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Technological Advances in Brain Stimulation Expand Uses for Research and Treatment

Noninvasive and dynamic approaches may allow more precise control of brain activity

WASHINGTON, DC — Advances in brain stimulation are transforming how neuroscientists study the brain and guiding novel approaches to the treatment of disease. New strategies revealed today offer safer, targeted means by which to study brain function, improve memory, and treat neurological and psychiatric disorders. The findings were presented at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The ability to affect brain activity helps scientists probe the function of the brain and treat dysregulation that underlies neuropsychiatric disorders such as Parkinson's disease. Deep brain stimulation uses an electrode implanted in the brain to activate specific regions, while other techniques such as transcranial magnetic stimulation and transcranial focused ultrasound deliver signals from outside the head to stimulate the brain without requiring surgery. As the technical capabilities of these approaches improve, scientists are exploring their potential to reach areas deeper in the brain, deliver customized stimulation, and study and treat diseases in new ways.

Today's new findings show that:

- Transcranial magnetic stimulation improves how well older adults recall object locations, providing a possible path for limiting age-related memory loss (John A. Walker, abstract 168.05, see attached summary).
- Transcranial focused ultrasound affects deep brain regions and influences primate behavior, suggesting its potential use in treating neurological disorders (Jan Kubanek, abstract 647.04, see attached summary).
- A portable headset can target transcranial focused ultrasound to excite deep brain regions in sheep, a first step toward stimulating specific brain regions in awake, moving animals (Seung-Schik Yoo, abstract 647.06, see attached summary).
- A brain stimulation system that simultaneously monitors and activates neurons in mice allows more targeted control of brain activity based on real-time neural changes (Noah Young, abstract 437.08, see attached summary).
- An adaptable deep brain stimulation device can auto-adjust its level of stimulation based on the severity of involuntary movement in Parkinson's disease, allowing for better management of symptoms and side effects (Nicole C. Swann, abstract 211.21, see attached summary).

"The advances presented today help expand what's possible with brain stimulation," said press conference moderator Helen Mayberg, MD, of Emory University School of Medicine, who pioneered the use of deep brain stimulation for treatment-resistant depression. "The range of techniques and the neuroscience advances presented not only provide potential new treatment strategies for our most severe neurological and psychiatric disorders, they also open the door to new ways of viewing and probing the brain to improve our understanding of feelings, thoughts and actions."

This research was supported by national funding agencies including the National Institutes of Health, as well as other public, private, and philanthropic organizations worldwide. Find out more about brain stimulation on *BrainFacts.org*.

Related Neuroscience 2017 Presentation

Clinical Roundtable: Advances and Challengers in Deep Brain Stimulation
Tuesday, Nov. 14, 8:30–11 a.m., WCC 206

Abstract 168.05 Summary

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Transcranial Magnetic Stimulation Improves Memory in Older Adults

Treatment increased ability to remember locations of objects

A painless and noninvasive brain stimulation technique may help improve some types of memory in older adults, according to new research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

One possible explanation for age-related memory loss is degradation of the neural connections between the hippocampus — a brain region involved in creating and storing memories — and the cortex. Weakening of these connections may lead to difficulties in creating new memories of specific events and the locations of objects, such as car keys. Scientists hypothesized that strengthening the connections between the hippocampus and cortex through a technique called repetitive transcranial magnetic stimulation (TMS) may help the storage of new memories. TMS delivers painless magnetic pulses to a particular region of the brain, changing the activity of the neurons within the targeted area.

To determine whether TMS could improve memory, 15 healthy adults over the age of 64 received TMS to a part of the cortex that communicates with the hippocampus for five days in a row. During a separate week, each participant received five days of sham treatment, in which the setup was the same but the stimulation was too low to influence the neural connections. Before and after each five-day session, participants were asked to remember pictures of everyday objects and pictures of outdoor scenes associated with each one. The adults' ability to recall the scenes associated with the objects improved after receiving TMS but not after the sham treatment.

"Our study demonstrates that TMS could potentially be used as a way to improve memory for older adults experiencing age-related memory impairments," said lead author John A. Walker, PhD, of Northwestern University. He added, "TMS can be used to probe the relationship between brain networks and memory experimentally, opening new doors to understanding the network-basis of cognitive decline in aging."

