

Neurotech

business report

from medical technology to commercial products

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In This Issue

Brown Researchers Develop Synaptic Imaging Tool: *The technique offers potential for future neurodiagnostic or neuromodulation devices. See page 1.*

Depression Market Poised for New Commercial Activity: *There are positive signs from vendors of both implanted and noninvasive therapies. See page 1.*

Neurotech Reports Announces Recipients of Gold Electrode Awards: *Kip Ludwig was named Neurotechnology Researcher of the Year. See page 3.*

Respicardia Announces FDA Approval of Device for Central Sleep Apnea: *The system stimulates the phrenic nerve and activates the diaphragm. See page 5.*

Vendor Profile: *Neurovalens Pursues Consumer Neurotech Market with Vestibular Nerve Stim. See page 6.*

Conference Report: *Entrepreneurs and Industry Veterans Take Part in 2017 Neurotech Leaders Forum. See page 7.*

Research Institution Profile: *Cleveland FES Center Expands its Focus to Novel Forms of Neuromodulation. See page 8.*

Departments

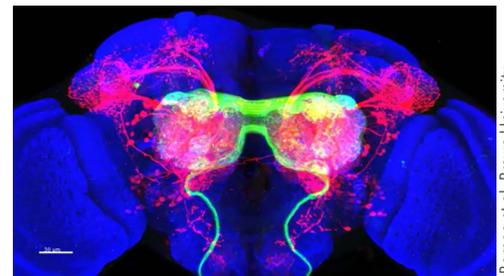
Publisher's Letter	2
Financial News	3
News Briefs	4
Research Highlights	5
Calendar	8
Contact Information.....	8

Brown Researchers Develop Synaptic Imaging Tool

by James Cavanaugh, editor

A team of researchers at Brown University has developed a new imaging technique that reveals neural connections. The method, called trans-Tango, may prove to be a valuable neurodiagnostic or neuromodulation tool in the years ahead, and in the meantime, offers researchers a glimpse at synaptic connections in real time.

In a study published in *Neuron*, the Brown team used trans-Tango to illuminate connected neurons in fruit flies, revealing previously unmapped gustatory circuits that link the taste-sensing organs to brain regions known to govern feeding behavior and memory. The technology is widely applicable, the researchers say, because trans-Tango doesn't depend on the neurotransmitters involved in a neural connection or on the types of neurons that are connected. As long as two neurons join at a synapse, trans-Tango allows investigators to label the cells connected to a starter neuron.



Barnea et al., Brown University

Trans-tango reveals olfactory circuits in the fruit fly by working across synaptic connections. Green cells are the ones researchers targeted with the technique revealing the red cells that were connected to them.

more on page 2

Depression Market Poised for New Commercial Activity

by James Cavanaugh, editor

The market for treating major depression and related psychiatric disorders with neuromodulation therapies, which had stalled in recent years after two failed clinical trials, seems ready to rebound. Several new vendors have announced new noninvasive brain stimulation devices and at least one established vendor of implanted devices released clinical data that holds out promise for new commercial activity.

A Swedish firm called Flow Neuroscience recently announced a new neuromodulation therapy for depression based on transcranial direct current stimulation. The system consists of a medical grade tDCS headset and a smartphone app that helps users change their daily routines and break the negative behavioral patterns that come with depression. tDCS is approved for treating depression in most of Europe.

At the recent Neurotech Leaders Forum, Fisher Wallace Labs described their new Kortex system, which includes both a tDCS headset and virtual reality goggles. The device also can use functional near infrared spectroscopy and EEG data to help predict treatment outcome and to customize the stimulation paradigm in real time. Fisher Wallace intends to market Kortex initially as a wellness device, but the com-

more on page 4

The News from Here

The Neurotech Leaders Forum, which took place in San Francisco earlier this month, has always been a great opportunity for us to get updates from some of the leading neurotech firms [see Conference Report, p7]. This year, we had an opportunity to inform the industry of some new goings on at Neurotech Reports.

To begin with, we announced that Jeremy Koff has joined the editorial staff of Neurotech Reports as senior contributing editor. Jeremy has been a medical device industry consultant for many years, with particular experience and expertise in neuromodulation and neuroprosthetic devices. Based in Los Angeles, he has worked for Advanced Bionics, Boston Scientific, Bioness, and other southern California device firms.

Jeremy will be heading up a new custom publishing operation that we announced at the Leaders Forum. This new venture allows us to produce custom publications and market research on behalf of clients in the neurotech industry. Examples are industry whitepapers, clinician surveys, interviews with key opinion leaders, patient preference studies, e-books, and web and video projects. Assisting Jeremy in this effort will be senior editor Jennifer French and this editor.

