

Academy Meetings

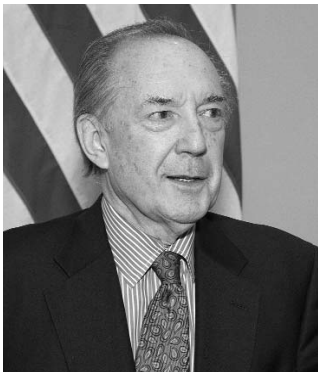


Advances in Brain Science: Implications for Therapy

Edward Scolnick and Robert Desimone

Introduction by Emilio Bizzi

The 1955th Stated Meeting, held at the House of the Academy on May 12, 2010



Emilio Bizzi

Emilio Bizzi is Institute Professor and Investigator at the McGovern Institute for Brain Research at the Massachusetts Institute of Technology. He has been a Fellow of the American Academy of Arts and Sciences since 1980. He was the 44th President of the American Academy.

Introduction

When I began working in brain research in the mid- to late 1960s, there were very few techniques available to study the brain. Through the years, I witnessed the progressive increase in new methods and techniques. Truly extraordinary is the progress made in the last fifteen years in molecular biology, genetics, computation, and imaging that has been utilized by brain scientists to understand the functions of the brain and develop new therapeutic approaches to neurological and psychiatric diseases. Tonight's speakers will describe the power, depth, and future of new approaches that have been integrated into the field of neurobiology.

The first speaker, Edward Scolnick, is Director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard. Previously, he was President of

the Merck Research Laboratory and Executive Vice President for Science and Technology at Merck & Company. At the Broad Institute, his research focuses on identifying genes that are relevant to bipolar disorder and schizophrenia. A distinguished scientist, Ed is known nationally and internationally and has been recognized by the National Academy of Sciences and the American Academy of Arts and Sciences.

Our next speaker is Robert Desimone. He is Director of the McGovern Institute for Brain Research and the Doris and Don Berkeley Professor of Neuroscience in the Department of Brain and Cognitive Sciences at MIT. Before joining MIT, Bob was Scientific Director of Intramural Research and Chief of the Laboratory of Neurophysiology at the National Institute of Mental Health.

He has achieved a very important goal in brain science, becoming the first person to identify the neural circuitry that is responsible for the processes we call *attention*. Attention has a primary role in sensory and motor activities and is extremely important for the substrate of learning. Hopefully, this function will be activated in your brain when he speaks.

Bob is a member of the National Academy of Sciences and a Fellow of the American Academy of Arts and Sciences.



Edward Scolnick

Edward Scolnick is Director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard. He has been a Fellow of the American Academy of Arts and Sciences since 1993.

Presentation

The goal of the program I oversee at the Broad Institute is to unravel the underlying causes of bipolar disorder and schizophrenia in order to develop better methods of diagnosis and treatment. The Broad Institute, located in the vicinity of the MIT Biology Department, the Brain and Cognitive Sciences Departments (including the McGovern Institute for Brain Research and the Picower Institute for Memory and Learning), and the Massachusetts General Hospital Psychiatry Department, is part of a community of first-rate neuroscientists, geneticists, and chemists – an environment that is necessary to advance our understanding of very complex diseases.

The lifetime prevalence of bipolar disorder and schizophrenia in the general population

is approximately 3 percent. Patients face a high risk of suicide and an enormous reduction in life expectancy, even when suicide is not a factor. The afflicted are typically young people just coming into the prime of their lives. Most importantly, because the underlying biology and pathogenesis of these diseases are not understood, patients are diagnosed, still today, simply by the symptoms they describe to their doctors. There is no biological, chemical, or physical quantitative test that helps doctors diagnose either disease. This reality is very unusual for any field of medicine today.

