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business report
from medical technology to commercial products

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In This Issue

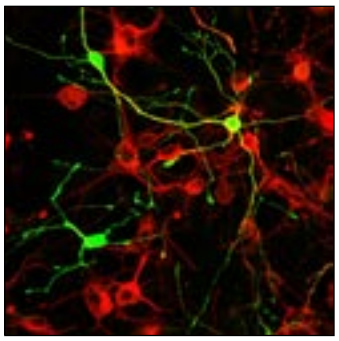
Departments

New Neuroimaging Tool Helps Locate Depression Circuit

by James Cavuoto, editor

A team of researchers at Stanford University has developed a new form of neuroimaging to help their quest to uncover the faulty brain circuits involved in depression. The technique, called voltage-sensitive dye imaging, allows intact brain circuits to be viewed in real time, enabling researchers to watch living neurons in action, across entire brain networks.

Writing in the July 6 issue of *Science Express*, the advance online publication of the journal *Science*, Karl Deisseroth, assistant professor of bioengineering and of psychiatry and behavioral sciences, along with Raag Airan, an MD/PhD student in Deisseroth's lab, described their effort to explain how a range of causes and treatments for depression converge.



Voltage-sensitive dye imaging process developed at Stanford helps researchers locate neuronal circuits involved with depression.

They found that in rats the differing mechanisms of depression and its treatment in the end appear to funnel through a single brain circuit. Changes in how the electrical signals spread through the circuit appear to be the cause of depression-related behavior, according to their study.

"I think this will help us make sense of how there can be so many different causes and treatments of depression," said Deisseroth. "It also helps us understand conceptually how something that seems as hard

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Task Force Addresses Access to New Neurotech Therapies

by James Cavuoto, editor

A newly organized task force representing clinicians, health service providers, payers, and neurotechnology vendors is seeking to expand the availability of neurotechnology devices for individuals with neurological and psychiatric disorders. The National Task Force on Consumer Access to Emerging Neurotechnologies held its inaugural meeting earlier this year and recently published a whitepaper specifically targeted to severe depression. Cyberonics, Inc., the Houston, TX manufacturer of vagus nerve stimulation systems, provided funding for the initial meeting but the group is currently seeking sponsorship from other neurotech device vendors.

The members of the new task force include several clinicians and academics involved with treatment-resistant depression, including Roger Haskett, a professor of psychiatry at University of Pittsburgh, Lawrence Cohen, a professor of pharmacotherapy at Washington State University, and Darin Dougherty from Massachusetts General Hos-

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Sharing the Task

The founding of the National Task Force on Consumer Access to Emerging Neurotechnologies is a promising development for the neurotechnology industry, as we report in our article on page 1 of this issue. Though the group's formation was no doubt inspired by a series of negative events surrounding Cyberonics' struggle to gain market approval and reimbursement for its vagus nerve stimulation system to treat refractory depression, we are heartened nonetheless by the goals and the efforts of the new organization.

In a short time, the task force has assembled an impressive membership drawing from the academic, clinical, payer, and mental health advocacy communities. They have also identified the key scientific, regulatory, financial, and political issues that stand in the way of delivering neurotechnology therapies to users who could benefit from them.

The task force wisely points out the dirty little secret of the neuropharmaceutical industry—that one third of individuals with depression are not successfully treated with currently available medications. This fact needs to be repeated over and over again to all who will listen, if for no other reason than to put into perspective the absurd standards by which neurotech devices are assessed.

It still astounds us that regulatory and reimbursement agencies would balk at a success rate of 40 to 50 percent for a therapy such as VNS or TMS for treatment-resistant depression when pharmaceutical therapies—in aggregate—exhibit at best a 67 percent success rate with the entire depression population. This is not only intellectually insulting, but a threat to the practice of psychiatry and the safety of a very sizeable patient population. If the government is so concerned with statistical evidence, they should pull from the market any individual antidepressant that fails to achieve the long-term success rate with TRD that VNS has achieved. Of course that would certainly make for some very angry pharmaceutical company executives. The notion that some regulators seem to have—if you can't help everybody we won't let you help anybody—is a perversion of government responsibility, in our view.

Clearly the task force members have their work cut out for them, beginning with the task of recruiting new sponsors. The head of the organization, Monica Oss of Open Minds, assures us this is a priority as it spins off to an independent 501(c)3 organization later this year.