We also announced that we will be updating and enhancing our Database of Neuromodulation products, which allows users to search for available and forthcoming products in a number of categories serving a number of neurological disorders. Basic information in the database will be available for free to clinicians, end-users, and vendors of neurotech products. Paid subscribers to *Neurotech Business Report* will receive enhanced access, which offers them more detailed information about companies and products in the industry, including regulatory and reimbursement status. To assist us in collecting information from the database, we've brought on Shivan Bhavnani, an experienced financial editor and analyst from New York.

Speaking of New York, we also announced we will be launching a new management and investment conference devoted to bioelectronic medicine in New York City next year. The first annual Bioelectronic Medicine Forum will take place on March 22. Watch this space for more details on the agenda and presenters.

Look for a new release of our market research report, *The Market for Neurotechnology: 2018-2022*, which will be published later this year. This significant update includes detailed information on several new players in the neurotechnology industry, as well as analysis of key market and technology trends. Finally, we also plan to release some new paperback titles in our Neurotech Press imprint in 2018.

For more information on any of these new activities, contact us at 415 546 1259 or editorial (at) neurotechreports.com.

James Cavuoto
Editor and Publisher

Synaptic Imaging

from page 1

Moreover, because trans-Tango works by instigating the expression of genes in connected pairs of neurons, it also has the potential to enable scientists to control circuit functions, said senior and corresponding author Gilad Barnea, an associate professor of neuroscience at Brown. Barnea began looking for a precise, reliable, and general way to visualize neural connections two decades ago. The application of trans-Tango that his team demonstrates in the new study is circuit tracing, but manipulations such as activating or shutting off connected neurons could become possible, too.

"trans-Tango provides genetic accessibility in the context of connectivity," Barnea said. "Our technique allows you to access the neurons that interact with the particular 'starter' cell you target."

The team is now working on developing a host of other applications of trans-Tango. These include using the system to manipulate behavior, developing the equivalent technique in mice, and making it work in reverse so that it employs incoming connections from other neurons just like it does outgoing connections. That's according to Mustafa Talay, a postdoctoral fellow who earned his Ph.D. in Barnea's lab and is co-lead author with Ethan Richman, a former undergraduate at Brown who is now a graduate student at Stanford.

trans-Tango works by genetically introducing an artificial signaling pathway into every neuron in the fly. The pathway acts like a switch in the neurons that can be thrown by exposure to a triggering protein. To operate trans-Tango, scientists genetically engineer the neurons of interest (starter neurons) to present this triggering protein on their synapses together with a protein that lights up the starter neurons in green. Expression of the trigger protein at the synapse causes connected neurons to light up in red, revealing the full extent of the connected neurons in the fly's nervous system.

In the gustatory system, for example, the team lit up connections extending all the way from peripheral taste-sensing starter neurons to connected neurons that projected into a brain region known

to control feeding behavior as well as to other regions thought to regulate memory.

By design, the system stops after just one stage of connectivity because if it continued endlessly, it would eventually light up the whole nervous system, Talay said. But the system is compatible with other cell imaging and targeting methods that can narrow down the number of connected neurons that respond to trans-Tango. In the new study, for example, the team combined trans-Tango with such techniques to specifically highlight individual connected neurons that respond to trans-Tango. In the new study, for example, the team combined trans-Tango with such techniques to specifically highlight individual connected neurons.

In many cases, revealing the full expanse that two connected neurons cover in a circuit can present deeply meaningful insights for neuroscientists. Not only did the team find novel connections in the gustatory circuitry of flies, but also they showed the different projections that various neurons in the olfactory system make, potentially clarifying how they carry out their distinct roles in connecting smell and behavior.

Neurotech Reports Announces Recipients of Gold Electrode Awards

Neurotech Reports, the publisher of this newsletter, announced the winners of the 2017 Gold Electrode Awards. The awards were presented at the 2017 Neurotech Leaders Forum in San Francisco earlier this month.

The award for best new product went to Medasense Biometrics Ltd. for its PMD-200 system for reporting an objective measure of pain. The award for most promising startup went to GiMer Medical. The award for most valuable financial professional went to Paul Grand of MedTech Innovator. The award for most useful nonprofit was presented to the Medical Device Innovation Consortium. The award for neurotechnology researcher of the year was presented to Kip Ludwig of Mayo Clinic.