Research was supported with funds from the National Institute on Aging.

Scientific Presentation: Sunday, Nov. 12, 8–9 a.m., WCC Halls A–C

Abstract 12431. Targeting hippocampal-cortical memory networks in elderly adults using noninvasive brain stimulation
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[2]Med. Social Sciences, Neurology, and Psychiatry, [3]Neurol., [4]Med. Social Sci., [1]Northwestern Univ., Chicago, IL; [5]Med. Social Sci., Northwestern Univ. - Chicago, Chicago, IL; [6]Norrthwestern Univ., Cognitive Neurol. and Alzheimer's Dis. Ctr., Chicago, IL; [7]Cognitive Neurol. and Alzheimer's Dis. Ctr., Northwestern University, Feinberg Sch. of Medici, Chicago, IL

TECHNICAL ABSTRACT: As one ages, memory declines across multiple domains, including associative memory. There are corresponding declines in functional and structural connectivity between the cortex and the hippocampus, the structure responsible for creating and utilizing associations in episodic memory. Here we examined whether stimulation of a parietal cortex location that is part of the hippocampal network would influence the function of this network in older adults. Elderly adults (N=15; ages 64-81 years) received 20Hz repetitive transcranial magnetic stimulation (rTMS) targeting the hippocampal-cortical network for five consecutive days. They were tested before and one day after stimulation using a memory task that measured object recognition and object-scene associative recollection. Participants learned pairings of objects and scenes during fMRI scanning. Old/new item recognition memory was tested for the objects followed an associative recollection test for the associated scenes. A wealth of previous findings indicates that memory for object-scene locations should be dependent on the hippocampal network to a larger degree than memory for the individual objects, and likewise memory impairments of aging are relatively specific for such associative information. We found that stimulation selectively improved object-scene associative recollection (p=.03), but not object recognition memory. These findings suggest that network-targeted noninvasive stimulation can selectively influence the function of hippocampal memory networks in elderly adults. As this network is disrupted in healthy aging as well as a host of other neurodegenerative disorders such as Alzheimer's Disease, these findings are therefore relevant to the development of non-invasive stimulation interventions for individuals with both healthy age-related and clinical memory impairments.

Abstract 647.04 Summary

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Transcranial Ultrasound Affects Monkey's Brain Activity, Influences Behavior

Finding paves way toward noninvasive treatment of movement disorders, chronic pain, depression

Ultrasound applied outside of the head can influence neurons in the primate brain, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. This noninvasive technique could be developed into a surgery-free way to target activity of brain areas affected by various neurodegenerative and psychiatric disorders.

Although ultrasound is well known as an imaging technique, it can also affect the activity of the cells at which it is directed. Recent experiments in anesthetized rodents revealed that transcranial ultrasound — pressure waves of high, inaudible frequency that penetrate the skull from outside the head — can change the activity of neurons even deep within the brain. New research assessed the approach in a nonhuman primate.

Researchers analyzed a macaque monkey's eye movements in response to a visual stimulus. The monkey was trained to look at either a right or left target, whichever appeared first. When ultrasound was focused on a visual area on the left side of the brain, the animal looked toward the right target more often; when the stimulus was focused on the right side, the animal looked toward the left target more often. The results indicate that transcranial ultrasound can stimulate deep neurons to affect perception and behavior.

"The finding that transcranial ultrasound can excite neurons to the extent that the effect is observed in a monkey's behavior paves the way to noninvasive stimulation of specific brain regions in humans," said lead author Jan Kubanek, PhD, of Stanford University School of Medicine. "This can facilitate the study of basic brain function and may further lead to convenient novel treatments of movement disorders, chronic pain, and depression."

