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Engineering Tomorrow's Responsive, Adaptable Neuroprosthetics and Robots

Findings illustrate rapid progress in prosthetic limbs and eyes as well as brain-machine interfaces

WASHINGTON, DC — Advanced prosthetic limbs and eyes as well as brain-machine interfaces are harnessing existing neural circuitry to improve the quality of life for people with sensory impairment, according to studies presented 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.

Millions of people around the world are unable to fully use their bodies or senses due to disease, injury, or amputation. At best, modern therapies and prostheses only partially restore function. Over the past 20 years, advances in biomedical engineering have led to the development of interfaces between prosthetic devices, the nervous system, and human tissue that are enhancing the effectiveness of biomedical devices.

Today's new findings show that:

- Neural signals from an extracted rodent spinal cord can control cultured muscle fibers in a petri dish, providing a new technique for studying how the nervous system directs movement (Collin Kaufman, abstract 781.11, see attached summary).
- A tetraplegic patient can learn to adapt neural activity to maintain control of a brain-machine interface in the face of technical challenges (Sofia Sakellaridi, abstract 777.06, see attached summary).
- Restoring sense of touch through an amputee's prosthetic hand improves motor skills, reduces phantom pain, and provides a sense of hand ownership (Jacob Anthony George, abstract 642.04, see attached summary).

Other recent findings discussed show that:

- A fully organic retinal prosthesis, made of layers of photosensitive polymers and silk, led to vision-related brain activity and behavior in blind rats (Jose Fernando Maya-Vetencourt, abstract 683.02, see attached summary).

"Unlike many pharmacological or biologic therapies to help people with neurological injuries or disease, engineering solutions have the potential for immediate and sometimes dramatic restoration of function," said press conference moderator Leigh Hochberg of Massachusetts General Hospital, Brown University, and the Providence VA Medical Center, and an expert in neurotechnologies. "It is really exciting to see how the growth of fundamental neuroscience and neuroengineering research over many years is leading to the creation of technologies that will help to reduce the burden of neurological and psychiatric disease."

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

Related Neuroscience 2017 Presentation

Techniques: Artificial Intelligence and Imagination: Exploring the Frontiers of Knowledge
Tuesday, Nov. 14, 1–2:10 p.m., WCC Hall D

Abstract 781.11 Summary

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Modeling How Motor Neurons Control Muscle Fibers in a Dish

Research may lead to next generation of soft robotics and adaptable cellular-based prostheses

An extracted rat spinal cord can dynamically control cultured muscle fibers in a petri dish, opening up avenues for developing soft robotics and models for studying neuromuscular degeneration. The study was presented 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.

Most robots depend on computer chips, electric motors, and metal joints to produce useful movements, but these rigid components often lack the versatility to interact with unpredictable or living environments, like the inside of the human body. On the other hand, robotics built with "soft" components that can flex and adapt to the local environment remain underdeveloped, and often have limited power and range of motion compared to more rigid robotics.

In this study, researchers cultured part of rat spinal cord in a petri dish and coaxed it to interface with a cultured muscle strip. They then assessed the system's ability to respond to classic biological regulators of muscle control, such as the neurotransmitter glutamate, which normally stimulates muscle contractions. This "neuromuscular junction in a dish" responded precisely and strongly to glutamate, contracting the fibers. The fibers stopped contracting in the presence of several drugs that inhibit muscle movement, similar to the mechanism in living animals.

"This system has neuron and muscle components that can respond to an external stimulus and generate an actuated force — it can locomote, it can move," said lead author Collin Kaufman, a graduate student in Martha Gillette's group at the University of Illinois, Urbana-Champaign. "The next step is trying to attach one of these devices to an actual living thing, seeing if they can control it themselves. It might also ultimately be used in areas where electronics would fail, [like highly radioactive sites], or situations where you need to have a softer touch, like during surgery."

The researchers are now developing an *in vitro* system for controlling opposing muscle fibers and artificial limbs using natural oscillations in spinal cord activity, which normally enable rhythmic motions such as walking and breathing.

Research was supported with funds from the National Science Foundation.

