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FUTURE OF HEALTHCARE

Neuroscience mapping brain connections

Discoveries could yield an understanding of and treatments for disorders such as autism, schizophrenia, depression and Parkinson's disease.

By Cassandra Willyard

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Inside the human skull lies a 3-pound mystery. The brain — a command center composed of tens advertisement of billions of branching neurons — controls who we are, what we do and how we feel.

"It's the most amazing information structure anybody has ever been able to imagine," says Dr. Walter Koroshetz, deputy director of the National Institute of Neurological Disorders and Stroke in Bethesda, Md.

For centuries, the brain's inner workings remained largely unexplored. But all that is changing. With the help of new tools, researchers are delving deeper into this complex organ than ever before. We're in a brainy age of discovery that could change our understanding of how the brain works and why, in some cases, it fails to do its job.

Scientists already have an intimate knowledge of brain anatomy, from the hippocampus to the amygdala. "We've mapped these in exquisite detail," says Arthur Toga, director of the Laboratory of Neuro Imaging at UCLA.

But those maps don't show how the regions connect. And it's this connectivity that enables the complex behaviors our brains perform so seamlessly.

The Human Connectome Project, a \$40-million endeavor funded by the National Institutes of Health, aims to plot these connections — both their structure and their function. "It's basically a Manhattan Project to try to establish the wiring diagram," Koroshetz says.

Calling it ambitious would be an understatement. In the 1980s, researchers spent a dozen years mapping 7,000 connections between the 302 neurons inside the worm *C. elegans*, an animal not exactly known for brainpower. The human brain contains more than 80 billion neurons and trillions of connections. The problem is further complicated by variability: No two brains are exactly alike.

But the payoff could be huge. In addition to gaining a deeper understanding of how normal brains process and store information, researchers also hope to find the root cause of disorders like autism and schizophrenia, which some neuroscientists suspect are the result of faulty connections.

Dr. Helen Mayberg, a professor of psychiatry and neurology at Emory University School of Medicine in

Atlanta, has spent the last 20 years probing the neural basis of depression, a difficult-to-treat disorder that affects millions of Americans. Mayberg's goal is to understand precisely what goes wrong in the brains of people who have the illness and, perhaps, relieve the problem by using electrodes to stimulate a particular region of the brain.

The quest began in the late 1990s, when Mayberg and her colleagues started scanning the brains of people with depression, treating them and scanning them again to look for changes in brain activity. The hope was to pinpoint the neural circuits involved in the disorder, and eventually they hit the bull's-eye: When antidepressants worked, the scans invariably showed a decrease in activity in a section of the prefrontal cortex called Brodmann area 25.

Next, Mayberg needed a way to block the activity of area 25. So she turned to a technique called deep brain stimulation, a therapy that helps calm the shaking that plagues people with Parkinson's disease. A neurosurgeon implants small electrodes that deliver a faint but steady stream of electricity that stimulates the deep reaches of the brain while calming down the trouble spot. A battery pack implanted under the skin near the collarbone provides the power source.

Deep brain stimulation isn't a magic bullet. It doesn't work for everyone, and the therapy requires brain surgery, which comes with a variety of risks.

But small studies conducted over the last several years suggest the therapy holds promise, and 2012 started with new validation. In January, Mayberg and her team published a placebo-controlled study that examined the approach for both major depression and bipolar disorder. After two years of stimulation, seven out of 12 subjects were in remission, according to the report in *Archives of General Psychiatry*.

"People didn't just get better, they were well," Mayberg says. Now the device's manufacturer has launched a randomized clinical trial to test the therapy in even more patients.

Other research groups are looking at stimulating different areas of the brain to treat depression and other disorders. In 2009, the Food and Drug Administration approved the technology for use in people with extreme obsessive-compulsive disorder.

Neurofeedback is another futuristic brain therapy that is already producing real results. Here's the premise: Functional magnetic resonance imaging machines, which watch changes in blood flow in the brain, can monitor brain activity in near real time. And if patients can see their brains working, maybe they can control the activity.

In an experiment published in 2005 in *Proceedings of the National Academy of Sciences*, researchers placed eight patients with chronic pain in state-of-the-art fMRI machines. A screen inside the machine displayed a flame that was linked to activity in the part of the brain that senses pain. When the pain center fired up, the flame grew. When that area got quiet, the flame shrank. The researchers asked study subjects to change the size of the flame by trying different strategies — for example, by imagining themselves relaxing on the beach. Overall, the group experienced a 64% drop in self-reported pain.

One of the study's authors launched a company called Omneuron to develop the technology.

"It's not entirely possible to predict exactly where this is all going," says lead author Sean Mackey, chief of Stanford University's Pain Management Division. Brain scanning is expensive. Perhaps researchers can figure out how to provide the same feedback using a less expensive EEG machine, Mackey says. Or perhaps patients could ultimately learn how to control pain without a machine.

Researchers are also investigating neurofeedback as a possible treatment for depression, attention deficit hyperactivity disorder, addiction and more.

Brain breakthroughs are already changing lives in amazing ways. Dr. Leigh Hochberg, a neurologist at Providence VA Medical Center in Rhode Island, is working to perfect an implanted device that has allowed a handful of paralyzed patients to control a robotic arm with only their thoughts. The device, called BrainGate, collects information from the motor cortex, the part of the brain that controls voluntary movement.

The system still needs to be refined and tested further, but Hochberg already has loftier goals in mind. "The dream is to one day reconnect brain to limb," giving paralyzed people the ability to use their own arms and legs, he says.

Even as these therapies progress, scientists are trying to dig deeper to understand exactly why they work. For instance, the electrodes in Mayberg's studies stimulate area 25, but they may be acting on other areas of the brain, too, through a complex web of connections that researchers are just starting to understand.

One thing seems clear: New discoveries in neuroscience tend to prompt new questions. Each time researchers manage to wrestle open a locked door, they find themselves facing another doorway.

As Koroshetz put it: "You thought you knew everything, and you were just in one room of the building."

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