The issues that Cyberonics has faced in the depression market with VNS will apply to Medtronic, St. Jude Medical, Neuronetics, Northstar, and other manufacturers of neurotechnology devices targeted at psychiatric disorders. We call on these firms to get on board with this task force, even if that means augmenting the membership beyond the initial group that Cyberonics funded.

James Cavuoto
Editor and Publisher

National Task Force
from page 1

pital. Also serving are representatives from Aetna Behavioral Health, Cigna Healthcare, PacifiCare Behavioral Health, United Behavioral Healthcare, and the U.S. Social Security Administration. Nonprofit organizations such as the Depression & Bipolar Support Alliance, the National Alliance on Mental Illness, and the World Federation for Mental Health are also represented on the task force.

The stated goals of the task force are to increase understanding of neurotechnology within the payer, provider, and consumer advocacy communities; to promote standardized clinical decision making criteria, consumer access, and reimbursement policies; and to promote parity and equity in consumer access to neurotechnology for individuals with mental health, behavioral health, and neurological conditions.

At the inaugural meeting, the task force focused specifically on depression, examining the state of current research on treatment efficacy, a standardized definition for treatment-resistant depression, the costs associated with TRD, and standards of scientific evidence. The members reported that existing depression treatment guidelines are outdated and do not address TRD. "It is clear that no one medication (or combinations of medication and/or cognitive therapies) is a panacea for all consumers, and the clinical predictors of treatment selection are weak," the group reported in its whitepaper. The publication pointed out that current guidelines do not address interventions for the 33 percent of individuals who do not respond to currently available therapies.

The task force reported that the annual costs to the U.S. associated with depression are about $83 billion, of which $26 billion relates to treatment costs, with the remainder due to lost productivity and lost earning resulting from suicide. Treatment costs for individuals with TRD were found to be six times greater than for those with treatable depression. The group also discussed the use of randomized controlled trials, currently the gold standard at the FDA, and advocated alternatives such as practice-based evidence.

Neuronetrix Names New CEO to Lead Alzheimer's Launch

Neuronetrix, Inc., the Louisville, KY developer of neurosensing systems, named Michael Reid as the new president and CEO. Reid succeeds John Barker, a company co-founder, who will remain an active part of the company on the board of directors. "We believe Reid's 14 plus years of medical and healthcare experience with the largest pharmaceutical company in the world (Pfizer, Inc.) and his direct experience in the Alzheimer's market gives him the ability to lead Neuronetrix to the next level," said Barker.

"Neuronetrix has a mission of revolutionizing the treatment of Alzheimer's disease by providing a point-of-care product that can be used by primary care physicians to screen and initiate therapy much earlier in the disease process," said Reid.

Even with several therapies available to treat Alzheimer's disease, there still is a significant gap between the onset of the disease and when a patient actually starts treatment. This treatment gap is directly tied to the challenges in diagnosing the disease early, before the significant loss of memory, cognition, and activities of daily living. Patients, doctors, caregivers, and the health-care industry are looking for and demanding a solution to this problem.

Over the last nine years, Reid led or directed teams responsible for generating sales revenue of up to $100 million. Reid also brings proven individual and leadership experience in launching eight medical products over the last 14 years. Three of those products deal directly with the central nervous system and one of those products is currently the most commonly prescribed treatment for Alzheimer's disease. In his tenure with Pfizer, Reid has won the company's top awards for performance in every position he has held as well as key leadership awards.

Dynatronics Acquires Six Key Distributors

Dynatronics Corp., the Salt Lake City, UT manufacturer of surface stimulation systems, announced that it has acquired six of its key independent distributors. The distributors are Rajala Therapy Sales Associates of Pleasanton, CA; Responsive Providers, Inc. of Houston, TX; Therapy and Health Care Products, Inc. of Girard, OH; Cyman Therapy, Inc. of Detroit, MI; Al Rice and Associates, Inc. of Jeffersonville, IN; and Theratech, Inc. of Minneapolis, MN. The acquisition of the six companies is anticipated to increase Dynatronics' earnings, excluding any one-time assimilation expenses during the first half of fiscal 2008. Adding sales of these distributors is expected to increase overall Dynatronics' revenue for the company's fiscal year ending June 30, 2008 by an estimated 80 percent. The six dealers generated approximately $19 million in combined revenues in 2006. After adjusting for the direct sales of Dynatronics products to these dealers, Dynatronics' overall revenues are expected to increase by an estimated $15 million. The total consideration paid for the six separately-negotiated acquisitions was approximately $8.3 million comprised of approximately $3.3 million in cash and 4.6 million shares of Dynatronics' common stock.

