect your visual experience. Specifically, if a group of neurons happens to respond unusually strongly, you should be more likely to perceive the visual features they encode (and respond accordingly on a perceptual task).

Britten, Newsome, and colleagues tested this hypothesis by determining whether they could predict monkeys' responses on the direction-discrimination task from the fluctuations in the responses of the MT neurons the authors recorded (Britten et al., 1996). Consider a situation in which they recorded from a neuron whose preferred direction is "up" on many trials of, say, a random 0% coherence stimulus. If the responses of this neuron contribute to a monkey's decision on these trials, then it should be possible to use its responses to predict the monkey's choice on each trial. On trials in which the neuron fires more than its average, the monkey should be more likely to report seeing upward motion than on trials in which the neuron fires less than its average.

The authors of this original study coined the term *choice probability* to describe the proportion of trials on which an ideal observer could predict the monkey's choices based on the neuron under study. In the context of a detection task, a similar metric is called *detect probability*. A choice probability of 1 would mean that the neuron could be used to perfectly predict the monkey's choice (figure 31.3 A). This would occur if the upward-preferring neuron fired more on every trial in which the monkey chose up than on any trial in which the monkey chose down. A choice probability of 0.5 would mean that the neuron is uninformative, so someone only looking at the responses of this neuron would have no idea which choice the monkey was about to make. This would occur if the distribution of responses on trials on which the monkey chose up were identical to the distribution when the monkey chose down.

The authors found that choice probabilities for individual MT neurons (whose tuning was well-matched to the task) were approximately 0.54, which was significantly greater than 0.5 but far from the perfect value of 1. Therefore, individual neurons carry some information about what the monkey is about to do, but not much. Neurons whose tuning does not match the stimulus to be discriminated or detected (e.g., a neuron whose preferred direction is not exactly up or down) have weak but significant detect probabilities (Bosking & Maunsell, 2011; figure 31.3B).

These weak choice probabilities are to be expected given how many neurons respond to any given stimulus. After all, many neurons presumably contribute to any percept, so no individual neuron should be terribly predictive of the monkey's choice.

The low but significant choice probabilities are surprising for two reasons, however. First is the observation we discussed previously: individual neurons carry nearly enough information to explain the monkey's performance on perceptual tasks. If the monkey only uses one or a few neurons to make a decision, those neurons should have very high choice probabilities. The low choice probabilities suggest that, instead, the monkey combines information from many neurons. This is a sensible strategy, but then why doesn't his performance reflect the benefit of the information encoded by all those neurons?

If the monkey indeed uses many neurons to make any decision, the second surprise is that choice probabilities are big enough to be detected at all. Trying to predict the monkey's decision from the one neuron that happens to be close to the electrode is like trying to predict the outcome of a presidential election by polling only the first person you encounter on the street. If many neurons or people vote in a decision or an election, that one person's opinion should carry very little weight in the election and should not tell you much about which way it will go.

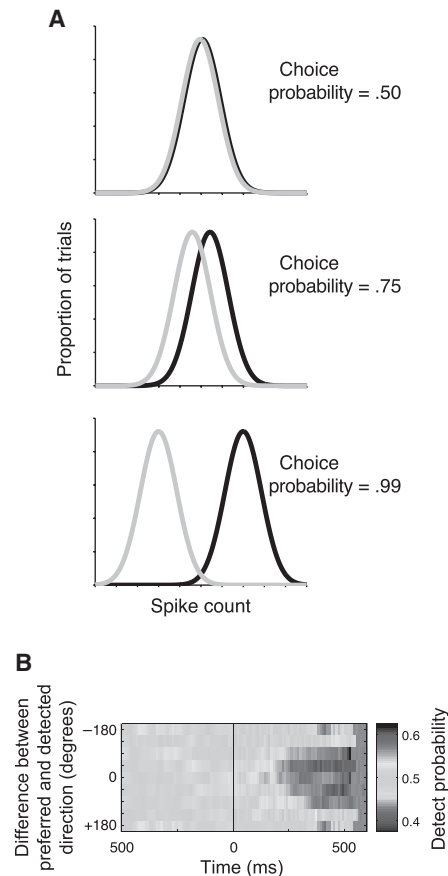


FIGURE 31.3 (A) Choice probability is calculated by comparing the distributions of neural responses on trials when the subject made each of two choices. This schematic shows pairs of distributions with different choice probabilities. (B) Choice probabilities (referred to as “detect probabilities” in this detection task) decrease for neurons whose preferred direction does not match the direction of motion being detected (adapted from Bosking & Maunsell, 2011). (See color plate 27.)

