ON THE BRAIN

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Bridging the Gap Between Molecular and Behavioral Science:
Harvard's New Center for Brain Science

A MAJOR THREAD has run through neuroscience for the past 50 years: understanding the components of the nervous system. Huge strides have been made in how these components – neurons – work and are wired, how they change chemicals to electrical signals, and how they send messages. Now, a new academic center at Harvard, the Center for Brain Science, will focus on studying these components to bridge the gap between molecular and behavioral science in an effort to better understand how neuronal activity affects behavior.

"While many aspects of both cognition and cellular and molecular biology are reasonably well understood at this point, the connections between these two levels of activity remain hazy," Joshua R. Sanes, Ph.D., the Center's director, said in a *Harvard Gazette* article announcing the creation of the Center. "The Center for Brain Science intends to explain human cognition and behavior in terms of the activity of individual cells and genes, linking human behavior with biological activity on a cellular and molecular scale."

The new Center will focus on the field of "systems neuroscience," the study of how the various components of neuroscience work together to account for our thoughts, perceptions and emotions.

With an interdisciplinary faculty from both the Faculty of Arts and Sciences (FAS) and Harvard Medical School (HMS), the Center will focus on three primary areas, says Dr. Sanes:

- Studying the neural circuits that provide the physical basis for behavior. No one has yet been able to map a neural circuit in the brain and tie it to a specific behavior, according to Dr. Sanes.
- Understanding the pathological and normal variations in individuals' behavior, including not only genetic differences but also environmental factors such as culture that affect behavior.
- Building the tools needed to understand the relationship between neural circuitry and behavior, including advanced imaging, theoretical and computational methods.

A Leader in Brain Science

Harvard University has long been a leader in brain science. FAS researchers are recognized for their studies of behavior, perception and brain development; HMS was the first medical school in the nation to establish a department of neurobiology. William James, a former FAS faculty member, founded the field of modern psychology. Research in cell and molecular biology and genetics at Harvard has always been at the cutting edge of science, with Nobel Laureates like George Wald, James Watson and Walter Gilbert among the faculty. And, at one point, almost every senior leader in the field of neuroscience – either at medical schools or university-based – was trained at Harvard.

"There is a tremendous reservoir of expertise present [at Harvard] at the reductionist levels of molecular and cellular neurobiology," says Carla Shatz, Ph.D., the Nathan Marsh Pusey Professor of Neurobiology and head of the Department of Neurobiology at HMS. "This reservoir is a key foundation for building a new synthesis of knowledge at the level of neural circuits and systems. It is an exciting time for systems neuroscience, and our

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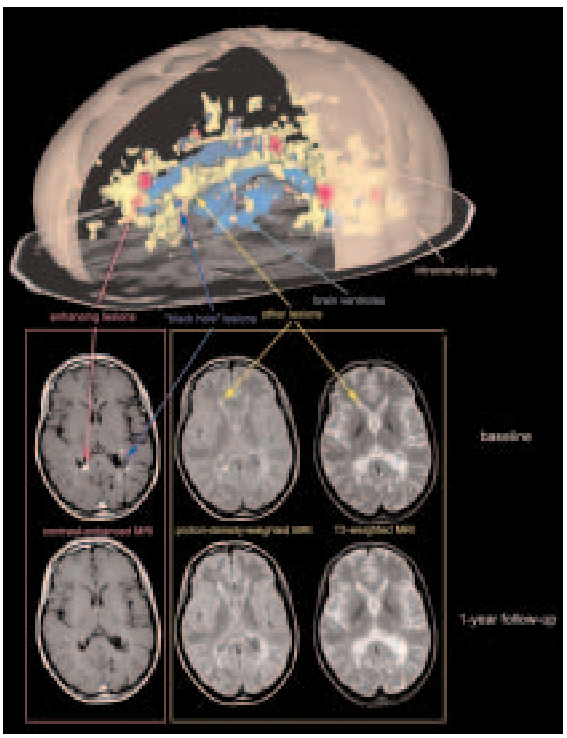
Imaging the Brain to Monitor MS

While the earliest descriptions of multiple sclerosis (MS) date to the 14th century, MS was first diagnosed in the mid–1800s. This unpredictable disease of the central nervous system can range from a relative benign form to one that results in significant disability.

