Building Better Brains

Neural Prosthetics and Beyond

Organizers: Richard Andersen (California Institute of Technology), P. Hunter Peckham (Case Western Reserve University), and Andrew Schwartz (University of Pittsburgh)Presented by the New York Academy of Sciences and The Aspen Brain Forum Foundation
Reported by Heather Berlin, PhD | Posted January 27, 2011

Overview

Neural prosthetics offer the promise of what was once unthinkable, the restoration of perceptive or movement ability in those who have lost it. But these devices offer much more than that. From September 23 through 25, 2010, researchers in all areas of the neural prosthetics field converged at the *Building Better Brains: Neural Prosthetics and Beyond* conference to examine ongoing work and the future of this exciting research avenue.

Throughout the course of the conference, it was clear that neural prothetics have the potential not only to mimic "ordinary" motor function more closely than ever before, but also to restore neurobiological connections, to reanimate paralyzed limbs by stimulating muscles directly, to facilitate the reorganization of neural connections to "work around" damaged areas, to improve recovery from some neuropsychological disorders, and much more. Researchers emphasized that these possibilities are only realized through the intersection of groundbreaking fundamental neuroscience research and innovative technological development, all of which must be grounded in critical analysis of the clinical, social, and ethical impact of the work. As presenters indicated during the conference, this analysis has already begun—with research into the histological impact of recording devices, the differential impact of ECoG- versus EEG-based brain–computer interfaces, the accuracy of yes or no responses from individuals in a vegetative state, and into the ethical ramifications of enhancing neural function in previously unimpaired individuals, to name a few areas speakers discussed.

The use and development of neural prosthetics will continue to raise difficult ethical and scientific questions, but, as the speakers in this conference demonstrated, these questions are often just as interesting, fruitful, and challenging as they are potentially confounding.

2010 Aspen Brain Forum Prize in Neurotechnology

The New York Academy of Sciences and the Aspen Brain Forum Foundation awarded two prizes of $7,500 each in unrestricted funds—one to senior scientist **Eberhard Fetz**, PhD (University of Washington) and one to a junior investigator, **Jose Carmena**, PhD (Helen Wills Neuroscience Institute at the University of California, Berkeley)—for innovation and excellence in the field of neurotechnology. We are honored to recognize the outstanding achievements of the winners and finalists for the Aspen Brain Forum Prize in Neurotechnology who were announced during the First Annual Aspen Brain Forum held in Aspen, CO on September 23-25, 2010. To read more about the Aspen Brain Forum Prize and the 2010 finalists and awardees, please click here.

Use the tabs above to find a meeting report and multimedia from this event.

Presentations available from:

Niels Birbaumer (University of Tübingen)
Kristen A. Bowsher (U.S. Food & Drug Administration)

Edward S. Boyden III (Massachusetts Institute of Technology)
Jacqueline C. Bresnahan (University of California, San Francisco)
Joseph Fins (Weill Cornell Medical Center)
Robert Fisher (Stanford University Medical Center)
Philip R. Kennedy (Neural Signals, Inc.)
Takashi Kozai (University of Michigan)
Eric C. Leuthardt (Washington University School of Medicine)
Helen S. Mayberg (Emory University School of Medicine)
Daniel Moran (Washington University)
P. Hunter Peckham (Case Western Reserve University)
Marc H. Schieber (University of Rochester)
Andrew B. Schwartz (University of Pittsburgh)
Krishna V. Shenoy (Stanford University)
Patrick Tresco (University of Utah)
Jonathan Wolpaw (Wadsworth Center, New York State Department of Health)

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This event was funded in part by the Life Technologies™ Foundation.

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Grant Support

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The project described is supported by Award Number R13NS071862 from the National Institute of Neurological Disorders and Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.

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Introduction

Neural prosthetics include any mechanical, electronic, optical, or molecular device that interacts directly with the nervous system and substitutes for, supplements, or enhances a function lost due to an injured or diseased part of the nervous system. The use of neural prosthetics to replace motor, sensory, or cognitive functions lost by disease or injury holds great therapeutic promise. However, neural prosthetics have not yet been widely used in humans. To address this issue, the most prominent researchers in the field of neural prosthetics came together on September 23–25, 2010 at The Given Institute in Aspen, Colorado to discuss their latest work and discoveries at the meeting entitled *Building Better Brains: Neural Prosthetics and Beyond* sponsored by the New York Academy of Sciences and

The Aspen Brain Forum Foundation.

This meeting highlighted the most cutting-edge developments in the field of neural prosthetics and included a review of the current obstacles to using neural prosthetics therapeutically, as well as the related ethical and regulatory issues. More specifically, the conference covered topics including; 1) presentation of the most recent advances in basic neurobiological research to inform development of neural prosthetics, 2) an overview of recent discoveries in bioengineering and materials that will allow for the development of neural prosthetic devices that function effectively within the human body, 3) discussion of how to improve upon the results of clinical trials of neural prosthetics, 4) how to use neural prosthetics to treat disorders, including not only neurodegenerative diseases and paralysis, but also depression and epilepsy, and 5) the unique regulatory and ethical problems that are associated with using neural prosthetics in people.

In sum, this meeting explored the development of neural prostheses and the next steps to transition them to human subjects. Over the past few decades scientists have done substantial research and development of neural prosthetic devices, mostly in non-human animals, and are now at the tipping point of starting widespread human trials. But efforts to transition neural prosthetics to humans are hampered by several important factors.

Engineering challenges are perhaps the most straightforward to overcome. The challenges here are to improve the reliability, fidelity, and lifetime of neural interfaces to be able to record salient neural activity over a period of decades to satisfy functional and safety criteria for clinical neuroprosthetic applications. Many strategies are applied to minimize the foreign tissue response to implanted electrodes, improve electrophysiological recording quality over long periods of time, and introduce new modes to interface the brain with. Several speakers at the Conference discussed recent developments in bioengineering and materials engineering.

On the basic science front, scientists have encountered further challenges. Though they have made some progress, neuroscientists still understand relatively little about how the brain actually works. To be able to translate brain function into external action for use in neural prosthetics researchers need to have a deeper understanding of the fundamental workings of the human brain and mind. The development and applications of neural prosthetic devices will primarily be restricted by a lack of understanding of which brain pathways can provide access to and can process large amounts of information. Hence, advances in basic neuroscience are of crucial importance to the development of neural prosthetic devices. A number of speakers discussed the current state of the science and the promising basic research that has a strong potential for translation to humans.

Finances present another major obstacle to the migration of neural prosthetic technology from the laboratory to human trials. Presenters queried where the money would come from for basic research and the application of this research in human trials. A number of funding sources have injected new energy into neural prosthetics development in the last few years, but conference participants agreed that more funding is needed to support this innovative research. As **Robert Fisher** from Stanford University School of Medicine quoted from a restaurant fortune cookie he once opened, "money spent on the brain is never spent in vain."

Whenever new technology is developed that can have a significant impact on mankind there are important ethical issues that need to be addressed in addition to the kinds of logistical challenges mentioned above. For example, when is it appropriate to test in human subjects a technology developed in non-human animals in the laboratory? Participants discussed this and similar questions as they considered the ethical implications of using neural prosthetics in humans.

Researchers covered a lot of ground at the conference—discussing everything from advances in basic research to the ethical issues surrounding neural prosthetics—but one theme reverberated throughout the talks as nearly every speaker expressed his or her excitement for the future of the field and for the potential applications of neural prosthetics. **Apostolos Georgopoulos** from the University of Minnesota Medical School summed up this sentiment poignantly in the closing remarks of his keynote address: "The thing I have learnt after all of these years (in research) is that the future is unimaginable, I mean it is everything. I am delighted to be here, but I am more jealous and envious of all the audience and the young people who really are going to write history."