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

Scientific Presentation: Wednesday, Nov. 15, 8:45–9 a.m., WCC 152B

Abstract 16443, Transcranial ultrasound impacts monkey choice behavior
J. KUBANEK[1], J. BROWN[2], P. P. YE[3], K. BUTTS PAULY[2], W. T. NEWSOME III[4];
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TECHNICAL ABSTRACT: Transcranial focused ultrasound (US) has the potential to non-invasively modulate neural activity in specific regions deep in the brain. Successful US neuromodulation has been reported by multiple groups using anesthetized rodents. This body of work opens the possibility that this method could be applied in awake behaving primates including humans. We used the macaque model to test whether 1) we can detect effects of US on behavior 2) long-term stimulation is safe 3) the neuromodulatory effects are excitatory, inhibitory, or a combination thereof. To do so, we engaged a macaque monkey in a stimulus onset asynchrony task in which the animal looked at either a rightward or a leftward target, whichever appeared earlier. US (270 kHz, 0.6 MPa, 300 ms) focused into either left or right frontal eye field (FEF) was applied through the intact skull and skin, 100 ms before the onset of the first target. We interleaved short blocks of trials in which US was applied and in which it was not. We found that US stimulation of left (right) FEF significantly shifted the animal's choices to the rightward (leftward) target. The contralateral nature of the effects suggests neuronal excitation within FEF. The effect was observed specifically when stimulating FEF and not when stimulating motor cortex. The effect was immediate and showed minimal hysteresis. There was no long-term bias in the animals' choices even after 8 days of stimulation of each region, which suggests that the stimulation was safe. The finding that transcranial US can excite neurons to the extent that the effect is observed in monkey's behavior paves the way to noninvasive stimulation of specific brain regions in humans.

Abstract 647.06 Summary

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Headset Delivers Transcranial Focused Ultrasound to Regulate Movement in Sheep

System demonstrates ability to stimulate specific brain areas with precision

A new headset can deliver transcranial focused ultrasound to activate or inhibit activity in targeted brain regions, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Transcranial focused ultrasound applies ultrasound waves to the outside of the head to target specific areas — as small as a grain of rice — deep within the brain. The ability to affect brain activity with such precision could enable treatment of various brain diseases, especially if such a technique could be used in awake, moving subjects.

To test the capacity of the technique in large animals, researchers created a lightweight ultrasound headset for sheep, which have skulls similar to humans' in shape and thickness. The system accurately predicted where the ultrasound waves would focus inside the brain, taking into account the curvature of the skull. It was also compatible with MRI, allowing the researchers to analyze functional effects of the ultrasound in the brain. Researchers tested the device on four anesthetized sheep and demonstrated that focusing ultrasound waves on the motor cortex activated the leg muscle while suppressing activity in the sensory area.

"The ability to stimulate a specific brain location with great precision, all without any surgery or medication, is expected to empower us to develop various new strategies to remedy diseases and conditions that are associated with neural systems," said lead author Seung-Schik Yoo, PhD, of Harvard Medical School. The team hopes to next test the headset in awake, moving sheep.

Research was supported with funds from the National Institute of Mental Health**.**

Scientific Presentation: Wednesday, Nov. 15, 9:15–9:30 a.m., WCC 152B

Abstract 2679. Wearable transcranial focused ultrasound system for region-specific functional neuromodulation (BRAIN INITIATIVE)
S.-S. YOO, W. LEE, P. CROCE, K. YOON, R. W. MARGOLIN;
Radiol, Brigham & Women's Hosp, Harvard Med. Sch., Boston, MA

TECHNICAL ABSTRACT: Advancements in focused ultrasound (FUS) techniques, with image-guidance for targeting the sonication focus to a specific region-of-interest, have allowed for the non-invasive transcranial delivery of acoustic energy to cortical as well as deep brain structures with an excellent spatial selectively of only a few millimeters in size (roughly the size of a rice grain). The main objective of our research is to develop a wearable transcranial focused ultrasound (tFUS) environment that reversibly modulates (either elicits or suppresses) region-specific neural activities of the brain using a large animal model (sheep).
We developed light-weight, MRI-compatible, single-element FUS transducers (one made with air-backed, lead zirconate titanate ceramics- 80 gram and the other made with Gas Matrix Piezoelectric, or GMP, material- 95 gram) both operating at 250 kHz. The transducers' housing diameter ranged 4-5 cm, and had focal lengths of 2-3 cm (from the exit plane of the transducer), allowing 'f-number' ≤1 for the formation of a sharp focus. The spatial dimension and their major operational characteristics (*i.e.,* acoustic output > 20 W/cm^2) satisfied the intended study requirement. Since the propagation of ultrasound waves is heavily affected by the geometrical shape of a skull, predictive computational tools are of great use for finding a precise localization of the focus. We also developed a computer-based numerical simulation that predicts the location of the acoustic focus as well as the degree of attenuation, and examined the feasibility of deploying multi-resolution approaches for simulating the acoustic propagation through the skull *via* finite difference time domain (FDTD) formulation. The translation of the implemented method to C-family programming language, augmented by utilization of the GPU (Graphic Processing Units), is currently underway to improve the computation speed compatible with real-time simulation (under 10 sec). We integrated the above FUS device with biological signal acquisition/stimulator system that acquire various electrophysiological responses, and assessed the performances of the resulting system among a few anesthetized sheep. As guided by the functional MRI information, sonication given to the M1 area created an EMG response from the hind leg muscle that is contralateral to the sonication. Non-invasive and controllable manipulation of region-specific cortical/subcortical activity in the brain will open new avenues not only for neuroscientific research, but also for clinical applications ranging from functional brain mapping to treatment of numerous neurological and psychiatric disorders.

