2006 ADVANCES IN BRAIN RESEARCH

Conversations with seven leading neuroscientists on timely topics in brain research

LIVINGSTONE | LICHTMAN | SEJNOWSKI | GRAFMAN | GROSSMAN | DELONG | GRAYBIEL

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CONTENTS

2006 Advances in Brain Research

BARBARA RICH, Ed.D., *Editor*

BRENDA PATOINE, *Interviewer/Writer*

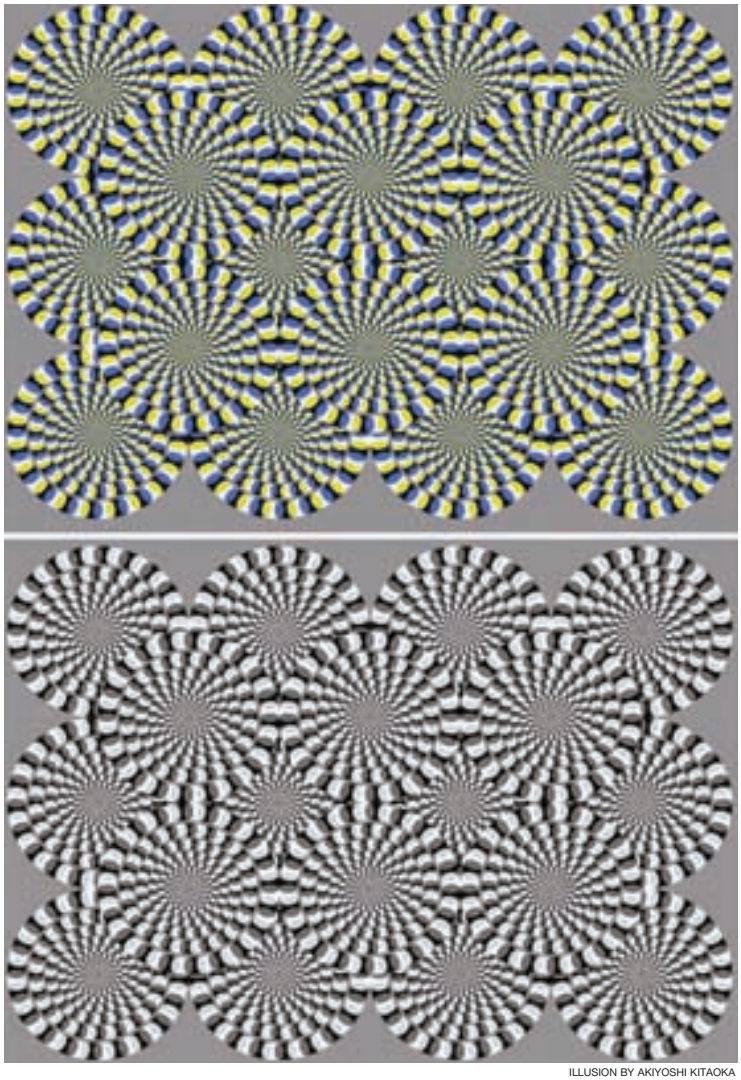
Errata: The figure on page 1 was published in the Journal of Neuroscience (Conway et al., JN25, 5651, 2005).
On page 6, it is the Vollum Institute, not the Vellum Institute; and Purkinje cells, not Perkinje cells.

Visual System Processing and Artistic Genius

MARGARET LIVINGSTONE, Ph.D.
Professor of Neurobiology
Harvard Medical School

Q: Your research focuses on how neurons in the visual system process different kinds of visual information such as form, color, depth, and movement. What have you found most surprising about how the brain "sees"?

Livingstone: I was most impressed by the fact that major aspects of our vision are colorblind. This is because the evolutionarily older "Where" subdivision of our visual system arises from colorblind retinal ganglion cells, but the newer, primate-specific "What" system can use color. The "Where" system, or the parietal part of our visual system, is responsible for carrying information about motion, depth, spatial organization, and figure/ground segregation. Lesions in this part of our visual system result in apraxias, or the inability to use visual information to guide motor behavior. The "What" subdivision is responsible for object recognition, face recognition, and color perception. Lesions in this temporal subdivision of our visual system result in agnosia (the inability to recognize objects), prosopagnosia (the inability to recognize faces), or central achromatopsia (complete loss of color perception). Artists have taken advantage of this subdivision of our visual systems for a very long time through their various discoveries concerning the different roles luminance and color play in art.



ILLUSION BY AKIYOSHI KITAOKA

Q: The image at left represents an optical illusion. What accounts for this?

A: Most people see movement in this static image, which was made by Akioshi Kitaoka, from Ritsumeikan University in Japan. We found that the critical feature for inducing this illusory motion is the luminance relationship of the static elements. Illusory motion is seen from black➠blue➠white➠yellow➠black. Compared to an average gray, black has a higher luminance contrast than blue, and white has a higher contrast than yellow. Since cells in the visual system respond faster to higher-contrast stimuli, the timing differences between white and yellow, and between black and blue, induce a motion illusion, with movement perceived in the direction from the higher-contrast element toward the lower (black➠blue and white➠yellow). Therefore the motion signals generated by the black➠dark-gray and the white➠light-gray pair are in the direction of the faster response to the slower response. This makes sense because such contrast-dependent timing differences would mimic the sequence of a stimulus that moved from the position of the higher-contrast element to that of the lower.

But the motion signals generated by the blue➠white and the yellow➠black pairs are in the direction from the slower response to the faster response, which is paradoxical. This paradox may be resolved by considering the fact that dark-

gray and white are opposite in sign of contrast from the average gray, as are light-gray and black. Element pairs that produce motion signals in a direction consistent with their timing differences have the same sign of contrast compared to the average gray, and element pairs that generate motion signals opposite to their timing differences are opposite in sign of contrast. Thus the pattern of responses to these static motion stimuli is analogous to the phenomenon known as "reverse phi motion," meaning that when their contrast is inverted, apparent motion-stimulus pairs appear to move in the direction opposite to their physical motion (Anstis, 1970). All four adjacent element pairs in the illusion generate a motion signal in the same direction, which is why the illusion is so powerful.

Q. Another interest of your laboratory is to use what you've learned about vision to explain some aspects of art. What do you think Leonardo da Vinci understood about color and light that neuroscience is just beginning to unravel?

A: Leonardo da Vinci produced an illusory dynamic quality in the Mona Lisa. People love this painting because her smile seems to come and go; her expression is so dynamic that she seems almost alive. When you look at a reproduction of this painting (or better still the original), look at her eyes and observe how much she seems to be smiling; then look directly at her mouth and see if she doesn't seem to be much less cheerful. Look back and forth between her eyes and her mouth and see if you don't see a systematic change in her expression.

Our brains convert flat images into a vividly three-dimensional experience by using the same cues a painter employs, plus stereopsis and relative motion.

The art historians said that her smile was blurry (sfumato) and therefore ambiguous, so her expression depended on the observer's imagination. But I find that her expression is systematically related to how far from her mouth my gaze is. Your central vision has much higher resolution than your peripheral vision; that's why you move your eyes when you read. You can see tiny detailed things much better than big blurry things with your central vision, but the reverse is true of your peripheral vision. Mona Lisa's smile is blurry, therefore it's much more apparent to your peripheral vision than to your central vision (see image). She seems to be smiling more when you're not looking directly at her mouth, and she stops smiling as soon as you look at her mouth. This gives the painting a dynamic, even coy, quality.

It is not clear to me whether Leonardo knew this explicitly. He wrote about a lot of his painting techniques and their scientific basis, but he never described this phenomenon explicitly. He was apparently very fond of this painting, and, as far as we know, he never did this again.

Q. You have suggested that stereoblindness—an impairment in one aspect of depth perception—might actually be an asset for artists, enabling them to better render 3-D scenes on a flat surface. What evidence have you uncovered that many famous artists might have had deficits in depth perception?