Basic Research with Strong Potential for Translation

Speakers:
Dawn M. Taylor, The Cleveland Clinic
Richard Andersen, California Institute of Technology
Andrew Schwartz, University of Pittsburgh

Eberhard Fetz, University of Washington
Marc H. Schieber, University of Rochester School of Medicine and Dentistry

Highlights

- Cortically-controlled prostheses can control various assistive devices such as robotic limbs, wheelchairs, computers, and the like.
- Some prostheses can even stimulate muscles to reanimate paralyzed limbs.
- Cognitive neural prosthetics can tap and decode high level cognitive factors: symbolic and contextual cues, reward expectation, effective value, internal models of dynamics, and cognitive states.
- Recurrent brain–computer interface (R-BCI) technology can be used to restore impaired neurobiological connections.
- Monkeys using R-BCI technology can directly control stimulation of their muscles and restore goal-directed movements to a temporarily paralyzed arm.
- R-BCI can be used to create synaptic plasticity, and reorganization of motor output can be induced by an artificial connection between two sites in the motor cortex.

The meeting began with an overview of the most recent advances in basic neurobiological research that can inform the development of neural prosthetics. The most common implementation of a neural prosthetic is to assist paralyzed individuals or those who have lost limbs. Neural prosthetics could aid, for example, an individual who can think about making movements but has a spinal cord injury that prevents him or her from sending the signals down the spinal cord in order to make those movements. Researchers are working towards developing an implantable microchip with electrodes to record from a population of neurons in the brain. Ideally that chip will wirelessly send the recorded neural signals out to a computer which can decode this information with appropriate algorithms and deploy it to control various assistive devices, such as robotic limbs, wheelchairs, or computers for browsing the Internet or typing messages. This technology could potentially even be used to stimulate muscles to reanimate paralyzed limbs.

Decoders are typically built by recording brain activity during actual or imagined movements, and then correlating that activity with various motor parameters such as endpoint position, velocity, joint angles, or movement goal. **Dawn Taylor**'s team at the Cleveland Clinic, Cleveland Veterans Affairs Medical Center, and Case Western Reserve University are conducting research to explore how to best make use of motor-related signals to control the actions of prosthetic devices. They have found that they can significantly improve neuroprosthetic control by decoding the aspect of movement that is most strongly encoded in the recorded neural signals and applying that decoded movement command to the control of a different, more-useful device action. Certain motor transformations are easily learned and can lead to smoother trajectories and more robust movement control.

A common approach to developing neural prosthetics, and one that several speakers discussed, is to implant microelectrodes into the motor cortex. Targeting this region makes sense since the motor cortex is responsible for sending out the commands that go through the spinal cord to animate the muscles. However, **Richard Andersen**'s research group at Caltech has taken a slightly different tack. They go one step before motor cortex signals and record from the areas of the brain (in the monkey) that first form the intentions to make movements (e.g., premotor and parietal cortices). These areas are more cognitive and code the goal of the movement rather than the precise limb movements needed to reach that goal. So the group can map a trajectory of the movement not only by decoding neural firing in the motor cortex, but also by decoding neural firing in 'higher' cognitive areas involved in movement planning.

Cognitive neural prosthetics that can tap into higher brain processing related to movement planning can also decode a number of high-level cognitive factors such as symbolic and contextual cues or reward expectation. In the future, depending on where the implants are placed, it may be possible to decode very high-level cognitive signals such as decision-making, attention, executive control, emotions, and language. Richard Andersen's group is now transitioning this cognitive approach to clinical trials in humans. One such trial tests bilateral control of robotic limbs as the somatosensory cortex is stimulated. This stimulation yields tactile feedback to aid the coordination of functions such as grasping. The other trial involves a communication interface to control a computer cursor for typing, sending e-mails, searching the internet, etc. The activity of small neuronal ensembles may eventually be decoded to help tetraplegic humans communicate using just their thoughts. Andersen's group is also working to develop wireless technology that can transmit signals directly out of the brain without cumbersome wires.

Another promising area of basic research with strong potential for translation is the work being conducted by **Eberhard Fetz** and colleagues at the University of Washington. Fetz discussed some of the exciting new applications

of recurrent brain–computer interface (R-BCI) technology, an interface that records activity in the brain and processes it through a computer chip to deliver activity-contingent stimulation back to the brain or to the spinal cord or muscles during free behavior. This "Neurochip" consists of a miniature, battery-powered electronic circuit that is connected to electrodes that record the activity of motor cortex cells and/or muscles and a programmable computer chip that can convert neural activity in real-time to electrical stimuli delivered to nervous system sites or muscles.

A promising application for this technology is to bridge lost biological connections, by creating an artificial recurrent connection (like that described above) that the brain can use. Since the brain can adapt to consistent sensory motor conditions it can learn to incorporate an artificial connection into normal behavior if that connection is used repeatedly and over an extended period of time. In a recent study, monkeys could directly control electrical stimulation of their temporarily paralyzed muscles by using the activity of their motor cortex neurons relayed via an artificial connection and could thereby restore goal-directed hand movements. Interestingly, the monkeys could learn to control the muscles with any motor cortex cells, whether those cells had been previously related to arm movement or not. This suggests that decoding may not be necessary for effective control if the subject is given sufficient time to learn new motor strategies.

A second application of R-BCI technology is to create synaptic plasticity through stimulation synchronized with neural activity, which can strengthen synaptic connections. Work by Fetz's lab in freely behaving primates has shown that reorganization of motor output can be induced by an artificial connection between two sites in the motor cortex. These changes of neural connections occurred over a day or two of continuous operation of the Neurochip implant that used action potentials recorded from an electrode in one part of the motor cortex to trigger electrical stimuli in another part of the motor cortex. The changes persisted in some cases for longer than one week. More recent work has demonstrated that stimulation of sites in spinal cord triggered from spikes of corticospinal neurons can strengthen the terminals of those neurons. Such activity-dependent stimulation may have practical applications in rehabilitation after spinal cord and/or brain injury by strengthening weakened neural connections.

Interestingly, the firing of neurons in the brain, particularly in the motor cortex, can become dissociated from what the native limb is doing. The cerebral cortex has no direct input from sensory receptors and no direct output to muscle fibers; everything is indirect and therefore dissociable if the intervening connections get disrupted. **Marc Schieber** of the University of Rochester and his colleagues are interested to see if there are limits to this dissociation, to probe questions about whether they can pick any neurons and dissociate them from their ordinary target of control and get them to control something else. They are also interested in whether there are factors that limit the brain's ability to reconfigure control in this way. Schieber's group has started studying these questions in monkeys. The results of these investigations will have profound implications for our understanding of how the cortex is organized and how it functions, and they will inform the development of neural prosthetics for neurorehabilitation in humans. Schieber and colleagues are trying to find features that affect the ability of small ensembles of motor neurons to control a closed-loop BCI, so that one day BCI devices could be effectively controlled by patients' own, albeit redirected, neural circuitry. So far they have found that the number of neurons and the location of those neurons matter to the efficacy of device control: ensembles of multiple neurons work better than do single neurons, and neurons that are farther apart can control devices better than can neurons close together.