Cyberonics Names New Chief Financial Officer

Cyberonics, Inc., the Houston, TX manufacturer of vagus nerve stimulation systems, announced the appointment of Gregory Browne as chief financial officer. Browne has served as both CEO and CFO for several publicly traded healthcare companies. Most recently, from 2002 to 2006, he was CFO at Amedisys, Inc., a home nursing company with revenues in excess of $600 million, during a period of substantial growth in revenue, profitability, and market capitalization. Previously, he served as CEO for Ramsay Healthcare Inc., a provider of psychiatric services, and Ramsay-HMO, Inc., a health maintenance organization. Immediately prior to joining Cyberonics, Browne worked with Tatum, LLC, an executive services company, and has also founded and served as president at PeopleWorks, Inc, a human resource outsourcing company. "The Board and I are delighted to welcome Greg to our senior management team, and we are confident that he will be an important contributor to the growth and success of Cyberonics," said Dan Moore, Cyberonics' president and CEO. "Greg's extensive financial experience in the health care industry, particularly within the capital markets, makes him an excellent choice."

Aspect Medical Announces Share Repurchase from Boston Scientific

Aspect Medical Systems, Inc., the Norwood, MA manufacturer of brain state analysis systems, announced that it had exercised an option to purchase 2.5 million shares of Aspect common stock held by Boston Scientific Corp. pursuant to the Termination and Repurchase Agreement between the two firms. The purchase price for the repurchase is approximately $37.7 million. Under the terms of the Termination and Repurchase Agreement, Aspect and Boston Scientific concluded their neuroscience alliance, Aspect purchased 2.0 million shares of Aspect common stock held by Boston Scientific for approximately $32.0 million and Aspect obtained the right, for a period of six months following the date of the Agreement, to purchase any or all of Boston Scientific's position in Aspect at a price of $15.00 per share, or the average of the closing prices of Aspect stock over the 10 trading days up to and including the date on which Aspect exercises its right to repurchase, whichever is higher. Following the repurchase, Boston Scientific's holdings in Aspect common stock will be approximately 1.5 million shares, or approximately 9 percent of the total number of shares of Aspect common stock outstanding. In accordance with the Agreement, Aspect retains the option to purchase additional shares from Boston Scientific at any time during the six month period subsequent to June 11. During this same period, Boston Scientific has agreed not to sell any of its Aspect stock, except to Aspect.

Aspect Medical Receives FDA Clearance for BIS View Monitoring System

Aspect Medical Systems, Inc., the Norwood, MA manufacturer of brain state analysis systems, announced that it has received 510(k) clearance from the U.S. Food and Drug Administration for the BIS View Monitoring system, the company's newest stand-alone monitor. BIS View offers customers a compact design and simplified operation for lower-acuity clinical environments with limited room for monitoring equipment. According to the new indication for use statement cleared by the FDA, BIS monitoring may be used as an aid in monitoring the effects of certain anesthetic agents and may be associated with a reduction in primary anesthetic use and a reduction in emergence and recovery time. Use of BIS monitoring to help guide anesthetic administration may also be associated with the reduction of incidence of awareness with recall in adults during general anesthesia and sedation.

Boston Scientific Announces Precision Plus Spinal Cord Stimulation System

Boston Scientific Corp., the Natick, MA manufacturer of neurostimulation devices, announced the launch of the Precision Plus Spinal Cord Stimulation system, a rechargeable neuromodulation device for treatment of chronic pain of the trunk, back, and limbs. Precision Plus provides physicians with EGL Scan, the first SCS lead scanning technology. The system also features an improved remote control and charger to simplify control of patient therapy. "Since the launch of the Precision system in 2005, we have delivered the technology and support infrastructure needed to gain more than 25 percent share of the pain management market," said Michael Onuscheck, president of Boston Scientific's Pain Management Business. EGL Scan (Electronically Generated Lead Scan) technology displays the relative position of implanted leads, within seconds and without using fluoroscopy or x-ray. The information from EGL Scan can be used to increase programming accuracy, which can lead to improvements in patient outcomes and treatment office operating efficiencies. The Precision Plus remote control and charger are completely cordless, eliminating the need for cumbersome cords and antennas. The remote control offers the industry's longest wireless range, enabling patients to adjust their pain therapy with simplicity and convenience. The charger is approximately 75 percent smaller and 85 percent lighter than competing chargers, making it convenient and discreet. The charger also features continuous temperature monitoring.