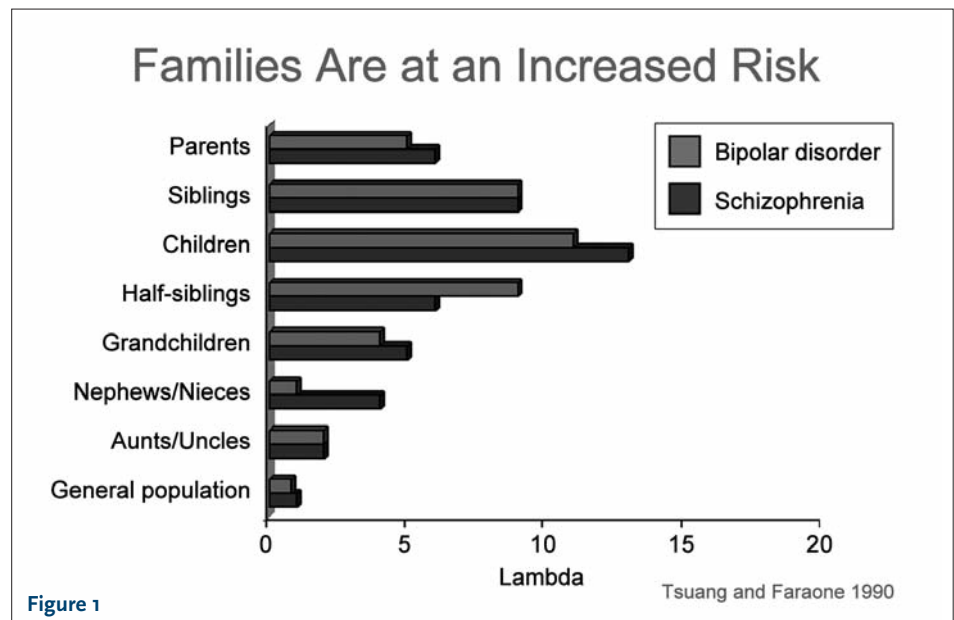
Because we do not understand the diseases' underlying pathogenesis, the drugs used to treat them are only minor modifications of pharmacological agents that existed more than sixty years ago. The field has been in such a difficult situation that, in the past year, three large pharmaceutical companies have shut down their programs for psychiatric research; they simply did not know what to work on.

The single largest reason for failure in pharmaceutical drug research is having to guess at underlying pathophysiology and biochemistry. On the other hand, once these are understood, scientists can usually make a medicine that will help many patients. For example, because of the progress made in the last two or three decades in understanding the molecular biology, genetics, and biochemistry of cancer, an enormous list

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of drugs – developed within the last fifteen years – has greatly improved the lives of patients with certain cancers. The drugs used to treat some cancers are targeted at the very genetic defect that drives cells to become cancer cells. These treatments are dramatically different from traditional chemotherapy, which was just as empirical thirty years ago as the field of schizophrenia and bipolar disease is today. Thus, developments in cancer treatment are proof that understanding the underlying molecular biology and genetics of a disease can radically improve the outlook for treatment.

Currently, the field has one significant clue about the etiology of schizophrenia and bipolar disorder: if you are a patient with one of these illnesses, your first-degree relatives' risk for having the illness increases sevenfold to tenfold (see Figure 1). That is your sibling, your brother or sister, or your parent. So these illnesses run in families.



In fact, the single greatest risk factor for developing one of these illnesses is genetic risk. But because these complex diseases are not amenable to methods used to study other genetic diseases, little progress has been made in deciphering the genes that cause them. Recently, however, the study of human genetics pioneered by my colleagues at the Broad Institute – Eric Lander, David Altshuler, Stacey Gabriel, and Mark Daly – and at other research institutes around the world has changed the landscape for studying genetic diseases.

With traditional, or Mendelian, genetic diseases, the disease-causing variance in the genome rarely occurs in the human population but has a very high penetrance when it does occur (meaning that people who have a mutation in a given gene are likely to contract the disease). Roughly two thousand Mendelian diseases have been described in many different fields of biomedicine over the last forty years, as family-based genetic-mapping studies have identified the genes that cause these diseases.

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But many human diseases are not Mendelian in origin. Rather, they are complex human genetic diseases in which multiple genes interact to elevate the risk or actually cause the disease. The methods for studying variances that are not Mendelian – that are risk-associated or causative – for complex genetic diseases have changed dramatically in the last five or six years. This progress began with the sequence of the human genome published in 2001 and was followed by a detailed map of the genome in 2005. Information from human genome sequencing has been used with new technologies to look for common variants that can increase the risk of disease and to find less common

variants using DNA sequencing methods. Whereas just two genomes were sequenced in 2001, it is now possible to sequence many genomes. As methods for sequencing advance rapidly while the associated costs fall, a wide spectrum of variants in the DNA that cause complex genetic diseases has become available for investigation. No longer is such research limited to Mendelian diseases. Outside the field of psychiatry, many epidemiological discoveries in these population-based, complex genetic studies have pointed investigators toward positions in the human genome (loci) on different chromosomes that provide clues on where to look for specific disease-causing sequence variants.

