The Boston Globe Magazine - THE MEDICAL ISSUE

Brain Power

As scientists move closer to understanding how the brain thinks, they're making strides toward finding what causes schizophrenia and other mental illnesses.

By Pamela Ferdinand | December 5, 2004

CHARLES, A 55-YEAR-OLD with schizophrenia, sits motionless and alone in the vaultlike chamber of a Charlestown laboratory. He leans back on a low-slung chair, and the white maw of an imaging machine swallows his head like a dryer in an old-fashioned hair salon - only this one contains more than 300 sensors bathed in liquid helium. Wires run down his neck from holes in a baby-blue cap where electrodes are pasted to his scalp and temples. He listens to a series of clicks, and, as his brain responds, red squiggles appear on a computer screen in an adjacent room.

The scanner system - called a magnetoencephalography machine or MEG - measures the faint magnetic fields emanating from his head as a result of brain activity, and it's the only one of its kind in New England. Scientists here are using it to see if the hearing part of a schizophrenic's brain works the same way it does in a healthy brain. The evidence suggests it does not, and the answer is vital not only to Charles but to 2 million other people with schizophrenia and their families.

In a few weeks, Steven Stufflebeam, a Massachusetts General Hospital neuroradiologist, will combine the results of Charles's MEG scan with measures of his brain's electrical activity, blood flow, and structure in hopes of better understanding how a diseased brain reacts to sound. Armed with this information, he will be as close as anyone has gotten to observing how a human brain thinks in real time.

Boston and Cambridge are leading the way in brain research, with an expanding constellation of neuroscience stars and new institutions, such as Harvard's Center for Brain Science and MIT's Brain and Cognitive Sciences Center, due to open early next year. MIT's new president, Susan Hockfield, is a neuroscientist, as are the provosts of Harvard and Tufts, and the new head of the **McGovern Institute** for Brain Research at MIT is **Robert Desimone**, former scientific director of the National Institute of Mental Health's Intramural Research Program, the largest mental health research center in the world. Looking around the region, **Desimone says, "I can't think of anywhere else on the planet where you have such a convergence of people and resources to make progress."**

They all have their work cut out for them. Neuroscience, in many ways, is still in its infancy, and the brain is perhaps the most complex machine in existence. But confidence is out there. "In five or 10 years,

when a person comes into my office and says, `I hear voices,' I can send this person for a test so that we can record brain activity to diagnose where the voices come from," says Stephan Heckers, director of the Schizophrenia and Bipolar Disorder Program at McLean Hospital in Belmont. "That will be possible. That's going to happen."

NEUROSCIENTISTS WERE once limited to observing behavior and dissecting brains. But now, they switch genes on and off like lights and observe the consequences in live animals from mice to the translucent zebra fish. They insert electrodes finer than hairs and record the activity of a single nerve cell or hundreds, predicting in advance which path a rat will take in a maze or reconstructing how a visual image is mapped on a monkey's brain. They compare the behavior of genetically engineered mice with the DNA of mentally ill humans. And they film nerve cells growing and changing over time.

"In the past, we uncovered and studied one gene at a time, one protein at a time, one neurotransmitter at a time," says Bertha K. Madras, a professor of psychobiology at Harvard Medical School who studies Parkinson's disease, substance abuse, and hyperactivity. "Now we can look at a collection of them simultaneously and try to figure out what is driving developmental disorders, learning, degeneration, progressive diseases, and, hopefully, regeneration. We can get the big picture."

The experiment with Charles, led by Stufflebeam and a Harvard psychiatrist, highlights this transformation: a boom in systems neuroscience, the synthesis of everything from genetics and cellular biology to psychology, mathematics, and physics to ultimately link the brain's tiny connections with our complicated behaviors.

Advances in genetics, new technologies that allow us to peer into the brain even as it performs tasks, and powerful methods of computing and crunching massive amounts of data fuel the latest push to integrate fields. Along the way, new ones are being generated, such as neuroeconomics, neuro-pharmaceuticals, and neuroesthetics, which combines brain imaging and genetic analysis to understand artistic creativity and our innate responses to art.

Most important, today's cutting-edge brain research is heading us toward a new generation of medical treatments while taking us closer to unraveling what it is to be human. Researchers surmise that a damaged brain one day could be retooled to heal itself, a tempting thought that comes with profound ethical implications.