Integra Supports Brain Trauma Foundation's Guidelines for Severe TBI

Integra LifeSciences Holdings Corp., the Plainsboro, NJ manufacturer of neurosurgical tools, announced its support for the third edition of the Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury. The Guidelines are nationally recognized and referenced by many of the leading trauma centers in treatment of patients with traumatic brain injury. The Guidelines were developed by the BTF in association with the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the AANS/CNS Joint Section on Neurotrauma and Critical Care, and incorporate the latest published research findings relevant to the diagnosis and treatment of severe traumatic brain injury. "We are very grateful for Integra's support of this publication," said Jamshid Ghajar, president, Brain Trauma Foundation, and Clinical Professor of Neurological Surgery, Weill Cornell Medical College. "Research has shown that not all brain damage occurs at the moment of impact. Damage frequently evolves over the ensuing hours and days after the initial injury. Research has proven that, in most cases, this secondary damage can be controlled using scientific, evidence-based treatment guidelines, which BTF has developed with medical organizations and physicians with expertise in TBI. By educating health care providers in the use of these guidelines, the BTF estimates that thousands of lives could be saved in the U.S., and many would be spared life-long disabilities."

Depression Circuit

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to get traction on as depression can have a really quantitative, concrete basis."

The work also may have implications for the search for new treatments for depression. "You can use that common pathway as the most efficient, most direct targeted way to find truly specific treatments," he said.

Deisseroth, who sees many depressed patients in clinic, said he has come to appreciate how the bumps in the road that most people see as normal obstacles in life become insurmountable hurdles to depressed people, causing them to lapse into helplessness.

Reasoning that the brain is essentially a complex electrical circuit, Deisseroth's team set out to test the theory of whether brain circuitry malfunction could be at the root of depression. To explore the idea in a precise, quantitative way, they needed to develop a visualization tool that was faster and sharper than brain imaging systems currently available, such as MRI or CT scans.

The Stanford system uses a fluorescent dye, sensitive to brain circuit activity, which the researchers introduce into the animal brain tissue. As dyed circuits light up and darken again in response to electrical activity, very fast high-resolution cameras capture the action. The researchers can observe how different stimuli received by the animal, such as a dose of an antidepressant drug, affect circuit operation.

The researchers used slices of rat brain, Deisseroth said, "like a computer repair technician would take out a circuit board" to test its functional properties. The brain slices, which remain active for many hours, came from parts of the hippocampus, a region long implicated in depression. They also tested slices from rats treated with the antidepressant medications fluoxetine and imipramine.

The team carried out the study using a standard rat model of depression. Even though the rats do not mimic the entire complexity of genetic and environmental causes of human depression, the animals exhibit similar symptoms and also get better from the same medications that work on humans.

In these rats, they found an alteration in electrical activity flow through the brain that could be corrected by human antidepressants. The extent that the signal spread through the brain sample was diminished in the "depressed" rats, a crucial finding that would not be apparent with other experimental methods, Deisseroth said. They needed to be able to image a whole circuit simultaneously—and very rapidly—to see the effect.

"What surprised me most was how specifically the measure tracked the depression-related behavior," said Airan. "We usually think of psychiatric disorders as fuzzy and intractable, and this study showed me that, with the right tools, we could really put psychiatry on a quantitative framework."

Leslie Meltzer, neurosciences graduate student and co-first author, searched for the cellular basis of these changes in circuitry. An obvious place to start, she said, was to look at the formation of new neurons in the hippocampus, a process that neuroscientists have suggested is at the root of how antidepressants work. What they found was that the growth of new neurons could account for the behavioral improvements seen from treatment as well as the circuitry changes. The converse was not true: Fewer new neurons in that region did not equal depression.

FDA Approves New Pulse Generators from Cyberonics Inc.