New Developments in Bioengineering and Materials

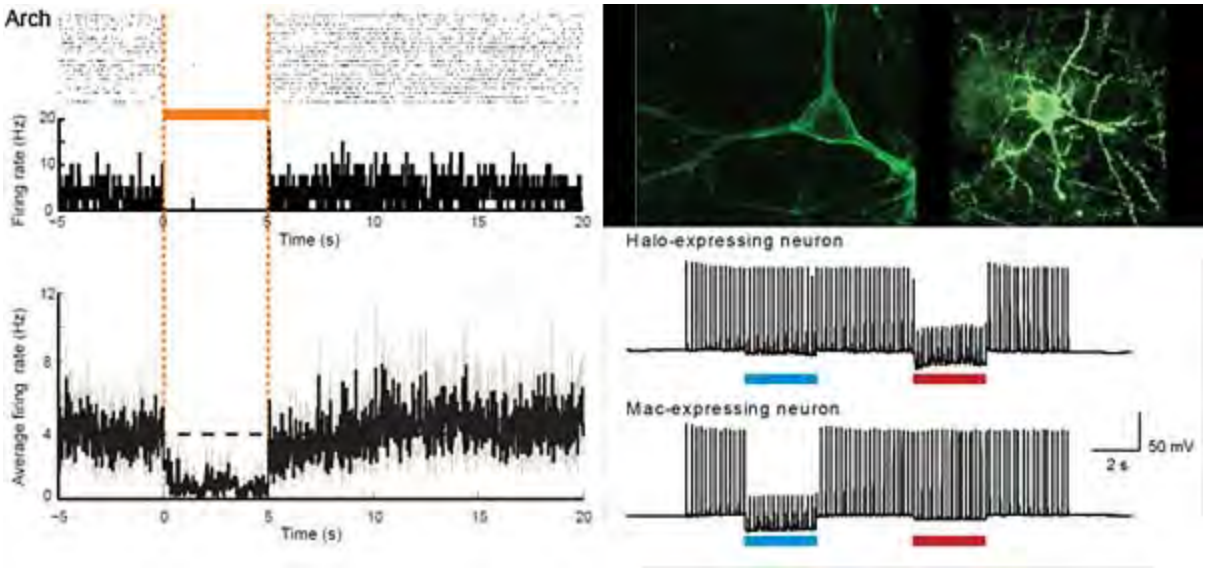
Speakers:
Edward S. Boyden III, Massachusetts Institute of Technology
Daryl R. Kipke (Presented by Takashi Kozai), University of Michigan
Patrick Tresco, University of Utah
Krishna V. Shenoy, Stanford University

Highlights

- Optogenetics allows researchers to manipulate neural circuits at high speeds and to control very specific brain circuits with different colored pulses of light.
- Researchers are developing new technology to detect both action potentials and neurotransmitter release.
- Ultra small, implantable 'microthread' electrodes will one day obtain a high fidelity neural recording reliably over long time periods.
- Neuroinflammation in response to implanted electrodes can be reduced by changing the implant's architecture.

Cutting-edge discoveries in bioengineering, genomics, and materials science are facilitating the development of new

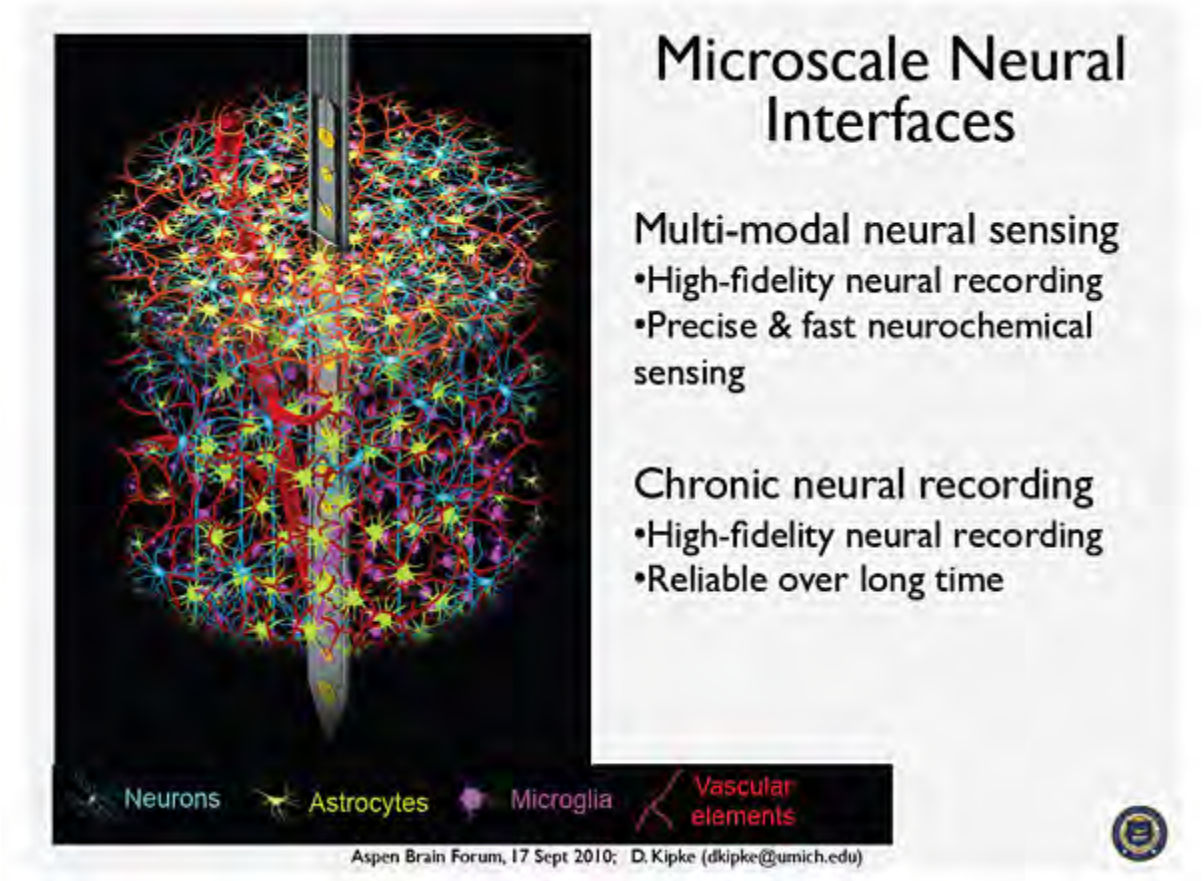
kinds of neural prosthetic devices that function effectively within the human body. For example, over the past several years **Edward Boyden** and his colleagues at MIT have developed revolutionary new technology that allows researchers to use light to control very specific brain circuits. His team developed genetically-encoded reagents, such as Channelrhodopsin-2 (a single-component light-activated cation channel from algae), that, when expressed in specific neurons in the brain, allow those neurons to be activated or silenced in response to pulses of colored light. This technique is appropriately called 'optogenetics' since it combines optical and genetic techniques to manipulate neural circuits at high speeds (activating or silencing in only milliseconds). Optogenetic reagents have been shown to be safe and effective in the mammalian brain for controlling neural circuit dynamics, and hundreds of researchers around the world are now exploring how these tools can be used to alter precisely the dynamics of the neural circuits that mediate sensation, movement, and emotion. In one study, presented by Boyden, researchers were able to erase fear in a mouse by targeting the prefrontal cortex with one of these optogenetic devices.



Molecules from different life forms can capture light and use it to change the electrical potential of neurons. Left, silencing of a neuron expressing the light-gated ion pump Arch, by yellow light. Upper right, photograph of neuron expressing Arch, fused to green fluorescent protein. Lower right, two neurons expressing Halo and Mac can be silenced with 2 different colors of light. (Courtesy of Edward Boyden)