"Ideally, you can look forward to a world in which people will die, but they will be alert and engaged until that day," says Phillip A. Sharp, a Nobel laureate and former director of the **McGovern Institute.**

A HEALTHY BRAIN is wet and spongy at about 3 pounds but solid enough to fit into a pair of cupped palms. Its major parts include the cerebrum, which encodes information and initiates responses, the cerebellum, which handles sensory input and voluntary movement, and the brain stem, which relays information to and from the spinal cord and regulates vital functions like breathing. Mental activity occurs when nerve cells (also called neurons) communicate with one another across a gap called a synapse via electrical charges and chemicals known as neurotransmitters. Our brains can make up to 10,000 connections per nerve cell, of which there are an estimated 100 billion.

There is far more we don't know about the brain than we know. One of the biggest hurdles is that brain research cannot be done inside the living human brain. That leaves neuroscientists like John Dowling to get at the genetic core of addiction by creating junkies out of tiny zebra fish, whose brains have surprising similarities to ours.

In Dowling's Harvard lab, postdoctoral fellow Tristan Darling places filter paper laced with cocaine at one end of a fish tank and exposes zebra fish to it for 20 minutes. The next day, the fish swim directly to the spot where the cocaine was found and spend about 85 percent of their time at that end of the tank. The lab, which has roughly 30,000 zebra fish, is now trying to isolate the gene responsible for their reaction to the drug.

"What is astonishing to me is that the zebra fish seem to show the same response to cocaine as humans do," Dowling says. "They find it pleasurable and attractive."

While experiments like these give scientists insight into the human brain, current imaging technologies offer other information, associating regions with computation, grammar, arousal, and depression. Yet imaging generally does not explain the brain's underlying mechanics. We don't know how many connections it takes to see or hear or smell. Or what it really means to pay attention, one of the brain's most complex activities and one of the first things to go wrong in a disorder.

The ambition of many neuroscientists is a three-dimensional map of the brain's circuitry, providing a detailed flow chart that shows how cell activity A gets to behavior B and predicting the detours. Even once that is accomplished, scientists will need to understand the impacts of disease, age, environment, and social interactions on our brains.

Says Earl K. Miller, a cognitive neuroscientist at MIT's Picower Center for Learning and Memory: "We don't even know what we don't know."

THAT SAID, SCIENTISTS have mapped the brain's basic anatomy, and they don't necessarily need a complete picture to start fixing what goes wrong. In the past 10 years, researchers have gotten a much better handle on specific genes, how neurons connect (they need to "fire together to wire together"), the way synapses work, how specialized areas process faces and numbers, and the importance of good activity to healthy brain maturation proving the cliche "use it or lose it."

Some of the greatest advances have occurred in understanding memory and learning, which can go awry in abnormal brains. Memory consolidation, once believed to be a one-step process, is now known to involve additional changes in our brains each time a memory is recalled. Emotionally charged events and facts are more likely to be remembered - and remembered in different ways - than neutral ones. Even forgetfulness, it seems, has a purpose: preventing mental overload so we can see the forest for the trees.

Strange as it sounds, it turns out that we can acquire new memories as we age, but older people tend to have more difficulty retrieving memories with limited cues. In one experiment that shed light on long-term memory recall, scientists at the Picower Center filled a small round swimming pool for mice with a milky liquid. They hid a small platform in the pool just below the surface, knowing that mice - which swim but do not like water - would climb onto it as soon as they found it. The objects around the pool offered several visual cues, including a door and window.

Two kinds of mice were trained for the task: normal mice and mice engineered to lack a specific gene only in cells in a tiny brain area responsible for spatial memory. After a week of training, normal mice swam to the platform within seconds, even with only one visual cue. But genetically altered mice swam in circles, unable to quickly find it with one cue. The scientists went on to pinpoint the brain cells most heavily involved and identified a gene, work that could ultimately lead to drugs for countering age-related memory decline, says center director Susumu Tonegawa, a Nobel laureate.

"We may be able to even treat Alzheimer's patients in the very early stage," he says.

Often associated with memory and learning deficits, mental illnesses are also better understood and have been redefined as extreme versions of the normal brain with biological deficits rather than purely psychological causes. Scientists now strongly suspect that most psychiatric disorders such as schizophrenia are due to the multiple small effects of many genes instead of the fault of one. And evidence shows that neurodegenerative disorders such as Parkinson's and Alzheimer's, age-related diseases characterized by nerve cell death, are associated with the buildup of toxic substances, such as abnormal clumps of proteins, made by the brain.

"Brain development and brain disease were areas of utter mystery 20 years ago and were pretty darn mysterious 10 years ago, but now we can begin to see the outlines of how most stages of development work, and of what goes wrong in quite a few neurological diseases," says Joshua R. Sanes, the director of Harvard's new center.

