In trailblazing translational research in pharmacy, medicine and computer science, scholars are applying their new knowledge of the brain and its complex workings to actively enhance human health

By Wendy Elliman

Perfecting Pulses

For over 25 years, three clusters of nerve cells deep in the brain have been Prof. Hagai Bergman’s research focus. A member of the Institute for Medical Research Israel-Canada (IMRIC) in the Hebrew University’s Faculty of Medicine and of the University’s Edmond and Lily Safra Center for Brain Sciences (ELSC), Bergman is an international authority on the basal ganglia, clusters which are the hub of human behavior.

The basal ganglia process information which comes from every part of the cortex to drive cognition, movement, emotions and learning, he says. “They funnel this input with memory and motivation to guide how we act. By tracking basic neuron responses in normal and in Parkinsonian animal lab models to tasks that involve assessing visual information, making decisions and acting on them, we’re gaining better understanding of the basal ganglia-cortical networks’ role in both health and disease.

“It’s this part of the brain whose function is lost in many dementias, so it’s a key area to search for changes associated with neurological disorders, such as Parkinson’s.”

It was Bergman, the Simone and Bernard Guttman Professor of Brain Research and president of the International Basal Ganglia Society, who first traced the development of the motor symptoms of Parkinson’s disease to the sub-regions of the basal ganglia. In 1990, he found that an area within the basal ganglia measuring just millimeters in diameter — the sub-thalamic nucleus — is overactive in this crippling neurodegenerative disorder, which attacks two people in every 100,000. His discovery led to the development of a procedure in which electrodes are implanted in this tiny area in order to deliver electric pulses or stimuli to override its faulty activity. Known as deep-brain stimulation (DBS), this hi-tech surgery was approved by the US Food and Drug Administration (FDA) in 2001.

Since then, surgeons in Israel, Europe and the US have drilled tiny burr holes in the skulls of thousands of patients with Parkinson’s disease — and, later, in those with other movement disorders, such as dystonia and dyskinesia. They insert two tiny electrodes at the end of a silicone-covered wire and feed it down to the sub-thalamic nucleus. The wire’s other end is slipped under the patient’s skin and connected to an implanted computer-mouse-sized electrical...
pacemaker. Over weeks and often months, the pacemaker is programmed to deliver pulses to the electrodes at the appropriate frequency and intensity.

“Every few months, the pacemaker must be adjusted to keep pace with disease-driven changes in the subthalamus,” says Prof. Bergman. “This means that for much of the time, it doesn’t function optimally. It was graduate student Boris Rosin from our lab who thought of a way to create a closed-loop system, in which the pacemaker continuously regulates itself — that is, it automatically adjusts the pacemaker’s function according to preset parameters.”

In Rosin’s experiments, the implanted electrode is preprogrammed to detect abnormal neuronal activity and is able to use the brain’s own electricity to trigger the appropriate stimuli to correct it. The concept has been proven and is now being developed for use.

This new strategy will not only control movement disorders more efficiently, but it also has exciting potential for other brain disorders. “In animal lab models, we’ve identified the specific neuronal signature for Parkinson’s, and are now trying to trace others,” says Bergman, who was awarded a prestigious ERC Advanced Grant for his research on basal ganglia and their disorders in 2012, and the Rappaport Prize for Excellence in Biomedical Research in 2013.

“Theoretically, wherever we’re able to identify such a signature, we can design an electrode to recognize the abnormal pattern and return it to normal brain activity in a closed-loop system.” This, he says, holds promise for neurological conditions such as chronic pain and Tourette’s syndrome, as well as for psychiatric illnesses such as obsessive-compulsive disorder, treatment-resistant depression and even schizophrenia.

“Together with Drs. Zvi Israel and Renana Eitan of the Departments of Psychiatry and Neurosurgery at the Hadassah University Medical Center, we’re part of an international multi-center study on this surgical treatment of depression and OCD,” says Bergman. “Five depression patients have been operated on so far. While these numbers are too small for firm conclusions, we’re greatly encouraged by the initial results of these surgeries.”

**Reverse Treatment**

“Road accidents, falls, sport and violence make traumatic brain injury (TBI) the most common cause of disability and death among 15- to 40-year-olds in Israel and the West,” says Prof. Esther Shohami of the Hebrew University’s School of Pharmacy and a former Dean of Students who currently serves as Student Ombudsman and is president of the Israel Society for Neuroscience.

“Despite worldwide research efforts that cost billions of dollars, there is no effective treatment for the secondary injury which follows trauma — too many of these patients decline and frequently die.”