The resolution to both of these apparent paradoxes lies in the fact that neurons (like voters ...) are not independent thinkers. If the noise in neural responses were independent, some neurons would fire more than average and some would fire less than average at any given moment. In this case, the mean of the population would remain relatively constant, so the noise would not have a big effect on the ability of the population to encode sensory information. Therefore, the monkey would have no excuse for not performing better on the task, and the average individual neuron would carry very little information about which option he would choose.

Instead, the noise in neuronal responses is shared, or *correlated*. Simultaneous recordings from multiple neurons have shown that when one neuron fires more than its average, nearby neurons are likely to be firing more than their average as well (for review, see Cohen & Kohn, 2011). If all of the neurons were doing the exact same thing, there would be no point in having more than one: the monkey

would do exactly as well as any one neuron, and every neuron would perfectly predict the monkey's choices. In reality, the correlation between the noise in the responses of nearby neurons is positive but weak. A model of the monkey's decision process suggests the observed correlations can explain the monkey's performance and the observed choice probabilities pretty well (Cohen & Newsome, 2009; Shadlen et al., 1996).

This model also makes the prediction that even if monkeys use a very large number of neurons to make a decision, neither their performance nor the ability of an ideal observer to predict choices from the responses of a group of neurons should improve after about 100 neurons. This prediction appears to be true. A recent study recording from about 80 sensory neurons simultaneously showed that those neurons were enough to predict the monkey's decisions on the vast majority of trials (Cohen & Maunsell, 2010).

It is tempting to interpret the existence of choice probabilities significantly greater than 0.5 as evidence enough that a group of neurons is responsible for perception. After all, recording from a few dozen neurons is enough to predict a monkey's actions almost perfectly. The problem is that correlated noise can lead to choice probability even when the recorded neurons have nothing to do with the decision, as long as their responses are correlated with the neurons that are. If the monkey makes his decision based on neuron A's response, but neuron B responds the same way as A, both could be used to predict the decision. (The same could be true of a nonvoter whose whims reflect the feelings of the nation as a whole.) The fact that significant choice probabilities have been observed almost every time they have been measured (for review, see Nienborg, Cohen, & Cumming, 2012), including in neurons whose tuning is very poor for the particular task, suggests choice probability may sometimes be present solely due to widespread correlated noise. Further evidence is therefore necessary to make the case that a group of neurons are responsible for, rather than simply correlated with, a perceptual decision.

Does activating the candidate neurons bias perception in favor of the stimulus property they encode? If a group of neurons is responsible for a percept, modifying their activity should change the percept. Since the work of Penfield in the 1950s, experimenters have used electrical stimulation to activate small groups of neurons. Penfield found that applying large currents on the surface of cortex could elicit reliable perceptions or movements depending on the location of the injected current (Penfield & Rasmussen, 1950). This work led to the creation of well-known maps of somatosensory and motor cortex (sometimes affectionately termed "homunculus maps," because they look like a small person). As stimulation techniques were refined, experimenters realized that smaller currents delivered by fine electrodes placed inside the cortex

of animals could lead to readily reproducible motor responses (for a review, see Graziano, 2006).

Newsome and colleagues used microstimulation to determine how activating small populations of MT neurons could bias the monkey's choice during the motion-direction-discrimination task (Salzman et al., 1990). This clever experiment relied on the fact that in MT, neurons located near each other tend to have similar preferred directions. Therefore, when the experimenters applied small currents, they could reasonably expect that they were modulating the activity of a group of neurons with similar tuning.

The authors put an electrode into MT, placed the motion stimulus in the receptive fields of the neurons they recorded, and had the monkey discriminate motion in the neurons' preferred direction from motion in the neurons' null direction. Unbeknownst to the monkey, the experimenters passed small amounts of current through the electrode on a subset of trials, which increased the firing rates of the neurons near the electrode tip.