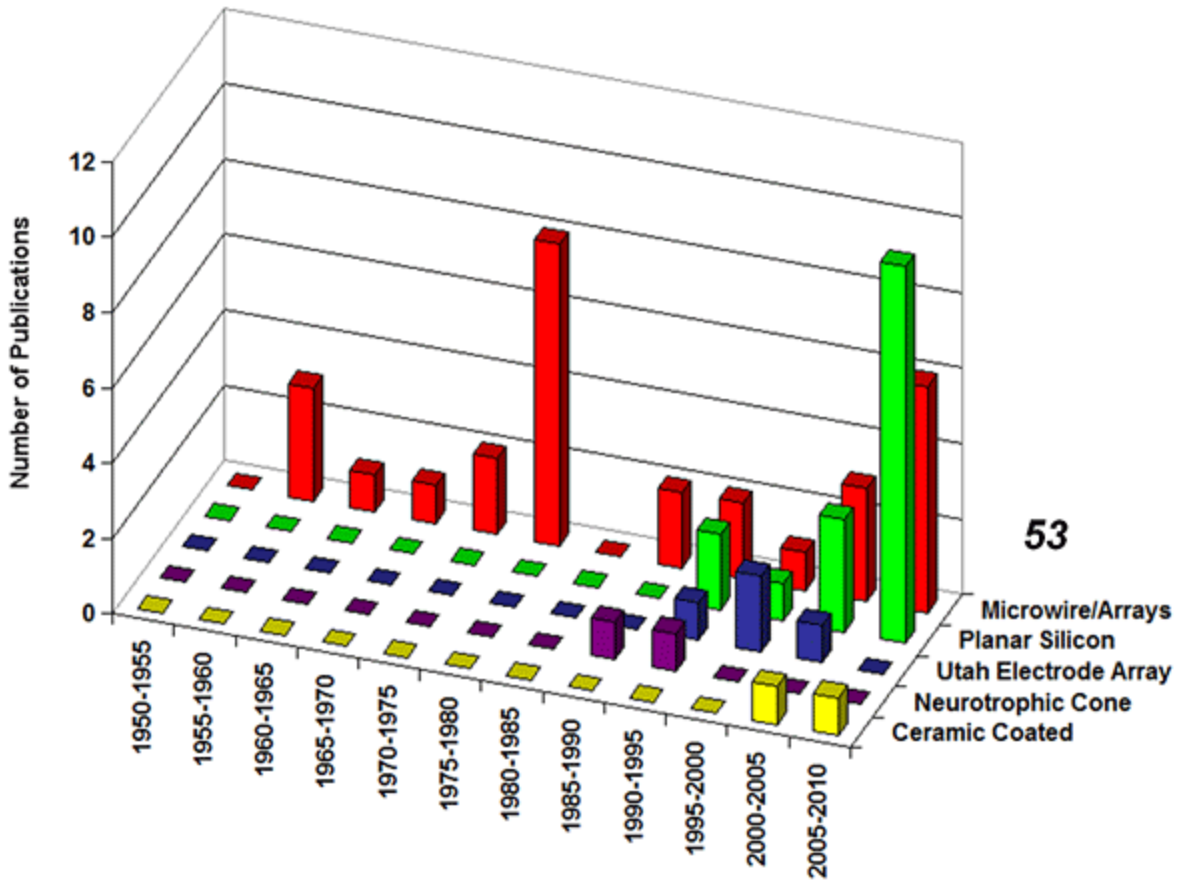
Most of the research in optogenetics thus far has been conducted in rodents and non-human primates, but investigators are now exploring the path to clinical use of this technology in humans. Optical control can, unlike DBS for instance, target specific cells and more precisely control neural circuits with fewer side effects, but it requires the delivery of a gene into the brain. Though difficult, this genetic transformation might be possible through gene therapy with adeno-associated virus vectors, which have been used in more than 600 people in 48 clinical trials without any serious adverse events resulting from the virus. So eventually researchers may be able to deliver these genes into the human brain and one day to develop strategies for optically activating or deactivating different circuits in the human brain. The ability to enter, via optogenetic control, information precisely into specific cell types and pathways in the human brain would support the creation of more powerful and flexible neural prosthetics, and would be useful in the treatment of neurological and psychiatric disorders, which often involve the over or under activation of particular neural pathways.

Takashi Kozai, working with **Daryl Kipke** and others at the University of Michigan, is developing technology for more precise, reliable, and high-fidelity implantable neural devices. These researchers are interested in microscale neural interfaces and, more specifically, in the tissue microenvironment surrounding the electrode. Kozai's and Kipke's research takes advantage of opportunities to use innovative materials, fabrication techniques and processes to make increasingly smaller devices that can be used to target ever more specific brain regions. They are also interested in understanding how better to integrate these devices into the tissue, and, as their efforts succeed their work is "starting to blur the line between bionic and abionic," that is to say, between biomimetic devices and the biological forms they mimic.



Visual representation of a microscale neural interface. (Courtesy of Daryl Kipke)

They are working on new technology to interface with the brain not just electrically, but also chemically at a micron spatial resolution with a short time scale so they can detect both action potentials and neurotransmitter releases. Traditionally investigators could only do one or the other so they had to choose to measure either action potentials or the release of neurotransmitter molecules. Advancing neural prosthetic technology, Kozai and Kipke are also developing an ultra small, implantable electrode to create a stealthy device designed to reduce the tissue response and record electrophysiology over time. Early results with microthread electrodes suggest it is possible to obtain a high fidelity, neural recording that is reliable over long periods of time.



Histological studies of the region around different recording electrodes. (Courtesy of Patrick Tresco)

The functioning of implanted neural devices that operate over very small distances in the brain depends on maintaining normal cyto-architecture and -function immediately adjacent to the implanted interface (e.g. the recording electrode). The surrounding tissue's response to the intrusion of implanted neural devices, which are foreign, possibly threatening bodies from the cells' perspective, may explain why clinical application of these devices has been challenging. There are surprisingly few histological studies of the effects of recording electrodes. However, the results of recent efforts to model and manipulate the tissue's foreign body response portend the acceleration of the clinical implementation of neural interfaces. **Patrick Tresco**'s group of the University of Utah conducted a quantitative histological analysis of the recording zone (the brain tissue in a 50–130 micron radius from the electrode surface; and measured tissue reactions that occurred in that zone in 10 rats. They found that electrode architecture influences the relative intensity and spatial distribution of the foreign body response and that changing the implant shape can therefore reduce the neuroinflammatory burden on surrounding cells. Applying these findings, the group is now working on making the electrodes very small to completely integrate them into brain tissue without initiating an inflammatory response.

Although prostheses have shown significant potential in proof-of-concept experiments with non-human animals and in initial human clinical trials, several potential barriers may slow down the translation of neural prosthetics into widespread clinical use. These barriers include the short length of time (just one or two years) implanted electrodes (in humans or monkeys) can record high quality neural signals and the slow speed and low accuracy with which cortically-controlled computer cursors and robotic arms move compared to natural arms. So far, cortically-controlled prosthetic devices have not been quite robust enough, for example, to run for hours on end or to work seamlessly across days and across multiple behavioral contexts without human technical intervention. These deficiencies could hamper efforts to employ such devices clinically at this juncture. However, work aimed at overcoming these logistical and technical barriers is underway in the labs of Krishna Shenoy and his colleagues at Stanford University and by other research groups elsewhere. Describing the results of one of his and his colleagues' investigations, a set of experiments with a 96-electrode array implanted in premotor and primary motor cortices of two rhesus monkeys, **Krishna Shenoy** said, "1) threshold crossing detection provides high signal quality for many years, and with low fluctuation; 2) a continuous-decode algorithm redesigned (using a feedback control perspective) can provide cortical-cursor control on par with typical computer-mouse control; and 3) multi-hour, multi-day, and multi-context operation is readily possible."

Translating Neural Prosthetic Devices to the Clinic

Speakers:
Jonathan R. Wolpaw, Wadsworth Center, NY State Department of Health
Leigh R. Hochberg, Providence VA Medical Center
John Donoghue, Brown University
Philip Kennedy, Neural Signals, Inc.
Eric C. Leuthardt, Washington University School of Medicine
Daniel Moran, Washington University
Niels Birbaumer, University of Tübingen
Philip Low, Neurovigil, Inc.
P. Hunter Peckham, Case Western Reserve University
Timothy J. Denison, Medtronic, Inc.
Jacqueline C. Bresnahan, University of California, San Francisco
Robert J. Greenberg, Second Sight Medical Products, Inc.

