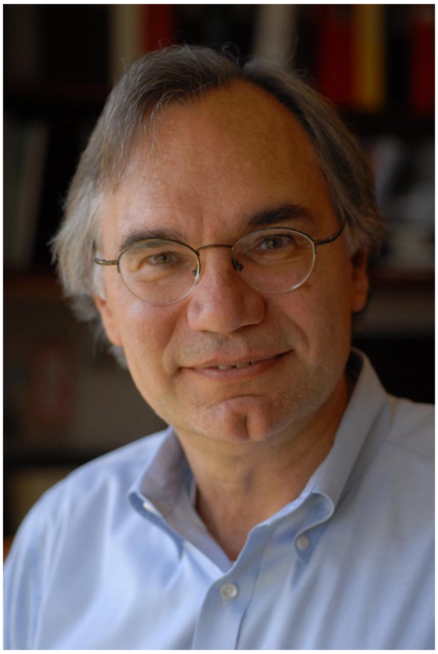
Profile of Richard A. Andersen

He won't be reading your mind anytime soon, but neuroscientist Richard Andersen does hope to eventually harness signals in the brain's planning circuits and use them to drive neural prosthetics that respond to a user's intent. Were the brain unable to coordinate goal-directed movements, like reaching for an object, everyday tasks would become unbearably slow. To keep such mundane tasks on track, the brain develops a prediction of a limb's current state based on feedback from the movement command, instead of relying solely on sensory feedback—a relatively slow process—to monitor muscle movement. Andersen, who was elected to the National Academy of Sciences in 2005 and is currently the James G. Boswell Professor of Neuroscience at the California Institute of Technology (Caltech; Pasadena, CA), studies how the brain integrates these signals and plans future movements. His Inaugural Article (1) describes how the brain's posterior parietal cortex (PPC) serves as a bridge from sensation to action and thus provides an attractive target for neural prosthetics.



Richard A. Andersen

Disc Jockey or Scientist?

Born in New Kensington, PA, in 1950, Andersen didn't remain there for long. "I moved around quite a bit," he explains. By the time he turned 16, his family had settled in the San Francisco Bay Area, but not before living in Louisiana, Ohio, and New York, moving wherever his father's career in chemical engineering dictated. "Although I didn't realize it at the time, I was receiving an in-depth science education every evening at the dinner table when my father discussed the technical challenges he faced each day." In high school, Andersen always enjoyed science and was seemingly training for a career in environmental engineering, with early science projects that included developing a fuel cell and studying the pollutants in San Francisco Bay. Later, in deciding his course of study at the University of California, Davis (UC Davis, Davis, CA), Andersen focused on what fascinated him most: human cognition. "College is that period in your life when you start thinking about yourself and what makes you tick," he says. "That's why psychology classes are so popular." Andersen chose to major in biochemistry, believing that psychology was too general to help him achieve a neurobiological understanding of higher-order brain functions like decision-making and planning. Neuroscience seemed like an obvious fit, but at the time, he explains, neuroscience did not really exist as a field of study.

For two summers during his undergraduate years, Andersen worked in Robert Scobey's laboratory at UC Davis, studying the receptive field properties of retinal ganglion cells. When not in the laboratory, he spent a fair amount of time at his university's radio station. He jokes that he figured he could become either a scientist or a disc jockey. While he greatly enjoyed music and hosting his jazz and blues radio show, he opted to enter the University of California, San Francisco (UCSF, San Francisco, CA) doctoral program after receiving his B.S. in 1973. He now remarks, "I think I made the right choice." At UCSF, Andersen worked with Michael Merzenich, who would go on to become a pioneer of the cochlear implant. Andersen studied the fundamental architecture of the auditory nervous system to clarify how the brain processes the sounds we hear. He remembers Merzenich as a very inspirational and supportive mentor who emphasized novel ideas in all his research. Also during graduate school, Andersen met his future wife, Carol, an audiologist, at a seminar on the workings of the inner ear.

Expanding the Senses

When the time came to choose a postdoctoral position in 1979, Andersen followed Merzenich's advice and applied to work with Vernon Mountcastle, one of Merzenich's own mentors and a preeminent neurophysiologist, then at the Johns Hopkins School of Medicine (Baltimore, MD). Mountcastle had discovered the cortical column: a shaft of neurons arranged vertically within the cortex. These columns, Andersen explains, are the "basic building blocks of the cortex." When Andersen began working in the laboratory, Mountcastle was employing a unique and difficult approach in the study of high-order cortical functions such as attention and goal-directed movements. The approach involved recording from single brain neurons in awake monkeys who were performing various tasks. This technique was opening a window on complex brain activity in real time. Andersen felt excited to extend his understanding of the cortex, going beyond his functional anatomical studies of audition to more physiological studies of other senses, including visual systems.