The monkey behaved as if the stimulation had increased the strength of the motion in the neurons' preferred direction, which can be seen in the leftward shift in the animal's psychometric curve (figure 31.4A). That this technique works is astounding: the currents used in this experiment should have modulated the responses of only tens or hundreds of neurons (Histed, Bonin, & Reid, 2009). The fact that tickling the responses of such a small number of neurons affects the monkeys' behavior in a measurable way is strong evidence that MT neurons underlie performance in the direction-discrimination task.

In other contexts, microstimulation has an even more astounding effect: it has been used to create a percept in the absence of a physical stimulus. Romo and colleagues trained monkeys to perform a two-interval somatosensory discrimination where the monkey's job was to indicate whether the second stimulus in a pair vibrated at a higher or lower frequency than the first (Romo et al., 1998). During most trials, a mechanical vibrating flutter stimulus was applied to the monkey's fingertips for both stimuli, but on some trials, one of the mechanical stimuli was absent and instead, electrical microstimulation was applied directly in somatosensory cortex. Amazingly, the animals were able to compare electrical and mechanical stimuli after training only on mechanical stimuli. This experiment provided strong evidence that the electrically stimulated somatosensory neurons encoded vibrotactile information that the animals could use to make decisions about stimulus frequency.

While microstimulation is a powerful tool for evaluating the causal contribution of neurons to perception, it is a relatively coarse method both temporally and spatially, and does not allow for the precise targeting of cell types or neuronal subpopulations. New techniques make it possible to precisely target particular neurons at particular times. In particular,

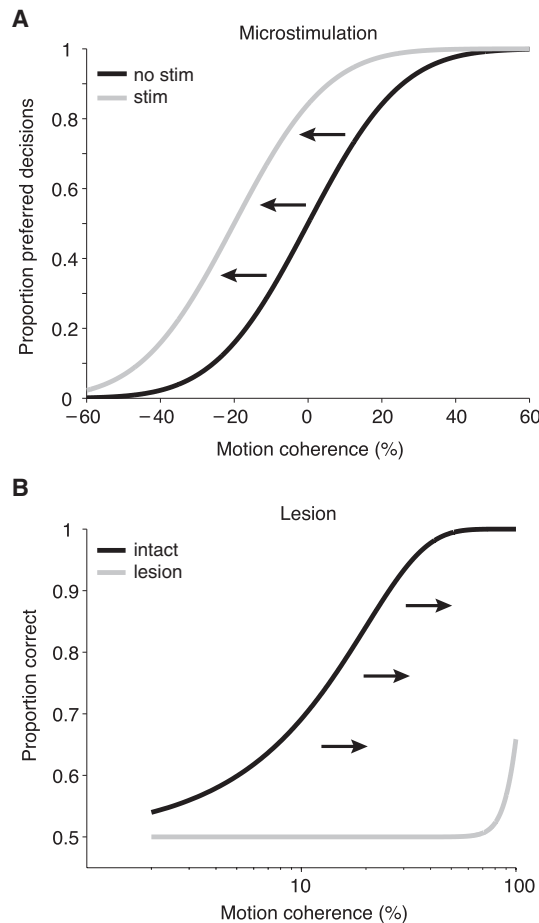


FIGURE 31.4 (A) Microstimulation biases the subject's choice toward the option that matches the preferred direction of the stimulated neurons (schematic based on the results of Salzman et al., 1990). (B) Performance on a motion-discrimination task is not much better than chance following ibotenic acid lesion of MT (schematic based on the results of Newsome & Paré, 1988).

the field of optogenetics allows researchers to use light to activate neurons that express proteins such as channelrhodopsin (ChR2; Luo, Callaway, & Svoboda, 2008; Peron & Svoboda, 2010; Scanziani & Häusser, 2009).

The greatest promise of these techniques lies in their potential specificity: in mice and some other species, ChR2 can be genetically expressed into particular subtypes of neurons in different areas or cortical layers or that project to different areas. Making these methods usable in monkeys is a topic of active investigation, and there have been some notable early successes (Diester et al., 2011; Han et al., 2009). A recent study was the first to demonstrate the behavioral detection of opsin-mediated neuronal signals in the primate brain (Jazayeri, Lindbloom-Brown, & Horwitz, 2012).