Particularly frustrating, she says, is an experimental drug that works well in animal models but does not help patients. “There is hard data that show that TBI and stroke trigger a massive release of glutamate, one of the brain’s most important and abundant chemicals,” says Shohami. “We know that this excess overexcites the brain and results in neuronal damage. For 15 years, pharmaceutical companies have invested in designing drugs to block the effect of glutamate. While many had good lab results, none has passed the critical phase 3 clinical trials.”

Prof. Shohami and her colleagues decided to find out why. They asked three key questions: Were the TBI models faulty? Is the concept of glutamate release wrong? Or is there a disconnect in translation from lab bench to clinical?

“We ruled out a problem in the first two, so knew it had to be the third,” she says. “With a colleague from Stanford University, we mapped the glutamate receptors the experimental drugs were designed to block and made a key discovery. The massive activation of glutamate receptors immediately after injury is temporary. Within hours, these receptor levels dwindle to levels far below normal. Thus, when administered according to the clinical protocols, the experimental drugs were further down-regulating glutamate activity.”

Why, then, had these drugs worked in the lab? “In every preclinical study,
they were administered either prior to injury or immediately afterward when glutamate levels were indeed too high,” says Shohami. “In the clinical trials, however, drug administration came hours later, after the patient had been admitted to hospital, examined and signed a consent form. Not only that: in almost every clinical trial, a second dose had been given two to three days later, without any indication that this was necessary. Many of the clinical trials, in fact, had to be halted prematurely because of adverse reactions.”

The researchers proved their concept by activating glutamate receptors instead of blocking them, something that could be done successfully 24 hours following injury. Their preclinical results were published in *PNAS* and subsequently highlighted by *Nature Neuroscience* in 2004. Three years later, they were in print again: they had identified a molecule that activates glutamate receptors in the antibiotic known as seromycin (d-Cycloserine). Developed in the 1960s to treat tuberculosis, seromycin is FDA-approved and has a long history of safe clinical use. Shohami and her team used the antibiotic to increase and regulate glutamate levels and, again, their results showed improved recovery following TBI.

“With funding from the Israel Defense Forces Medical Corps, we were ready for clinical trials,” she says. In November 2012, they launched the trial as a multi-center, randomized, double-blind study, led by the Hadassah University Medical Center’s Neurosurgery Department. Over the course of a year, they plan to recruit about 100 patients, aged 18 to 55, with mild to moderate traumatic brain injury. Cognitive function, executive function and memory will be evaluated on admission, and again after three and six months. They anticipate that a single dose of seromycin within 24 hours of injury will lead to significantly improved recovery within six to 12 months.

“We’re encouraged and excited about this project, both for traumatic brain injury patients and for the promise we believe it holds as a new approach to alleviating a range of brain disorders,” says Prof. Shohami. “Glutamate mediates a wide array of brain activities — from chronic pain, memory impairment and Parkinson’s disease to post-traumatic stress disorder, psychosis, fear, anxiety, schizophrenia, drug addiction and obsessive-compulsive disorder. We believe that learning how to control it may provide a new way to help such patients.”

**Surgical Precision**

In keyhole brain surgery, probes, catheters and needles are inserted through a tiny burr hole in the skull. Without any direct visibility, neurosurgeons must then navigate the tangle of blood vessels and neurons to reach their target. While preoperative MRI mapping, anatomical knowledge and extensive experience optimize the neurosurgeon’s preparation, inadvertent brain damage nonetheless occurs in one in 10 such surgeries.

That, however, is about to change with software that plans the neurosurgeon’s safest possible insertion trajectory, starting from where exactly to drill and ending at the target. “We’ve built a navigation system which overlays the patient’s MRI images with data from other advanced brain-mapping procedures, such as fMRI and MRA,” says Prof. Leo Joskowicz, head of the Computer-Aided Surgery and Medical Image Processing Laboratory at the Hebrew University’s Selim and Rachel Benin School of Engineering and Computer Science and a member of ELSC.

“Existing surgical planning systems
rely on two-dimensional images and show only brain structures,” he says. “Ours factors in blood vessels, critical brain structures such as the ventricles, sensitive functional regions that influence vision, movement and language, and the tracts that relay orders between the cerebral cortex, spinal cord and muscles.” The result is a three-dimensional map showing a surgical insertion trajectory which is not necessarily the shortest but is always the safest — the most distant from critical structures, with zones marked in green and red indicating where incisions can or cannot be made.