Cyberonics, Inc., the Houston, TX manufacturer of vagus nerve stimulation systems, announced that the DemipulseT and Demipulse DuoT Generators for use in the company's VNS therapy were approved by the U.S. Food and Drug Administration for commercial release.

The Demipulse generators are 43 percent smaller in volume than the Model 102 generators and incorporate greater functionality, including continuous projection of time to end of service, improved diagnostics, such as direct lead impedance measurement, and faster communication with a programming system.

Feinstein Researchers Identify Two Distinct Parkinson's Networks

Parkinson's disease, which causes tremors, rigidity, and slowed movements in a million Americans, also targets another brain network that regulates cognitive thought and the ability to carry out everyday tasks. David Eidelberg, head of the Center for Neurosciences at The Feinstein Institute for Medical Research, and his colleagues measured and quantified this network of brain regions during a five-year study of newly diagnosed Parkinson's patients who agreed to be followed several times over the course of the study. The new report appears in an online version in the journal *Brain*. The technology is precise enough to diagnose the two brain networks—one that regulates movement and the other cognition—in individuals, and Eidelberg said that it could be used to assess the degenerative disease process and the person's response to treatments. The study also shows that standard drugs used to treat Parkinson's alter the areas involved in movement but not those that regulate cognition. The network that grows abnormal over time includes pre-frontal cortex, the same region that is hard-hit in mild cognitive impairment. But Eidelberg said that the symptoms in the two diseases are quite different. Thinking that medicines used for Alzheimer's might help normalize this network, they gave Parkinson's patients eight weeks of treatment. It didn't work. In 1999, the researchers recruited 15 patients with early stage Parkinson's and signed them on to get brain scans at different points throughout the study. Some were on medicines and some were not. The first networks to be identified were no surprise: The basal ganglia, thalamus, and brain stem that regulate movement. The scans they used identified areas in this motor network that showed decreased metabolic activity and some areas that had increased metabolic activity. Over time, the cognitive network became apparent. And as the disease progressed and symptoms worsened, this network also took its toll. They are now testing other treatments, including deep brain stimulation, to see if it can impact on the cognitive network.

German Researchers Uncover Mechanism of Pain Distraction

German researchers have pinpointed the brain region responsible for pain's ability to affect cognitive processing. They have found that this pain-related brain region is distinct from the one involved in cognitive processing interference due to a distracting memory task. Ulrike Bingel and colleagues at the University Medical Center Hamburg-Eppendorf published their discovery in the July 5, 2007 issue of the journal *Neuron*. To search for the region responsible for pain's ability to usurp attention, the researchers asked volunteers to perform a cognitive task involving distinguishing images, as well as a working memory task involving remembering images. The researchers asked the volunteers to perform the tasks as they experienced different levels of pain caused by the zapping of their hands by a harmless laser beam. During these tests, the volunteers' brains were scanned using functional magnetic resonance imaging. The experiments identified the lateral occipital complex as the cognitive-related area affected by both "working memory load" and pain. This finding was expected, since the LOC is known to be involved in processing images. The researchers next sought to identify the brain region by which pain affects the functioning of the LOC. They theorized that the best candidate for this region was one called the rostral anterior cingulate cortex . This region is known to be involved in the brain's processing of pain, and it is part of the anterior cingulate cortex, which plays an important role in "executive" functions such as attentional control. Indeed, fMRI scans indicated that the rACC is the center through which pain influences the LOC. By contrast, they found a working memory load affects the LOC through a different region, the inferior parietal cortex. The researchers noted that the modulation of visual processing by pain that they observed in their fMRI studies is behaviorally relevant, because as their fMRI scans showed pain affecting the LOC, they also observed a parallel impairment of accuracy in subjects' recognition of the images.

Vendor Profile

Afferent Corp. Targets Sensory Signals as Novel Neurorehabilitation Strategy

by David Pope, editorial director

Afferent Corp. of Providence, RI, is pioneering a new class of neuromodulation devices that target afferent, or sensory, signals from the peripheral nervous system. Unlike most current neuromodulation devices that use electrical stimulation to activate the efferent neural pathways of the central nervous system, Afferent's technology uses electrical or mechanical stimulation to increase sensory feedback from mechanoreceptors in skin, muscles, tendons, and ligaments. Building on early studies that demonstrated subthreshold sensory stimulation enhances tactile sensation and balance control in adults, Afferent initially is focusing on developing platforms for stroke rehabilitation, diabetic neuropathy, and improving balance and gait in elderly people.