At Hopkins, in addition to mastering the fairly new technique of using tiny wires to record activity from individual neurons in the monkeys, Andersen remarks that he learned the importance of scientific rigor and the joy of discovery. "Dr. Mountcastle appeared in the lab every day and had a habit of asking all of his postdocs, 'What did you discover today?' Naturally, no one wanted to disappoint him!" Andersen's most important work from his Hopkins studies was the discovery of what he terms "gain fields." In the process of deciphering how the brain integrates information about the direction of gaze and visual stimuli imaged on the retinas, Andersen happened on a universal way that the brain performs computation (2, 3). Neurons have visual "receptive fields" and will only respond when light stimulates circumscribed areas of the retina. But, of course, the retina is mobile. Andersen found that the same location on the retina can be stimulated for different gaze directions, leading to the same response from a neuron, even though the stimulus is at a different location in space. Andersen and Mountcastle found that a second signal existed, coding the direction in which the eyes were looking. This directional signal combined with the visual signals, and the interaction explained how locations in space can be specified, indepen-

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 8170.

dent of the direction of gaze. The gain field discovery—finding that the brain integrates signals multiplicatively—proved unexpected; "It was a bit serendipitous, but it makes perfect sense in hindsight."

Coordinated Moves

Andersen took his first faculty position in 1981, joining the Salk Institute (La Jolla, CA). At the time, researchers were beginning to approach neuroscience from a more theoretical perspective, viewing information such as neuronal impulses as signals to be processed in complicated circuits and beginning to understand that signals in the brain are processed in parallel by large, complex neural networks. "There are networks that contain multiple nodes and many cells, each carrying a little bit of the story," explains Andersen. "For that reason, you need to combine theoretical and computational approaches with experimental data to understand what is going on." Among the colleagues who exerted theoretical influence on Andersen at Salk was Francis Crick. In addition to sharing his own thoughts on the nature of the brain, Crick and some of his close colleagues formed a seminar group known as the "Helmholtz Club," made up of neuroscientists from around Southern California. Andersen and other young researchers in the area were introduced to scientists from around the world with similar theoretical interests. One study to arise from this cross-pollination club of theorists and researchers was the Zipser–Andersen Neural Network Model, one of the first neural network models to account for neural data (4). This artificial neural network showed how gain fields can accomplish calculations in a straightforward and parsimonious fashion. While recording from monkeys in the laboratory to further investigate gain fields, Andersen found evidence that the PPC also plans movements, often seconds before they are made, a feat he calls a "neural correlate of intention" (5). This finding marked a new role for the parietal lobe, a portion of the brain generally believed to act primarily as an integration center, processing signals from multiple inputs but with no role in action. Andersen's work established the role of the parietal lobe in movement planning.

In 1987, Andersen left the Salk for the Massachusetts Institute of Technology (MIT; Cambridge, MA). While at MIT, he felt keenly influenced by Emilio Bizzi, a preeminent motor neurophysiologist who had recruited him to the university and was the chairman of the Department of Brain and Cognitive Sciences. By this time, Andersen had begun research on how the senses of hearing, balance, and vision are integrated for the control of movement (6, 7). During his MIT years, Andersen also began to study motion perception. "We looked at how you see shape from motion as you navigate through the world," he says. Andersen likens the navigation effect to the opening sequence of the movie "Star Wars," with stars rushing by. In experiments that extended to his next move to Caltech, Andersen examined how the brain separates visual motion due to movement of the eyes from visual motion due to movement of the whole body through the environment (8). In other words, Andersen sought to understand how the brain produces stability or "the illusion thereof." He also began studying how motion is interpreted as three-dimensional shapes—the so-called "structure from motion"—and found that the middle temporal area is one of the earliest regions in which neural activity accounts for the perception of structure-from-motion (9, 10).

"The major aspect of my teaching is training scientists."