In his laboratory at the Center for Neurological Imaging at Brigham and Women's Hospital, Charles R. G. Guttmann, M.D., an assistant professor of radiology at Harvard Medical School, is using quantitative analyses of magnetic resonance imaging (MRI) scans to better understand the natural progression of MS and to aid in the assessment of new therapeutic approaches to the disease.

MS is a disease in which inflammation of the white matter of the brain is associated with destruction of tissue that results in hardened lesions of the brain. These lesions include destroyed myelin, the fatty insulation that covers nerve cells in the brain and spinal cord and facilitates message transmission between the brain and spinal cord and the rest of the body. Myelin destruction leads to slowed or blocked transmission of these neuronal signals, which can result in diminished or lost function, including muscle weakness, vision problems, spasticity, tingling sensations, speech impediments and cognitive impairments. Each case of MS displays one of several patterns of symptoms and courses of progression, the erratic effects of which can take a toll on patients' quality of life.



Example of multi-channel automated image segmentation. Example slices of a three-channel MRI acquisition are shown. From left to right: Contrast-enhanced MRI, proton-density-weighted MRI and T2-weighted MRI.

Baseline and 1-year follow-up exams are shown. The three-dimensional model shows segmentations of the intracranial cavity, the ventricular system and different types of white-matter lesions. Image courtesy of Dr. Dominik Meier, Center for Neurological Imaging

Dr. Guttmann says researchers don't know exactly why these lesions appear in the brain, why they appear where they do, or why one lesion can be small and resolve while another is large and pseudotumoral in the same patient.

"MRI can help answer these questions," he says. "There's no other way to look into the brain at this level; it is the most sensitive technique for viewing pathological changes in the brain of a living patient."

MRI Tracks Lesions, Disease Progression

A noninvasive, computerized image of internal body tissue, MRI is often used in conjunction with a contrast agent to distinguish new MS lesions from old lesions.

Quantitative MRI image analysis enables researchers and clinicians to measure brain components such as normal and damaged white matter, gray matter and cerebrospinal fluid, all of which are implicated in MS. Using methods developed for *in vivo* (in a living body) quantitative tissue analysis, Dr. Guttmann and his colleagues have demonstrated correlations between changes in white matter abnormalities and changes in clinical status, represented by scales of disability and cognition. Such a linkage, he says, established quantitative MRI as a valid measurement of disease progression in clinical trials evaluating the efficacy of novel MS treatments.

Dr. Guttmann was on a team of HMS scientists who developed a more precise method of measuring changes in the brains of MS patients by combining stacks of two-dimensional MRI images to construct a 3-D image of the brain. From these images, the volume of MS lesions can be measured over time to determine quantitatively if the lesions are growing.

Other imaging techniques are used as well to help track changes in the brains of MS patients and to monitor progression of the disease, including:

- Magnetic resonance spectroscopy, which yields information about the brain's biochemistry, specifically the chemical N-acetyl aspartate, low levels of which can indicate nerve damage.

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Remembering President Reagan

In June, our country mourned the passing of one of our greatest leaders, President Ronald W. Reagan. Diagnosed with Alzheimer's disease, Reagan's courageous public announcement of his diagnosis helped increase public awareness of the field of neuroscience and of this degenerative brain disease over a decade ago. In November 1994, in a letter released to the American people, Ronald Reagan announced that he was diagnosed with Alzheimer's disease and recognized the horror to come. "So now, we feel it is important to share it with you. In opening our hearts, we hope this might promote greater awareness of this condition. Perhaps it will encourage a clearer understanding of the individuals and families who are affected by it." Reagan's open disclosure about Alzheimer's disease raised public consciousness and brought greater attention to the need for significantly more scientific research on the causes of this devastating disease.

In recognition of their courage and contributions to increasing awareness about neuroscience, Ronald and Nancy Reagan were awarded the David Mahoney Prize in June 1995. Presented by the Harvard Mahoney Neuroscience Institute, the David Mahoney Prize is awarded to an individual who has brought the importance of research and education about the human brain to the attention of the public. As the first recipients of this award, the Reagans were honored for their extraordinary leadership in educating the public of the importance of finding a cure for this devastating disease. At the Mahoney Prize award ceremony in New York City on June 5, 1995, David Mahoney emphasized that "we must continue to raise public awareness of our achievements in brain research. President and Mrs. Reagan have again taken the lead in a major cause, and we are in their debt."