Highlights

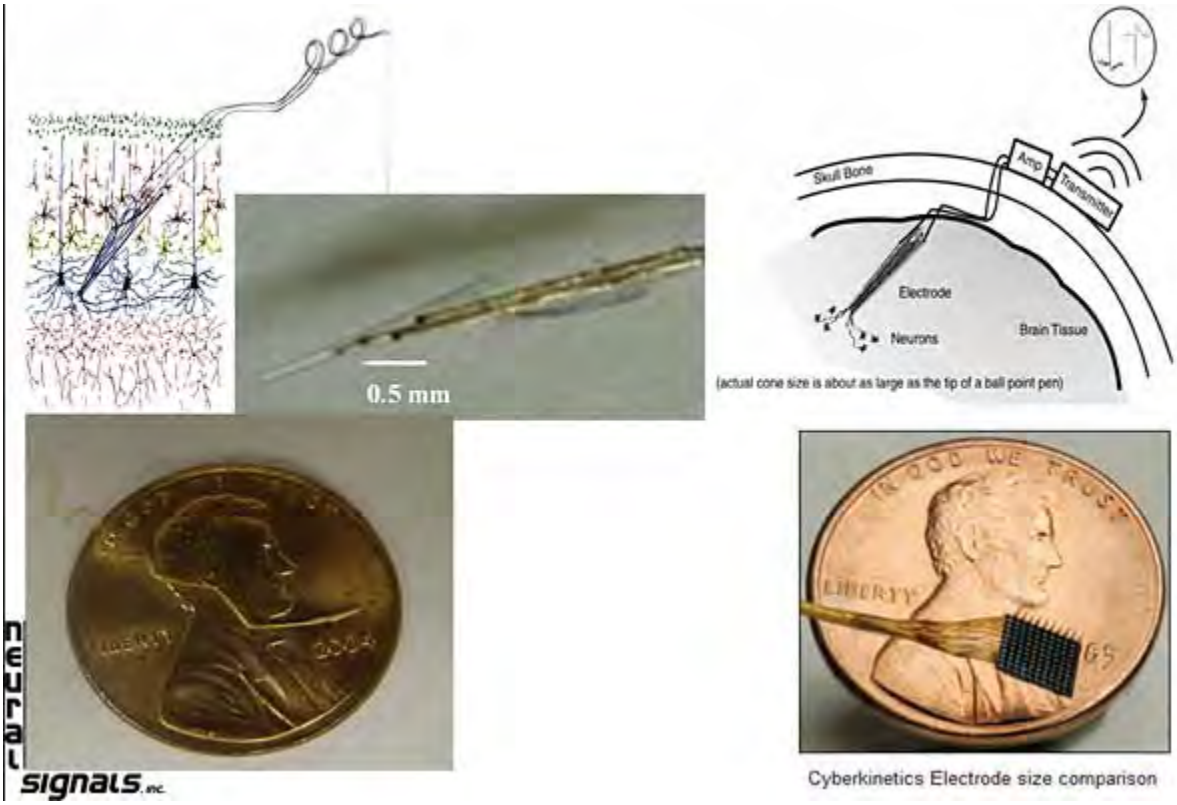
- A "neurotrophic electrode"—where neuropil is grown into the electrode instead of poking an electrode tine into the existing tissue—has been shown to provide a stable, useful signal for up to 5 years after implantation.
- Neurotropic electrodes help locked-in state (LIS) patients produce computer-generated speech sounds (with 80% accuracy).
- The BrainGate pilot clinical trial, using the BlackRock microelectrode array, demonstrated almost 5 years of use of an implanted neural interface system for control of external devices by a person with tetraplegia
- High frequency oscillations are heterogeneous and can thus be used as signals for ECoG-based BCI control in humans (e.g. controlling a cursor with thoughts alone).
- ECoG-based BCIs may be a more effective, more stable, and less traumatic tool for those with severe motor disabilities (and even for LIS patients) than is EEG-based BCIs.
- Bilateral stimulator telemeter systems help upper and lower extremity neuroprostheses restore full arm mobility and levels of standing and ambulation.
- The Argus® II implant (Second Sight™ Medical Products, Inc) bypasses defective photoreceptors and stimulate remaining, viable retinal cells in people who are retinally blind.

Over the past decade, preclinical research has shown that healthy, non-human primates can control virtual and physical devices with neural activity (spike patterns and extracellular field potentials) using implanted multielectrode BCIs that allow for the execution of movements like grasping and reaching. Researchers **Leigh Hochberg**, **John Donoghue** and others at Providence VA Medical Center, Harvard Medical School, and Brown University are now translating this ground-breaking research into pilot clinical trials of an intracortical neural interface system called BrainGate2. They are testing the ability of people with tetraplegia to control, using BrainGate2, the movement of a cursor on a computer screen or other assistive devices just by thinking about moving the device with their own hand. The device consists of a 4 × 4 mm array of 100 microelectodes placed in the precentral gyrus and motor cortex, regions of the brain responsible for the planning and execution of movements. The signals, which can be actions potentials, multi-unit activity, or local field potentials, are brought out by a pedestal through the skin and decoded by a number of algorithms. A 56-year-old woman in a locked-in state (LIS)—where a patient is awake, alert, and cognitively intact as far as evoked potential and fMRI can show, but is nonetheless unable to move or communicate—from a brainstem stroke at age 42, used the BrainGate2 system to point-and-click around a keyboard on a computer screen to select to letters, conducting the first ever BCI-Google chat. This is an extremely promising start, though there is a need to increase device speed and reliability and to develop better decoding algorithms to enhance the process.

These researchers also showed continuous state, one- and two (and a half)-dimensional control using BrainGate2 of an assistive robotic arm and hand for very precise reaching and grasping by a person with tetraplegia. In addition to providing better control systems for prosthetic limbs, they also hope one day to reconnect brain to limb to restore natural limb control to people with paralysis. Already, they can demonstrate continuous control of a 6-muscle dynamic arm simulator, but they hope to expand this to an 18-muscle arm that would give 3-D control. They are also working towards making the neural sensor device fully implantable, in much the same way as are cardiac pacemakers or Deep Brain Stimulation devices, and wireless, with the ability to transmit information through the skin with infrared.

Applying this technology could also improve our ability to understand, monitor, and hopefully predict epileptic seizures.

However, while single-unit neuron activity recorded directly from the brain provides perhaps the best multi-dimensional signal for BCI control, attaining long-term stability of single unit recordings has only recently been improving. While many people are studying proposed issues such as glial encapsulation, a process by which the electrode becomes insulated by glial cells or cellular debris and consequently isolated from their target nerve cells, most of the challenges seen in recording to date have actually been attributable to engineering failures rather than to changes at the cellular level. Single-unit recordings require implanted electrodes, but many in the field believe that the potential benefit of these technologies will outweigh the risks of surgery.



Size comparison between the Neurotrophic electrode and a Cyberkinetics electrode.
(Courtesy of Philip Kennedy)

