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Contacts: Emily Ortman, (202) 962-4090
Anne Nicholas, (202) 962-4060

Envisioning the Future: New Therapies in Development

Animal experiments show path to potential applications for diseases and disorders

CHICAGO — Advances in neuroscience are bringing treatments that once seemed impossible a step closer to reality. Research released today demonstrates the promise of brain-machine interface, deep brain stimulation, and other strategies to improve and even restore nerve function in neurological disorders. The findings were presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Today's new findings show that:

- A newly created non-human primate model of artificial vision could allow for testing of neural prostheses, which may one day may help restore sight to blind people (Nathan Killian, abstract 428.10, see attached summary).
- Deep brain stimulation for Parkinson's and other brain diseases may be optimized with an automated system that measures neurotransmitter levels, according to animal studies (Kendall Lee, abstract DP06.02, see attached summary).
- Chemicals that can confer light sensitivity to specific retinal cells enter the neurons through a membrane pore, with the potential of one day restoring vision after blinding diseases (Richard Kramer, abstract 138.09, see attached summary).

"Blindness, Parkinson's disease, and chronic pain are among the many devastating conditions that arise from defects in the nervous system. The findings presented today bring us closer to new therapies that once seemed unthinkable," said moderator Andrew Schwartz, a professor at the University of Pittsburgh and a pioneer in the field of neural prosthetics. "These experiments in animals are necessary and important steps on the pathway to new human treatments."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find out more about new tools for treating neurological disorders at *BrainFacts.org*.

Related Neuroscience 2015 Presentation:
Symposium: Early Reports from the BRAIN Initiative Frontline: Advancing Technologies to Accelerate Our Understanding of Brain Function
Monday, Oct. 19, 8:30-11 a.m., S100A

Abstract 428.10 Summary

Lead Author: Nathan Killian, PhD (573) 864-3564
Massachusetts General Hospital nkillian@mgh.harvard.edu
Boston

A Next Step Toward Visual Prosthetic Device

Animal model of artificial vision may help with creation of better visual prostheses

The dream of restored vision for blind people using neural prostheses is moving forward, but progress is slow because not all necessary experiments can be performed in humans. Now scientists have created a non-human primate model of artificial vision that may help speed development of this therapy, according to research released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Nearly 40 million people worldwide are blind. Researchers have been working for years to develop visual prostheses that will allow blind people to see by stimulating brain structures such as the retina, thalamus, and visual cortex. The prosthetic devices stimulate multiple points in the brain, with the stimulation of each point producing a "pixel" to create a bigger image. However, scientists must test implanted brain-stimulating devices and cannot do so on humans. In an effort to create an appropriate animal model for the testing of such devices, researchers in Boston trained macaque monkeys to use a simulation of artificial vision to recognize the letters of the Roman alphabet.

The researchers simulated artificial vision by projecting points of light on a screen to create letters. This approximates what would be "seen" when using prosthetic brain stimulation. The monkeys were trained to recognize letters from these images. As the monkeys examined the images, they actually controlled the points of light with their eye movements, allowing them to explore different parts of the letters in fine detail. The researchers tracked the monkeys' eye movements with an infrared camera. Then the primates were presented with a pair of letters — one matching the test letter and one other letter — and they had to learn to hold their gaze on the matching letter in order to earn a reward. The animals learned faster when the points of light were more densely packed and when they made more rapid eye movements, perhaps providing them with more information. These insights will help guide the design of human visual prosthetics. The next step will be to test implanted devices that directly stimulate the brain to simulate vision.

"We believe that this animal model will serve to accelerate device development, thereby helping to bring better visual prostheses to blind patients sooner," said lead author Nathan Killian, PhD, of Massachusetts General Hospital.

Research was supported with funds from the National Eye Institute, the Phyllis and Jerome Lyle Rappaport Foundation, the NIMA Foundation, Peter D. Pezaris, and William and Lori Goldenthal.

Scientific Presentation: Monday, Oct. 19, 2-3 p.m., Hall A

428.10, A non-human primate model of artificial vision
***N. J. KILLIAN**[1,2], M. VURRO[1,2], S. B. KEITH[1,3], M. J. KYADA[1,3], J. S. PEZARIS[1,2];
[1]Neurosurg., Massachusetts Gen. Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Northeastern Univ., Boston, MA