Boston Scientific Announces Financial Results for Third Quarter

Boston Scientific Corp., the Marlborough, MA manufacturer of neuromodulation systems, reported financial results for the third quarter ended Sept. 30, 2017. Sales for the quarter were \$2.22 billion, a 5.6 percent increase compared to the prior year. Neuromodulation revenue was \$154 million, an 11 percent increase compared to \$138 million in the previous year. Net income was \$283 million (20 cents per diluted share), compared to \$228 million (17 cents per diluted share) in the third quarter of 2016. “Our global team is delivering strong performance as we continue to invest in a deep and innovative portfolio and expand into faster-growing markets,” said Mike Mahoney, chairman and CEO of Boston Scientific.

NeuroPace Announces \$74 Million Funding Round

NeuroPace Inc., the Mountain View, CA manufacturer of brain stimulation systems, announced that it closed a \$74 million round of funding led by the KCK Group and OrbiMed Advisors. This funding provides the resources necessary to expand commercialization of the NeuroPace RNS system, a device approved by FDA to treat adults with partial (focal) onset seizures that are not well controlled by medication alone. “With this additional funding, we now have the resources necessary to substantially accelerate adoption of RNS system and improve quality of life for hundreds of thousands of patients in the U.S. alone who live with uncontrolled, disabling seizures,” said Frank Fischer, NeuroPace CEO. The RNS system is the first closed-loop brain-responsive neurostimulation system designed to prevent epileptic seizures at their source. It treats seizures by continuously monitoring brain waves, detecting unusual activity, and automatically responding with imperceptible electrical pulses before seizures occur. Physicians can program the detection and stimulation parameters of the implanted RNS neurostimulator non-invasively to personalize therapy for each individual.

Neural Analytics Receives \$10 Million Contract from DoD for TBI Detector

Neural Analytics, Inc., the Los Angeles, CA manufacturer of brain sensing systems, announced that the Department of Defense has awarded the company a \$10 million contract to develop and supply a portable, point of injury device for assessing combat-related traumatic brain injury. The contract was awarded by the U.S. Army Medical Research and Materiel Command. Neural Analytics will partner with the DoD to develop its Lucid System within the next 18 months to measure and monitor physiological parameters relevant to moderate-severe TBI and to operate in prolonged field care scenarios. Battelle, headquartered in Columbus, OH, will provide technical and advanced engineering expertise enabling ruggedization and miniaturization suitable to meet military requirements. The system is expected to operate as a single, portable unit with minimal required training and maintenance. “We are honored to continue our partnership with the U.S. Army to further advance point of care injury management of brain health,” said Leo Petrossian, co-founder and CEO of Neural Analytics.

Aleva Neurotherapeutics Announces \$13 Million Series D Round

Aleva Neurotherapeutics, the Lausanne, Switzerland manufacturer of DBS systems, announced that it has raised \$13 million in a series D financing round. The round was led by Forrestal Capital, a fund with specific experience in neurological devices. Aleva’s existing investors also participated in the round. The proceeds will be used to complete the acquisition of CE Mark for Aleva’s directSTIM DBS device. The results of Aleva’s directSTN pilot study were published in *Brain* and strongly suggest the potential of directional stimulation in improving surgical outcomes. “We would like to thank both our new and existing investors for this significant support towards the registration of our products, designed to deliver improved therapeutic outcomes for Parkinsons patients,” said André Mercanzini, founder of Aleva.

EnteroMedics Changes its Name to ReShape Lifesciences Inc.

EnteroMedics Inc., the St. Paul, MN manufacturer of obesity neuromodulation devices, announced that the company has formally changed its name to ReShape Lifesciences Inc., with the NASDAQ symbol RSL. The new name reflects the company's expansion and growth into a full-scale provider of medical devices to address the continuum of care for obesity and its associated health conditions. The company's portfolio, designed to help patients lose weight and live a healthier life, includes two FDA-approved devices, the vBloc system and ReShape Integrated Dual Balloon system, as well as the Gastric Vest System, an investigational device. "Our new name, ReShape Lifesciences, conveys our commitment to customers and patients as a long-term partner helping address obesity and its associated comorbidities. The name exemplifies our core mission of enhancing and extending life for patients," said Dan Gladney, president, CEO, and chairman of the board. "With the recent acquisitions of ReShape Medical, Inc. and BarioSurg, Inc., we have transformed from a single-product company to a comprehensive provider of multiple effective, innovative, and minimally-invasive obesity solutions for our patients and physician-customers."