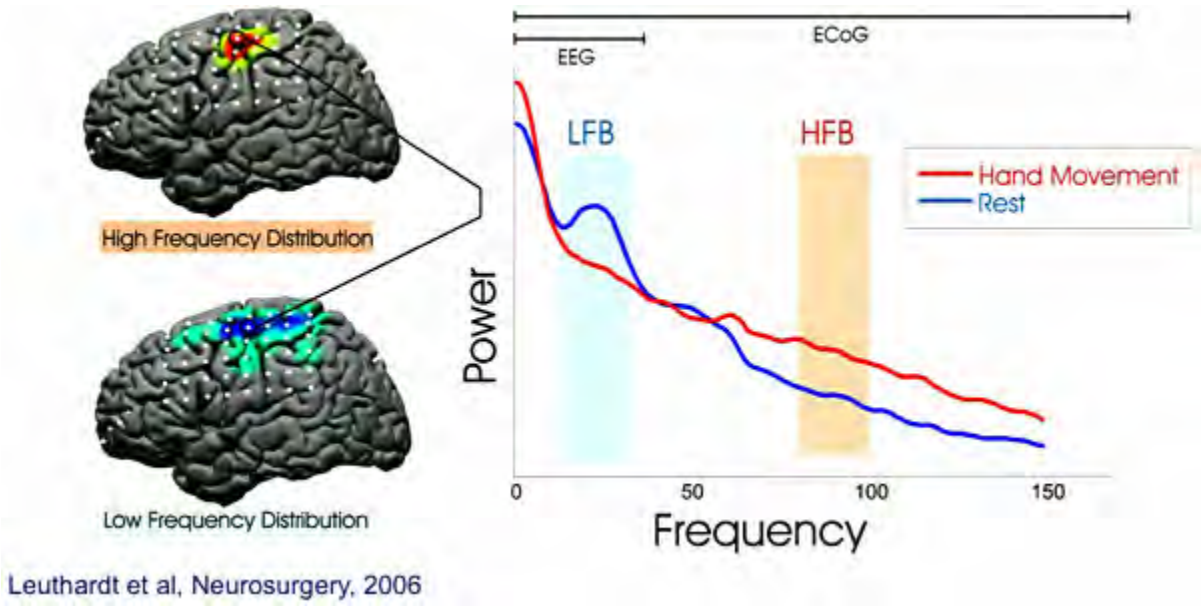
One possible way to form a stable connection between brain and electrode, which is needed for implants to be successful for the lifetime of the recipient, is to allow neuropil tissue to grow into the electrode rather than poking a sharp electrode tine into the neuropil region. "Neurotrophic Electrodes" of this sort have been shown to provide a stable, useful signal for up to 5 years (and counting) after implantation. This kind of electrode is made of Teflon-insulated gold wires fixed to a hollow glass cone with trophic factors, proteins that promote nerve cell growth, to entice neurites into the tip of the cone. In a few weeks the trapped neurites become myelinated, and the wires can record action potentials firing along the myelinated neurites.

Using this device, locked-in state (LIS) patients could use their thoughts/neural signals to move a cursor on a monitor to select a word, and, with feedback training, to select nodes on a computer screen that can generate speech sounds (with 80% accuracy). Because the patients' brains must also adapt to the use of the device, neural plasticity is crucial to prosthetic efficacy, as **Philip Kennedy** of Neural Signals Inc. explained. This new "neuropil" technology may prove to be a better brain interface because the electrode endures over many years, the signals are stable and functional long-term, and the algorithms are able to detect patterns of neural activity.

Less invasive approaches: EEG and EcoG

This session covered another option for BCI control in humans: EEG, a non-invasive technique where relatively large electrodes are placed on the scalp surface to record electrical activity emerging from the cerebral cortex underneath. But a relatively large area of cortex (~6 square centimeters) needs to be active all at once to be "picked-up" by the electrodes on the scalp, and it can take months to train such large cortical networks for BCI control. So, unfortunately

control of BCI devices with EEG activity currently has limited resolution and requires extensive training.

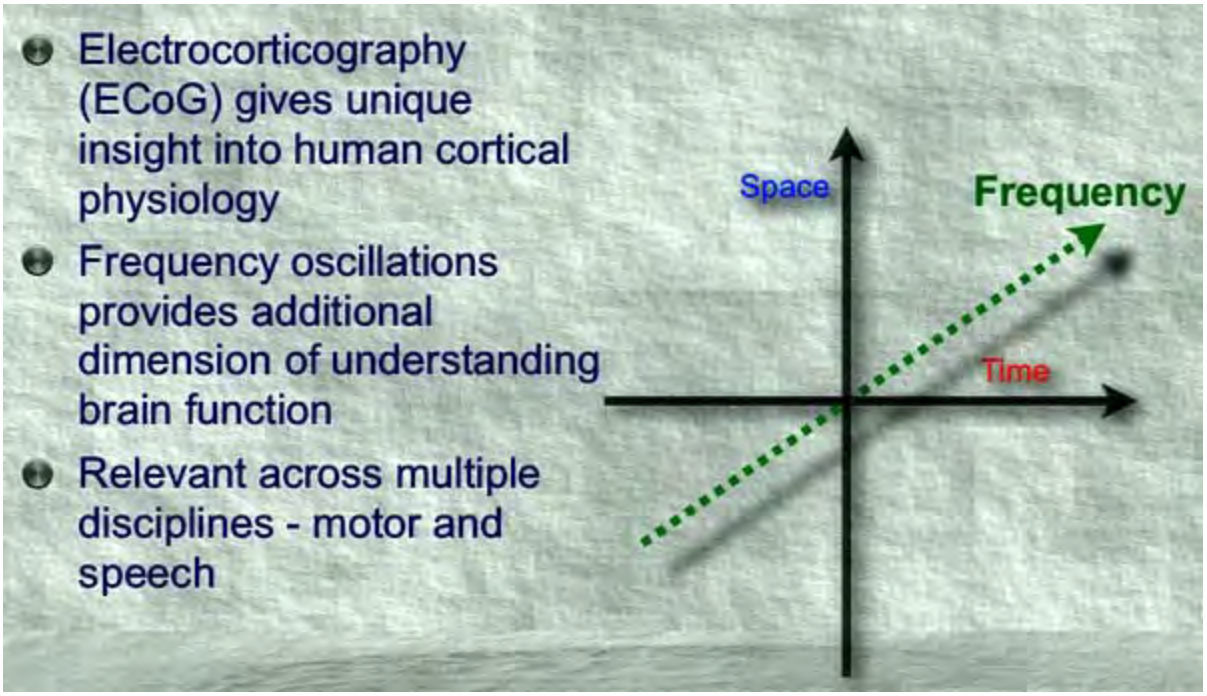


Left: High frequency signals are distributed over a smaller anatomic area than are low frequency signals. Right: The High Frequency Band (HFB) is detectable by ECoG but not by EEG, and these high frequency signals show higher power is associated with greater activity. (Courtesy of Eric Leuthardt)

Recent research by **Eric Leuthardt** and colleagues at Washington University suggests that electrocorticography (ECoG)-based BCIs may be a more effective tool for communication and control than EEG-based BCIs in people with severe motor disabilities. ECoG-based BCIs are also potentially more stable and less traumatic than BCIs that use electrodes to penetrate the brain to record single-neuron activity. Instead, ECoG technology involves an electrode grid placed directly over the surface of their brain to record neural activity, and thus requires much smaller neural ensembles (~1–2 square mm) to be active at one time. Also, the electrode space is coarse (1 cm electrode spacing, electrode size is 2.3 mm in diameter) so fewer electrodes are needed. Though still an invasive technique because it requires a craniotomy (surgical incision into the skull) to implant the electrode grid onto the surface of the brain, ECoG is less invasive than BCI implants because the grid does not penetrate the cortex. It is worth noting that ECoG is already a very common procedure in clinical practice for identifying the locus of epileptic seizures. Another interesting difference between techniques is that while EEG usually picks up lower frequency oscillations, ECoG gives access to higher frequency rhythms that tend to be confined to relatively small areas of the cortex, so researchers can pinpoint areas of activation in relation to different cognitive tasks.

The utility of the high frequency range

Research is advancing knowledge of even the fundamental science behind neural signals in this high frequency range. Most studies to date have treated amplitude changes for signals with frequencies above 30 Hz as homogeneous, but **Daniel Moran**'s work at Washington University in non-human primates shows that epidural ECoG in high frequencies (60–200 Hz) is highly correlated with ensemble single unit activity, and can modulate 50%–75% of baseline power for BCI control. In just one week, Moran's group trained a monkey to draw circles with a 2-D computer cursor using just two randomly selected electrodes, biofeedback and neural adaptation of microECoG signals over "cortical control columns" just a few millimeters in diameter. Also advancing the study of high frequency neural signals, Leuthardt and colleagues have shown that that high frequency (gamma rhythm) oscillations are non-uniform and can thus be used as signals for ECoG-based BCI control in humans (e.g. controlling a cursor solely with thoughts). Taking advantage of the EcoG monitoring already required to locate seizure foci for surgical resection in epilepsy patients, the group tracked neural signals associated with simple speech and motor tasks. These investigations showed that independent and non-uniform power changes occur in narrow bands throughout the high frequency (30–530Hz) range of signals. Each cognitive task was accompanied by power changes in distinct frequency bands, and analogous power changes in separable frequency bands within the same cognitive task differentiated cortical regions. As these results have demonstrated, further research on cortical activation for BCIs may need to account not only for electrode location and the timing of signal detection but also for the frequency range of that collection.



