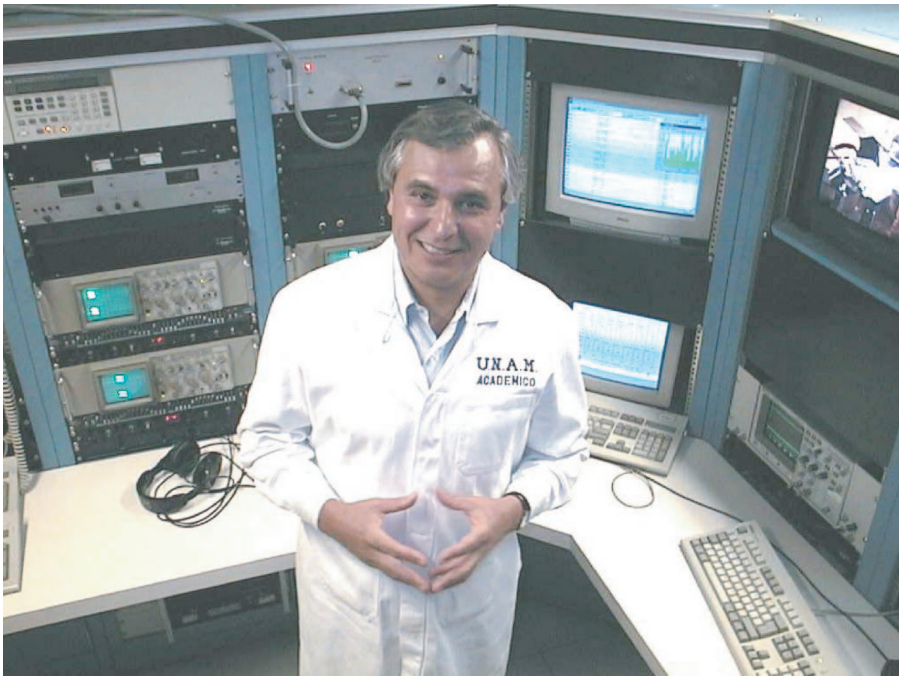
Profile of Ranulfo Romo

In the study of the brain, decoding the mechanisms behind perception and awareness has long posed a difficult problem. Neuroscientist Ranulfo Romo has spent much of his career tackling this problem, investigating how neurons generate the signals that lead to perception of touch stimuli. Elected to the National Academy of Sciences as a foreign associate in 2005, Romo is a Professor of Neuroscience at the National Autonomous University of Mexico in Mexico City. In his Inaugural Article in this issue of PNAS (1), Romo and colleague Victor de Lafuente examine how, in the brain's cortex, the processing of a sensory stimulus evolves over time during perception.



Ranulfo Romo

Biology of Man

Romo was born in 1954 in the small town of Ures, Sonora, in northern Mexico. His father was a farmer, and, as a young boy, Romo was keen on nature. "I was really interested in biology. When I went to secondary school I had a very good teacher in biology who taught about plants and animals, and I had a pretty good idea I wanted to study biology," he says. "I was really interested in the biology of man, so I decided to study medicine to focus my interest in understanding the physiology and anatomy of human beings. I thought I could be a good physician and eventually do some research."

With these interests in mind, Romo entered medical school at the University of Guadalajara (Guadalajara, Mexico). He recalls his disappointment, however, "I thought the physiology professor was an investigator. After he gave the first lesson, I went to the back of the book to see the references, and his name wasn't there. He was simply reading the textbook. I said to myself, 'This man is not an investigator,' and I discovered that the university had no research." Romo called his parents and told them he was going to leave because he wanted to pursue research at the National Autonomous University of Mexico. "So I spent a year with my parents doing nothing with my life and waiting for admission," he says.

In 1974, Romo was finally accepted to medical school at the National Autonomous University of Mexico. On the first day, he was surprised to find out that the physiology professor was truly a physiologist. "I said to myself, 'Finally, I will be in touch with a man who does research,'" says Romo. He immediately asked the professor whether he could work in his laboratory, but the professor refused, saying he needed people with experience. "I was very disappointed. I asked him whether I could simply go to his lab and watch experiments and help by doing anything," says Romo. After several attempts, he was accepted into the laboratory. "I was very happy, and I immediately knew a medical career was a second option. I wanted to become a scientist, not a physician," he says.

Sleep research was prevalent in Mexico in the early 1970s, and Romo entered this field of study during this time. While in medical school, Romo began his own related research projects. "I studied lizards to see whether I could find the first elements of producing paradoxical [REM] sleep. I managed to do some experiments and publish a couple of papers at the age of 19 (2). Over the years, I have seen some people working on phylogenetic analysis of sleep cite my papers (3). So they were not lost," he says.

Move to Motor Control

After finishing medical school in 1978, Romo studied epilepsy and parkinsonism with Francisco and Marcos Velasco, at Mexico's National Medical Center in Mexico City. "I became very interested in the pathways of the brains, which produce, for example, motor control, and the disorders produced when those pathways vanish," he says. With a new interest in neurotransmitters and motor control, Romo wrote in 1981 to the neurochemist Jacques Glowinski at the Collège de France in Paris. "I was very interested in locating the cells associated with parkinsonism. I spent 3 years for my Ph.D. there studying dopamine release, the molecule associated with parkinsonism," says Romo (4–6).