Nexeon Medsystems Receives SBIR Grant to Develop Stimulation for Asthma

Nexeon Medsystems Inc., the Dallas, TX manufacturer of neuromodulation systems, announced that it has received a Phase I Small Business Research Innovation grant from the National Heart, Lung and Blood Institute to develop a neurostimulation therapy for asthma in collaboration with researchers at Oregon Health Sciences University. The funding award was granted due to the merits of the proposed development plan for a novel asthma treatment related to airway constriction. This therapy would be a second-line defense for patients whose current medications do not adequately treat their asthma. Current studies are looking to demonstrate the ability of both VNS and auricular VNS to induce airway response improvements that are predictive of a clinically meaningful effect in humans. Will Rosellini, Nexeon's CEO commented, "We are excited to expand the utilization of either external or implantable neurostimulation solutions for the treatment of various disorders." Nexeon is engaged in multiple clinical trials with its Auricular Vagus Nerve stimulator and is finalizing development of its implantable neuromodulation system. The system is anticipated to receive European commercial approval in 2018 and begin parallel clinical trials in the U.S.

LivaNova Announces FDA Approval of Next-Generation VNS Therapy

LivaNova plc, the London, U.K. manufacturer of neuromodulation systems, announced it received U.S. FDA approvals for its latest VNS system, which consists of the SenTiva implantable generator and the next-generation VNS therapy programming system for the treatment of patients with drug-resistant epilepsy. SenTiva is the smallest and lightest responsive therapy for epilepsy. The new programming system features a wireless wand and new user interface on a small tablet. Together, the components offer patients with drug-resistant epilepsy a physician-directed customizable therapy with smart technology and proven results to reduce the number of seizures, lessen the duration of seizures, and enable a faster recovery. "We created SenTiva and the accompanying VNS therapy programming system based on feedback received from patients and physicians to ensure ease of use, better patient care and cost effectiveness," said Jason Richey, LivaNova's president of North America and general manager of the neuromodulation business franchise. "VNS therapy is the first and only system that is FDA approved for drug-resistant epilepsy in children as young as four years of age." SenTiva is the first epilepsy device of its size to include detect-and-respond mode, designed to prevent seizures before they start and automatically deliver extra therapy to stop them.

Depression Market

from page 1

pany is planning a 150-patient randomized control trial for depression and other psychiatric disorders.

Meanwhile, Neuronetics Inc., the first firm to market a magnetic stimulation system for treatment of depression, recently signed a distribution deal with Japanese pharma company Teijin. Teijin will distribute the product in Japan.

In the implanted device segment, Abbott, which earlier this year acquired St. Jude Medical, released long-term data from the company's BROADEN study of DBS of area Cg25, which failed a futility analysis in 2013. Newly published data in *The Lancet: Psychiatry* reported that DBS may offer some patients an option for managing their chronic, treatment-resistant depression. The authors concluded that after 24 months of stimulation, nearly half of all DBS patients responded to the therapy. Of these patients, 26 percent of patients experienced remission of their depression; a remission rate that steadily grew over time.

While the BROADEN study initially found no statistically significant difference in efficacy between the stimulation group and the control group after six and 12 months, after the initial 12-month study, 77 of 90 participants entered into a four-year follow-up study. Within that follow-up study, the authors found that patients receiving DBS therapy saw response and remission rates of 29 percent and 14 percent at 12 months, 53 percent and 18 percent at 18 months, and 49 percent and 26 percent at 24 months, respectively.

"Innovation within the field of neuroscience takes time and is filled with opportunities to learn, adapt and learn again. This study is a strong example of how our therapies can contribute to the innovation taking place within the broad field of neuroscience," said Allen Burton, medical director within Abbott's neuromodulation division. "We applaud the researchers who led this study and look forward to future advancements to support the care of people suffering from chronic, treatment-resistant depression."

"While I am disappointed by the initial results, I'm encouraged by the long-

term outcomes seen in this trial, which are consistent with previous and ongoing experience with DBS outside of this clinical trial,” said Helen Mayberg, professor of psychiatry, neurology, and radiology at Emory University in Atlanta, GA. “There are refinements to optimize DBS delivery that may prove useful to understand these findings and move the therapy forward. For example, we now know that implantation method and directionality matter for optimal patient outcomes. We look forward to seeing what new innovations, such as use of advanced imaging to guide the implantation and use of directional leads, can do in the future.”

Other DBS manufacturers are looking at the depression indication with interest. At a recent investor’s day presentations, executives at Boston Scientific pointed to OCD, depression, and Alzheimer’s disease as potential new directions for DBS.