In the last 25 years, the number of Americans with Alzheimer's has risen from 500,000 to 4.5 million. Since the disease affects nearly half of those 85 and older, the Alzheimer's Association predicts that a six-fold increase in the next 45 years is likely. It estimated that by the year 2050, Alzheimer's will have struck some 15 million Americans.

David Mahoney with Nancy Reagan as Dr. Daniel Tosteson, former Dean of the Faculty of Medicine at Harvard Medical School, presents her with the David Mahoney Prize.

The Harvard Mahoney Neuroscience Institute, established by David and Hildegarde Mahoney in 1990, supports scientific investigation and maintains ongoing communication efforts to increase public awareness of the critical importance and the promising future of neuroscience. The Institute seeks to accelerate the pace of scientific discoveries, broaden public understanding of the importance of these discoveries, and to increase the funding that makes them possible.

New insights into Alzheimer's disease may come tomorrow or they may take years. The task before us, translating our enhanced knowledge of the development and function of the brain into novel and groundbreaking treatments, requires the continued commitment of research funds. Thanks to President and Nancy Reagan for their public support of the urgency of this effort, scientists have made important strides in our understanding of Alzheimer's disease. The Harvard Mahoney Neuroscience Institute continues the effort.

Looking for the Nature of Human Nature
We're Born with a Lot on Our Minds

By William J. Cromie
Harvard News Office

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STEVEN PINKER is looking into peoples' brains to try to see what's on their minds. The Johnstone Family Professor of Psychology at Harvard disagrees with those who think that, at birth, it's nothing.

Some people assume that a new mind is like a blank slate. Interactions with family, toys, media images, and whatever else is in the environment create impressions on the slate that make you what you are. Pinker wonders why that idea has had so much appeal. "Many studies suggest that we are born with our brain already wired to learn language," he notes. "There is also evidence that we come into the world with certain expectations about objects, space and numbers, and with a capacity for emotions, such as love, hate, anger, and disgust."

Pinker is skeptical, however, of the claim that human brains come with a "God module," an innate capacity for belief in an all-knowing Grand Designer. Does the mind have a soul, or does it make one up?

One of Pinker's favorite examples of research leading to the conclusion that a new mind isn't blank comes from a study done by Nancy Segal, now a visiting scholar at Harvard, and her collaborators. It involves pairs of identical twins separated at birth. One twin of a male set was brought up as a Catholic in a Nazi family in Germany, the other was raised as a Jew by an adoptive father in Trinidad. When they finally met in their 40s, they were wearing identical blue shirts with epaulets. Both had rubber bands around their wrists. Both flushed the toilet before using it as well as after. Both liked to sneeze in crowded elevators to watch other people jump.

The minds of twins

Pinker's own research includes a twins' study that focuses on why some kids acquire language more quickly than others. He and his colleagues track several hundred pairs of twins, whose mothers keep diaries of their language development.

It turns out that identical twins, who both have the same genes, are more closely synchronized in language development than fraternal twins, who only share half their genes. That's evidence, Pinker insists, for a genetically influenced clock, that is, for brain slates that come with rules for language development.

A related area of his research deals with how children use grammar. They apparently come into the world trying to master rules that call for adding "ed" to a verb to form a past tense. If you want the past tense of "talk" or "walk," you just add "ed." "Mommy talked to me." "Daddy walked the dog."

But what about all those irregular verbs like "go," "bring," and "find"? Children usually start by over-applying the rule and saying things like, "doggie goed," "daddy bringed," "I finded." This shows that they are not just imitating their parents' speech. Rather, they have unconsciously ferreted out a rule of grammar and are applying it creatively, albeit incorrectly. Some kids start making such errors before age 2, others don't do it until they are almost 3. Pinker and his colleagues have found evidence that some of this variation depends on the ticking of the genetic clock.

A similar test examines when children begin to put together microsentences like "all gone milk," "want cookie." They don't hear their parents say things like that, so they must be combining language elements in their own minds. Putting together such sentences represents the first glimmer of grammar. This, too, apparently depends of the organization of their not-so-blank slates.

"Parents often write to me to ask why their child is not talking yet," Pinker notes. "They worry that it's their fault for not talking enough to the child." He assures them that there's not necessarily anything wrong, it may be just a matter of timing, when genes turn on and off.