There are four particularly spectacular discoveries in human genetics that have significantly changed several fields of medicine in the last two or three years. The first code to be cracked was that of age-related macular degeneration, a common disease caused by a variant in the genes of the complement biochemistry pathway (a system that helps clear pathogens from the body). The second is Crohn's disease, or ulcerative colitis, which is caused by genetic defects in the autophagy pathway (a pathway in the cells that allows cells to engulf and destroy various proteins and microorganisms). These breakthroughs have led to new approaches to treatment that were unknown prior to three years ago.

Third, an amazing discovery made by investigator Stuart Orkin at Children's Hospital Boston has paved the way for new approaches to treating sickle cell hemoglobin, a defect in the sequence of the amino acids that make up hemoglobin, causing it to crumble and sickle under low oxygen conditions. It has long been known that an elevated level of a fetal form of hemoglobin called hemoglobin F (HbF) protects patients from the sickling event. But no one has been able to figure out why certain patients have elevated levels of fetal hemoglobin. Using new methods in human genetics, Orkin discovered a gene called BCL-11 that affects how DNA is made into protein and transcribed. The discovery immediately spawned new approaches to increasing the activity of this protein and, therefore, levels of HbF – a potentially phenomenal new treatment for sickle cell hemoglobin.

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Finally, investigator Sek Kathiresan of Massachusetts General Hospital recently discovered a gene that involves the intracellular degradation of the unwanted form of low-density lipoprotein cholesterol. Again, genetic studies pointed researchers to a particular place on a chromosome and allowed them to unravel the molecular biology.

What has psychiatric research uncovered in the last two or three years? We are beginning to understand some of the underlying genetics of schizophrenia and bipolar disorder. First, scientists have discovered rare structural variations in the genome, or copy number variants, that increase the risk for many diseases. We all carry two copies of our genes, our copy number variant is either less than or more than these two copies. The methods that I outlined above allow geneticists to look for copy number variance in human DNA samples. Large deletions on a number of chromosomes and duplications of other regions of the chromosomes, among other changes, have significant effects. Not only do patients with such deletions or duplications have an increased risk for schizophrenia or bipolar disorder, but they also have many other clinical symptoms of abnormal brain function. (At this point, we do not understand what causes that variability.)

We have also learned that some of these variants are inherited from parents. Sometimes the parents are well even though they carry genetic changes; sometimes they are ill. Some changes are *de novo*: they are dependent on mistakes made in how DNA and cells are reproduced in the formation of an embryo; the changes are at times new to a given person and in some instances inherited from parents. We have discovered a genetic mechanism that accounts for these