TECHNICAL ABSTRACT: Simulations of artificial vision have been used in human subjects to guide the design of visual prostheses. However, there is presently no animal model of artificial vision that permits both implant experimentation and studying the viewing conditions experienced by human visual prosthesis implant recipients. To this end, we created a non-human primate (Macaca mulatta) model of simulated artificial vision. The animals (N = 3) controlled a simulation of artificial vision based on a retinotopic array of phosphenes (artificial points of light, each phosphene being a proxy for an implanted electrode). The model paradigm used a two-alternative forced-choice task to describe artificial vision performance. The stimuli to be recognized were the 26 letters of the Roman alphabet (Stelio typeface) presented on a computer screen at one of five letter size and decomposed by one of six simulated gaze-contingent phosphene patterns. The simulated phosphene patterns had from 29 to 890 phosphenes in the central 10 degrees of visual angle. The animals first visually explored a letter using changes in gaze location to shift the phosphene pattern (cue phase). They then chose by gaze fixation (choice phase) between the same letter (correct choice) and a non-matching distractor (incorrect), both presented in the clear. We previously found that normal humans required no training to perform this task (Bourkiza et al., 2013). However, the animals required extensive training to learn to use phosphene vision for letter recognition; over 100 days of training were required for each animal to reach their peak performance levels. Humans and animals performed similarly on some conditions, e.g. humans and 2 of the 3 animals achieved approximately 75% correct for letters at a visual acuity level of logMAR 1.0 (20/200 Snellen acuity) using patterns with about 400 phosphenes in the central 10 degrees (the third animal reached this level at about logMAR 1.3). As the phosphene count decreased, the task became inherently more difficult and corresponding decrements in performance were seen. All three animals performed significantly better than chance ($p < 0.05$, binomial test) with 54 central phosphenes at the lowest visual acuity level tested (logMAR 1.9). Useful discriminability disappeared with the next most difficult pattern tested (29 central phosphenes). Performance levels on these highlighted conditions are part of the complete performance surface that describes the optotype sizes and phosphene counts required to obtain useful visual acuity in this model paradigm. These parameterizations will help guide the design of visual prostheses utilizing retinotopic phosphene patterns.

Abstract DP06.02 Summary

Lead Author: Kendall Lee, MD, PhD
Mayo Clinic (507) 284-2816
Rochester, Minn. lee.kendall@mayo.edu

Optimizing Deep Brain Stimulation

Wireless automated system measures neurotransmitters, adjusts stimulation

Getting the best results from deep brain stimulation (DBS) usually requires frequent adjustment of the stimulation pattern based on a patient's response to treatment and a bit of guesswork. But now researchers have designed a way to optimize the treatment. They designed and tested in animals a system that measures fluctuations in the brain's production of neurotransmitters and automatically adjusts the stimulation pattern accordingly — potentially making DBS more effective and more efficient. The research was released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Deep brain stimulation involves electrical stimulation through an electrode implanted deep within the brain and is an effective treatment for certain types of neurologic disorders such as Parkinson's disease. However, clinical success depends on the careful selection of the stimulation parameters, such as amplitude, frequency, and duration of the electrical impulses delivered through DBS. Too much or too little electrical stimulation can have a major impact on brain chemistry and thus on patient response to DBS therapy. Currently, health care professionals must make adjustments to the stimulation programming, which is costly, time consuming, and based on subjective feedback and observations of symptom relief, rather than on objective markers. But the newly designed system would eliminate that need, potentially improving the effectiveness of DBS and lowering costs.

DBS changes the brain's levels of neurotransmitters, the neurochemical signals neurons use to communicate. For patients with Parkinson's disease, an electrode is implanted into a brain region called the striatum, where stimulation is thought to improve symptoms by regulating levels of the neurotransmitter dopamine. The researchers built a system that continuously measures levels of dopamine in the brain and automatically makes adjustments to the stimulation pattern to evoke specific neurochemical responses associated with therapeutic outcomes. They tested their newly built wireless system, called WINCS Harmoni, in rodents, swine, and non-human primates.

"Our preliminary results in animals show that by monitoring real-time changes in brain chemistry we can automate and optimize the parameters of stimulation," said Kendall Lee, MD, PhD, lead author of the study. The system has the potential to reduce over- or under-stimulation and thus to improve the therapeutic outcomes of DBS.

Research was supported with funds from the National Institute of Neurological Disorders and Stroke and the Grainger Foundation.

Scientific Presentation: Tuesday, Oct. 20, 8 a.m.-noon, Hall A

DP06.02, Closed-loop control of dopamine release evoked by deep brain stimulation
K. H. LEE[1], *J. LUJAN[1], J. K. TREVATHAN[2], K. E. BENNET[1];
[1]Neurologic Surgery, Mayo Clin., Rochester, MN; [2]Mayo Grad. Sch., Rochester, MN

TECHNICAL ABSTRACT: Background: Deep brain stimulation (DBS) is an effective neuromodulation technique for treatment of neurologic and psychiatric disorders. Clinical DBS outcomes depend on empiric clinical programming to identify optimal stimulation parameters. As a result, DBS devices are often programmed with suboptimal settings that can result in limited benefits, early battery depletion, or side effects. Recent studies suggest that changes in endogenous neurotransmitter concentration are associated with therapeutic DBS, and could therefore serve as biomarkers of stimulation efficacy. Thus, developing a control system that exploits the dynamic nature of the brain to modulate stimulation is paramount to improving the efficacy of DBS therapy. Here, we present a control algorithm that relies on neurochemical feedback to fine-tune DBS, thereby improving the selection of stimulation parameters, which when combined with characterization of neurochemical baseline levels, will improve therapeutic outcomes of DBS. Methods: We developed a closed-loop algorithm that utilizes fast scan cyclic voltammetry (FSCV) to continuously monitor striatal dopamine dynamics and automatically adjust stimulation parameters in anesthetized rodent, swine, and non-human primate models of DBS. To achieve this, we characterized the kinetics of stimulation-evoked striatal dopamine responses using mathematical models of release, reuptake, diffusion, and adsorption. We used features extracted from these models to train a multi-layer artificial neural network (ANN) on the inverse relationship between stimulation parameters and evoked dopamine responses. The trained ANNs relied on existing dopamine levels and prior stimulation-evoked responses to predict stimulation parameters required to achieve target dopamine levels. We compared target dopamine responses and stimulation-evoked responses using regression analysis. Results: The trained ANNs learned the non-linear relationship between neurochemical responses and the stimulation parameters needed to achieve them. The ANNs trained on model features were able to predict stimulation parameters required to achieve target dopamine levels. Conclusions: Our results demonstrate that ANNs can characterize stimulation evoked neurochemical dynamics. Additionally, our results show ANNs can be used to dynamically predict neuromodulation parameters as a function of target and existing dopamine levels, demonstrating the feasibility of neurochemical feedback for closed-loop DBS. Ultimately, this work will bring forth new therapeutic strategies for sustaining optimal patient specific neurochemical levels in disease states.