Abstract 437.08 Summary

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Real-Time Monitoring Allows More Targeted Control of Brain Activity in Mice

Stimulus intensity increases or decreases according to brain state

Neuroscientists have developed a way to regulate brain activity levels based on real-time fluctuations in neural activity, according to new animal research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The technique, which simultaneously monitors and activates neurons, may help scientists study brain networks and how they are disrupted in different disorders.

Although activity in the brain is constantly changing, many brain stimulation techniques deliver a single, pre-determined level of stimulus intensity. Without accounting for the dynamic nature of the brain, experiments using brain stimulation may be unreliable and stimulation-based treatments ineffective. A better approach would determine the needed stimulus intensity based on moment-by-moment measurements of activity in the brain area of interest.

To generate an adaptive stimulation control system, researchers used genetically altered mice that possessed one gene that caused neurons to fluoresce when they were active and another gene that allowed the same cells to be controlled by light. By monitoring fluorescence, the system determined the appropriate amount of light needed in any given moment to attain the desired level of activity.

"If brain activity in a particular region decreases, our system steps on the gas and provides more stimulation; if activity increases, the control system eases off the pedal and lets activity levels calm down," said lead author Noah Young of Stanford University. "We anticipate this kind of artificial regulation of brain activity to be a key tool in studying dysregulation disorders of brain activity in future studies."

Research was supported with funds from the National Science Foundation and Howard Hughes Medical Institute.

Scientific Presentation: Monday, Nov. 13, 4–5 p.m., WCC Halls A–C

Abstract 16470. All-optical closed-loop feedback control of targeted neuronal populations in awake animals
N. YOUNG, C. K. KIM, M. INOUE, Y. S. KIM, K. DEISSEROTH;
Stanford Univ., Stanford, CA

TECHNICAL ABSTRACT: Stimulation of targeted neural cells and tissues can be achieved with varying degrees of temporal precision and cell type specificity. Most stimulus strategies used today are "open-loop" in that they ignore ongoing activity and other features of the momentary brain state. For many applications, however, it is desirable to make real-time adjustments to stimulus intensity and waveform based on ongoing activity in the same or other brain areas[1], though this has proven difficult to achieve with electrical methods due to large stimulation artifacts and a lack of cellular specificity. Here we present an all-optical setup for applying stimulation to defined subsets of neurons in closed-loop, leveraging the advantages of genetically-targeted population recording/control. We co-expressed spectrally-separated opsin and fluorescent Ca^{2+} indicator in genetically-defined subpopulations of neurons in behaving mice. Ca^{2+} responses (serving as a proxy for cellular activity) were recorded using the Frame-Projected Independent-Fiber Photometry (FIP) method described previously[2]. Opsin excitation was achieved by laser through the same optics used for activity recording. This system exhibited a stimulation artifact below 3% of total signal. Surprisingly, we found that simple PID control was sufficient to bring activity within 20% dF/F of a predetermined setpoint. These results demonstrate the utility of approximating population neural activity (as a single time-varying scalar) in behaving animals with a linear plant model.

Abstract 211.21 Summary

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New Adaptive Deep Brain Stimulation Technique Offers Individualized Treatment for Parkinson's

Implantable device tailors stimulation to accommodate changing symptoms

A new approach to deep brain stimulation self-adjusts to deliver the ideal amount of stimulation in patients with Parkinson's disease, according to new research released today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The approach could lead to better management of symptoms with fewer side effects.