Respicardia Announces FDA Approval of Device for Central Sleep Apnea

Respicardia Inc., the Minnetonka, MN manufacturer of neuromodulation systems, announced that it received U.S. FDA approval of its remedē system, a transvenous implantable neurostimulation system that stimulates the phrenic nerve, and engages the diaphragm to restore natural breathing during sleep in patients with central sleep apnea. The regulatory approval was based on findings from the remedē pivotal trial, which demonstrated that transvenous neurostimulation with the remedē system can significantly reduce the severity of CSA, improve sleep, quality of life, and patient satisfaction. The data from the pivotal trial were published in *The Lancet* in September 2016.

The remedē system is indicated for the treatment of moderate to severe CSA in adult patients. “We are thrilled the remedē system received FDA approval and are excited to provide this safe and effective therapy that is proven to improve the quality of life for CSA patients,” said Bonnie Labosky, president and CEO of Respicardia.

UCLA Researchers Demonstrate Stimulation Enhances Memory Recall

Neuroscientists at the David Geffen School of Medicine at UCLA have discovered precisely where and how to electrically stimulate the human brain to enhance people’s recollection of distinct memories. People with epilepsy who received low-current electrical pulses showed a significant improvement in their ability to recognize specific faces and ignore similar ones. Eight of nine patients’ ability to recognize the faces of specific people improved after receiving electrical pulses to the right side of the brain’s entorhinal area, which is critical to learning and memory. However, electrical stimulation delivered to the left side of the region, tested on four other people, resulted in no improvement in the patient’s recall. The study builds on 2012 UCLA research published in the *New England Journal of Medicine* demonstrating that human memory can be strengthened by electrically stimulating the brain’s entorhinal cortex. The researchers followed 13 people with epilepsy who had ultrafine wires implanted in their brains to pinpoint the origin of their seizures. The team monitored the wires to record neuron activity as memories were formed, then sent a specific pattern of quick pulses back into the entorhinal area. Using the ultrafine wires allowed researchers to precisely target the stimulation but use a voltage as low as one-tenth to one-fifth as strong as had been used in previous studies. The study suggests that even low currents of electricity can affect the brain circuits that control memory and human learning. It also illustrates the importance of precisely targeting the stimulation to the right entorhinal region. Other studies that applied stimulation over a wide swath of brain tissue have produced conflicting results. Electrical stimulation could offer promise for treating memory disorders like Alzheimer’s disease. The study was published in the journal *eLife*.

Thync Reports Positive Results from Psoriasis Stimulation Trial

Thync Global Inc., the Los Gatos, CA manufacturer of noninvasive neuromodulation systems, reported positive results from a pilot study evaluating the use of its proprietary neuromodulation technology to treat psoriasis. The study showed that compared to a placebo group, patients using Thync’s neuromodulation technology had a significant reduction in redness, scaling, and itchiness of their plaque psoriasis after four weeks. There were no reported side effects. These results demonstrate the potential of a noninvasive, systemic bioelectronic approach to treating an autoimmune skin disorder. In the single-blind study that enrolled 28 patients, 15 of the 18 subjects in the treatment group (83 percent), reported at least a 50 percent reduction in psoriasis symptoms after four weeks. Six patients out of 18 reported more than a 75 percent reduction of these symptoms. In comparison, after four weeks, only 2 of 10 patients within the active placebo control group reported at least a 50 percent reduction in symptoms. The difference in psoriasis symptom improvement between the treatment and control groups was highly statistically significant. Both groups included patients with mild to severe psoriasis. “This is the first study that demonstrates the effectiveness of a neuromodulation technology in treating a dermatological condition,” said Sumon Pal, chief scientific officer of Thync. “We are excited that we may have a new treatment paradigm for the millions of patients that suffer from this debilitating disease. Our next step is to generate clinical data through collaborations with leading institutions such as the University of California, San Francisco.” In the study, patients used Thync’s neuromodulation system for at least 10 minutes a day for four weeks. The system is worn on the neck and uses proprietary neurostimulation algorithms that painlessly stimulate specific nerves to systemically modulate the autonomic nervous system. The improvement of psoriasis symptoms was reported on a weekly basis. The primary endpoint of the study assessed the percentage of patients using the Thync system who achieved a significant improvement of symptoms compared to an active placebo group at week four.