Developed by graduate students Miri Troppe and Ruby Shamir with colleagues from the Hadassah University Medical Center led by Dr. Yigal Shoshan, the prototype was tested in a retrospective study at Hadassah in summer 2012. Senior and junior neurosurgeons planned the surgical trajectory, first using MRI images only and then the new software. The latter approach significantly shortened planning time and increased trajectory distance from the nearest blood vessel by an average 1.5 millimeters. The difference was especially marked among junior surgeons whose skills were upgraded to expert level — thanks to the innovative software. “The concept has been proved,” says Joskowicz. “Compensating for brain shift is one of the most challenging problems in image-guided craniotomy,” says Prof. Joskowicz. The prototype he and his Technion colleagues have developed comprises a pair of calibrated, synchronized, digital cameras trained on the brain’s exposed surface. “We use two cameras to reconstruct what happens in 3-D, the same way that two eyes work,” he explains. “The cameras track the brain surface by extracting landmarks, such as the splitting of small blood vessels, from the video stream and use this to gauge how much it shifts.”

Working on a brain model, the researchers have successfully demonstrated their technique for real-time visual tracking of brain shift on its surface during craniotomy. They are now developing a biomechanical model that will use the surface-shift data to assess the impact on the inner part of the brain — which is the surgeon’s target.

The Pain Chain

Neurobiologist Alexander Binshtok spent the first decade of his professional life as a physiotherapist, focused on relieving the chronic pain which afflicts more than one in five adults in the West. “I saw that patients with chronic inflammatory or neuropathic pain rarely respond well to available treatment,” he says. “I decided to study pain’s molecular mechanism in order to develop better therapies for a pandemic which causes great suffering and costs national...”
Binshtok pursued a doctorate in neurobiology at the Hebrew University, followed by a postdoctoral fellowship at Harvard University and Massachusetts General Hospital. In 2010 he joined IMRIC in the Hebrew University’s Faculty of Medicine and he is also a member of ELSC. The pain therapy he has developed has been hailed by fellow scientists as a major medical discovery.

Binshtok’s work stems from his pioneering elucidation of the underlying molecular, cellular and neuronal network-related mechanisms of pain. He and his colleagues went on to find a way to block pain without numbing other sensations, freezing muscles or affecting blood pressure.

“Based on our knowledge that pain fibers express a specific type of ion channel,” he says, “we looked for a way to use these channels to get an impermeable anesthetic into the pain fibers — and, thereby, block pain selectively. Our preclinical studies suggested that a single injection combining capsaicin — the “burn” compound in chili peppers, capable of opening the channels — with a membrane-impermeable derivative of the local anesthetic locadine would control pain for several days without any side effects.”

The 2007 Nature article in which Dr. Binshtok and his colleagues described this work was subsequently ranked among the top neurology research publications of all time. Their discovery is now in commercial development with Endo Pharmaceuticals, with expected applications for debilitating inflammatory pain, post-surgical pain and labor pain. Binshtok published an article on an adaptation of this approach that blocks itching in Nature Neuroscience in May 2013.

He also has several more major projects to combat chronic pain in his research pipeline. One, based on the similarity between the mechanisms driving pain and epilepsy, has led him to study the effect of anti-epilepsy medication on inflammatory pain. “We’ve found that substances released during inflammation acutely activate pain neurons; we’re examining whether proven epilepsy treatment will ameliorate this,” he says. He is likewise looking at the interaction between neurons and glial cells — the latter comprise 90 percent of the brain and are tasked with supporting and protecting neurons — in both chronic pain and epilepsy.

A longer-term endeavor for Binshtok — who was awarded a prestigious ERC Starting Grant in 2011 — is his plan to track the body’s pain pathways. “Chronic pain is a disease of the central nervous system, involving the brain and spinal cord,” he says. “The difficulty is that pain pathways change constantly since neurons themselves are altered chemically and structurally by processes such as learning and memory.” Using advanced imaging technologies, Binshtok plans to identify the central neuronal networks that transmit information to the brain from the body’s primary sensory neurons, create models of these networks and then track how the neurons behave in chronic pain.

He leaves describing his most “futuristic” project until last: building molecular nanorobots from threads of DNA to monitor and block chronic pain.

“Interaction with living organisms at cellular and molecular levels is currently achieved with drugs,” he says. “Our aim is to create an ‘intelligent’ drug — one programmed to, say, count to 10 before engaging its target, to communicate with other drugs, or to calculate drug molecules at the target site.”

With partial funding from the German-Israeli Project Cooperation Foundation (DIP), Binshtok heads a bi-national team of researchers in Israel and Germany working on this project. “We are currently proving the concept by showing that such DNA robots can sense abnormal neuronal activity and release compounds to block it,” he says. “The challenge will be to translate our work into a therapeutic approach.”