Does inactivating the candidate neurons cause deficits in perception? If a group of neurons underlie a percept, suppressing their

activity should cause a deficit in perception. The brain is remarkably flexible, and removing or inactivating large portions of cortex can have surprisingly subtle effects on behavior. Nevertheless, to make a strong statement that a group of neurons are responsible for a percept, it is necessary to show that inactivating them has a measurable effect on a subject's perceptual ability, even if it's a transient one.

To determine whether MT neurons are necessary for motion-direction discrimination, Newsome and Paré used ibotenic acid to completely remove MT in one hemisphere (Newsome & Paré, 1988). Removing MT almost completely abolished the monkeys' ability to perform the direction-discrimination task (figure 31.4B), suggesting that under normal circumstances, MT is critical for performance in this task. Interestingly, the monkeys' performance improved almost to pre-lesion levels within a few weeks, suggesting that motion signals from elsewhere in cortex can be recruited to guide behavior in the absence of MT.

While lesion studies can provide clear answers, they are a relatively crude approach for asking whether a group of neurons are necessary for a percept. It is usually not possible to measure performance on perceptual tasks for a while after the lesions have been made, and, as the MT results show, subjects may eventually be able to learn alternate strategies to make up for the missing areas. Because reversible inactivation experiments can be performed on a relatively fast time scale, such manipulations may solve this problem by not allowing for sufficient time for the animal's brain or behavioral strategy to adjust to a long-term deficit. Using muscimol, a GABA agonist, Chowdhury and Deangelis (2008) replicated the findings of Newsome and Paré, showing that the monkeys' performance returned to normal after the drug had sufficient time to wash out two days after injection. Further, because they could allow MT to recover after muscimol was applied, the authors were able to ask questions about how an area's role in a percept might change with training on different tasks. They found that MT's role in a particular type of depth judgment depended on whether monkeys had first been trained on a different, finer-grained depth discrimination.

Technological advancements are making possible even more precise inactivation and lesion methods. For example, Schlieff and Wilson (2007) used a genetic approach to lesion specific, highly selective olfactory receptor neurons in the fly brain. Flies are innately attracted to certain odors, but removing these neurons made them no longer interested in the odors encoded by the removed receptor neurons.

While genetic approaches are still in their infancy in primates, researchers have begun to use rodents to combine cutting-edge genetic techniques with electrophysiology and perceptual tasks. A recent study from Znamenskiy and Zador (2013) harnessed many of the techniques we have

discussed in the previous sections to provide an impressive amount of evidence linking corticostriatal neurons to decisions about the frequency of a tone stimulus. The authors used excitatory channelrhodopsin and inhibitory archaerhodopsin to demonstrate that the activity of neurons in auditory cortex that project to the striatum biases decisions either toward or away from the choice represented by the set of neurons expressing each opsin type, respectively.

Do the candidate neurons underlie perception or a planned motor response? Neurons that underlie perception should correlate with the subject's choices regardless of the way that the subject communicates that choice. The responses of neurons that encode a planned motor response could correlate with choices for a trivial reason that has nothing to do with perception. In the most common version of the direction-discrimination task, the monkey signals that he perceives upward motion by moving his eyes up and downward motion by moving his eyes downward. Imagine recording from a motor neuron responsible for upward eye movements. The responses of that neuron would be perfectly correlated with the monkey's choice; high firing rates would signal upward choices, and low rates would signal downward choices.

One straightforward way to ensure that a set of neurons is correlated with perception rather than simply a planned motor response is to ensure that their responses carry sensory information and correlate with choices regardless of the motor output used to signal the choice. MT neurons have choice-probability and signal-motion information in the motion-discrimination task regardless of whether choices are signaled with eye movements (Britten et al., 1992, 1996) or hand movements (Nichols & Newsome, 2002). In principle, the responses of the same neurons could be responsible for perception and a motor plan, so the requirement should not be for identical responses for different motor outputs. Rather, some aspects of the response (e.g., early in the behavioral trial) should not depend on the motor output used to signal the choice.

Examples of systems for which the link between sensory neurons and perceptions is most well established

To our knowledge, MT and the motion-direction discrimination task represents the only system for which all of the above questions have been answered in the affirmative. However, there is growing evidence linking other brain areas with specific percepts. Two other experimental systems have proven to be particularly fertile grounds for linking sensory neurons to perception.