Neurovalens Pursues Consumer Neurotech Market with Vestibular Nerve Stim

by James Cavuoto, editor

Neurovalens Ltd., a neurotech startup based in Northern Ireland, has developed a noninvasive vestibular nerve stimulation system that the company intends to market to consumers. Although the product is positioned as a general wellness device, which may make for a smoother regulatory pathway, the company is touting the system's ability to help users lose weight.

Neurovalens' Modius device works by activating the vestibular nerve, indicating to the body that it is physically active, helping users achieve their weight management goals. The externally worn device stimulates the vestibular nerve through sticky gel pads attached behind the ear.

The company recommends users wear the Modius device for 45 to 60 minutes per day. Used five days per week, the device produces results within a few weeks, according to the company.

Neurovalens cites a 2002 article in *Proceedings of the National Academy of Sciences* by a research team at Johns Hopkins University that suggested a linkage between the neurovestibular system and homeostatic regulation. In a more recent laboratory trial, 15 human volunteers received vestibular stimulation while various assessments of both its immediate and longer-term impact were carried out. An initial study looking at the effects of repeated stimulation over a period of 16 weeks, in nine of these subjects, observed a significant reduction in body fat as measured by whole body DXA scans.

The average reduction in abdominal fat in the active group was about 8 percent with the range being between 2 and 14 percent. This was statistically different from the control group and none of the volunteers changed their diets or exercise. In the immediate term, providing just one hour of vestibular stimulation was found in six fasted subjects to increase the secretion of the hormones insulin and leptin, while simultaneously decreasing appetite. Interestingly, even though these subjects fasted, this response would typically be observed after eating a meal.

Outside the laboratory setting Modius

has been used by people with varying lifestyles. The most significant result was seen in BODPOD scans at Ulster University, Coleraine. Over the period of one year, regular use of a Modius prototype, with an active and healthy lifestyle, brought about a 44 percent reduction in body fat, with a simultaneous 2-kg increase in lean muscle mass in one participant.

Vestibular stimulation in general, due to its influence on the brain and endocrine system, has been researched as a therapeutic intervention in diabetes, high cholesterol, thyroid dysfunction, and as a means of reducing stress and anxiety. Modius activates the vestibular system using a small electrical pulse. This activation then proceeds through to the brainstem and onwards into the hypothalamus. The hypothalamus is a crucial area in how the brain maintains stable internal physiological processes within the body, part of which includes fat storage and appetite.

The company believes there is a "set-point" in the hypothalamus that acts to regulate body fat. This control system modifies feeding behavior and metabolic rate, in order to maintain body mass composition within set parameters and does so in order to optimize energy utilization. As such, deviations too far in either direction from the set-point are strenuously resisted. Thus, not only is it hard to change body mass composition via diet and exercise but even if you can, maintaining the new leaner composition in the long term is typically doomed to failure, as the brain, in effect, fights against the change.

Several areas within the hypothalamus are implicated in regulating this set-point, but a particularly vital one appears to be the arcuate nucleus with its populations of pro-opiomelanocortin, and agouti-related peptide/neuropeptide Y co-expressing neurons. These neurons are part of the central melanocortin system, which acts by responding to circulating hormones, nutrients, and neuronal inputs. In the case of the POMC neurons, the response is anorexigenic with a decrease in food intake and an increase in

energy expenditure. Conversely, the orexigenic AgRP/NPY neurons act antagonistically to this.

CEO and co-founder Jason McKeown led Neurovalens through the InvestNI "Propel Programme," where they were awarded Company of the Year 2015. Chief scientific officer and co-founder Paul McGeoch is a neurosurgeon and proposed the idea of using vestibular stimulation to modulate body mass composition while doing a post-doctoral fellowship in brain science at the University of California in 2010.

After securing seed funding of £1.1 million from InvestNI, Angel CoFund, Beltrae Partners, and TechStart NI, the company conducted an Indiegogo campaign that raised \$1.6 million. Neurovalens plans to sell the device for less than \$250. "We believe there are tens of millions of people who will find they can become leaner through use of the Modius device," said McKeown. "We also know that neuroscience and technology can be combined to affect all sorts of other health issues which in effect gives our company a very robust product pipeline."

Neurovalens' advisory board includes V.S. Ramachandran, director of the Center for Brain and Cognition and distinguished professor with the psychology department and neurosciences program at the University of California, San Diego. Another advisor is Tom Bilyeu, the co-founder of Inc. 500 company Quest Nutrition—a unicorn startup valued at over \$1 billion—and the co-founder and host of Impact Theory. Tom's mission is the creation of empowering media-based IP and the acceleration of mission-based businesses.