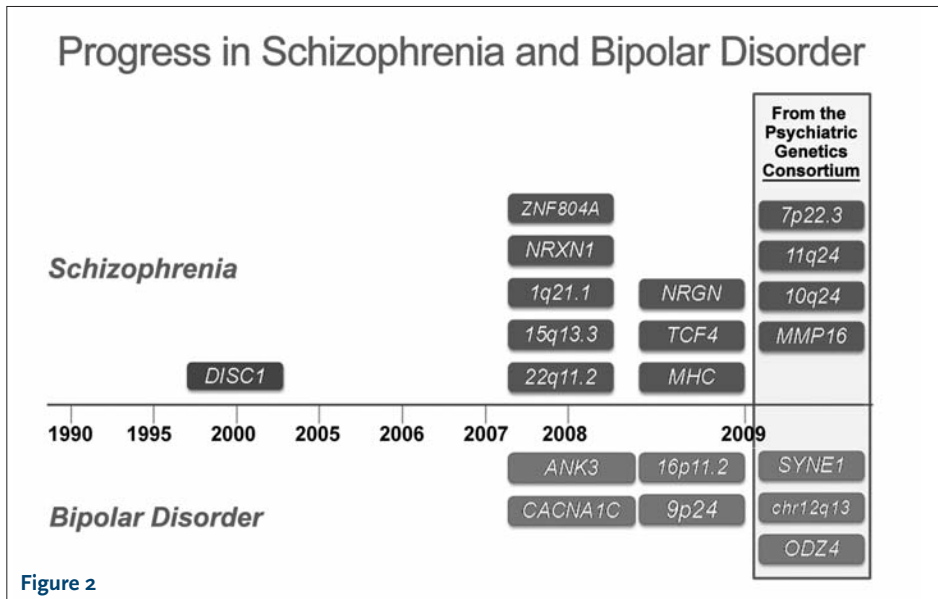


Figure 2

kinds of copy number variants. James Lupski, a geneticist at Baylor College of Medicine, has studied the neurologic diseases Charcot-Marie-Tooth disease and Hereditary Neuropathy with liability to Pressure Palsies, both caused by reciprocal changes in a gene on chromosome 17. Lupski found rare mutations in the gene that occur because anatomical peculiarities predispose this region of the genome to mistakes.

Another insight that has recently emerged involves the chromosomal regions I described earlier and the clinical spectrum of the disease associated with them. In some cases, extra copies of the gene cause schizophrenia; in other cases it causes autism. In some instances, it's the reverse: a loss of copies leads to autism in some and schizophrenia in others. At this point, we can conclude that autism, which affects very young children, and schizophrenia and bipolar disorder, which affect teens and young adults, share some genes as part of their pathogenesis. We do not yet understand this. With detailed DNA sequencing, we hope to begin to sort it out.

In addition, common variants in twelve specific genes or gene regions that confer risk have been found in population-based studies in just the last couple of years (see Figure 2). Using these methods and DNA sequencing, we can begin to unravel the genetic architecture of bipolar disorder and schizophrenia and open up new ways for both treatment and diagnosis.

A recent article in *Science* articulates that we are at an inflection point in this field with the genetic methods available.¹ The policy piece argues for a large-scale approach to genetics to unravel the pathogenesis for the first time in a complete way. Indeed, it is now only a matter of time and money be-

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fore we have sequenced thousands of samples to decode the underlying biochemistry of these diseases. We can study these complex genetic diseases in model organisms, create models of the human diseases in mice, and even study them in cell culture.

¹Huda Akil, Sydney Brenner, Eric Kandel, Kenneth S. Kendler, Mary-Claire King, Edward Scolnick, James D. Watson, and Huda Y. Zoghbi, "The Future of Psychiatric Research: Genomes and Neural Circuits," *Science* 327 (5973) (March 26, 2010).

One illustration of what we hope to accomplish is the recent announcement by a pharmaceutical company that it may have a drug to improve the clinical symptoms of patients with Fragile X Syndrome, a Mendelian genetic brain disease. MIT investigator Mark Bear, a pioneer in the field, has worked out the pathophysiology of that gene's effects, and treatment that was shown to correct the phenotype in mice may have also improved the lives of many patients with Fragile X. This type of breakthrough is the paradigm for what we hope will happen in psychiatric illness.

How are stem cells used to study psychiatric disease in cell culture? Three years ago, a Japanese group headed by Dr. Shinya Yamanaka discovered that human skin cells can be transformed into pluripotent stem cells in culture. Pluripotent stem cells can be programmed to develop into neurons in various parts of the nervous system. Using this technique, we will be able to study the process of neural differentiation in patient samples, knowing the genetic background. As genes are discovered that predispose patients to these illnesses, we will be able to study the pathophysiology and biochemistry that is going wrong not only in animals, or in living brains, but to a degree, in cell culture. We have a comprehensive program in place at the Broad Institute and the Stanley Center for studying patient samples and human genetics. I am not trained as a human geneticist, and I cannot express enough thanks to Eric Lander, David Altshuler, and their colleagues for giving us the opportunity to set up this program.

If you take nothing else from this presentation, I want you to remember that until the last two or three years, gaining a foothold on the pathophysiology of schizophrenia and bipolar disorder was impossible. Now, even though the challenge remains and will still take painstaking work by many scientists, we no longer lack an intellectual approach, something we could never say before.

How long will it take to decipher the full range of genetic causes, understand the neurobiology, and develop treatments? Your guess is as good as mine. But it's now doable; that's what has changed.



Robert Desimone

Robert Desimone is Director of the McGovern Institute for Brain Research and Doris and Don Berkey Professor of Neuroscience at the Massachusetts Institute of Technology. He has been a Fellow of the American Academy of Arts and Sciences since 2001.