In 1984, Romo met Wolfram Schultz and joined him as a postdoctoral researcher at the University of Fribourg (Fribourg, Switzerland). "I talked to him about whether we might be able to do some recordings of dopamine cells in behaving monkeys and see whether those neurons really encode something associated to motion," says Romo, who spent 3 years performing research with Schultz. "I was very, very happy because at last I could do neurophysiology," says Romo.

According to Romo, the leading idea in those years was that dopamine cells in the substantia nigra were associated with motor control. No studies showing this association were available, apart from the negative effects obtained when destroying such cells. However, Romo explains, "When we went to the cellular recordings in behavioral tests, we found those cells did not encode motion. Wol-

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 14266.

fram and I were very surprised. It was a very negative result for us that the cells were not very active when the monkey was performing voluntary movements."

Instead, Romo and Schultz found that the dopamine cells were associated with encoded reward. "That was very unexpected. That was the first study that associated dopamine cells with motivation and reward. It took us about 5 years to publish the paper because nobody was going to buy this idea that those neurons were not associated with movement, but reward," Romo says (7, 8).

Mexico via Baltimore

In 1987, Romo wrote to neuroscientist Vernon Mountcastle at Johns Hopkins University in Baltimore, MD. With no research positions open in Mexico, where Romo hoped to return, he felt his best option was to obtain another postdoctoral position. "I wanted to learn psychophysics and how to study the cerebral cortex. In those years, Mountcastle was the [leader] of neurophysiology in the United States. He had a lot of experience, and I thought in moving from Europe to the United States, not only was I going to get good training, but [I could] negotiate my return to Mexico City."

Although 69 years of age and nearing retirement at the time, Mountcastle wanted to carry out new experiments in the somatosensory system. "I was also interested in the somatosensory system because Wolfram and I had observed that dopamine cells could respond to touch," says Romo (7). Reflecting on his research stint under Mountcastle, Romo says, "I received the best training a person could get working with him from early morning to late in the evening, Monday to Sunday. It was a wonderful experience to me, because the man behaved as a postdoc, eager to do something every day."

In Mountcastle's laboratory, Romo trained monkeys in sensory discrimination of vibrotactile stimuli, taking the animals to the limits of discrimination and measuring thresholds (9). Neurophysiological studies were conducted by introducing electrodes into the cerebral cortex and recording from single neurons. The monkeys held a vibrating touch pad in one hand and used a set of push buttons to indicate differences in the pad's fluttering with the other hand. Romo continues his research today with similar experimental designs.

At the end of the 1980s, Romo searched in vain for a research position in his native Mexico. His wife, Ana Cecilia de Romo, had a friend, Nancy Carrasco, at Albert Einstein College of Medicine in New York, NY, who learned of his difficulties. Carrasco contacted Antonio Peña, the director of the Institute of Cellular Physiology at the National Autonomous University, Romo's alma mater. Peña contacted Romo and eventually hired him. In 1989, Romo was appointed a full professor at the university and has remained there since.

"I decided to return to Mexico for personal reasons. I wanted to give myself a chance in Mexico. We knew in those years that research was not very well developed in Mexico and that the country needed some," Romo says. Over the years, he has been able to gather the proper equipment needed to conduct research at international standards in Mexico. Romo says that the only difference between performing research in Mexico versus the United States it that postdoctoral positions are not as attractive in his native country. "It might be attractive coming to my lab, but you need a science culture and environment to provide excitement to young colleagues," he explains.

Romo's recordings could predict whether the monkey would make the proper detection before it declared its choice.

Returning to Mexico, Concentrating on Touch

Upon his return to Mexico, Romo resumed experiments on the somatosensory system. "The field of sensory perception was and still is dominated by the visual modality," he says. "So I thought by concentrating on touch I could add something new to what people knew about sensory processing and decision-making," says Romo (10, 11). "In essence, the sensory discrimination task has two components, two stimuli separated in time. But once a stimulus is gone, this information has to be stored in the brain, so the question is, 'Where and how does this happen?'"

Although the brain must store a copy of a stimulus that is already gone, when a second stimulus is introduced, the brain must compare the information of the second stimulus against the working memory copy. "I think this is key to understanding perception because when you see an object, the sensory input is providing information about the object, but you recognize this object because you compare the representation against sensory experience, which is stored in working memory," Romo says. In studying this area, Romo identified cells that store or reflect the content of the sensory information (12) and decoded the signals of these cells (13).

With the working memory and sensory cells identified, Romo put it all together (14, 15). "If monkeys compared the sensory information with the sensory information stored in working memory, you should be able to decode in the responses of these cells the memory signals, the sensory input and the comparison of both, and how they evolved in time to produce a decision that produces the motor response in the animal. This is what we discovered in the late 1990s and early 2000s," Romo says (16–18). "I think they were beautiful studies because we could track the sensory processing, we could track the working memory processing, and we could track where in the brain the two signals are melded together in order to produce a decision signal that drives the motor response of the monkey. In fact, we were reading the monkey brain, the monkey mind, just by listening to cells," he says. Romo's recordings were so precise that by looking at the neural signals they could predict whether the monkey would make the proper detection before it declared its choice.