Neurovalens

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Market: Consumer Neurotech
Founded: 2013
Privately held
CEO: Jason McKeown
CSO: Paul McGeoch
CCO: Tony Wilcox

Entrepreneurs and Industry Veterans Take Part in 2017 Neurotech Leaders Forum

Staff report

More than 100 neurotechnology industry professionals attended the 17th annual Neurotech Leaders Forum, held in San Francisco earlier this month. On day one, keynote speaker Tom Insel, former NIMH director and president of startup Mindstrong Health, gave attendees an overview of recent efforts to establish objective measures of mental health.

Insel described some of the problems inherent in current methods of assessing mental health. “When you ask someone with a mental illness ‘How do you feel?’ you’re talking to someone who by definition is not an accurate responder,” he said. Insel described his firm’s smartphone-based “digital phenotyping” that capitalizes on 45 measures of keyboard and scroll patterns to create digital markers of mental health. “These digital features are surrogates of mental health,” he said.

A session on funding tools for neurotech vendors included Stephanie Fertig from the NIH, Renee Ryan from Johnson & Johnson Development Corp., and Faz Bashi, an angel investor. Ryan said that neuromodulation is an important area for J&J since it touches all three of the firm’s business areas. JJDC has invested in CVRx, Inspire Medical, and several other neurotech startups. Bashi warned entrepreneurs to stay away from “science projects masquerading as companies.” He said that since many smaller firms have already been acquired by strategics, much of the available capital is not reaching early-stage companies.

A lively session devoted to neurotech M&A activity featured Jeff Erb from Medtronic, Scott Drees from Nuvectra and attorney Mark Lindon, who has represented the Mann Foundation and some of the Mann spinoffs. Erb explained how Medtronic’s new organizational structure—based on indications and not on technologies—impacted the way acquired firms are assimilated. Drees advised neurotech entrepreneurs looking to be acquired by a larger firm to take a long-term view. “Don’t run a company to sell it—run the company to be successful,” he said. Lindon mentioned that mergers are a lot like dating. Some can be love at first sight

while others involve longer-term casual dating scenarios. Regardless, the devil is in the details, he advised attendees.

NBR senior consulting editor Jeremy Koff moderated a session called “Supplier-Side Economics” devoted to outsourcing. Contract manufacturing is growing at an 11 percent rate, he said. Finding the right fit with a vendor is important. Really knowing what you have and what you need can make the process much easier. Representatives from Cirtec Medical, Velentium, and Regulatory & Clinical Research Institute each described how their firms could offer valuable services to neurotech startups and established firms alike. All warned to look out for scope creep.

In a session on brain stimulation, Doug Weber, formerly with DARPA and now with University of Pittsburgh and Battelle, highlighted previous work from the Battelle team in BCI-FES. But he would like to see it go one step further. “What we need are more practicable solutions.” He would like to optimize recovery through targeted neuroplasticity. Ian Cook from the Semel Institute for Neuroscience at UCLA summarized some of his commercial and research background in novel forms of brain stimulation.

John Parker, CEO of Saluda Medical, was the keynote speaker on the second day of the conference. Neuromodulation is 50 years old, but he believes that technology development will accelerate in the next five years. The increase in battery capacity and the drop in power consumption in implanted devices allow for more complexity, he said. This opens the door for more sophisticated closed loop systems. The elegant feature of the closed loop system is that the sensing electrode recomputes stimulation parameters to keep dosage within the therapeutic window. In the end, this makes it more comfortable for the end user. Saluda recently implanted their 100th patient, a milestone for a new startup company.

A session devoted to direct-to-consumer neurotech featured executives from Fisher Wallace, NeuroMetrix, and Posit Science. FW offers a tACS system which is FDA cleared for depression, anxiety,

and insomnia. Co-founder Kelly Roman believes we are nearing a tipping point in scientific evidence for medical devices. “It all begins and ends with the brain.” FW is launching the Kortex device in November. They raised \$200,000 through a crowdfunding site selling the device as a wellness version intended for stress and sleep.

Shai Gozani talked about his experience marketing the Quell wearable TENS device direct to consumer. NeuroMetrix sells it online, through brick and mortar retailers, and cable channels like QVC and HSN. Gozani said that Best Buy has been the best performing retail outlet but they still cut into your margins. The advantages of direct to consumer are the ability to have a direct conversation with the consumer, avoiding reimbursement issues, and the ability to offer diverse promotions and sell through multiple channels. The distinct disadvantages of direct to consumer is that it is difficult to build awareness, and there’s a high acquisition cost per customer. The margins are low and there is a high cost for returns and negative reviews. Henry Mahncke from Posit said he was satisfied with recent FDA announcements regarding regulation of software as a medical device.