A full slate

What else might be on the slate besides an ability to learn rules for breaking sounds into words and combining them in sentences?

Experiments by Elizabeth Spelke, a professor of psychology at Harvard, suggest that babies come into the world with certain expectations about the stability of objects and with some knowledge about laws that govern them. Given the task of locating themselves after being turned around in a room, infants appear to locate themselves and objects by using cues like the shape of the room. Adults don't orient themselves this way, but rats and hamsters

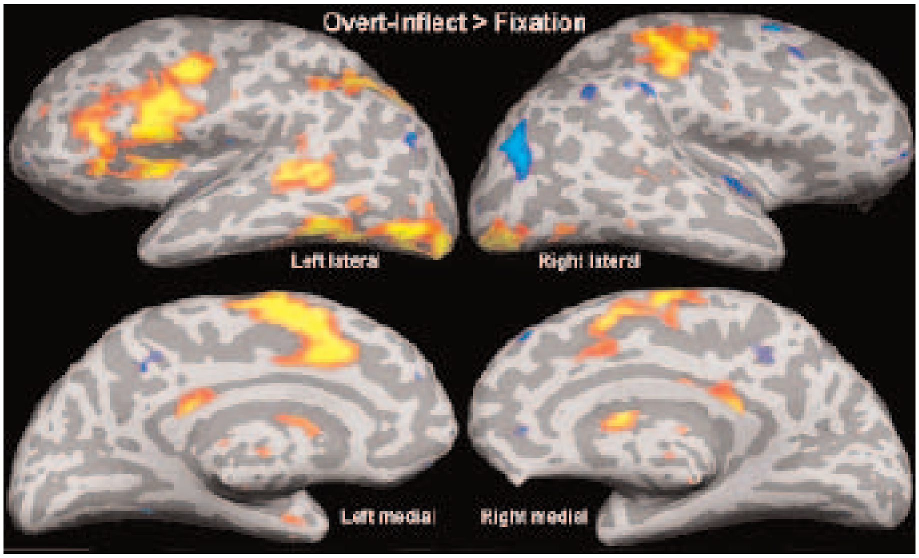

Image of functional magnetic resonance imaging scan of people reading and conjugating verbs, from a study being conducted by Pinker and Sahin.

do. This suggests that newborns have a primitive inborn capacity that gives them information about objects before they learn about them from parents or experience.

Spelke's work also hints that we come into the world with some concept of numbers, possibly inherited from our evolutionary predecessors. When two objects are placed in a box, infants will reach in twice, not once or three times. Monkeys do the same thing, as demonstrated by Spelke's and Pinker's colleague, psychologist Marc Hauser. It appears that both infants and monkeys can add or subtract numbers up to three without any help from their parents.

To the list of things that might be on a newborn's mind, Pinker adds an ability to conceive of other people as having their own thoughts and feelings, rather than as objects like robots or wind-up dolls. That's a capability lacking in children with autism, an inherited deficit. In other words, autistic kids lack the genetically shaped intuition written on a normal slate.

Finally, Pinker believes, humans are born with some capacity for emotions and social relationships. He believes this involves things like love, hate, guilt, anger, disgust, gratitude, and a capacity for trust and solidarity toward friends and family.

Gods in your head

Pinker draws the line at an inborn belief in God or gods. He doesn't look for this God module in brain scans, but he does discuss the subject in his 1997 book "How the Mind Works." (He also continues to gets lots of mail about it.) In his latest book, "The Blank Slate: The Modern Denial of Human Nature," he takes on the larger question of why many people believe in a soul that is separate from the physical activity of the brain, something for which, he says, no evidence exists.

Pinker notes that a God module in the brain fails to offer any direct evolutionary advantage, as counting and language do. "So, it's likely," he comments, "that religious belief is a byproduct of other faculties of the mind. If the mind explains the behavior of other people by positing they have minds, it's a short step to posit that minds, like souls and spirits, aren't tied to other peoples' bodies."

Pinker also argues that religion should not be considered a source of higher ethics and moral guidance. He points out that religion "has given us stonings, witch burnings, crusades, inquisitions, jihads, fatwas, suicide bombers, and mothers who drown their children." He cites passages from the Bible that, he believes, make it "a manual for rape, genocide, and the destruction of families."