A: We have two eyes that are horizontally displaced, so they see the world from two slightly different perspectives. As Leonardo da Vinci noted centuries ago, these viewpoints produce two distinct retinal images. Try this: hold your two index fingers up with one about ten inches from your nose and the other a dozen inches away, directly behind the first. Now look at your fingers out of one eye at a time and you will notice that the two "scenes" vary significantly. The brain uses these differences between the retinal images, in addition to other monocular depth cues, to estimate distance and generate a rich perception of depth.

This phenomenon, known as stereopsis, is just one important cue for depth perception; others include perspective, shading, occlusion, haze, and relative motion. Our visual system integrates all of these cues, enabling us to navigate through our environment. In paintings, though, only the monocular static cues can contribute to the illusion of depth; stereopsis and relative motion reveal that the canvas is actually flat. So the next time you find yourself looking at a painting rich in depth cues, stand at arm's length and try closing one eye; you may experience more of the illusion of depth that the painter was trying to achieve.

The ability of painters to translate the three-dimensional world into two dimensions is remarkable. Perhaps more astonishing, however, is the curious feat our visual systems perform in enabling us to perceive the visual world as three-dimensional in the first place. The brain's only visual input comes from a pair of two-dimensional images; the retinal images are, after all, flat. Our brains then convert these flat images into a vividly three-dimensional experience by using the same cues a painter employs, plus stereopsis and relative motion.

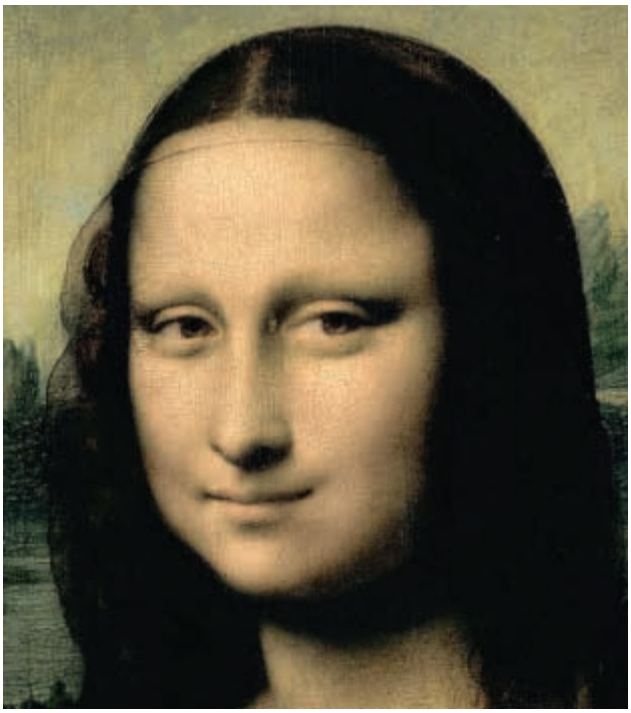
Just as stereopsis is a hindrance to the viewer who wants to see all the depth the artist put into the painting, it can also be a hindrance to the artist trying to depict three-dimensional scenes on canvas. Art teachers often instruct students to close one eye when viewing a scene in order to flatten it. I have therefore suggested that stereoblindness might prove an asset

IMAGES COURTESY OF MARGARET LIVINGSTONE

rather than a handicap to an artist. A person lacking stereopsis might become more sensitive to other (monocular) depth cues, such as shading, perspective, and occlusion—precisely those cues artists can render in paintings.

Stereoblindness is not a prerequisite for artistic talent. Yet the notion that stereoblindness might prove an asset for painters demonstrates the broader possibility that other aspects of brain organization considered detrimental under some conditions might offer advantages under other circumstances. Indeed, many talented artists, musicians, mathematicians, and engineers are dyslexic. It is often thought that the over-representation of dyslexics among artists and musicians represents a compensation for failure in conventional academic fields. Yet growing evidence suggests that the correlation may be based, in part, on a positive correlation between dyslexia and extraordinary talent.

Bevil Conway, himself a stereoblind artist, and I have suggested that a number of very talented artists might have been stereoblind, a notion based on looking at photographs of them and finding that their eyes are misaligned. Stereopsis requires precise eye alignment; therefore, people whose eyes are misaligned usually have poor or no stereopsis; they have fine depth perception because they use other depth cues to gauge distance and depth. We recently suggested that Rembrandt was likely to have been stereoblind because he usually portrays himself as having divergent eyes. Misaligned eyes might seem like a stylism in a painting, except for the fact that the same eye is usually deviated in all Rembrandt's self portraits, and the opposite eye deviates in his etchings. Since an etching is reversed in the printing process, this mirror reversal of his eye deviation between the paintings and the etchings suggests that the deviating eye was something in his physiognomy that he accurately portrayed. ■



DETAIL OF THE MONA LISA, BRIDGEMAN ART LIBRARY

The elusive quality of the Mona Lisa's smile can be explained by the fact that her smile is almost entirely in low spatial frequencies, and so is seen best by our peripheral vision. The three images at top have been filtered to selectively show (left to right) very low, low, and high spatial frequencies. When you look at Mona Lisa's eyes or the painting's background, you see a smile like the one on the left or the middle, and you think she is smiling. But when you look directly at her mouth, your brain registers an image that looks more like the panel on the right, and her smile seems to vanish.

Optical Imaging for the Study of Normal Brain Function and Disease

JEFFREY LICHTMAN, Ph.D.
Professor of Molecular and Cellular Biology
Harvard Medical School

Q: Your laboratory has pioneered new optical imaging techniques that enable you to visualize synaptic connections directly in living animals, essentially eavesdropping on the brain at work, in real time. What has surprised you most from the results you've seen so far?

Lichtman: Our aim in looking at nerve cells in their natural setting is precisely to learn things that could not be anticipated (and hence are surprising). We have been surprised by almost everything we have seen. Perhaps most inspiring is the sheer beauty of the cellular organization of the nervous system.

Q: How do these imaging techniques work? What key advances have led to their development?

A: The field of in vivo imaging depends on fluorescent probes that give off light of one color (say yellow) when illuminated with a different color light (say blue). The power of this approach is that by using filters that only pass the fluorescent color (e.g., yellow) a researcher can see the labeled cells on a dark background. This high contrast allows very small or dimly labeled objects to be visualized—much the same way stars are easier to see at night than during the day. Over the past several years this approach has gotten a big boost from the discovery that a gene from a bioluminescent jellyfish can be incorporated into the DNA of many cells to cause neurons in many different species (including mammals) to fluoresce. This green fluorescent protein gene has since been modified to shift the fluorescent spectrum, so that now there are also yellow, cyan, red and other color fluorescent proteins. We are now involved in generating transgenic mice that express a wide range of different fluorescent colors in individual neurons. These mice permit us to see synaptic circuitry in vivo in living animals that are anesthetized.

Q: What impact are these methods having on basic neuroscience research?