In brief, the advantages of ECoG measurements over traditional EEG measurements.
(Courtesy of Eric Leuthardt)

Leuthardt and colleagues advanced the application of ECoG and decreased training time for using neural prosthetics. They were able to show that patients could use ECoG signals correlated with imagined and real speech and motor tasks to gain closed-loop control of a one-dimensional computer cursor. The whole process was both rapid, requiring training periods of just 3–24 minutes, and accurate, achieving target accuracies of 73%–100%. In an extension of this analysis to two dimensions, tests showed that patients using the ECoG activity of imagined or actual motor tasks could also control a computer cursor rapidly (training periods of 12–36 minutes) and with average success (53%–73% accuracy in a 2-D, four-target center-out task). For patients with little training (~30 minutes), high levels of multidimensional control are therefore possible with high frequency gamma rhythms. And these frequencies can convey information about cognitive intent as well. In another study, seven epilepsy patients monitored with ECoG were given a simple word repetition task: see or hear a word and then repeat it. The investigators could separate out stimulus onset and hearing, reading, and speaking, by the changes in high frequency bands (as high as 530hz) measured by one 2.3 mm electrode over patients' sensory motor cortices. Further, patients could move a ball on a computer monitor with just one microelectrode transmitting a single high frequency band to articulate either "oo" or "ah."

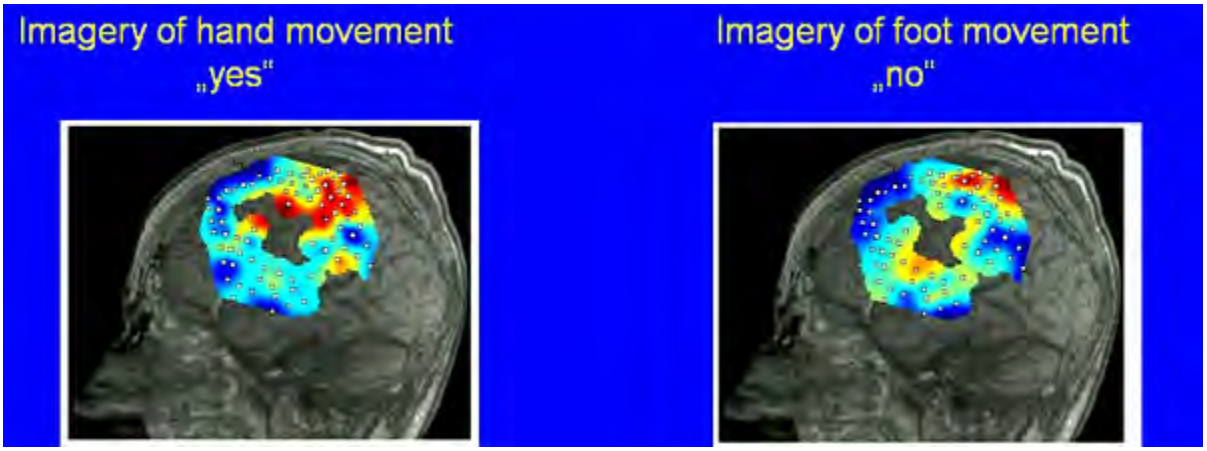
ECoG is a unique way to study human cortical physiology directly and to investigate translational applications in the brief window of time researchers have to test out BCI paradigms in humans. High frequency oscillations are not, as some had expected, uniform, and they convey significant information about cognition and cortical location, which tests of motor and speech physiology have shown. Inspired by these promising results, researchers are also examining the high frequency range for information about levels of attention and consciousness. Minimally invasive ECoG-based BCIs, which can combine high performance with clinical and technical practicality, may therefore be a favorable option for the control of neuroprosthetic devices in humans.

Restoring communication

One purpose of BCI devices is to restore the capacity for communication for those who are completely paralyzed. Patients with severe brainstem stroke or advanced amyotrophic lateral sclerosis (ALS, colloquially known as Lou Gehrig's disease) can suddenly or progressively enter into a locked-in state (LIS). Using noninvasive EEG-based BCI for verbal communication, ALS patients have shown successful, but slow, communication up to and even during the LIS, where they still have intact vision and eye movements and can get positive visual feedback. These patients can, over the course of about a minute, select a letter by moving a cursor on a computer screen and can ultimately spell words. The completely locked-in state (CLIS), characterized by a lack of eye movement, vision, and visual feedback, a compromised somatosensory system, a dependence of auditory communication, artificial respiration and feeding techniques, and an altered though present circadian rhythm, does not seem to disrupt cognition according to evoked

potential and fMRI analyses. It is nonetheless very difficult to show BCI control in patients in this state, and it remains to be seen whether patients who transition from LIS to CLIS paralysis can transfer the control they had learned from one state to the other.

In a series of studies **Niels Birbaumer** of the University of Tübingen and his colleagues found that non-invasive EEG-based BCIs can allow for brain-derived communication in paralyzed and LIS patients, but not in CLIS patients. Voluntary regulation of neural activation (controlled by thought) for communication (yes/no) was possible with BCI technology in all stages of paralysis except in the CLIS. But, the high spatial resolution and increased signal-to-noise ratio in ECoG signals, combined with the short training periods required, may offer an alternative for communication in the CLIS. For example, epileptic patients using ECoG signals derived from motor-related areas were able to spell their names by moving a cursor on a computer screen to select letters within only one or two training sessions simply by imagining moving their tongue to select a letter and their hand or foot to eliminate a letter. And they could write a letter without any training within just 20 minutes.



Differential activation of areas of the brain for imagined hand (left) or foot (right) movement.
(Courtesy of Niels Birbaumer)

Prompted by these initial results, researchers then implanted the ECoG grid in two CLIS patients. Although there were no positive results from the first patient, there were from the second patient. And, as in Leuthardt's work (described above), the high frequency patterns were of greater use to and therefore more employed by the patients than lower frequency patterns for the aurally-learnt task, which required them to imagine different movements to indicate 'yes' and 'no' . But the statistical difference between the affirmative and negative imagined movements was not enough for useful, reliable communication. Another limitation on this kind of communication is that, if a person is in a paralyzed state for a long time, his or her voluntary thinking and capacity to form the intent to move may actually go into extinction. For this reason the researchers used a semantic classical conditioning paradigm instead, which is reflexive but still responsive. Instead of thinking about movements, patients use their conditioned behavior to respond implicitly to stimuli.