In a session devoted to bioelectronic medicine, Daniel Chew from Galvani Bioelectronics said that neuromodulation offers pharma vendors a neural control method to complement existing methods of signaling control and immune control. Galvani’s ultimate vision is devices that are selective, smart, and small, he said.

Kip Ludwig from Mayo Clinic stressed that human data and human biomarkers are very important, pointing out the anatomical difference between rat and canine vagus nerves.

Entrepreneur presenters included Dan Rizzuto from start-up Nia Therapeutics, which is developing a memory restoration therapy for early-stage Alzheimer’s disease. Nia is developing a fully implantable cranial implant. The timing of stimulation is “critical,” he said. Tina Chang from GiMer Medical described her firm’s batteryless ultrahigh frequency SCS system for pain.

Cleveland FES Center Expands its Focus to Novel Forms of Neuromodulation

by Jennifer French, senior editor

When this publication first profiled the Cleveland FES Center more than 10 years ago, the center was unique for its collaborations and unquestionably a premier research institution in neuroprosthetics. Today, the center still thrives on collaboration but has expanded and diversified its role in the neurotechnology field.

During the recent “State of the FES Center 2017” talk, executive director Robert Kirsch stressed that success is based on enabling trans-disciplinary collaborations. Case Western Reserve University, MetroHealth Medical Center, University Hospitals, Cleveland Clinic, and the Louis Stokes Cleveland VA Medical Center partner to develop the technology that holds the institutions together. Notably, Kirsch highlighted the renewal of five years of funding from the U.S. Department of Veterans Affairs’ Rehabilitation Research and Development Service to support the Center of Excellence.

Total funding for the FES Center jumped to \$23 million in 2016-17, up from \$18 million the prior year. The bulk of that funding is from the NIH, followed by support from the VA and foundations

and industry. Industrial partnerships, overseen by Andrew Cornell, are a significant pathway forward. “The focus of the FES Center has always been to provide function. In order to do so, we need industrial partners,” he said. With vendors such as Cirtec Medical, Synapse Biomedical, Bal Seal, and Ardiem Medical, these relationships are viewed as the way for the center to make “societal impact.” In the spectrum of medical device development, the “sweet spot” for the FES Center is concept to first in human. Later stages of translation to larger clinical trials, standard of care, and clinical practice are transferred to existing companies, start-ups, or the new Institute for Functional Restoration.

The FES Center employs 66 investigators with specific expertise in modeling, technical development, surgical techniques, and regulatory consulting. Research centers around four areas: movement restoration, pain mitigation, brain health, and autonomic systems. Movement restoration has been the mainstay of the center since its inception. New technologies are helping restore meaningful function and integrating with

modern control systems. In 2016, investigators implanted a networked neuroprosthetic system. This fully implanted system enables multiple functions within one system. Earlier this year, the center demonstrated the first system to combine implanted FES-based arm and hand function with an intracortical BCI, allowing a person with severe paralysis to use his hand by thought. An FES-evoked cough system for those with weak pulmonary function can also be integrated with diaphragm pacing, merging both independent breathing and cough in one system.

A recent diversification is the brain health program. The program is focused on the development of novel technologies to tap into brain plasticity. Over the last five years, the center expanded research into autonomic physiology. Modulating the autonomic nervous system has the potential to address hypertension, gastric function, migraine, autonomic dysreflexia, and bowel and bladder disorders. Dennis Bourbeau is leading the effort to develop a noninvasive genital nerve stimulation approach to improve urinary continence and bowel motility.

Calendar

Nov. 11-15	Neuroscience 2017, Washington, D.C. Contact Society for Neuroscience, sfn.org
Dec. 1-5	American Epilepsy Society Annual Meeting, Washington, D.C. Contact aesnet.org
Jan. 11-14	NANS 2018, Las Vegas, NV. Contact neuromodulation.org
Mar. 22	Bioelectronic Medicine Forum, New York, NY. Contact Neurotech Reports, 415 546 1259.
Jun. 25-27	Neural Interfaces Conference, Minneapolis, MN.
Jul. 17-21	EMBC '18, Honolulu, HI. Contact IEEE Engineering in Medicine and Biology Society, embs.org
Aug. 28-31	IFESS 2018. Nottwil, Switzerland. Contact International Functional Electrical Stimulation Society, ifess2018.com

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