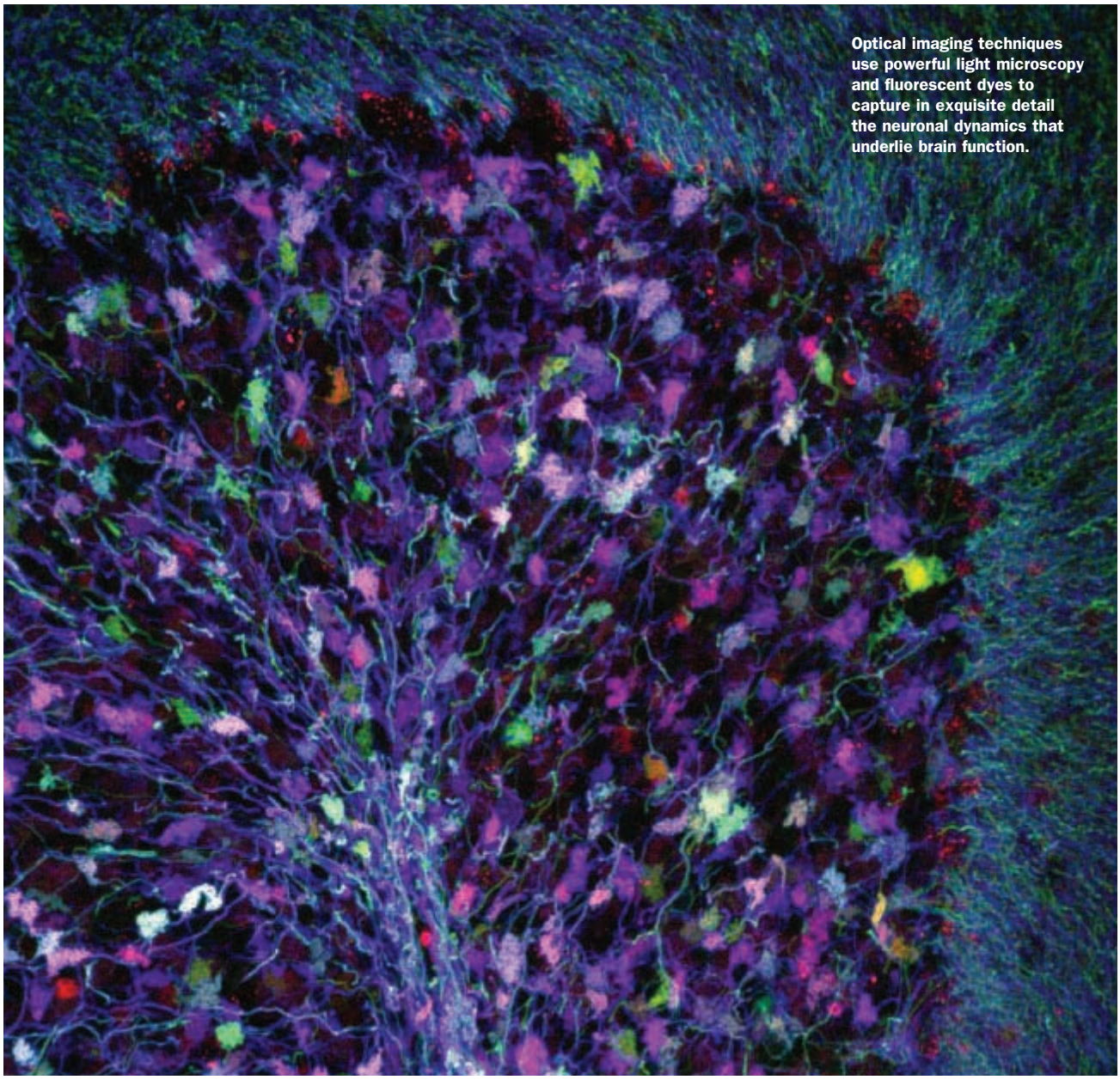
A: One critical aspect of the nervous system is its dynamic properties. For example, questions such as how long a synaptic connection lasts, or how the nervous system ages, have been difficult to study without tools that allow the same neural structures to be imaged over time. These labeling and imaging methods provide the first straightforward means of asking these questions. Although we have been doing this type of in vivo time-lapse work for over twenty years, things got much more interesting (and easier) when jellyfish genes became available.

Q: You've examined the process of synaptic development in laboratory animals, tracking the wiring up of the nervous system in mice over minutes, weeks and months. What has this work revealed about the fine-tuning of synapses during development?

A: We see that the final pattern of connections emerges after the vast majority of neuronal connections are trimmed away. This trimming appears to be the consequence of competition between different neurons vying to remain connected to the same target cells. Although we have studied this phenomenon in only a few parts of the nervous system, there are hints that this trimming back may be a general feature of the young brain. As this trimming occurs in the early postnatal life of a mammal, the resulting reorganization of neural circuits may allow an animal to select the subset of connections that are best tuned to the tasks the animal is being called upon to do. In this way the loss of connections may be central to learning. In the broadest sense, this idea argues that, of the many things we could become, we become who we are through a process of selective trimming back of neural circuits to a much smaller subset of brain circuits that allow us to do a few things well.

Q: You and others have begun applying these imaging methods to neurological disorders, including spinal cord injury and amyotrophic lateral sclerosis (ALS). How have they helped advance our understanding of these conditions, and do you foresee wider application to diseases?

A: Yes, the idea that diseases might be studied from the inside out by documenting the pathological processes and observing disease progression over time inside an animal allows a more direct and clearer picture of what is actually going wrong. I can imagine that virtually all disease models in animals will one day be studied this way.



Optical imaging techniques use powerful light microscopy and fluorescent dyes to capture in exquisite detail the neuronal dynamics that underlie brain function.

IMAGE COURTESY OF TAMILY WEISSMAN, JEAN LIVET, AND JEFF LICHTMAN

For example, we've applied in vivo, time-lapse imaging to a mouse model of ALS to investigate how motor nerve fibers degenerate in the disease and how some of these motor axons attempt to compensate for the loss of nerve signaling from the brain. With the high-resolution images, we were able to show that there are two distinct populations of motor neurons, one group with axon branches that are clearly degenerating, and one that is undergoing compensatory reinnervation. This work suggests that if we can identify the factors that protect certain motor neurons from degenerating and/or induce their regeneration, it might be possible to design therapeutic strategies that enhance these processes.

We've also used these imaging methods to track the degeneration and regeneration of axons in living mice over the course of several days following spinal cord injury. We found that within 30 minutes of the injury, axons die back hundreds of micrometers, from both ends of the severed axons. In addition, many axons attempt regeneration within 6 to 24 hours of the spinal cord lesion, a growth response that begins robustly but ultimately fails, seemingly as a result of the axons' inability to navigate in the right direction. These results show that this type of time-lapse imaging can be useful for understanding the degenerative processes that follow spinal cord injury and for evaluating therapies aimed at enhancing regeneration. ■

A New View of Synaptic Transmission

TERRENCE SEJNOWSKI, Ph.D.

Francis Crick Professor, The Salk Institute for Biological Sciences

Howard Hughes Medical Institute Investigator

Professor, University of California, San Diego

Q: You recently published research that bucks the conventional wisdom about nerve signal transmission at the synapse. Specifically, you have evidence for "ectopic release" of neurotransmitters, i.e., evidence that these chemical messengers are released not only at a single "active zone" at the synaptic cleft, but also that they diffuse more broadly at other sites beyond the recognized receiving site. Why is this work important?

Sejnowski: Our results provide evidence for a different concept of the synapse. The textbook view of the synapse describes it as a place where rifle-like volleys of neurotransmitter are launched from one defined region of the sending neuron (the "active zone") to another defined target on the receiving neuron. In contrast, our data suggest that the synapse can act like a shotgun, firing buckshot-like bursts of neurotransmitter from multiple locations outside the active zones to reach receptors arrayed beyond the known receiving sites.

A study published a couple of years ago by Craig Jahr and colleagues at the Vellum Institute in Portland, Ore., showed ectopic release from Perkinje cells in the cerebellum onto a specific type of glial cell. While that's not neuronal transmission, it showed that ectopic release can happen between a neuronal structure and a glial structure in the central nervous system. We were able to show for the first time that it happens between two neurons, at a neuronal synapse.

Q: For this study, you used a computer model to reconstruct the architecture of the synapse and reproduce the act of neurotransmitter release at that synapse. Why did you choose this approach?

A: The computational modeling played a crucial role in achieving the result we found; it is really what makes this initiative unique. Without the model we couldn't link together the anatomy and the physiology; it's kind of the glue that allows those to be put together in the same framework.

Physiologists have for a long time been recording from neurons to track the electrical impulses that underlie the transmission of nerve signals at the synapse. Meanwhile, anatomists, who examine the synapse from a purely structural point of view, see a great variety of geometry. In the case of the type of nerve junction we've studied, called a calyx synapse, the presynaptic terminal appears as a cap on top of the surface of the cell body, or soma. Coming out of the soma are little fingers like a shag rug, with the cap on top of this shag rug. You can also see the vesicles that store neurotransmitter in the presynaptic terminal in electron micrograph pictures.