FOR CHARLES, WHO HAS heard voices in his head for the past 20 years, there have been few milestones. Antipsychotic drugs, while improved, have operated on the same chemical targets in the brain for decades. They have side effects, lose potency, if they work at all, and they do not treat all symptoms, which can make the world a confusing and sometimes dangerous place.

"It's no fun," says Charles, who requested that his last name not be printed.

Evie Barkin, a 59-year-old from Newton, agreed. Barkin lived with severe bouts of depression most of her life, just like her mother, until she found a therapist and effective medication. Prozac recently stopped working for Barkin, but she switched to another drug and is grateful the future will probably offer more choices. "There's so much research going on, and so much hope," says Barkin, the executive director of McLean Hospital's Jonathan O. Cole Mental Health Consumer Resource Center. "The new generation will have it easier."

The next generation also will benefit from our fundamentally altered understanding of the brain. Once considered a hard-wired black box after adolescence, the brain is increasingly viewed as able to adapt and learn in ways that mirror its early, rapid development.

Evidence continues to emerge that the adult brain changes according to genetics and experience, compensating for damaged regions, growing new neural circuits, and strengthening or weakening existing ones. For example, the adult brain adjusts to process language, and one study showed that people who learn to play the violin as adults develop more brain area for controlling finger movements.

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Scientists are beginning to see those changes on the smallest scale, offering even more therapeutic possibilities. With technology used by only a handful of labs, Elly Nedivi, a molecular biologist at the Picower Center, is finding change in single nerve cells - more than previously suspected - in real time, in living adult mice.

The task of collecting data recently fell to Wei-Chun Lee, one of Nedivi's graduate students. In one corner of a lab cloaked with black curtains, Lee gently anesthetized a mouse, whose brain lay permanently exposed under tiny windows embedded in its head. He then placed the mouse on a black tray and slid it under an optical microscope designed by Peter So, an MIT mechanical engineer.

By following the brain's blood vessels like a road map, Lee says he can probe the same target cells every week. When the images from deep inside the mouse brain are put together in a 3-D film, they look like an ocean where axons and dendrites - the long arms of nerve cell transmission - are the green tentacles of seaweed.

Indeed, scientists say the brain's plasticity offers great promise for the prevention, treatment, and possible delay or reversal of debilitating conditions. There is little talk of cures for severe mental diseases, but a new generation of targeted drugs and therapies is on the horizon, including new classes of medications for schizophrenia. Scientists also are seeking early detection methods for disorders now diagnosed by observing subjective symptoms or motor disabilities. In Parkinson's, for instance, neurodegeneration starts years before symptoms appear, while schizophrenia is typically diagnosed after a psychotic episode.

It's still hard and expensive to find genes that increase the risk of developing bipolar disorder, but it's no longer impossible, and researchers say future diagnostic techniques

will probably combine chemical tests, genetic screens, brain scans, and memory exams.

There are hints of progress for some of the more common diseases, too. In Alzheimer's research, promising results have been shown with cholesterol lowering drugs called statins, and vaccines to stop the build-up and/or promote the removal of neurotoxins. Scientists also are exploring the possibility of a common theme among many illnesses that could be alleviated by drugs with unified targets.

Neuroprotective and neuroregenerative drugs could be commonplace one day, as could cognitive enhancers to boost mental power, embryonic stem cell therapies to maintain or increase neurons, and braincomputer interfaces (now being tested) that allow someone to command a computer or a prosthetic device simply by thinking about it a science fiction tale come true.

ALTHOUGH IT'S TOO EARLY to know exactly where neuroscience will take us, the moral and ethical questions of probing and manipulating the brain lie ahead. "Brain fingerprinting," a scientifically shaky technique that claims to detect lies via brain waves, is admissible in court, brain scans are being collected in databanks, and neuromarketing companies are using imaging to gauge consumer preferences. At stake is privacy and access, among other issues, and the Center for Cognitive Liberty and Ethics in California, a nonprofit law and policy institute, is calling for freedom of thought to be recognized as a 21st-century human right.

The extent to which we understand the brain also will shape our conversations about the larger questions of nature versus nurture, free will, and individuality. We are left to wonder: What is consciousness and awareness? Can a brain ever really understand itself? And what if we are on the wrong track entirely, missing fundamental pieces of the puzzles?

"That's what makes it so fun, honestly, to be a neuroscientist," says Mark F. Bear, a Picower Center scientist who studies how experience modifies the brain. "It's still a romantic era where big discoveries are made."

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