Scientific Presentation: Wednesday, Nov. 15, 3–4 p.m., WCC Halls A–C

7984. Engineering a bio-inspired, three-dimensional spinal cord-skeletal muscle soft robot

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TECHNICAL ABSTRACT: Biorobotics refers to the fabrication of hybrid machines that combine abiotic and biological components for a wide variety of possible functions. These may include the ability to sense their environment, process signals, and produce force. Recent work in the field of biorobotics has focused on developing a musculoskeletal biological machine that can produce motion in response to controllable external signaling. Here, we report the development of a muscle-cell actuator on a 3D-printed hydrogel skeleton now under explicit neuronal control. This multi-cellular system is able to generate small muscular forces by harnessing the emergent properties of vertebrate nervous systems. Chemical stimulation of the spinal cord with glutamate resulted in muscle contractions that were blockable by dual application of APV and DNQX, as well as treatment with curare. Immunohistochemical staining demonstrated clustering of nicotinic acetylcholine receptors at points of neuron-muscle contact that may indicate the presence of neuromuscular junctions that developed during the co-culture period. Bioengineered soft robots offer many potential biomedical applications such as providing tissue-based testbeds for disease models, creation of a "peripheral nervous system on a chip" device for drug safety and efficacy testing, and eventually to the development of forward-engineer life forms.

Abstract 777.06 Summary

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Brain Adapts to Maintain Control Over a Brain-Machine Interface

Research points to rapid but limited plasticity in active manipulation of neuroprosthetics

When a brain-machine interface makes errors, the human brain can rapidly adapt to correct those mistakes, according to a study presented 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.

For people who are no longer able to move any of their limbs, brain-machine interfaces (BMIs) represent a rare opportunity to at least partially regain lost motor and communication abilities. BMIs still face many technical difficulties however; for example, the longer a patient has cortical implants, some devices may record less neural activity, with a decreased ability to translate that neural activity into physical movements.

In this study, a woman with tetraplegia was implanted with a 96-electrode array in her anterior interparietal cortex, a brain region involved in the planning of movement. Over the course of about 100 trials, she learned to control a cursor using her thoughts alone — in such interfaces, the computer learns to translate specific patterns of neural activity into concrete physical actions, such as moving a cursor to the right or left. The researchers then introduced "perturbations" to the brain-machine interface, changing the computer's response to the woman's neural signals. For example, neural activity that had previously produced upward motion of the cursor might now produce leftward motion.

For "short-distance," or minor, perturbations, the woman was able to adapt to the perturbations and regain her intentional control over cursor movement. For "long distance" perturbations, which produced more severe errors in cursor movement, however, she was unable to overcome the introduced impairments in cursor control. The study suggests that, at least for minor errors, the brain's inherent ability to use innate activity patterns in new ways may help people better control their BMIs.

"If a brain area is more flexible than others, and can generate more combinations of innate activity patterns, then it may be a better region for collecting neural activity to control BMI devices," said lead author Sofia Sakellaridi, a postdoctoral scholar in Richard Andersen's group at the California Institute of Technology. "Understanding the limits of learning is important for rehabilitation therapies for people who suffer from stroke or other brain injuries. Restoring neural functions after brain trauma may also require patients to generate specific neural patterns of activity."

Next, the researchers intend to assess the plasticity of other brain regions, such as primary motor cortex and premotor cortex, during the learning of BMI use and following the introduction of errors to BMI mapping.

Research was supported with funds from the Tianqiao and Chrissy Chen Brain-Machine Interface Center at Caltech, the Boswell Foundation, the Swartz Foundation, and the National Eye Institute.

Scientific Presentation: Wednesday Nov. 15, 2–3 p.m., WCC Halls A–C

9723. Why learning can be difficult? A brain-machine interface study with a tetraplegic human

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<u>TECHNICAL ABSTRACT</u>: The ability to learn new skills and adapt to current environmental demands is essential in human and animal behavior. Recent brain-machine interface (BMI) studies in non-human primates have contributed to our understanding of the mechanisms by which changes in neural activity improve behavioral performance. Studying these processes in humans would represent a significant step forward as only humans can be instructed about a task and provide verbal reports of how they solve a task. In the current study, we explore the mechanisms of learning in a participant with tetraplegia (C3-C4 10 years post injury) who is implanted with a 96 channel microelectrode array in the anterior intraparietal (AIP) cortex. We examined how AIP learns to compensate for errors by perturbing the mapping between neural activity and cursor movement in a 2D cursor control task. Each session started with learning the lower dimensional neural space (intrinsic manifold) which captured the co-modulation patterns among the neural units during an initial brain control session. After a number of trials, the mapping from neural activity to kinematics was perturbed within the intrinsic manifold, preserving the relationships among the neural units but altering the way in which these relationships