Presentation

Understanding the brain is a problem of astronomical proportions. The number of neurons in the brain is approximately equal to the number of stars in the Milky Way. The number of connections between neurons – the synapses – is even larger. (I once read a magazine article in which the author gushed that there are more synapses in the brain than there are atoms in the universe. Somehow I think that isn't quite right, but it is a very large number.) In a system this complex, there are many opportunities for error. Beyond schizophrenia, bipolar disorder, and the other psychiatric disorders that Ed mentioned, there are neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and autism that have enormous societal and financial impacts. There are no cures, only partial treatments that work in some, but not all, patients. The need for new treatments is enormous.

What, exactly, is taking so long? Even though we are making genetic discoveries in these disorders – from the genes themselves to the proteins that genes create, to the formation of neural circuits, to the thousands of neural circuits in the brain – understanding all these components is a long, arduous task. But it is not my goal tonight to depress you. It is my goal to tell you that, as Ed pointed out, brain research has changed radically in

just the last five years. We are the beneficiaries of revolutions in genetics, in systems of neuroscience (understanding how neurons interact with each other in the brain), and in how we understand these large brain systems through the use of brain imaging and intact human subjects. These developments are fundamentally changing how we approach diseases.

Studies of disease models, particularly those in animals, have begun to focus on the neural synapse, where neurons communicate with each other and where much can go

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wrong. Synapses regulate how different parts of the brain talk to each other. Inside each synapse are many proteins. Studies show that a number of brain disorders seem to involve, at least in part, some of the proteins that make up these synaptic structures. One example of the synapse as a target for neuropsychiatric disorders is the work of Guoping Feng, a scientist at Duke University who will become an associate member of the Broad Institute in Summer 2010. Guoping has been studying two proteins, Shank and SAPAP3, and how they function in synapses.

Human genetic studies have implicated the SAPAP3 gene in obsessive compulsive disorder (OCD) and the Shank gene in autism. Guoping has created animal models to investigate how these mutations might affect neural circuits and then how they might be treated. For example, he introduced the mutation in the SAPAP3 gene in mice. As a

result, the mice groom constantly, a symptom that is reminiscent of the obsessive hand washing sometimes observed in people suffering from obsessive compulsive disorder. Just as in the human disorder, which is treated with antidepressants that have a mild positive effect on OCD, the mice, when given an antidepressant, reduce their obsessive grooming. Even more promising, because Guoping knows the genetic cause of the behavior, he can replace the gene (a type of gene therapy) in exactly the part of the circuit that he has identified as critical for this behavior. Through this genetic rescue, he has in fact largely resolved the behavior, raising the possibility of gene therapy in this disease and pointing us toward targets for drug therapy as well.

Guoping also found that when he studied animals with mutations in the Shank gene, they seemed to have social abnormalities somewhat reminiscent of what we might expect to see in a patient with autism. A normal mouse will gravitate to a new mouse that is placed in its enclosure. Mice with the mutation, by contrast, have no interest in the new mouse nearby. They stay on their own. Guoping is now studying these mice to identify a means of rescuing this kind of phenotype.

Even more surprising is a discovery by neuroscientists Edward Boyden, now at the MIT Media Lab and the McGovern Institute, and Karl Deisseroth of Stanford University that has allowed us to make neurons sensitive to light. They discovered that by taking a light-sensitive protein from an amoeba (the amoeba uses these light-sensitive molecules to steer), packaging it in a virus, and using that virus to infect the neurons in the brain, they could make the brain's neurons become sensitive to light. This finding allowed them to control neural activity with light using a fiber-optic probe to stimulate the neurons. We now have the ability to control many microfibers in the brain, targeting specific cell types, and we are acquiring the ability to play the neurons in the brain the way a pianist would play a piano, which is a tremendous research tool with very important therapeutic implications. It has been used to study obesity and mechanisms underlying sleep, Parkinson's disease, and depres-

sion, but perhaps the most immediate potential therapeutic application is with blindness.