Anatomical studies indicate that there are specialized regions at the synapse called active zones where you find pre- and post-synaptic specializations. These are the classic synapses you see in textbooks—a nice simple picture with the receptors in the post-synaptic density, the vesicles lined up ready to be released by an electrical signal moving down the nerve fiber. The question is, where are the neurotransmitters coming out, where are they being released? You can't tell by looking at a static picture. So here you have anatomy on one hand giving you a very complex picture of that synapse, and on the other hand you have the physiologic recordings indicating the functional signaling, but how do you actually connect the two? That's what we did. Mark Ellisman at the National Center for Microscopy and Imaging Research in La Jolla, Calif., reconstructed the anatomy of the synapse in exquisite three-dimensional detail, then we used the computer model to release vesicles from different locations throughout that area.

Q: What specifically did the computer model indicate?

A: We modeled minis—miniature synaptic potentials—which occur spontaneously in cells in various sizes and shapes. By measuring the minis from actual cells, then feeding those measures into the model, we were able to test our hypothesis that the majority of the neurotransmitter release actually occurred outside the active zone. Using the model, we varied the probability of release outside the active zone from 0% to 100%, with 0% modeling a scenario in which all release occurs in the active zone and 100% being all release outside the active zone. We found that if you restrict the release of neurotransmitter to those active zones where its release is traditionally expected, that you cannot reproduce the distribution of amplitude in these mini synaptic potentials that occurs in reality. The probability that matched the actual distribution occurs when 90% of the vesicles are released outside the active zone. That is very strong evidence for ectopic release.

This is surprising to a lot of people because no one really expected it, although there is a evidence in the literature pointing in that direction. So now we actually have the smoking gun.

Q: Given this evidence for a new view of neurotransmitter release at the synapse, what are the next steps in this line of research?

A: The question now is why: what is the purpose of ectopic neurotransmitter release? Also, how widespread is it? Is this something that happens outside this particular synapse? We suspect so, for a couple of reasons. The synapse we studied is in the chick ciliary ganglion, where neurons innervate the pupils of the eye, a part of the autonomic nervous system. Humans have these same synapses, even though the neuron structure is different.

I suspect that ectopic release is much more common than we have realized. My hunch is based on the fact that there are many extrasynaptic receptors outside the active zone; they've been known to exist for a long time. Certain types of receptors—GABA receptors for example—are more prevalent outside than inside the active zone. No one has ever been able to pin down the reason for this. There have been suggestions that maybe there is spillover, that some neurotransmitter spills outside of the cleft during release, and if it gets out far enough from the cleft it can activate these extrasynaptic receptors, but it's very difficult to actually prove that. But if I'm right, if our result holds for some of the other synapses in the central nervous system, then it could be that those extrasynaptic receptors are directly activated by neurotransmitter release from vesicles that are outside the active zone.

This is the future of neuroscience...in order to understand brain function you have to be able to synthesize a tremendous amount of data.

Q: If, as you suggest, this type of ectopic release is common, why hasn't it been seen before?

A: It's very difficult to get direct evidence of ectopic release—or even for traditional neurotransmitter release at active zones, for that matter. In the neuromuscular junction, which is the only synapse where there is direct evidence, scientists stimulated the nerve and froze it at the moment it released the vesicle. By doing so at the precise instant of release, they were able to capture "omega figures," partially fused vesicles, at the point where they've joined the membrane but haven't collapsed yet after releasing their neurotransmitter load. These "figures" were in exactly the space they were expected to be, at the active zones where the vesicles are lined up. This was a heroic experiment, done back in the 1970s. It's extremely difficult to do that in a central synapse or in the middle of the brain: there is just no access. You can't freeze the brain quickly enough.

That's why we've turned to indirect methods, such as the computer modeling. This approach enables us to create very accurate, very detailed computer simulations that incorporate all of the quantitative data from the kinetics of receptors, the locations of the receptors, the detailed geometry of the synaptic cleft, the space between neurons, and so on. All of that data has been painstakingly gathered over many years, from many different laboratories—it's all in the literature. The model is the essential glue that holds it all together. Without the glue to hold the data together, you don't know what they imply.

Q: Does this type of complex computational modeling represent our best hope for ever truly understanding the essential dynamics of brain function, given the innate complexities?

A: This is the future of neuroscience. Neuroscientists are really good at being reductionists, at taking things apart. We're really good at identifying the molecules and all the different pieces of the puzzle, and even, to some extent, at determining how they interact with one another. However, in order to understand brain function, you have to be able to synthesize a tremendous amount of data. You need to take all those pieces and put them together and reconstitute the function so that you know if you have all the right pieces put together in the right way.

We worked on just one synapse; tackling the more complicated brain is going to be much more difficult. Still, I think the very same approach can be used inside the brain to try to gather all the knowledge that has been painstakingly gained in all the neuroscience labs around the world, and to integrate all that data and all those quantitative measurements into the sort of models that we're building. Then we can see if the model behaves the same way as real tissue. If it does, we're on the right track. If not, then we're missing something, and that may be just as interesting, or even more interesting, because we can use it as a discovery tool to figure out what needs to be added or what's missing or what's wrong.

My lab is now collaborating with Mary Kennedy at Caltech, Karl Svoboda at Cold Spring Harbor Laboratory, and Richard Weinberg at the University of North Carolina to take the next step and model synapses at the dendritic spines of pyramidal cells in the hippocampus, which are thought to be important for learning and memory. Our goal is to try to reconstruct what goes on inside the dendritic spine, and see if we can understand what occurs when calcium enters through the NMDA receptor and triggers a cascade of biochemical reactions, leading to a change in synaptic strength. So this is the synapse we'll be tackling next with the computer modeling approach, with the goal of a better understanding of how the brain accomplishes the feat of learning at the synaptic level. ■

The Prefrontal Cortex and Frontal Lobe Disorders

JORDAN GRAFMAN, Ph.D.
Chief, Cognitive Neuroscience Section
National Institute of Neurological Disorders and Stroke (NINDS)

Q: You've been studying the brain's frontal lobes for 25 years and have called the prefrontal cortex the "crowning achievement" of the human brain. Why?

Grafman: I began studying the human prefrontal cortex right after completing my doctoral degree in Human Neuropsychology at the University of Wisconsin-Madison. I was studying Vietnam Veterans with penetrating missile wounds at Walter Reed Army Medical Center and began receiving letters and phone calls from the spouses of the patients describing problems in day-to-day functioning that the spouses felt would not be detected by our general test battery. These included problems ranging from behaving inappropriately in social situations to not being able to effectively design or carry out a plan. These observations, along with the evidence that our "tests of frontal lobe functions" were not sensitive or specific enough to pick up impairments in many of our patients, led me to contact some of the key investigators in cognition (e.g., Alan Newell) and neuropsychology (e.g., Tim Shallice) who I thought had a "handle" on these issues. While they were generous with their time and comments, I wasn't satisfied with the approaches being taken and began my own long journey to try to better characterize what role(s) the prefrontal cortex plays in human behavior.

The human prefrontal cortex... is a crowning achievement of the human brain...and is a work in progress.

My research indicates that the human prefrontal cortex is especially designed to store in long-term memory the features that are unique to large structured sets of sequential events such as themes, morals, and plans. This enables us to put off immediate gratification, and allows us to out-think faster and stronger competitors. These observations form the foundation for the notion that the human prefrontal cortex is a crowning achievement of the human brain and that, like the rest of the brain, is a work in progress.

Q: You consider the prefrontal cortex to be the seat of "social cognition" and possibly "moral cognition" as well. What do these terms mean and what leads you to these conclusions?

A: Social cognition refers to the long-term memories we access when we interact socially with others, and that guide our social behaviors in routine and novel situations. These long-term memories contain information about how we accomplished social goals—from obtaining permission to do something, to taking leadership, to collaborating on a project—and incorporate information about perception and action. Moral cognition is a specific example of social cognition that pertains to ethical, legal, and "folk" justice, beliefs, and rules.

My colleagues and I (and others) have argued that the prefrontal cortex is uniquely suited to manage social and moral cognition because it aids us in controlling our immediate reactions to a stimulus (like a face or gesture) and is critical for forecasting the consequences of a current behavior on a long-term goal. While other species have social cognitive abilities and some rudimentary features of moral cognition, social cognitive abilities reach their peak in humans (as does the anatomy and physiology of the prefrontal cortex). Like the prefrontal cortex, social cognition only matures in the second decade of life and shows some decline in old age.