Views like that have won him such honors as Humanist Laureate and the Emperor's New Clothes Award from the Freedom from Religion Foundation.

Pinker himself considers looking at religious beliefs from a nonreligious point of view as part of solving the puzzle of how human nature works. "In my research and thinking about the brain, language, and mind," he explains, "I'm trying to determine what the mind is and how it fits into a larger, coherent, scientific picture of the nature of things."

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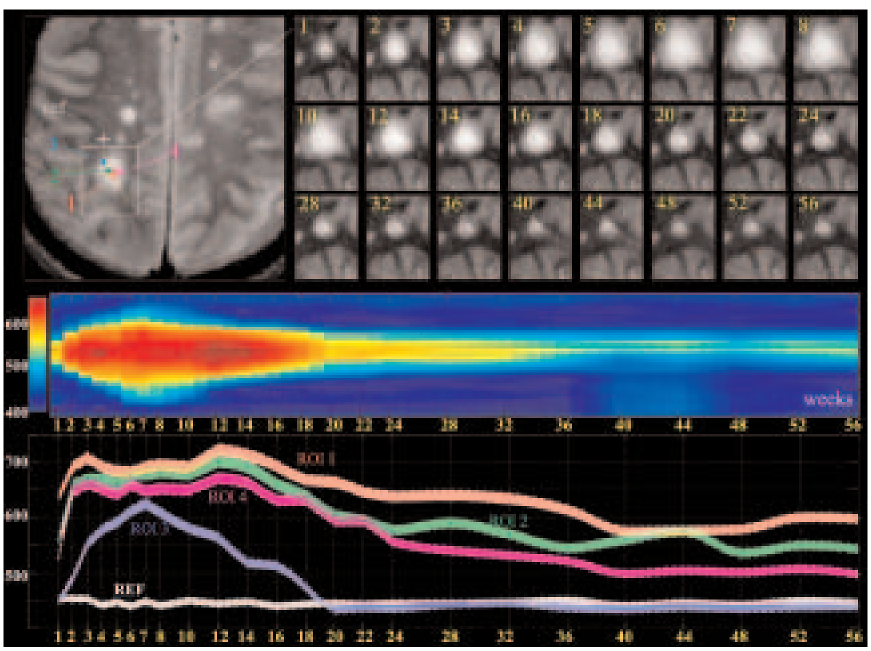
- Magnetization transfer imaging, which detects white matter abnormalities before lesions can be seen on standard MRI scans by calculating the amount of "free" water in tissues (demyelinated tissue shows increased levels of "free" water particles).
- Diffusion-tensor MRI, which produces three-dimensional images of the nerve fiber bundles in the brain's white matter (white matter fiber tracts). Understanding the relationship between MS lesions and specific fiber tracts is expected to yield a better understanding of the genesis of clinical MS symptoms.
- Functional MRI, which measures brain activation in response to a given stimulus, such as the performance of a cognitive task. Through observations using functional MRI some researchers have suggested that the brain is able, at least in part and temporarily, to compensate for some disruption caused by MS lesions.

The combination of these MRI tools allows unique in vivo investigations of MS and is yielding otherwise inaccessible insight into the disease, says Dr. Guttmann. Since MRI is done in vivo and is thought to be fairly safe, changes can be detected in the brains of living patients over time. MRI can also depict lesions in 3-D and 4-D (time-lapse movies of changes in 3-D lesions over time), as well as image the entire brain rather than small sections. MRI's drawbacks include a lower specificity to the various components of a lesion (inflammation, degeneration and repair elements) and lower resolution of brain structures than provided by microscopy tissue examinations that can only be performed after death or on tissue obtained through a biopsy or surgical excision. Dr. Guttmann says that comprehensive examination of MS includes the use of MRI and other imaging, immunological, genetic and clinical testing.



Example of time-series analysis of lesion dynamics as apparent from serial MRI. The dynamics of a single lesion, studied with weekly to monthly exams over a 1-year period, is shown. Profiles for local point samples are plotted (bottom) and a pseudo-color rendering of the lesion dynamics is shown along a cross-section (middle), indicated by a yellow line. Different levels and rates of recovery are apparent within a single lesion. Image courtesy of Dr. Dominik Meier, Center for Neurological Imaging

Database Yields 'Natural History' of Disease

For several years, Dr. Guttmann has served as the project leader of the MRI, image analysis and informatics component of a large serial follow-up study of MS patients designed to understand the natural course of MS and treatment effects by analyzing lesion distribution and morphology.