In 1994, the same year he received the Alden Spencer Award from Columbia University (New York, NY) for outstanding research contributions in neural science, Andersen accepted a position at Caltech. "That's where I got interested in reach movements." Up to this point, Andersen had focused on eye movements. He found two regions in the parietal lobe that were separately specialized for eye movement and reach and named them the lateral intraparietal area (LIP) and the parietal reach region (PRR), respectively (11, 12). Looking back, he sees his work converging on hand–eye coordination, an ability that is exquisitely developed in primates, including, of course, humans. He found that LIP and PRR code eye and hand movements in the same visual coordinates, suggesting that these plans are early and abstract in nature (13, 14). In the premotor cortex, an area in the frontal lobe, his research group found an even more abstract and highly processed representation of the hand, target, and eyes, in which all three are coded relative to one another (15). This relative reference frame may be basic for hand–eye coordination. Recently, Andersen has been looking at the mechanisms for making decisions, in particular those involving "free choice," where the monkeys can choose between alternatives. These experiments are intended to pinpoint where decision-making and planning occur (16), and how information flows between cortical areas during decision-making (17).

Monkey Business

Andersen's interest in planning and decision-making led to a natural extension of the research to a practical application: neural prosthetics. Andersen aims to record intent and use it to control assistive devices. He explains that most work in the area is done in the motor cortex, but his group is looking more abstractly at the intention of the subject by using computers or robotic limbs that can elaborate the desired movement. "Monkeys can control machines with just their thoughts." But Andersen can go deeper. "We can even tell what the monkey expects." The researchers could tell what the monkeys expected for a reward, including the type of liquid reward ("Tang is a favorite"), how big it might be, and how often it is delivered (18).

In his Inaugural Article (1), Grant Mulliken, Sam Musallam, and Andersen report on their study of intention and how the brain plans movement, investigating how a region of the brain develops a representation of arm movements that overcomes long sensory feedback delays. The PPC, which includes the PRR, is a functional bridge between the areas that sense input, such as visual cues, and those that direct motor function. Because sensory input alone is generally too slow for the subject's PPC to develop an estimate of the state of their hand during movement, the researchers investigated whether downstream motor movement information is harnessed by the PPC to anticipate the next state of a movement. The neural activity measured while monkeys operated a joystick to move a cursor toward a target showed that the PPC develops a "forward state" representation of action, with neurons encoding an estimate of both the current direction of the cursor and its future direction. Because the PPC develops a continuously updated forward representation of action for goal-directed movement, Andersen believes it would be an attractive target for the development of neural prosthetics.

Besides prosthetics, another relatively new direction for the Andersen laboratory lies in incorporating functional magnetic resonance imaging (fMRI) studies, but in monkeys rather than people. fMRI is used mostly in humans, and it is an indirect, and thus difficult to interpret, reflection of brain activity. By

Andersen indulging in his favorite hobbies: teaching and science.

performing the same fMRI experiments in monkeys and humans, and then recording neural activity directly in the monkeys, Andersen can better interpret the human data. "The monkey fMRI studies are a bridge to help us understand what's happening in humans." Several of their just-completed studies using this new technique are already beginning to shed light on how the human brain works. The imaging studies are also being extended to paralyzed human subjects to target areas for electrode implants in paralyzed patients for use in neural prosthetics applications. Eventually, Andersen hopes to obtain U.S. Food and Drug Administration approval for human prosthetic studies, with clinical studies first planned for quadriplegic patients.

The Andersen laboratory comprises approximately 20 postdocs, students, and staff. "For a monkey lab, it's on the large size." But Andersen thrives on the company. "The major aspect of my teaching is training scientists." He likes the daily contact in the laboratory better than standing in front of a class. "It's nice because you know them throughout their careers and don't just see them once." He encourages students to look at new ideas and be creative, but to maintain a rigorous approach. And of course the monkeys are part of the crew, too. Andersen remembers David Baltimore, then Caltech's president, touring the facility, eyeing the jars of nuts, fruit, and Tang—all rewards for the monkeys—and joking that one would never see these sorts of supplies in a molecular biology laboratory. Andersen respects the primates that make his work possible. He sees them as colleagues, an integral part of the team. "They're here five years working with us, sort of like graduate students," before they (unlike graduate students) retire to an animal sanctuary. Andersen does regret that he no longer has time for daily work in the laboratory. Although he used to perform experiments, programming, monkey training, and surgeries himself, "the lab got too big, with too many directions, and I ran out of time in the day." "Now I'm more of a director." But that doesn't mean Andersen is far from his work. "My main hobby is science," he says.

Tinsley H. Davis, *Freelance Science Writer*

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