In addition, brain damage in the prefrontal cortex due to head injuries, strokes, and dementing illnesses (among other brain disorders) often result in altered social cognitive abilities. Patients with lesions in the prefrontal cortex may behave inappropriately in public, violating social rules such as personal space maintenance, social contracts, or inappropriate verbalizations. The earliest example of this comes from the famous brain-injured patient Phineas Gage, but many modern-day Gages have been reported in great detail, highlighting the unfortunate case histories of these patients.

Finally, functional neuroimaging studies now routinely identify the importance of the prefrontal cortex for mediating social and moral behavior in studies examining all kinds of social behavior.

Q: What have you learned about how the brain processes "good" attitudes vs. "bad" attitudes? Does it surprise you that the underlying circuitry is so distinct?

A: We have been very interested in studying social attitudes, including stereotypes, because they are examples of simple associative knowledge that can influence behavior—often outside an individual's awareness. My colleagues and I think that these attitudes are rudimentary forms of more complex social behaviors and therefore are likely to be stored in the ventromedial prefrontal cortex. We have data from patient studies and from fMRI studies in normal volunteers that support this inference. But the picture can become more complicated once you distinguish among types of attitudes.

For example, we have found a hemispheric asymmetry underlying good and bad attitudes, with negative attitudes being more strongly associated with right frontal lobe activity and positive attitudes with left frontal lobe activity. While at first this might seem surprising, in fact, there is accumulating evidence that the right hemisphere appears to be much more involved in various forms of avoidance behavior, whereas the left hemisphere appears to be much more involved in approach behavior. Our attitude data would fit nicely into that view. Of course, the devil is in the details, and we want to know what underlying representations and mechanisms might mediate such a distinction.

Q: NINDS has just completed a Phase 1 study showing that electrical stimulation ("direct current polarization") of the frontal lobes is safe and can enhance verbal fluency in healthy adults. What are the prospects for using this approach to treat frontal lobe disorders, such as frontotemporal dementia (FTD)? Does this suggest a day when we might selectively "tickle" groups of neurons to enhance a deficient (or desired) cognitive or social trait?

A: Based on our findings with normal volunteers, we are cautiously optimistic about using direct current (DC) polarization to modulate cortical cognitive functions. We have begun studies to use DC polarization in patients with frontotemporal dementia (FTD) to try to improve their language fluency. Even a small change over a short period of time would be welcome since there are few treatment alternatives for FTD.

DC polarization is safer than transcranial magnetic stimulation (TMS), another stimulatory therapy under investigation, although it may not have the same precision as TMS for local/regional stimulation. Nevertheless, TMS is tied to the laboratory because of the equipment required, whereas DC polarization requires only a small battery pack about the size of an iPod. Another advantage to using DC polarization is that even though the stimulating pad that is placed on the scalp covers a fairly large region of the brain, the therapy is still more focal than current drugs, and doesn't have the unintended side effects that drugs may have.

Although we hope that it has some therapeutic efficacy (additional, larger trials in patients will determine this), the possibility that DC polarization could be used to do something like boost a student's test-taking ability is a long way down the line. Moreover, any artificial enhancement of cognition carries with it the same ethical issues that using steroids in sports competitions would have, in terms of setting new standards of achievement.

Functional neuroimaging studies now routinely identify the importance of the prefrontal cortex for **mediating social and moral behavior.**

Q: How can your group's research shed light on diseases like FTD?

A: My section at the NINDS (and our collaborators, including John Hardy at the NIH and Dino Ghetti at the University of Indiana) is one of several laboratories throughout the world studying frontotemporal dementia. Like other laboratories, we are collecting medical histories, information on environmental exposures, genetic information, structural and functional brain images, and neuropsychological data. We also hope to eventually have brain tissue from autopsies.

We have several goals in studying patients with FTD. We hope to better understand the pathophysiology of the various subtypes of FTD so we can develop symptomatic interventions in the short term. In the long run, we hope to better characterize the molecular biological signatures of the various FTDs so that molecular-level interventions that address the underlying pathology can be fashioned. Given that so many of our patients have agreed to autopsies, we should be able to eventually provide improved information about the differential diagnosis of the FTDs for clinicians to use. Last but not least, we will employ experimental cognitive tasks to study the cognitive and behavioral deficits these patients exhibit, which will not only inform us about the manifestations of FTD, but will also teach us about the normal functions of the prefrontal cortex and anterior temporal lobes. ■

Frontotemporal Dementia and Language Processing

MURRAY GROSSMAN, M.D.
Associate Professor, Neurology
University of Pennsylvania

Q: You've been at the forefront of efforts to improve diagnostic accuracy and medical management of frontotemporal dementia (FTD). What is FTD and why is better diagnosis a concern?

Grossman: Frontotemporal dementia is an umbrella term that encompasses several different neurodegenerative conditions, any of which can affect the frontal and temporal parts of the brain and impair language and cognitive functioning. In the past it was called Pick's disease. A definitive diagnosis of FTD can be made only after examining brain tissue on autopsy, and this has hampered our ability to provide patients with the best possible treatments. Very important work is now underway to try to sort out what kinds of techniques we can develop and what kinds of biomarkers we can use to identify the specific histopathologic conditions causing FTD during life.

I am confident that we will develop treatments in the near future that will change the natural history of progressive neurodegenerative conditions like FTD.

Improving the diagnostic accuracy of FTD is not a trivial issue, for several reasons. It's certainly important from a research perspective to improve our understanding of brain-behavior relations, but it's also crucially important because we are making rapid advances in developing substances that can treat the conditions that cause FTD. It is essential that doctors have the tools necessary to make an accurate diagnosis during life, so that therapeutic substances can be administered to the appropriate patients.

We're also trying to make the diagnosis earlier. This too is very important, not only from a purely scientific perspective but from a treatment perspective as well. It's clear in any progressive neurodegenerative condition that the earlier we intervene, the earlier we start a treatment, the greater the likelihood that a better outcome will be achieved for the patient. We'd like to be able to identify people earlier, when they don't have full-blown disease but only have some of the initial inklings of what might be coming in the future. If we can intervene at that early point, we're going to do much better than if we wait for the disease to fully manifest.

We can draw an analogy to Alzheimer's disease. There is a pre-Alzheimer's state called Mild Cognitive Impairment, or MCI. This condition is marked by memory difficulty but little impairment in other cognitive domains and reasonable independence in activities of daily living, so people can manage relatively well. Alzheimer's involves memory difficulty as well as deficits in other cognitive domains sufficient to interfere with day-to-day functioning. If we can slow the onset of Alzheimer's disease by five years, it is estimated that we can substantially reduce the frequency of the condition in the population.

We're trying to do the same thing in FTD, that is, to identify people who have some of the very earliest signs of FTD so that we can treat the condition early. This may be even more important in FTD because of the relatively early onset of the condition, when families are still young and haven't yet developed the social and financial resources to deal with a slowly progressive neurodegenerative condition. Our strategy for identifying the earliest features of FTD is to study families where there is a higher risk for the development of this condition. We are also hoping to study the subgroup of MCI patients without memory difficulty, that is, the MCI patients with subtle problems in other cognitive domains.

Q: You've recently published a report suggesting a new technique for determining the levels of the protein tau in the cerebral spinal fluid of patients with FTD. How might this kind of work improve clinical practice?

A: The crucial issue is that we need to find better ways to identify the earliest signs of dementia, and we want to do this with as much specificity as possible. Since tau plays such a crucial role in the pathophysiology of FTD, we think that developing a diagnostic marker for tau has great promise in FTD. If, for example, we can determine during life that the

protein tau is accumulating abnormally in the brain, then we can administer a treatment specifically directed at tau, as my colleagues John Trojanowski and Virginia Lee are currently proposing at the University of Pennsylvania (see below). Knowing the underlying cause of a dementia—whether it is tau or something else—is the first step toward curing the condition. That is really our goal. One step is learning to deliver the substance to the appropriate patients, and a biomarker like the tau level in CSF can help us identify the appropriate patients.