Motion direction is a relatively low-level feature of a visual stimulus, but the same experimental methods used in the MT experiments have been used to link the activity of

neurons in inferior temporal (IT) cortex, in both humans and monkeys, with the perception of higher-level features like faces. Early electrophysiological experiments identified neurons in primate IT that were extremely selective for faces compared to other complex objects (Desimone, Albright, Gross, & Bruce, 1984). The existence of small clusters of face-selective IT neurons was revealed by work from Doris Tsao and colleagues, who used functional imaging to guide their electrophysiological recordings and identified patches in macaque temporal cortex that were overwhelmingly selective for faces, even compared to other similar shapes (Tsao, Freiwald, Tootell, & Livingstone, 2006). Functional imaging in humans has also revealed patches of cortex in the ventral stream that are highly selective for different object categories, such as faces (Kanwisher, McDermott, & Chun, 1997). Activity in these regions may be used during perceptual decisions about complex object categories like faces and houses (Heekeren, Marrett, Bandettini, & Ungerleider, 2004), but it is currently unknown whether individual IT neurons in humans or monkeys can be used to predict choices in a face-discrimination task in a manner that is directly analogous to the choice-probability studies performed in MT.

However, the results of lesion and microstimulation studies strongly implicate IT cells in face perception. Prosopagnosia, famously documented by Oliver Sacks and others, is a well-described condition in humans thought to result from damage to the temporal lobe in which patients are completely unable to recognize or identify faces. To test whether activity of inferotemporal neurons is sufficient to lead to the percept of a face, Afraz and colleagues performed an analogous experiment in primate IT to the one performed by Newsome and colleagues in area MT. These authors trained monkeys to perform a task where they reported whether an image contained a face or not (Afrac, Kiani, & Esteky, 2006). This task was made difficult by adding various amounts of noise to the image set that degraded the clarity of the images, thus making them harder to discriminate. Similar to the results of the MT study, the authors found that microstimulation in face-selective portions of cortex led the animals to report seeing a face in a noisy stimulus more often than when stimulation was not applied.

With the advent of increasingly sophisticated molecular, genetic, and imaging techniques has come a strong interest in developing both rodent and rat models for linking the activity of neurons to behavior. Progress on this front has been made across a range of tasks and sensory modalities, including visual (Carandini & Churchland, 2013) and auditory (Brunton, Botvinick, & Brody, 2013) discriminations. Of particular interest is a series of work linking the activity across multiple brain areas in rats to olfactory discriminations.

Uchida, Mainen and colleagues have demonstrated that rats can accurately discriminate between mixtures of odor pairs with just a single sniff (Uchida & Mainen, 2003). Neurons in the olfactory bulb, the target of olfactory receptor neurons in the nose, exhibit odor-specific selectivity and have been shown to reliably distinguish between small sets of odorants on similarly brief time scales to a sniff, as well as to correlate with reaction times during an odor-discrimination task (Cury & Uchida, 2010).

Piriform cortex, also known as olfactory cortex, receives input from the olfactory bulb and is a candidate for a cortical region that is involved in odor discriminations. A recent study recording activity in piriform cortex during an odor-mixture discrimination demonstrated that the activity of fewer than 100 neurons was sufficient to accurately predict behavioral performance and reaction time. This study also interestingly revealed that noise correlations among these neurons were extremely low, highlighting a potentially important difference between olfactory and visual processing (Miura, Mainen, & Uchida, 2012).

The systems for which the most progress has been made linking sensory neurons to perception tend to have at least two things in common. First, experimenters have designed psychophysical tasks that allow them to measure subtle changes in specific perceptual abilities. Second, the brain areas under study (in the primate visual system, at least) tend to be organized so that neurons with similar tuning tend to be located near each other in the brain. This certainly has experimental benefits, because techniques like microstimulation or chemical inactivation that are accessible in primates can be used to affect small groups of neurons with, for example, only a preference for upward (and not downward) motion. New techniques such as optogenetics may remove this technical requirement. It will be interesting to see whether anatomical organization is required for certain perceptual abilities, or whether areas with anatomical organization have been well studied simply because it is technically easier to do so.