affected cursor kinematics. The distance between the original and the perturbed map characterizes the degree of difficulty of the BMI perturbation task - i.e., the longer the distance, the more challenging it is to learn to adapt to perturbations. The participant was instructed to employ a constant strategy of making attempted thumb movements to modulate neural activity. The perturbation was successful in causing an immediate and lasting decrement in performance. Over the course of a session, the participant could regain proficient control of the cursor for easy (i.e., short distance) perturbations. However, the performance often remained impaired for difficult (i.e., long distance) perturbations suggesting that learning did not occur. Importantly, the participant often reported that she compensated for errors caused by the perturbations by re-aiming to different directions. These results suggest that people adapt to perturbations in BMI tasks by exploring new cognitive strategies. When finding new strategies is challenging (or even impossible), AIP either cannot learn, or needs a more extensive period of training, to generate new patterns of activity to compensate for errors.

Abstract 642.04 Summary

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Restoring Touch Generates Sense of Ownership Over Prosthetic Hands

Findings indicate numerous benefits of pairing motor and sensory functions in prosthetic devices

Restoring the sense of touch to a person with a prosthetic hand not only improved motor skills and reduced phantom pain but also provided a better sense of “ownership” over the device, according to 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.

Most prosthetics cannot replicate the multifaceted sensory experience of using one’s own limb, leading as many as 50 percent of upper limb amputees to abandon their prostheses over time. Scientists are now building technologies aimed at restoring aspects of hand movement that go beyond motor control, including somatosensation, or the sense of touch.

In this study, researchers fitted an amputee with a prosthetic hand that he could control with his thoughts, decoded from electrical signals recorded from his remaining arm muscles. Then, they implanted electrodes into his arm’s remaining nerves that had previously detected somatosensory input from the hand. Stimulating through these electrodes caused the amputee to feel natural sensations on his missing hand, and he could use these sensations to guide movements such as opening a door.

Connecting the sense of touch to movement produced a “unique reaction” in the amputee, according to Jacob George, the lead author of the study and a graduate student in the lab of Gregory Clark at the University of Utah. Upon reaching out and touching a door, for example, he exclaimed, “Oh my God! I just felt that door,” and began to stroke the door, saying he could feel his finger sliding down the door. The subject gained an “entirely different perspective, where now, it’s really his hand,” George said. Another subject also reported reductions in phantom pain.

The researchers are now preparing to test their system in a cohort of subjects who will be able to take the system home and use it in everyday settings. George hopes this test will demonstrate that a fuller experience of using a prosthetic hand provides a “unified solution to a variety of different ailments” in amputees, including depression, phantom pain, and inconsistent motor control.

Research was supported with funds from the Defense Advanced Research Projects Agency and the National Science Foundation.

Scientific Presentation: Wednesday Nov. 15, 8:45–9 a.m., WCC 150A

3065. High-resolution somatosensory feedback in a human amputee allows sensorimotor discrimination, increases prosthesis embodiment, and reduces phantom pain

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TECHNICAL ABSTRACT: The long-term goal of these studies is to provide rich, biofidelic tactile and proprioceptive feedback from an advanced prosthetic hand after prior amputation in humans. Here we report on S6, our most recent of six human subjects. S6 received two 100-electrode Utah Slanted Electrode Arrays (USEAs; Blackrock Microsystems) implanted chronically (12 months) in residual median and ulnar nerves for stimulating sensory fibers and recording from motor fibers after a long-term (13-y) transradial amputation, as well as an array of intramuscular electrodes for electromyographic (EMG) recordings from residual extrinsic hand muscles (Ripple, LLC). Sensory percepts were mapped by passing increasing current through individual USEA electrodes (biphasic, 200-μs pulses; 100-200 Hz, 200-500 ms trains) until the subject reported a percept (location, type, and intensity), or until stimulation maximum (< 100 μA). Experiments were conducted either in a MuJoCo (Roboti, LLC) virtual reality environment; or with a simple sensorized, motorized physical prosthetic hand (Open Bionics); or with a more advanced, sensorized, motorized prosthetic hand (DEKA) having 6 DOFs and 19 receptive fields. S6 reported up to 119 different primary or secondary USEA-evoked cutaneous (e.g., pressure, vibration) or proprioceptive percepts (e.g., movement or tightening). The evoked percepts covered most of the phantom hand (although representation was sparse for the index finger tip); corresponded to normal afferent fiber distributions; and were typically perceived as enjoyable by S6. Percepts showed within-session stability, and more than half maintained location stability when retested at ≥ 1 month. S6 also used sensory feedback evoked by biofidelic afferent fiber stimulation to guide motor control of the DEKA hand (Kluger et al., SFN17). S6 could discriminate between “soft” foam blocks and “hard” plastic blocks in a sensorimotor task using the DEKA hand (15 successes in 18 trials). S6 also showed objective evidence of embodiment of both the Open Bionics and DEKA hands, as measured by proprioceptive shift from the amputated hand to the prosthetic hand and by responses to survey questions. Stimulation of sensory fibers also resulted in a 23.2% reduction in subjective phantom pain scores for S6 (from 3.75 ± .14 to 2.88 ± .18, $p < 0.005$). The emerging ability to provide a relatively complex repertoire of high-count, high-resolution somatosensory inputs may enhance sensorimotor control, increase prosthesis embodiment, and reduce phantom pain for amputees, ultimately improving the adoption of advanced neuroprostheses.