Other biomarkers also may be useful, including neuropsychological approaches, clinical questionnaires, brain imaging scans, and other biological markers in the cerebrospinal fluid and blood. These also can be used to determine whether or not an etiologically specific treatment is successful in changing the progression of the condition, since biomarkers also can be used to monitor whether there is a response to the treatment. In this way, biomarkers can be used longitudinally to follow individuals over time to track the disease.

Q: Why is tau a target?

A: Tau is one of the abnormal proteins implicated in the cause of FTD. Tau accumulation occurs in about 40 percent of patients with FTD, although the accumulation of tau has several different manifestations. In other FTD patients, there is a remarkable depletion of tau.

Tau is a microtubule-associated protein. Microtubules are microscopic networks of tube-like structures that run along the inside of a nerve cell's surface. They help distribute metabolic substrate around the neuron, and help neurons maintain their shape. In FTD and other neurodegenerative conditions, these proteins can degrade or they can accumulate abnormally and block physiologic function. Eventually this process leads to neuronal atrophy and neuronal death.

My colleagues at the University of Pennsylvania, Virginia Lee and John Trojanowski, are working on the development of substances that will help compensate for the abnormal accumulation of tau in neurons. The substances they are developing are designed to stabilize the microtubules and restore normal function, supporting the role that tau plays in the stabilization and aggregation of microtubules. They published a paper in 2005 in *Proceedings of the National Academy of Sciences* demonstrating the efficacy of this class of substances in an animal model of FTD that they developed. The substances under investigation are attenuated versions of the anti-cancer treatment Taxol. Their development was triggered by the realization that Taxol, when used at doses needed to treat cancer patients, has a side effect: it causes microtubule aggregation. At much lower doses, this kind of substance may be useful for aggregating microtubules, essentially serving the function that tau normally performs in neurons.

Q: Your basic laboratory research is focused on understanding the neural basis of complex language processing. How does that relate to FTD?

A: I became interested in this area because the two major manifestations of FTD include a disorder of language and a disorder of social comportment and personality. I'm interested in both of those areas—how our brains let us communicate linguistically and socially—so it was a natural progression to study diseases that affect those crucial centers of the brain.

Knowing the underlying cause of a dementia—whether it is tau or something else—is the first step toward curing the condition. That is really our goal.

There are very specific kinds of difficulties in language that can be seen in patients who have FTD. This includes patients who have an aphasia—a disorder of language—and patients who do not have an obvious aphasia. In the subgroup of FTD patients with aphasia, we think that there are two major manifestations. One involves impaired semantic memory, or difficulty with the meaning of words and objects. FTD aphasics thus can have significant difficulty understanding the meaning of common words like "chair." A person with this manifestation of FTD might say, "Chair? I've heard that word. What is chair?" It's as if the page from the patient's mental dictionary for chair has been ripped out. We hope to study this difficulty so that we can develop effective speech and language therapies for these patients. These therapies are based on understanding the nature of the semantic impairment and using functional imaging techniques like fMRI to help understand which brain regions are not contributing to word meaning. Moreover, in our work we've found that other healthy brain regions are helping to compensate for some of these difficulties, and we want to support this mechanism with speech and language therapy.

Another kind of language problem in some aphasics with FTD is difficulty with grammar. We use grammar to construct the sentences we use when we speak. Language is more than just single words that reference an object in the world; language also involves stringing these words together in sentences so we can talk about complex concepts, describe who does what

to whom, in a manner that does not depend on the order of word use or the order in which things occur in the world. That kind of grammatical process can fall apart in another group of aphasic patients with FTD.

A third group of FTD patients doesn't have an obvious language deficit. They can understand the meanings of words, and their grammar is quite good as well. So these FTD patients have no obvious difficulty speaking or understanding single words and sentences. Instead, they have difficulty with discourse, the ability to tell the story. We recently completed a study with a University of Pennsylvania colleague, Sherry Ash, that looked at the ability to narrate a story based on a wordless picture book, the kind of book you might use with children who are at the very beginning stages of reading. When these patients try to tell the story by looking at the pictures, all they can do is describe what is on the page. They don't have any sense that the pages can be integrated into a story. This holds true for their day-to-day conversations as well. Their speech can be tangential and meander from topic to topic without much organization.

To help us understand the neuroanatomic basis for difficulties such as this, we take detailed MRI images of their brains and correlate their difficulty integrating elements of a story into a larger whole with specific brain abnormalities we identify on the scans. For example, this type of language deficit is associated with the frontal and temporal regions of the right hemisphere, the side of the brain that we don't ordinarily associate with language.

Q: How might knowledge of language processing in the brain impact clinical management of FTD?

A: I can give you a couple of examples of how we can use language to help understand and treat patients with FTD. If we want to make an early diagnosis of FTD, for example, it becomes critical to discover exactly the right measures of language to see whether there are some specific problems marking a risk for developing FTD. So the idea is to take what we know about these language processing deficits and apply that to some early diagnostic procedures. We can't put everybody in an MRI machine or do a lumbar puncture on everybody to sample cerebrospinal fluid. Instead, we can interview people, talk with them, and try to ascertain a pattern that is sensitive enough to accurately select those who are more likely to have FTD. Then we would be in very good shape to identify people for whom it would make sense to follow up with more invasive or more expensive techniques to better determine whether FTD is likely.

I am confident that we will develop treatments in the near future that will change the natural history of progressive neurodegenerative conditions like FTD. If that confidence is well founded, we have to start developing therapies for treating the residual language difficulties that may remain. Doing this effectively requires a detailed understanding of the neural basis of language and figuring out ways to help people. We're just beginning to understand the neural systems that are compromised when we see a language processing impairment. The goal, of course, is to try to repair the brain, so that these networks can be utilized as fully as possible.

Some patients seem to tap into compensatory mechanisms ... other parts of the brain that are functioning reasonably well can assume some responsibility for the parts of the brain that are not functioning well.

Our imaging studies have shown that some patients seem to tap into compensatory mechanisms that optimize their remaining language skills. In other words, other parts of the brain that are functioning reasonably well can assume some responsibility for the parts of the brain that are not functioning well. It seems clear that there is great opportunity for compensation, and some of the behavioral therapies in development are trying to take advantage of this. Essentially, we're talking about a specific set of mental exercises. We are in the early stages of developing such a program of behavioral therapy. It is incredibly exciting to work in an area that takes advantage of the rapid growth in our knowledge of both the biological basis for a profound neurodegenerative condition and the source of difficulty for the most human of acts, speaking. It is satisfying to know that we are moving forward in our ability to help individuals with these profound conditions. ■

The Basal Ganglia and Surgical Treatment of Motor Circuit Disorders

MAHLON R. DeLONG, M.D.
Professor, Department of Neurology
Emory University School of Medicine

Q: You've spent much of your long career studying the basal ganglia (BG). Why has this cluster of brain structures captured your attention, and how has scientific understanding of the basal ganglia progressed in recent years?

DeLong: The brain structures that comprise the basal ganglia—the putamen, caudate nucleus, globus pallidus, substantia nigra, and subthalamic nucleus—have long been an enigma to researchers, and they remain so. Even today, with all of the sophisticated methods we have for studying the anatomy and physiology of the brain, we have much yet to learn about what role these structures play in normal brain function. In fact, we have more information about how the basal ganglia contribute to movement disorders than about what they do in the normal brain.

That said, our understanding of the basal ganglia has progressed significantly in recent years, driven by a number of major research advances that have elucidated their anatomic organization and their functional significance both to normal motor function and to a spectrum of movement and neuropsychiatric disorders. These findings come from anatomical studies and recordings of neural firing patterns in animal models of disease (especially the primate model of Parkinson's disease); from functional brain imaging studies of patients and animal models; from observations seen in the operating room during neurosurgical procedures on patients; and from physiologic studies that map the rates, patterns, and frequencies of nerve signals both within the BG and between the BG and interconnected brain regions, especially the cortex and thalamus.