Afferent's technology is based on work by James Collins, professor of biomedical engineering at Boston University, who showed that low-level stochastic, or random, vibrations improved sense of touch. Collins went on to demonstrate that generating a subthreshold noise in the sensory pathways with a random electrical stimulation improves detectability of weak mechanical stimuli. These two experiments and others indicated that either mechanical vibrations or electrical stimulation can be used to enhance tactile sensation.

Sensory neurons adapt and cease to respond to constant or regular periodic input—for instance, we become unaware of the touch of clothing. But when exposed to random noise, sensory neurons are unable to adapt and remain in a heightened state but below firing thresholds. In physics, the use of random noise to improve the performance of a nonlinear system is called stochastic resonance, and the phenomenon has been studied in laser pumping and chemical reactions. It also has been used to explain climatic fluctuations and how crayfish sense predators in turbulent water. Collins was the first to demonstrate stochastic resonance in the human sensory nervous system.

In 1999 entrepreneur Jason Harry, who had served as vice president of research engineering at NMT Medical, Inc. which specialized in cardiovascular implants, licensed the stochastic resonance technology from Boston University and received help from the Community Technology Fund—the university's technology transfer incubator. The following year the company Harry founded, then named Sensory Technologies, received assistance and funding from the Rhode Island state-financed Slater Center for Biomedical Technology and raised $1 million from Pharos LLC, an investment firm headed by George Hatsopoulos, founder of Thermo Electron Corp.

The initial goal was to develop shoe insoles and possibly gloves or sleeves for treating neuropathy in diabetics and improving balance in the elderly. Then in 2001, Harry decided to switch to developing products that would accelerate healing of sports injuries in the hope that this market would attract investors. The name of the company was changed to Afferent Corp. to emphasize how its technology differs from other neurostimulation technologies. The sports medicine effort failed to gain the interest of investors, and Harry had to downsize his company to himself and his first employee, James Niemi. The new focus was the development of products for rehabilitating stroke survivors and improving balance in elderly patients. Harry admitted that the firm had difficulty deciding which products to develop first because the technology could be applied to so many neurological dysfunctions.

At the beginning of 2003 the Slater Center, Boston University, and Pharos gave the company $300,000 to continue operations until a Phase II SBIR grant from the National Institute of Child Health and Human Development was finalized. The $750,000 grant for product development and clinical testing of technology to improve balance in elderly people was announced in August. Afferent had previously been awarded Phase I grants from various NIH agencies. In 2004 Afferent received another $750,000 Phase II SBIR grant from the National Institute of Neurological Disorders and Stroke to advance product development and clinical trials of the technology for stroke rehabilitation and for animal testing. By 2007 Afferent had received a total of $2.5 million in grants from the NIH.

A Series A round led by New Science Ventures raised $4 million in 2004 from Point Judith Capital Partners, Long River Ventures, Village Ventures, and Nitta Corp. of Japan, a developer of industrial robotic products including pressure and tactile sensors. All of Afferent's previous institutional investors also participated.

Several pilot clinical studies at the Spaulding Rehabilitation Center and Beth Israel Deaconess Medical Center, both Harvard affiliated, provided evidence that imperceptible electrical stimulation improved sway balance and tactile sensations in older adults, in patients with stroke, and in patients with diabetic neuropathy. Other pilot studies showed that applying mechanical vibrations to the soles of the feet improved sway balance in the elderly and in stroke and diabetic patients. Animal studies are being conducted at Brown University and the Canadian Centre for Behavioural Neuroscience at the University of Lethbridge, Alberta. Post-stroke rehabilitation clinical studies are underway at Northwestern University's Feinberg School of Medicine and at the Rehabilitation Institute of Chicago, and Afferent is negotiating additional post-stroke rehabilitation trials at other leading centers.

Harry, the founding CEO of Afferent, stepped down in 2006 and brought in a seasoned medical device industry executive, David Hable, as CEO and president. Hable formerly was worldwide president of Codman & Shurtleff, a neurosurgery medical device division of Johnson & Johnson. He also served as CEO and president of Brainsgate Ltd., an Israeli neurotech firm developing a novel technology based on stimulating the sphenopalatine ganglion to induce cerebral vasodilation.