Ed Boyden has collaborated with a group at the University of Southern California, led by neuroscientist Alan Horsager, that has used these light-sensitive molecules to try to cure blindness in mice. They inserted the light-sensitive molecules in the layer of cells in the retina beyond the photoreceptors (see Figure 1), so that other cells in the retina, cells that are not normally sensitive to light but are healthy, become sensitive to light. As an example of some of the early results, when a mouse goes into a water maze, it would normally head toward the lit arm of a maze. But a blind mouse has no idea what to do. When a blind mouse has this light-sensitive molecule put into its retina, it heads for the light. Further testing is needed to determine whether these mice can recognize patterns, among other tasks. But tests done thus far appear extremely promising with regard to therapeutic applications, particularly for diseases such as macular degeneration, retinitis pigmentosa, and diabetic retinopathy, in which the photo receptors degenerate.

Some people have damage to the retina that goes beyond the photoreceptors. We have

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started to think about communicating information directly into the higher levels of the brain, but because the higher levels of the brain require highly processed information, this effort presents a much more complex problem. We have to understand a lot more about these higher processes to begin thinking about a neuroprosthesis for more complex sensory disorders.

But there are, in fact, other promising applications for neural stimulation. For example, there are applications to relieve depression, to treat Parkinson's disease, to help people

with spinal cord damage control their limbs and, potentially, to help people who have lost arms and legs control robotic limbs (a significant problem for injured soldiers returning from Iraq).

Interacting with the brain at these higher levels requires better neural models for higher brain function. Fortunately, there has been recent progress in this endeavor. For example, investigator Tomaso Poggio (of the McGovern Institute and the Brain and Cognitive Sciences Department at MIT) and his colleagues have used computer algorithms to model how the brain processes visual information and recognizes complex objects. These computer algorithms recognize objects with performance similar to people recognizing objects under the same conditions.

I want to switch from animals and computers and talk about work in human beings, namely brain imaging. Scientists experimenting with brain imaging are beginning to capitalize on the knowledge acquired in genetic experiments. Investigator John Gabrieli, of the McGovern Institute and the Brain and Cognitive Sciences Department at MIT, has studied brain activation in people placed in a brain scanner and instructed to do nothing. What do people do when they're asked to do nothing? They think; they self-reflect. John and others have found that such activity in the brain is not random. Rather, there is a characteristic pattern of activity in certain brain structures that communicate with each other, and that activity can be mapped (see Figure 2). In patients with schizophrenia, brain imaging reveals that a similar system is activated, but the activity is expanded. The implication is that this increased activity is related to the over-thinking and self-rumination that occurs in the schizophrenic subject. The application for genetics is the finding that scans of the first-degree relatives of patients with schizophrenia show an intermediate pattern of brain activity. These relatives share some genes with their schizophrenic relatives, which gives us some hope that we will be able to identify the specific brain systems that are influenced by specific genetic variations. Now that we have begun to identify specific disease genes in psychiatric populations, we

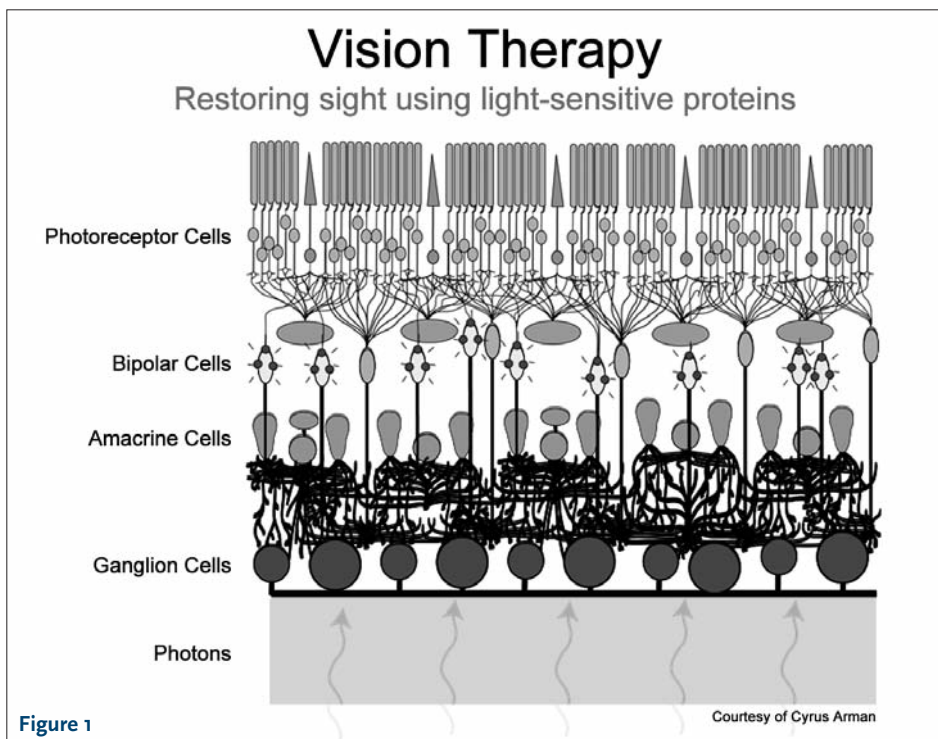
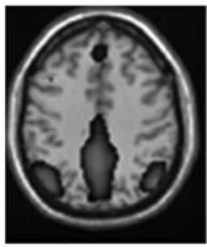
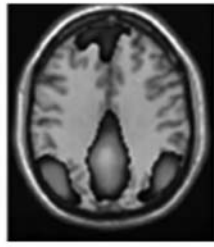