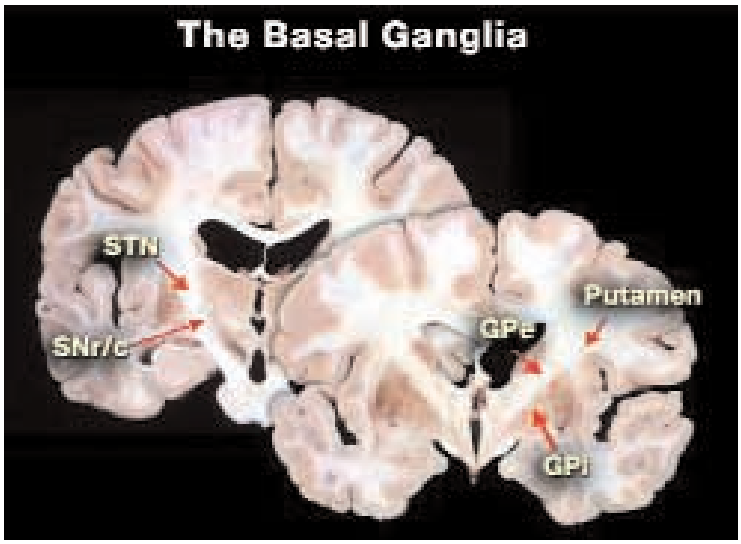


IMAGE COURTESY OF MAHLON DeLONG

The basal ganglia comprise a group of interconnected nuclei of nerve cells deep in the forebrain, including the subthalamic nucleus (STN); the substantia nigra pars reticula and pars compacta (SNr/c); the globus palladum externa (GPe) and globus palladum interna (GPi), and the putamen.

Q: What have we learned about the basal ganglia's role in motor control as a result of this ongoing research?

A: From this growing body of research has evolved an ever-clearer picture of the brain's "motor circuit." As my colleagues and I first proposed a decade ago, the BG are not merely "funnels" that relay information from the cortex to the thalamus. Rather, the structures of the BG form parallel segregated pathways for neural signals traveling to and from the cortex, essentially forming a loop that both feeds information to and receives information from the cortex. In fact, virtually every part of the cortex projects to some piece of the basal ganglia.

One can, therefore, think of the basal ganglia as key components of circuits, with the cortex and thalamus at either ends. Nerve signals traversing this circuit originate in the motor and sensory fields of the cortex, located in the pre- and post-central gyri of the frontal cerebral cortex—an area long known to be crucial for normal movement and somatosensory processing. (This area is often depicted in brain illustrations as distorted maps of the body that represent the neural real estate devoted to motor and somatosensory functions of each body part.) From this cortical starting gate, nerve signals travel to the putamen, where they activate striatal output neurons. The signals then take one of two routes on their journey to the thalamus: an indirect route that circuits through the rear parts of the striatum, the external pallidum and subthalamic nucleus, then on to the internal pallidum; or a more direct route to the internal pallidum that bypasses the first two stops. Once signals reach the thalamus, they project back to the cortex. Thus, the thalamocortical circuit consists not of a single loop, but of a series of subcircuits. Importantly, the output signals from the BG are inhibitory—meaning they quell, rather than activate, neural firing in their target neurons—

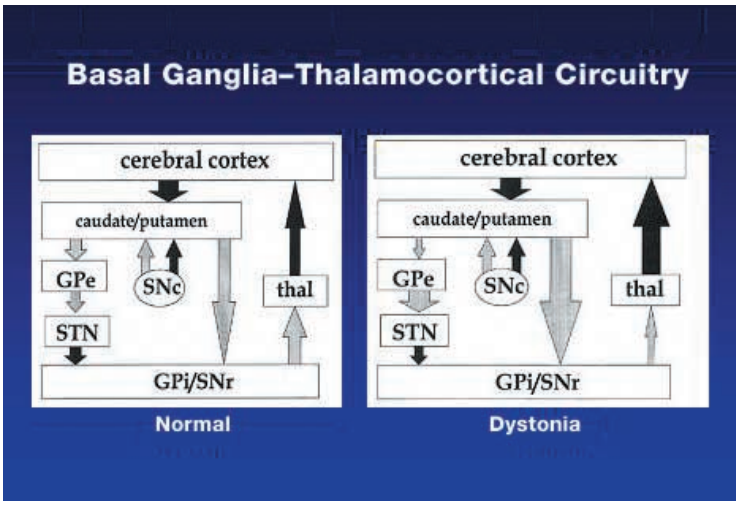


IMAGE COURTESY OF MAHLON DeLONG

Normal basal ganglia circuitry (left image) connecting the cerebral cortex to the thalamus is disordered in dystonia (right image), with some pathways abnormally underactive and others overactive, as indicated by smaller and larger arrows in the right image.

giving the BG a powerful inhibitory drive. This fact has been critical to applying therapeutic approaches to the treatment of motor disorders.

Q: How have these understandings about the basal ganglia contributed to new therapies for people with movement disorders?

A: The study of motor circuits in the brain, particularly in the basal ganglia, is a good example of how fundamental basic science contributes to our understanding and treatment of neurodegenerative diseases. Over the past decade there has been a renaissance in neurosurgical approaches to the treatment of movement disorders such as Parkinson's disease. In general, it appears that many movement disorders, including Parkinson's, Huntington's, dystonia and Tourette's syndrome, result from disturbances in specific circuits that connect the cerebral cortex, basal ganglia and thalamus—in other words, they can be viewed as "circuit disorders." In Parkinson's disease, for example, physiologic studies in primate models and functional neuroimaging studies in patients have revealed distinctive widespread alterations in the activity of neurons in this motor circuit, including changes in the rate of neuronal discharge, changes in the pattern of discharge, such as signal "bursts" or abnormally synchronous nerve firing, and signal oscillations in low-frequency ranges (i.e., beta waves vs. the usual gamma waves). Together, these changes disrupt information processing in the motor circuit and result in the clinical features of Parkinson's.

The study of motor circuits in the brain ... is a good example of how basic science contributes to our understanding and treatment of neurodegenerative diseases.

Interrupting the motor circuit at the level of the subthalamic nucleus or the internal pallidum by surgical ablation can dramatically reduce the abnormal motor disturbances. But ablative surgery has significant drawbacks: it is non-modifiable; it carries a risk of functional loss as well as permanent complications in movement or vision, and it may interfere with or render future treatments less effective.

Deep Brain Stimulation (DBS), a therapy that applies chronic high-frequency stimulation to the same subcortical structures that have been the targets of surgical ablative approaches, can also ameliorate the abnormal movements associated with Parkinson's and other movement disorders. DBS, however, has the advantage of being less invasive and destructive, and of being adjustable and reversible. Although DBS was initially believed to block the activity of neurons at the site of stimulation, it now appears that it acts by stimulating axons and replacing the abnormal basal ganglia output with a more tolerable pattern of nerve signaling.

Q: Deep Brain Stimulation has been most widely applied to Parkinson's disease, but is being increasingly applied to other neurologic disorders as well. What are the prospects for wider application of DBS?

A: The success in treating Parkinson's with DBS has led to successful treatment of other disorders, most notably dystonia, a devastating disorder of abnormal sustained muscle contractions. Unlike Parkinson's, no neuronal degeneration occurs in dystonia; instead, the disorder appears to result from abnormal neuronal plasticity. Both surgical ablation and DBS are highly effective treatments for dystonia, but, in contrast to DBS for Parkinson's, it may take weeks to months for dystonia patients to realize the maximal benefit. This suggests that the mechanism of action of these procedures in dystonia is a slow "re-tuning" of the neuronal circuits.

Recently, DBS has also been employed with some success as treatment for Tourette's syndrome and obsessive compulsive disorder, and is also being studied as a therapy for depression and epilepsy. While more work is needed to better define the optimal protocols for these conditions and to show concrete, consistent benefits, in my view DBS remains one of the most promising and intriguing approaches for the treatment of the major movement and other neurologic disorders. ■

The Basal Ganglia: Moving Beyond Movement

ANN M. GRAYBIEL, Ph.D.
Walter A. Rosenblith
Professor of Neuroscience
Massachusetts Institute of Technology

Q: You have focused your research on the basal ganglia (BG) for many years. Why are you interested in this group of brain structures?