Harry moved to the position of executive vice president and chief technology officer. James Niemi, who previously had worked with Harry at NMT Medical, is now VP of research, and Scott Kellogg is VP of product development. The company has eight employees, and plans to add staff as the products under development approach commercialization.

Although Afferent is initially concentrating on the stroke, diabetic, and elderly balance markets, the company sees its technology as a new class of devices for treating a variety of chronic neurological dysfunctions. In addition to the immediate benefit of improving the sensitivity of mechanoreceptors, the company is pursuing the possibility that subthreshold sensory stimulation can produce permanent changes in neural pathways and restore functions in the brain through the process of neuroplasticity. One of the critical factors in successful recovery of function after stroke or brain injury is the flow of appropriate sensory information from the peripheral limbs. Increasing the sensitivity of the sensory pathways with either electrical or mechanical stimulation could improve standard rehabilitation efforts. If current animal and human studies show positive results, Afferent plans to initiate a pivotal study to determine the benefits in stroke rehabilitation of combining sensory stimulation with physical therapy.

Mechanical and electrical stimulation devices are both under development. A device that combines mechanical and electrical stimulation is being investigated. In such a device, a mechtrode on the skin would generate surface mechanical stimulation to the skin and electrical stimulation to deeper structures. Another approach being developed by Afferent is the use of implanted electrodes to boost sensorimotor functions in patients with more severe sensory loss and motor dysfunction.

The company's technology base attracted the attention of a major orthopedics company, Stryker Corp., which invested an undisclosed amount in Afferent in January 2007. For its investment, Stryker gains an insider's view of the technology as it unfolds. The deal was negotiated by Stryker Development, which finds new business opportunities for its parent.

According to Hable, the Stryker investment is an important validation of Afferent's technology. "They see the neuro area as an attractive, strategic market, both for stand-alone applications and for areas that are complementary to their existing product lines," he said in an interview with *Neurotech Business Report*.

Stryker's revenue was $5.4 billion in 2006, and about one-third came from outside the U.S. It operates two major divisions, orthopedic implants, and medical and surgical equipment. Stryker also operates almost 500 outpatient physical therapy centers in the U.S. When Afferent is ready to market a vibrating insole or an electrical stimulation device to improve balance in the elderly, it is possible that Stryker's physical therapy centers would be an ideal way to reach a large customer base. Similarly, when Afferent develops implanted devices, Stryker's orthopedic group might offer to market them.

The Stryker deal also will help smooth the way for Afferent's Series B round, which is expected to raise $15 million for product development and clinical trials that could pave the way for FDA approval of Afferent's first product.

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Founded: 2000
Market: Sensory stimulation
Privately held
President and CEO: David Hable
Founder: Jason Harry

Conference Report

Neuroscientists and Philosophers Discuss Consciousness at ASSC Meeting

by James Cavuoto, editor

Several hundred researchers and academics attended the 11th meeting of the Association for the Scientific Study of Consciousness June 22-25 in Las Vegas, NV. While much of the program was devoted to more abstract presentations on human consciousness, several presenters discussed the use of neurotechnology tools as a means of measuring and evaluating brain states.

Among the featured lecturers at the conference was Michael Gazzaniga from UC Santa Barbara. Gazzaniga spoke on the structure of human consciousness, proposing a theory that conscious experience emerges from the dynamic interactions of specialized component processes via a distributed neuronal network. His model seeks to address the dichotomy presented by the segregation of neural processing into specific brain regions on one hand and the integrative multi-modal processes that overcome modular segregation on the other hand.

Alison Gopnik from UC Berkeley addressed the question of consciousness in babies, arguing that babies are more conscious than adults since there is less inhibition of phenomenological experience.

Several clinical specialists used their experience with neurological disorders as a platform for evaluating conscious states. Fabien Perrin from the Laboratoire de Neurosciences Sensorielles in Lyon, France, presented a paper on sensory discrimination in patients with severe brain damage, Perrin and colleagues used electrophysiological studies with 14 brain-damaged patients. He noted a P300 response to hearing the patient's own name in locked-in individuals or minimally conscious state, and most of the patients in a vegetative state.