Figure 1

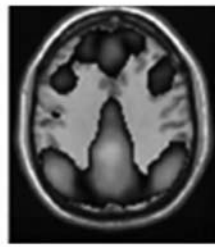
Combining neuroimaging with genetics



Normal controls



First-degree relatives



Schizophrenics

Figure 2

can advance efforts to pinpoint the specific neural circuits that are influenced by mutated genes in these populations.

MRI technology can be used not only as a diagnostic tool but also as a kind of therapy itself. Patients use feedback from their own brain imaging patterns to learn to control the activity in their brains. The basic idea is to place subjects in the scanner, measure their brain activity, and (now that computer systems are fast enough) extract this information in real time. It can be used to create what is called a flame representation of the amount of activity in some patients' brain structures. As the flame increases, the activity there increases; as the flame dies down, the activity decreases. Patients in the scanner are instructed, basically, to try to make the flame go higher. Over time, patients learn to do this. They don't know how they do it or what they're doing, but they learn to do it. We know that in some brain disorders, people have altered patterns of activity in the brain. The question is, can they learn to renormalize their own brain activity patterns through training?

The first application of this retraining technique was in people suffering from chronic pain. In these subjects, there is abnormal activity in the anterior cingulate cortex. Patients underwent training sessions in which they learned to adjust the activity in their own anterior cingulate cortex. Most important, in the post-test run, they do not receive any feedback but have learned, over days or weeks, to control the activity in this part of the brain. Tests have shown that pain perception in these patients changes

over time, so they are learning to control their own perception of pain. The \$64 million question is, can this approach be applied in other disorders, such as depression, or cognitive disorders? In a pilot study at MIT, subjects are learning to control the activity in one of the reward centers of the brain, the nucleus accumbens. Activity in that center is known to be low when regulated in people suffering from depression.

We now have the ability to control many microfibers in the brain, targeting specific cell types, and we are acquiring the ability to play the neurons in the brain the way a pianist would play a piano, which is a tremendous research tool with very important therapeutic implications.

Now that we know that people who do not have depression can regulate the activity in their nucleus accumbens through this feedback, the question is whether people suffering from depression could learn to elevate their mood by controlling their own brain activity. The best outcome would be an approach that allows patients to be their own therapist and, potentially, independent from drugs.

Everything that I have discussed has required collaboration across disciplines and institutions. Indeed, the science of the future depends on breaking down the silos and on people working together. A physical example of this metaphor is the former grain silos of the Quaker Oats Company in Akron, Ohio, where the company used to store their grains. Of course, it is no longer necessary to have silos in the middle of a city, and so they have broken through the silos and turned them into a hotel and conference center. Thus, this structure has evolved to keep pace with modern times, just as science is evolving to keep pace with changing times in which we all are becoming more interactive.

Question

I noticed that Dr. Scolnick broke down the cancers into different types. Is the same required for schizophrenia and bipolar disorder? It seems that progress is slow because you are treating schizophrenia as if you were trying to treat all cancers with one drug.