A major part of this study is an "image-centric" database of more than 5,000 MRI scans of the brains of many hundreds of MS patients. The MS Project started more than 14 years ago, with MS patients, over a one-year period, receiving weekly, then biweekly and finally monthly MRIs to track the progression of their disease.

"This dataset is unique," says Dr. Guttmann, "in that it provides a weekly follow-up with untreated MS patients. It gives us a rare glimpse into the natural history of MS."

In addition to MRI images, the database also includes patients' immunological and clinical information to help researchers understand the pathological underpinning of MS and help clinicians monitor the progression of the disease in individual patients.

Next Steps

Dr. Guttmann and his colleagues at the Center for Neurological Imaging are in the early stages of research on other MS imaging techniques. One study is examining time series analysis, a direct analysis of MRI intensity signals over time in long-term follow-up to determine the underlying pathological processes of MS. Another study is investigating differential morphology, an image analysis approach that yields exact counts of the total changes that have occurred in the brain, as well as where and what kind of changes have taken place. Researchers are also developing a Disease Activity & Severity Index, which focuses on coordinating variables to create a common reference for disease activity (the extent of currently active disease) and disease severity (the extent of visible damage that has occurred).

While there is currently no cure for MS, Dr. Guttmann says the research being conducted at the Center for Neurological Imaging and in the MS Project is geared toward bringing to the bedside better clinical treatments for MS. His working hypothesis is that MS is not a single disease, but a combination of diseases, with different causes, that yields a single clinical picture. With MRI technology, he and his colleagues hope to make the distinction clearer between different forms of MS in order to eventually enable treatments to be better tailored to the individual patient.

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faculty at Harvard Medical School look forward to working with our new colleagues in the Center for Brain Science."

A Multidisciplinary Center

The Center for Brain Science will build upon this expertise by drawing faculty from across Harvard – neurobiologists, neurologists and psychiatrists from HMS and biologists, evolutionary biologists, chemists, computer scientists, physicists and engineers from FAS.

"One of the strengths of the Center," says Dr. Sanes, "is that a number of departments not normally involved in neuroscience will be involved. We'll recruit people with skills that traditional neuroscientists don't have, but these individuals will have a strong interest in neuroscience."

Dr. Sanes, a neurobiologist who pioneered the study of synaptic development, as well as molecular and genetic approaches to nervous system analysis, will direct the Center. Faculty members from FAS, HMS and some Harvard teaching hospitals sit on the Center's steering committee.

"Part of [Harvard President Lawrence] Summers' agenda is to get Harvard to work together," says Dr. Sanes, "and the Center is one manifestation of this."

Genesis of the Center

The field of neuroscience has grown in relevance in the past decade or so. The field of neurology, traditionally one of diagnostic rigor but little, if any, therapeutic potential, has been transformed by the neurosciences. Promising treatments are now in clinical trials for such conditions as Alzheimer's disease, spinal cord injury, amyotrophic lateral sclerosis and a host of other neurodegenerative diseases. In addition, advances in our ability to shape behavior and understand the neurobiological bases of addiction, criminal behavior and sexual preference have implications far beyond the fields of medicine and science.

The effort to establish a center to tie together the disparate fields involved in systems neuroscience began in 1999 when Harvard made a major investment to bridge the gap between molecular and behavioral science, focusing on genomics, imaging and mesoscale structures, and neuroscience. The new Center for Brain Research will bring much of this together to study the brain and nervous system – from sensation and perception, learning and memory to the molecular, genetic and cellular make up of the nervous system – in a multidisciplinary approach to neuroscience.

"We're not inventing systems neuroscience," says Dr. Sanes, which has been around for the past half-century or so. "We want to contribute by doing something a little different. One way is to focus a lot of resources on a few central issues. Another is to bring together groups that have traditionally not had much to do with each other. We don't yet know exactly what will come of it, but we firmly believe that these are ways for Harvard to make a difference."

In the end, says Dr. Sanes, focusing on simple neural circuits and behaviors will lead to new insights on how the brain works and could pave the way for significant medical breakthroughs to treat a wide range of brain diseases and conditions.

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