Deep brain stimulation (DBS) has been a valuable treatment for Parkinson's by helping to quell the abnormal movements that are characteristic of the disease. However, traditional DBS delivers a constant level of stimulation and is not able to adapt to how a patient's symptoms may vary over the course of a day. As a result, a patient may sometimes receive too little stimulation, failing to control symptoms, or too much, causing side effects such as worsening of involuntary and uncontrolled movements, known as dyskinesia.

In order to match stimulation to variations in patient symptoms throughout the day, researchers and engineers developed a novel implantable device that can both provide DBS and record activity from the surface of the brain. Similar to a cardiac pacemaker, this adaptive device can auto-adjust its level of stimulation based on a physiological signal — in this case, brain activity related to dyskinesia. A high dyskinesia signal indicated greater likelihood of unwanted side effects and caused the device to reduce the stimulation level; a low signal indicated a higher chance of symptoms returning and triggered an increase in stimulation. The device was tested in two patients, both inside and outside of the lab. Neither reported any discomfort, adverse events, or worsening symptoms. Additionally, the battery used up to 45 percent less energy than traditional DBS, an important advantage since battery replacement requires surgery.

"Our study showed that totally implanted, adaptive deep brain stimulation is feasible and can be used at home in patients," said lead author Nicole C. Swann, PhD, of the University of Oregon. "Adaptive stimulation represents one of the first major advances in DBS technology since this technique was first introduced for the treatment of Parkinson's disease 25 years ago."

Research was supported with funds from the National Institute of Neurological Disorders and Stroke and the University of California President's Postdoctoral Fellowship Program.

Scientific Presentation: Sunday, Nov. 12, 1–2 p.m., WCC Halls A–C

Abstract 8933. Closed loop deep brain stimulation for dyskinesia control in Parkinson's disease
N. C. SWANN[1], C. DE HEMPTINNE[1], M. C. THOMPSON[3], S. MIOCINOVIC[4], A. MILLER[1], R. GILRON[1], J. OSTREM[2], H. J. CHIZECK[3], P. A. STARR[1];
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TECHNICAL ABSTRACT: Introduction – Deep brain stimulation (DBS) is an effective treatment for Parkinson's disease (PD), but has limitations. One shortcoming is that though PD is a dynamic disorder with symptoms that wax and wane, DBS therapy is continuous and constant. This can result in sub-optimal symptom control or stimulation-induced adverse effects. One way to mitigate this limitation is to adjust stimulation based on changing symptoms – creating "closed loop DBS". Here we used a totally implantable device capable of long-term recording and stimulation (Activa PC+S). We used signals from motor cortex electrocorticography (ECoG) to update DBS stimulation. Specifically, we adjusted stimulation based on a previously identified narrowband gamma oscillation (~80 Hz) associated with involuntary hyperkinetic movements (dyskinesia). Dyskinesia can occur as a result of stimulation or medication. Methods – We tested closed loop DBS in 2 PD patients who experience dyskinesia and are implanted with Activa PC+S. Stimulation changes were triggered either via an internal algorithm (both patients) or via streaming to an external computer (in 1 patient). For both patients we adjusted stimulation within a safe voltage range specified by the patient's neurologist. For each patient a threshold for gamma power was set. When gamma power exceeded this value, DBS voltage was reduced. When gamma power dropped below the threshold, voltage was increased. For 1 patient, clinical rating scales were obtained before the closed loop session started and every 20 minutes during the session. Patient symptoms were monitored with video recordings, accelerometry, electromyography, and commercially available wearable sensors. Results – We implemented closed loop DBS in 2 patients experiencing dyskinesia during short runs of 10 minutes to 1 hour. For both patients we observed multiple instances where the algorithm appropriately adjusted the voltage in response to gamma power. For the longest run which occurred during dyskinesia there was an approximately 39% and 26% reduction in power usage for each patient respectively. For all sessions, there were no adverse effects. Discussion – We have demonstrated the feasibility of implementing closed loop DBS in PD patients using an ECoG signal related to dyskinesia. In all our patients we had no adverse events and patients did not report any discomfort. We demonstrated a battery use reduction in our short sessions. We are currently testing clinical efficacy based on blinded clinical ratings. Future directions will test closed loop DBS in longer sessions (up to 1 week).