Edward Scolnick

The way to break down these psychiatric disorders is to break them down genetically. Genetic categories that cause different types of schizophrenia will eventually be identified. It is very clear that they are heterogeneous categories, as your question implies. In other words, there is a spectrum with classical schizophrenia on one end, classical bipolar disorder on the other, and every variation imaginable in the middle. Eventually, there will be genetic categories and then additional biomarkers to go with those genetic categories.

Question

Does theory have a significant role in brain science? Given that the instruments available from mathematics and physics concern such complexities, has there been any transfer of those instruments into your field?

Robert Desimone

Tomaso Poggio is a good example of a scientist trained as a physicist who has now turned his attention to brain problems. I would invite him to share his thoughts on that issue.

Tomaso Poggio

There have been attempts to develop theories at the several different levels that are needed to fully understand the brain, some quite successful and some less so. For instance, the Hodgkin-Huxley model describes spike production and propagation in neurons and axons – in other words, how electric signals are generated and transmitted. This is a theory that, once supported by experiments, became a milestone in neurobiology. At a higher “computational” level, it is important to understand how the brain solves problems such as perception, language, and reasoning: in other words, how the brain produces intelligence. At this level, we are starting to make progress but we have not managed yet to program computers to behave or think at the same level as our brains do. Understanding intelligence and how to reproduce it in machines is, I think, the most difficult problem in science; we will get there, but it will take some time. I also think neuroscience will inform computer science and not the other way around, as people predicted a few decades ago.

Emilio Bizzi

Why do patients with schizophrenia express the disease in their late teens?

Edward Scolnick

Today, that question is unanswerable. Scientists speculate that a pruning of synapses occurs during the late teens or early adult years that somehow tips the balance. There are clear endocrine changes that occur at that time. As we learn more about the genes, we hope to begin to formulate an answer.

Question

How do you treat a genetic disease like autism if it exists from birth but is not expressed until the child is already two or three years old?

Edward Scolnick

I think the recent progress in treating Fragile X syndrome, which I mentioned briefly, illustrates the treatment paradigm that we hope to coordinate for diseases like autism. Fragile X is a Mendelian disease, which

means that it is caused by a mutation in a certain gene that, in effect, silences that gene. The mutation is present from the beginning of the baby’s life. In tests with mice, it is present throughout the mouse’s development from baby to adult. Afflicted children and mice have a variety of behavioral abnormalities because of malfunctioning synapses. In other words, the connections are there but are not working properly because the protein is not functioning. Even

Genetics has changed many fields of medicine, with new methods of diagnosis and treatment.

though the problem is developmental, it can be partially corrected, at least in mice, and perhaps now in humans. The brain is very plastic. Once we understand the cause of malfunctioning and can identify the pathways, it will be possible to look for ways to correct the functioning. If the circuits are constructed abnormally, however, and are themselves connected to wrong places, the problem will be much more complicated. But if the circuits are connected properly, I think there will be a way to correct the functioning.

Robert Desimone

A recent study that followed children diagnosed with autism reported that roughly one-third of kids with an early diagnosis of autism improved to the point that they no longer have an autism diagnosis. As Ed mentioned, the brain is very plastic and receptive to change and perhaps even educational approaches, whatever the problem. So there’s certainly hope that even the older kids will be helped.

Emilio Bizzi

Recently, the cells in the pancreas that do not normally produce insulin have been changed into insulin-producing cells with the insertion of three genes. This, to me, is a fantastic discovery. Do you see potential for that approach in the field of brain science?

Edward Scolnick

Though conceivable, transdifferentiation would be difficult to achieve in the brain. But as Bob pointed out, the related ability to study and manipulate circuits is important.

Question

It sounds as though the psychiatric profession is going to be profoundly challenged by these discoveries, more so perhaps than we might imagine any other medical subspecialty being abruptly challenged by scientific discoveries. What are your thoughts on that issue?

Edward Scolnick

I agree that in psychiatry, and certainly in psychiatry departments at research institutes, methods for diagnosis and treatment will change dramatically. Professional training programs will change as well.

Broadly speaking, the biologic driving force for biological science has been genetics, enormously enabled by physics, chemistry, engineering, and computer science, but the intellectual driving force has been genetics. Genetics has changed many fields of medicine, with new methods of diagnosis and treatment. I predict similar changes occurring in psychiatry within the next five to ten years. Psychiatry departments in medical schools should start thinking now about how they plan to adapt their educational programs. ■

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