General themes and future directions

As our knowledge of the link between sensory neurons and specific percepts has become more developed in recent years, a few conceptual themes and unanswered questions have emerged.

STUDIES OF SINGLE NEURONS MISS CRITICAL INFORMATION For technological reasons, most studies linking the responses of sensory neurons to perception focus on recordings from one neuron at a time. However, the responses of a large subset of the thousands of neurons that respond to any sensory stimulus are thought to underlie any percept. The logic is that we can learn about how big groups of neurons

respond at one time (as in actual behavior) by recording how individual neurons respond over many behavioral trials and using computational models to figure out how the responses of many neurons are combined. Although these types of studies have been hugely informative, recent studies have shown that this assumption does not always hold.

New technology makes it possible to record from groups of neurons simultaneously, and early results suggest that measuring the responses of many neurons at once is very different than combining information from individual neurons recorded on separate days. For example, we discussed earlier that shared or correlated noise can make measurements of choice-probability misleading. Those same correlated responses can have big effects on the amount of information a group of neurons encodes, although different models of how the responses of many neurons are combined make different predictions about whether correlations hurt or help (Abbott & Dayan, 1999; Shadlen et al., 1996). Correlations depend on the sensory stimuli (Aertsen, Gerstein, Habib, & Palm, 1989; Ahissar, Vaadia, Ahissar, & Bergman, 1992; Espinosa & Gerstein, 1988; Kohn & Smith, 2005), learning (Ahissar et al., 1992; Gutnisky & Dragoi, 2008; Komiyama et al., 2010), and behavioral state and cognitive factors like attention (Cohen & Maunsell, 2009; Cohen & Newsome, 2008; Mitchell, Sundberg, & Reynolds, 2009; Poulet & Petersen, 2008; Vaadia et al., 1995). That so many factors affect correlations strongly suggests that they are important, but future theoretical and experimental work will be needed to determine their exact role in encoding sensory stimuli.

Recording from large groups of neurons has another advantage: it gives experimenters a snapshot of the sensory information available to a subject at a given moment rather than the average responses to many repetitions of the same sensory stimulus. It has long been known that cognitive factors and motor planning can affect the responses of sensory neurons, but the role these factors play likely differs from moment to moment and can be obscured by averaging across many trials (for review, see Desimone & Duncan, 1995; Maunsell & Cook, 2002; Maunsell & Treue, 2006). The differences in the conclusions that can be drawn from studies that record many neurons at a single moment compared to one neuron over a long period of time are an area of active investigation.

NOT ALL NEURONS ARE THE SAME Neurons come in many anatomical and physiological subtypes. Neurons differ in their pattern of connections, whether they are inhibitory and excitatory, whether they fire tonically or in bursts, and a host of other factors. Most of the studies we have discussed rely on extracellular electrophysiology. This technique makes it very difficult to determine the subtype of the neuron under study. Most models of neural circuits posit very different

roles for neurons with different properties (e.g., inhibitory vs. excitatory neurons), but there is little experimental data on how they function in behaving animals. New technology, including optogenetics (Luo et al., 2008; Peron & Svoboda, 2010; Prakash et al., 2012; Scanziani & Häusser, 2009; Zeng & Madisen, 2012) and improved imaging tools (Helmchen & Denk, 2005), will make it possible to understand the role of different classes of neurons in neural computations.

THEORETICAL MODELS ARE IMPORTANT As monitoring the activity of large numbers of neurons becomes easier and easier, having a theoretical framework for interpreting all of these data becomes more and more critical. The dominant, and really only, framework for relating sensory neurons to perceptual decisions comes from work by Shadlen and colleagues (1996) modeling decision making in the motion-discrimination task. This model has significantly helped researchers to make sense of the physiological data. For example, it pointed to correlated variability as the source of choice-predictive signals in individual MT neurons. It is in many ways a high-level model, however, and does not take into account factors like cell type, dynamics, or the pattern of connections different neurons make. As data sets get more sophisticated, new theoretical frameworks will be necessary to convert data into understanding.

Tremendous progress has been made on both theoretical and experimental fronts since Parker and Newsome wrote their landmark review in 1998. As the field continues to progress, their rubric has become more important than ever. It is only through a principled application of the technological advancements discussed above that we will improve our understanding of the relationship between neural activity and perception.

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