Limits of Perception

In the past couple years, Romo and de Lafuente have examined how detections are represented in the monkey brain at the limits of perception, when the same stimulus is perceived only 50% of the time (19). Romo found that sensory neurons in the primary somatosensory cortex simply fire as a function of the stimulus quantity and have no relation to the detection performance. "They cannot tell you something about why the monkey did or did not detect it with the same stimulus quantity," he says.

The finding went against the common assumption that the primary somatosensory cortex is involved in detection performance. So Romo and de Lafuente looked elsewhere in the brain for this activity. "We made a radical movement. We went to the frontal lobe to compare the responses of primary somatosensory cells with responses of neurons in the medial prefrontal cortex. We found that neurons there strongly covary with the detection performance," he says.

In his PNAS Inaugural Article (1), Romo and de Lafuente look at the detection steps that occur between the primary somatosensory cortex and the neurons that encode the detection. "We propose that information from the primary somatosensory cortex is little by little transformed to areas like the medial premotor cortex. It's a gradual transformation of this sensory representation. The transformation strongly correlates with detection performance," Romo says.

Explaining the brain's activity, he says, "You feel that you perceive something abruptly, but what you see in the activity of neurons in different positions in the network [is] they gradually build the neural correlate associated to this abrupt sensation that you detect as something." He and de Lafuente also propose that multiple transformations occur in the brain. The signals received in the primary somatosensory cortex are passed to the posterior parietal lobe, the secondary somatosensory cortex, and then on to the frontal lobe. "You can see the contribution of these different cortical areas to the detection performance," he says, "and the one that correlates the most is the medial premotor cortex." Romo and de Lafuente compared the responses of neurons from different parts of the brain and found they could calculate the probability of obtaining a detection response based on the signal from a particular brain region.

All of this research comes down to solving what Romo calls one of the simplest problems in cognitive neuroscience: How do we detect things and the differences between them? Romo says neurophysiologists must develop experiments that make neural and psychophysical measurements at the same time. "We are not addressing how the circuits are working in real time. We are recording neurons one after the other, and we do *a posteriori* reconstruction of their functions," he says.

To observe how neural circuits work in real time, Romo says new experimental techniques are needed. "We are investing a lot of time and money in order to sample many hundreds of neurons simultaneously from different cortical areas because we would like to see how local and distant circuits communicate information in real time and how the sensory percept is built up in a single trial," he says. "It's an immediate challenge for the lab and any lab working on sensory, memory, or motor problems." As an analogy, Romo says, "In the square plaza here in Mexico City, people gather for a meeting—you may have 100,000 people associated with a single event. So the question is if you see all these people as single units, what are they sharing at the same time? I'd like to have an idea about this. I don't know what the end will be, but certainly there will be interesting results."

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1. de Lafuente V, Romo R (2006) *Proc Natl Acad Sci USA* 103:14266–14271.
2. Lozoya X, Romo R (1975) *Arch Invest Médica (Méx)* 6:455–466.
3. Romo R, Cepeda C, Velasco M (1978) *Bol Inst Estud Médicos Biol (Méx)* 30:13–18.
4. Romo R, Cheramy A, Godeheu G, Glowinski J (1986) *Neuroscience* 19:1067–1079.
5. Cheramy A, Romo R, Godeheu G, Baruch P, Glowinski J (1986) *Neuroscience* 19:1080–1090.
6. Romo R, Cheramy A, Godeheu G, Glowinski J (1986) *Neuroscience* 19:1091–1099.
7. Romo R, Schultz W (1990) *J Neurophysiol* 63:592–606.
8. Schultz W, Romo R (1990) *J Neurophysiol* 63:607–624.
9. Mountcastle VB, Steinmetz MA, Romo R (1990) *J Neurosci* 10:3032–3044.
10. Romo R, Ruiz S, Crespo P, Zainos A, Merchant H (1993) *J Neurophysiol* 70:2690–2694.
11. Ruiz S, Crespo P, Romo R (1995) *J Neurophysiol* 73:525–537.
12. Hernández A, Salinas E, García R, Romo R (1997) *J Neurosci* 17:6391–6400.
13. Romo R, Brody CD, Hernández A, Lemus L (1999) *Nature* 399:470–473.
14. Salinas E, Hernández A, Zainos A, Romo R (2000) *J Neurosci* 20:5503–5515.
15. Hernández A, Zainos A, Romo R (2000) *Proc Natl Acad Sci USA* 97:6191–6196.
16. Hernández A, Zainos A, Romo R (2002) *Neuron* 33:959–972.
17. Romo R, Hernández A, Zainos A, Lemus L, Brody C (2002) *Nat Neurosci* 5:1217–1225.
18. Romo R, Hernández A, Zainos A (2004) *Neuron* 41:165–173.
19. de Lafuente V, Romo R (2005) *Nat Neurosci* 8:1698–1703.