Abstract 683.02 Summary

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Organic Retinal Prosthesis Restores Visual Function in Rat Model of Adult Blindness

Research may lead to development of functional retinal prosthetics in humans

Scientists have developed an organic artificial retina that restores vision-related brain activity and behavior in a rat model of blindness, according to recently published research presented 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 loss of rod and cone photoreceptors in the retina is a leading cause of human adult blindness, but implantable prosthetic retinas have proved difficult to engineer. In this study, researchers developed an organic retinal prosthesis made from layers of photosensitive polymers and silk, which is both benign to the human and rat immune system and fully functional. Researchers carefully implanted the material into the retinas of rats bred to model retinitis pigmentosa, a disease that leads to blindness via the progressive loss of photoreceptors.

The rats tolerated the implants well, showing no swelling or disruption to the anatomy of the eye over the course of the study. Within 30 days of implantation, the rodents regained several key aspects of visual sensation, including the pupillary reflex (when the pupil contracts or expands to adapt to light and dark), electrical activity in the retina, and a tendency to avoid light. The team also detected neural signals that usually indicate visual sensation in the rats' visual cortices. These improvements lasted for 10 months after the implant.

"The progressive degeneration of retinal photoreceptors due to single mutations in any one of over 240 identified genes is one of the major causes of adult blindness in humans," said lead author Jose Fernando Maya-Vetencourt, a research scientist in Fabio Benfenati's group at the Instituto Italiano Di Tecnologia. "The experimental findings obtained so far highlight the possibility of developing a new generation of fully organic, highly biocompatible, low cost, and functionally autonomous photovoltaic prostheses for subretinal implantation to treat degenerative blindness."

The researchers are now adapting their organic, photosensitive prosthesis for use in a swine model of blindness, which will better model surgical procedures in people, and could moving the device towards Phase I clinical trials.

Research was supported with funds from the European Commission, Telethon Italy, Fondazione Cariplo, Compagnia di San Paolo, the Italian Ministry of Health, Istituto Italiano di Tecnologia, the Ra.Mo. Foundation, and Rare Partners.

Scientific Presentation: Wednesday, Nov. 15, 9–10 a.m., WCC Halls A–C

1726. A fully organic retinal prosthesis restores vision in a rat model of degenerative blindness

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TECHNICAL ABSTRACT: The degeneration of photoreceptors in the retina is one of the major causes of adult blindness in humans. Unfortunately, no effective clinical treatments exist for the majority of retinal degenerative disorders. In this work we report on the fabrication and functional validation of a fully organic prosthesis for long-term in vivo subretinal implantation in the eye of Royal College of Surgeons rats, a widely recognized model of retinitis pigmentosa. Electrophysiological and behavioural analyses revealed a prosthesis-dependent recovery of light sensitivity and visual acuity that persists up to 6-10 months after surgery. The rescue of the visual function was accompanied by an increase in the basal metabolic activity of the primary visual cortex, as demonstrated by positron emission tomography imaging. Our results highlight the possibility of developing a new generation of fully organic, highly biocompatible and functionally autonomous photovoltaic prostheses for subretinal implants to treat degenerative blindness.