Graybiel: The question really should be how could I not be interested in the basal ganglia. They are endlessly interesting because it turns out they are involved in an amazing range of behaviors. That fact has only been appreciated in recent years, in part because of the location of this cluster of nerve cell nuclei deep in the forebrain. Before brain imaging came along, the BG were essentially off-limits because it was really difficult to get in there.

As a result, the basal ganglia were long thought of purely as motor structures involved in normal movement and in movement disorders, such as Huntington's disease and Parkinson's disease. Then a few people began to realize that they were also involved in neuropsychiatric disorders. One example is obsessive compulsive disorder (OCD), which can involve compulsive repetition of movements, but which also has a psychological element. About the same time, it began to become clear that the BG are deeply involved in addictive kinds of behaviors, from habitual risk-taking to drug addictions that highjack the brain's reward system and are very difficult to overcome.

Q: It seems that the more that science learns about the basal ganglia, the more evidence there is for their involvement in all sorts of behaviors. What's the latest?

A: The latest thing that is really fascinating is that parts of the BG have now been implicated in social behaviors like love and affection. This probably reflects the fact that people have realized that dopamine, the very neurotransmitter that becomes depleted in Parkinson's disease, signals "reward" to the brain. So it's not a big step to go from thinking that we have a place in the brain that is activated by highly pleasurable behaviors to the idea that our brains can capitalize on that activation to train our behaviors toward things that are rewarding or pleasurable—the idea of "that felt good; do it again." A vast amount of learning, including social learning, is related to just "doing it again." The extreme of that is addiction, but the less extreme form may explain a whole array of human behaviors. In the social realm, for example, it's human nature that if someone is nice to you, you associate with them, and if someone is not nice to you, you don't.

Q: How are the basal ganglia involved in generating habitual thought patterns?

A: I'm high on the idea that maybe in addition to behavioral habits—habits that can be thought of as "action habits"—we also have habits of thought, habits of mind. My guess is that the BG help produce those and lay them down, just as they do behavioral habits.

So, one of the long-proposed roles of the BG is to help the lower-level motor regions of the brain stem and spinal cord generate patterns of nerve activity that subserve various motor behaviors. Our idea is that essentially the same kind

A vast amount of learning, including social learning, is related to just "doing it again." The extreme of that is addiction...

of circuit applies to the cerebral cortex. The BG in this case project upstream, to high-level centers in the neocortex that control complex cognitive functions such as planning and reasoning. It may be that they help lay down and select patterns of cognition, so the BG modulate not just motor pattern generators, but also thought pattern generators, or cognitive pattern generators.

Q: What have you learned about how basal ganglia circuits adapt and re-adapt as habitual behaviors change?

A: We are doing a lot of work in our lab now trying to teach animals habits, and we've been really stunned with the plasticity of the BG. We're looking at the activity of neurons in the striatum, which is in a key position to be involved in this habit-forming business, because it is the main part of the BG that receives the reward-related dopamine input on the one hand, and it gets massive inputs from the neocortex on the other hand. You've got the information flooding into the striatum and the dopamine signals saying either "yes, that's good, do that again," or "no, don't do that again." If these output pathways are right, a behavior gets stamped in bit by bit.

We've found that when this happens behaviorally, the firing of the neurons changes dramatically. When an animal is learning something new, such as turning a lever just the right way in order to get a reward, it initially learns by trial and error – called "exploration." When the animal has figured out how to turn the lever to successfully receive the reward, that's called "exploitation." Based on the results we have so far, we're beginning to think that there is neural exploration and neural exploitation in the brain.

much more selectively, especially at the beginning and end of the procedure that is being learned. When you take away the reward, the more selective patterns disappear. If you then give the reward back, boom! The patterns come back again right away.

People who have bad habits that they are trying to break know this phenomenon intuitively. If you're trying to quit smoking, you don't want to go to a place where you always smoked. I think we're seeing the representation of that in

I'm high on the idea that maybe in addition to behavioral habits — habits that can be thought of as "action habits" — we also have habits of thought, habits of mind.

When the animal starts out on a new task, he doesn't yet know what information is salient, so essentially everything is important. Correspondingly, neurons in the striatum fire at almost everything, looking for clues as to which activity proves rewarding. As the animal learns, the neurons quiet down: they stop firing at everything and start firing much,

the brain. To me, that's very exciting, because if we can get a handle on what happens, then we can try to manipulate the process. And if we can manipulate it in an animal, then we may be able to produce a therapy, or some way to reduce the overwhelming power and strength of these highly ingrained habits.

Q: What might such a therapy look like?

A: Deep Brain Stimulation (DBS) is now being applied not just for motor disorders, but also for some disorders in the realm of psychiatry, so it's clearly not crazy to think that DBS might help in breaking addictive or compulsive habits. Ideally, one hopes that there could be a pill, that a pharmacologic therapy could be developed that somehow mitigates or interrupts these patterns of activity in the brain's reward system. Toward that end, it would be ideal to be able to screen these patterns, both their development and their disappearance or lack of disappearance, when different drugs are being tested to look for drug effects. In addition, our lab is now trying to identify the genes involved in these pathways, which could lead to new drug targets. While dopamine is a principal actor in the reward story, there are many other molecules that are downstream from dopamine, and maybe one of these could be targeted.

It's a very, very hopeful time for research in these areas. I believe there are deep commonalities between the movement disorders in which the BG are involved and this habit-forming system that we've been studying, which at first seems kind of strange to think about. I'm convinced that a better understanding of the neural plasticity of this system will be key to advances on both sides. ■

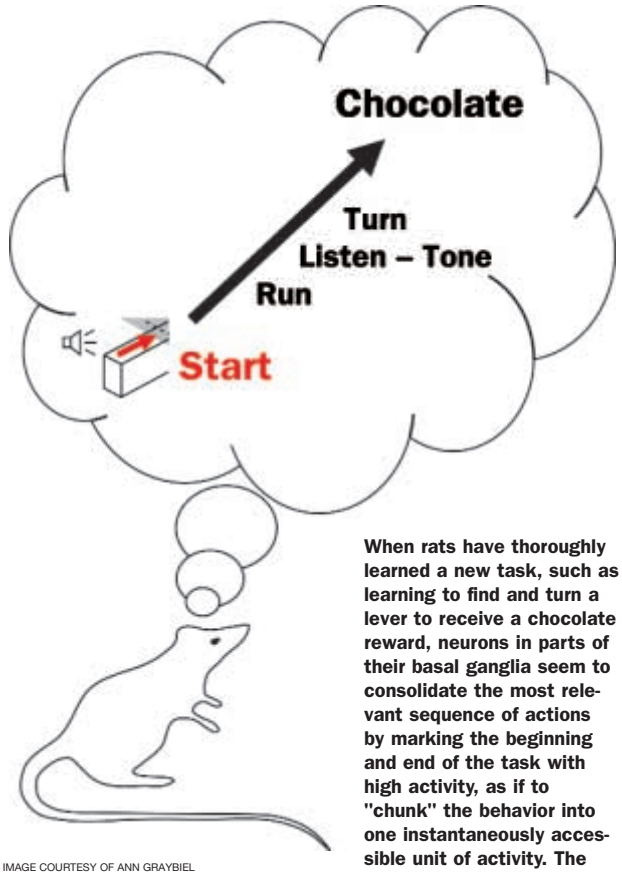


IMAGE COURTESY OF ANN GRAYBIEL

When rats have thoroughly learned a new task, such as learning to find and turn a lever to receive a chocolate reward, neurons in parts of their basal ganglia seem to consolidate the most relevant sequence of actions by marking the beginning and end of the task with high activity, as if to "chunk" the behavior into one instantaneously accessible unit of activity. The finding has implications to the formation of habits, both good and bad.

A Resource For Journalists

The News Office of the Dana Foundation provides a free resource service to journalists seeking background information and experts in neuroscience. *Advances in Brain Research* is available as part of this service. The News Office also publishes briefing papers throughout the year on brain-related research.

The Web site at www.dana.org provides reporters with current publications about the brain, links to validated sites about brain disorders through the BrainWeb and Brain Information section, and access to the Press Box.

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745 Fifth Avenue, Suite 900
New York, NY 10151