Abstract 138.09 Summary

Lead author: Richard Kramer, PhD
University of California, Berkeley (510) 407-7424
Berkeley, Calif. rhkramer@berkeley.edu

Chemical Compounds Have Potential to Safely Restore Sight After Blinding Diseases

Using mice, researchers discover how chemicals enter specific neurons to confer light sensitivity

Some degenerative blinding diseases rob people of their sight by attacking the retina's light-sensing cells, called rods and cones. But what if light sensitivity — and sight — could be restored? A class of chemicals called azobenzene photoswitches might hold that promise, and scientists have now discovered how these chemicals enter specific neurons in the retina to confer light sensitivity, according to findings in mice presented today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Age-related macular degeneration and retinitis pigmentosa are among degenerative diseases that kill rods and cones, leaving other non-light-sensing retinal cells intact. Previous work from researchers at University of California, Berkeley, showed that azobenzene photoswitches can bestow light sensitivity on retinal ganglion cells (RGCs), which normally cannot sense light. Azobenzenes interact with ion channels, proteins that regulate the flow of charged particles in and out of cells, thereby regulating neurons' excitability. When the chemicals accumulate in neurons, the ion channels become highly light-sensitive, so that light causes neurons to fire excitatory signals.

Typically, RGCs send signals from the rods and cones to the brain's vision centers via the optic nerve. But when the chemicals accumulate in RGCs, the newly light-sensitive cells then evoke sight without the need for rods and cones by signaling directly to the brain.

Now the researchers have shown in mice that the chemicals enter neurons through a protein pore called P2X. When the team blocked the P2X channels, the retinal ganglion cells didn't become light sensitive after applying the photoswitch chemicals. The researchers also determined that, after the death of rods and cones, retinal ganglion cells increase the number of P2X pores they make, for reasons unknown. The increase in pores allows more photoswitch chemicals to enter these cells. "Remarkably, the pore is abundant in retinas in which rods and cones have died, but sparse in retinas with healthy rods and cones," said lead author Richard Kramer, PhD. "This implies that photoswitch compounds will work in diseased tissue but have few side-effects in healthy tissue."

"These findings make photoswitch compounds promising candidates as vision-restoring drugs in humans with degenerative blinding diseases," Kramer added.

Research was supported with funds from the National Eye Institute, the Foundation Fighting Blindness, and the Thome Foundation for Macular Degeneration Research.

Scientific Presentation: Monday, Oct. 18, 8-9 a.m., Hall A

138.09, Cell-type-specific mechanism employed by photoswitch compounds to re-animate the blind retina
***R. H. KRAMER**, I. TOCHITSKY, V. MESEGUER, Z. HELFT, N. GALLERANI;
Univ. California Berkeley, Berkeley, CA

TECHNICAL ABSTRACT: Azobenzene photoswitches, such as AAQ, DENAQ, BENAQ, and QAQ, can confer light sensitivity onto retinal ganglion cells (RGCs) in blind mice. The high-sensitivity, fast kinetics, and low toxicity of these compounds make them interesting candidates as vision-restoring drugs in humans with degenerative blinding diseases, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). Remarkably, photosensitization is manifest only in photoreceptor-degenerated strains of mice, but absent from wild-type mice with intact rods and cones. Here we show that P2X receptors (ionotopic receptors for ATP) mediate the entry of photoswitches into RGCs where they associate with voltage-gated ion channels, enabling light to control action potential firing. While photoswitch compounds differ in which ion channels they affect, all of the compounds require membrane permeation through P2X receptors, whose gene expression is up-regulated in degenerated retina. Ordinarily membrane-impermeant fluorescent dyes also penetrate through P2X receptors to label a subset of RGCs in degenerated retina. Dendritic mapping and patch-clamp recording of dye-filled cells suggests that only the OFF-RGCs are labeled and re-animated; On-RGCs are unaffected. Hence P2X receptors are a natural conduit for cell-type specific delivery of photoswitches to restore visual function in degenerative blinding disease, reinforcing their potential as drugs for treating advanced stages of RP and AMD.