George Mashour from the department of anesthesiology at the University of Michigan spoke of his experiences using tools such as Aspect Medical's BIS index for depth of anesthesia. While the incidence is rare, in about one to two cases out of 1000, surgical patients may be aware of intraoperative events without the presence of any objective indices. Labeling these individuals "inverse zombies," Mashour discussed the challenge of ensuring the absence of qualia and its implications for the study of human consciousness.

Stephen Macnick from the Barrow Neurological Institute in Phoenix, AZ presented an intriguing paper on the role of feedback in visual masking, visual awareness, and attention. Macnick and his colleague Susana Martinez-Conde examined the neurophysiological mechanisms accompanying visual masking tasks in primates. They propose a feedforward model of visual masking, suggesting that the ratio of feedback versus feedforward connections in the visual system may be explained solely by the critical need for top-down attentional modulation.

Barrow Neurological Institute Performs Leading-Edge Research in Clinical Setting

by James Cavuoto, editor

Barrow Neurological Institute of St. Joseph's Hospital and Medical Center in Phoenix, AZ is internationally recognized as a leader in neurological research and patient care. Established in 1962, Barrow treats patients with a wide range of conditions, including brain and spinal tumors, cerebrovascular conditions, and neuromuscular disorders.

In addition to its clinical specialties, Barrow features several research laboratories. The Atkinson Pain Research Laboratory, led by Bud Craig, studies connections from the spinal cord to the brain that are involved in bodily "feelings." The main connection originates in a spinal region called lamina I. Quantitative analyses of lamina I spinothalamic neurons indicate that they serve as "labeled lines" that generate feelings of sharp pain, burning pain, warm, cool, itch, muscle ache, sensual touch, and other sensations related to the body's physiological condition.

Anatomic work in the laboratory shows that lamina I neurons project their axons first to autonomic spinal and homeostatic brainstem regions, then to a specific thalamocortical relay nucleus called VMpo, which is found only in primates and is greatly enlarged in humans. Craig's work also shows that stimulation of the vagus nerve causes activity within the same pathway. This finding supports the idea that pain is a reflection of the homeostatic processes in the brain that evolve to maintain the body's health.

Current work in the laboratory addresses the integration of pain, temperature, itch, and visceral representations within the insular cortex of the primate; the role of the medial thalamus and anterior cingulate cortex in the inhibition of pain by cooling; the association of deep dorsal horn cells with sensorimotor integration (considered for more than 30 years to be pain cells by others); the role of lamina I spinothalamic neurons in injury-induced sensitization (hyperalgesia); and the characterization of lamina I spinobulbar neurons involved in brainstem homeostatic mechanisms.

The Neural Physiology Laboratory, led by Jie Wu, studies the function and pharmacology of recombinant nicotinic acetylcholine receptors transfected into a cloned cell line and natively expressed nAChRs in neurons of the central nervous system using patch-clamp whole-cell and single-channel recordings. Wu's lab also looks at cellular and molecular mechanisms of epileptogenesis in different epilepsy animal models and epilepsy patient brain tissues, using electrophysiological techniques combined with cellular and molecular biological methods.

The Laboratory of Visual Neuroscience, headed up by Susana Martinez-Conde, investigates the aspects of the neural code that relate to visual perception. One of the ways the lab addresses this is by correlating the eye movements that occur during visual fixation with the spike trains that they provoke in single neurons. Since visual images fade when eye movements are absent, it makes sense that the patterns of neural firing that correlate best with fixational eye movements are important to conveying the visibility of a stimulus. The lab has found that bursts of spikes are better related to fixational eye movements than single spikes alone. This suggests that bursts of spikes are more reliable signals than are single spikes.

Calendar

Aug. 23-26	29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Lyon France. Contact IEEE EMBS, embc07.ulster.ac.uk
Sep. 15-20	2007 Congress of Neurological Surgeons Annual Meeting, San Diego, CA, contact CNS, neurosurgeon.org
Sep. 26-27	BMES 2007, Los Angeles, CA. Contact Biomedical Engineering Society, http://bme.usc.edu/bmes2007.
Oct. 25-26	Neurotech Leaders Forum, Newport Beach, CA. Contact Neurotech Reports, 415 546 1259.
Nov. 3-7	Neuroscience 2007, San Diego, CA. Contact Society for Neuroscience, sfn.org.
Nov. 10-14	IFESS 2007, Philadelphia, PA. Contact IFESS, ifess.org.

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