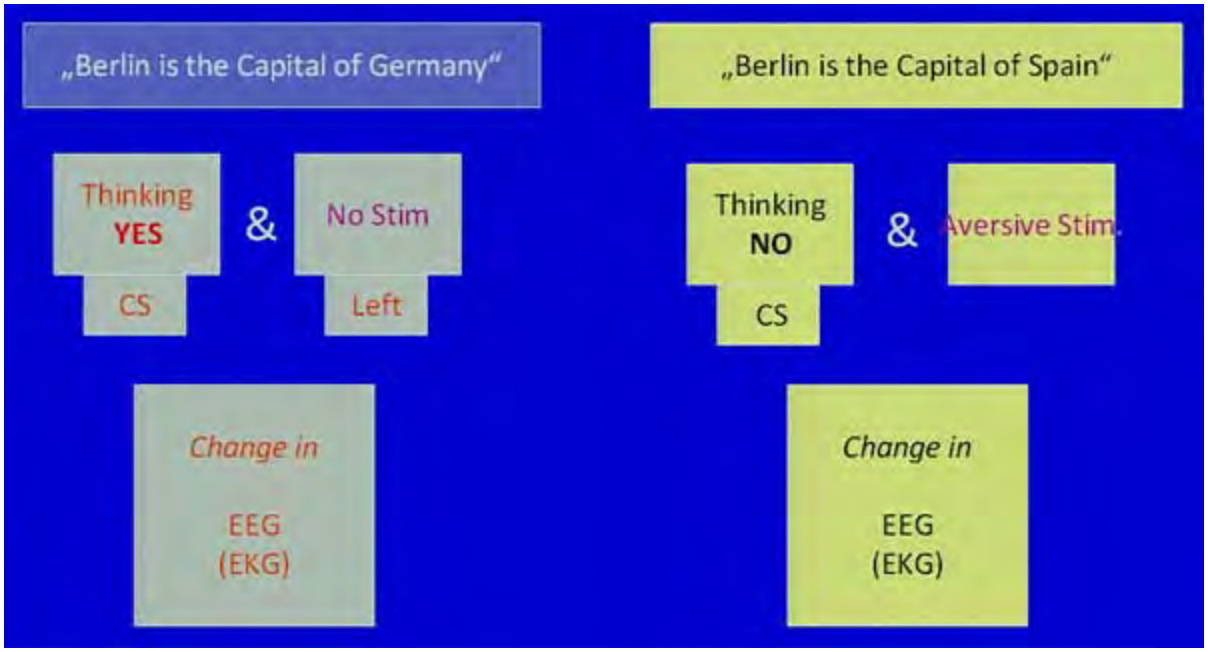


Diagram of the semantic classical conditioning paradigm. (Courtesy of Niels Birbuamer)

Two patients with ALS on the verge of becoming completely locked-in but who still had eye movements were presented hundreds of prompts that have yes or no answers. They were told, for example, "Berlin is the capital of Germany," and if they thought 'yes'—the conditioned stimulus (CS)—they were given a tactile non-aversive stimulus, the unconditioned stimulus (US). If, when told "Berlin is the capital of Spain," for example, they thought "no"—also the CS—then they were given an aversive electric stimulus. The researchers took EEG measurement and looked for reliable differences between the aversive and non-aversive stimulus situations . And after some training, in just over one week, researchers could discriminate between 'yes' and 'no' answers with about 70% accuracy based on the patients' EEG patterns. The ability to distinguish affirmative and negative responses allowed the researchers to ask more open-ended questions, interspersed with questions like those above to which researchers knew the answers. Patients were asked "do you feel pain?", "do you want to live?" Though interesting, the patients' recorded answers to these questions may prove somewhat unreliable, at least until researchers can improve their ability to determine the patients' truly-intended 'yes' and 'no' responses.

Restoring motor control

In order to restore even partial motor control for paralyzed patients, it is often important to move beyond motor cortex stimulation to record neural signals in or to stimulate target muscles. Transmission in target muscles, however, requires the development of an analogous but often quite different set of neural prosthetics technologies.

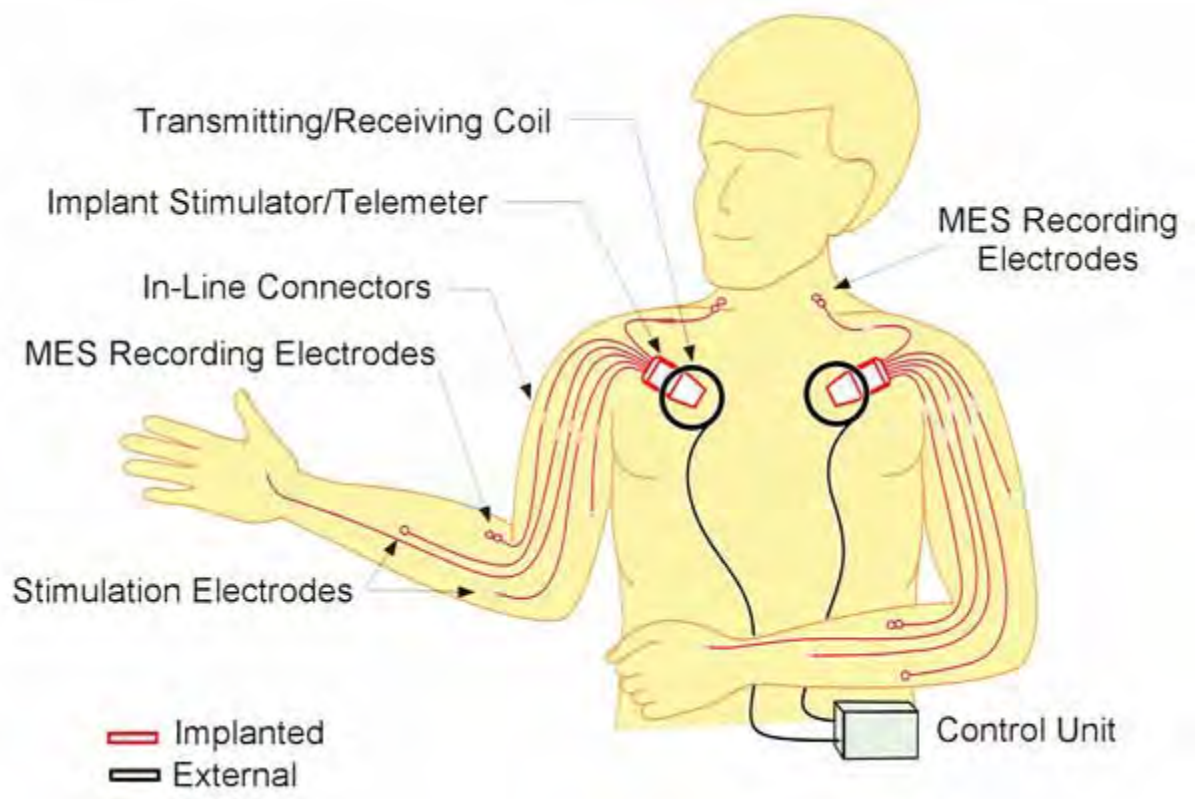


Diagram showing the placement of the components of a bilateral implanted stimulator telemeter system.
(Courtesy of P. Hunter Peckham)

Hunter Peckham of Case Western Reserve University works on this very set of technologies, and at this conference he discussed examples of upper and lower extremity neuroprostheses from his research that restore full arm mobility and levels of standing and ambulation in otherwise paralyzed individuals. These particular prostheses use a bilateral stimulator telemeter system, which involves multiple electrodes implanted in target muscles to record or stimulate neural signals, and a control unit outside the body. Current upper extremity prosthetics depend on residual (non-paralyzed) muscles as their primary means of action, but these muscles lack sensory feedback so control of them is complicated. **Geoffrey Ling** and **David Clifford** at the Defense Advanced Research Projects Agency (DARPA) are working on shifting from muscle- to neural-based control of the prosthetics and providing for sensory feedback, which will greatly enhance the extent to which any prosthesis is truly a "replacement" limb.

In addition to target muscles and regions of the motor cortex, **Jacqueline Bresnahan** of UCSF explained that there are also large assemblies of neurons in the spinal cord that can be stimulated by neural prosthetic devices to enhance recovery. Neural prostheses can train and enhance the activity of these neurons by delivering pharmacological stimulation in the form serotonergic agonists that drive locomotion or direct spinal cord stimulation (at L2 and S1 over the dorsal aspect of the spinal cord). The best locomotion/stepping can be elicited by stimulating with a combination of the two. Understanding the properties of the neural circuits that remain after spinal cord injuries and how those residual circuits might be activated to improve recovery is critical for the development of effective prosthetics devices.

Restoring sight

Along with helping to restore motor function, neural prostheses can also be used to help restore damaged or lost sensory functions like hearing and vision. **Robert Greenberg** of Second Sight® Medical Products, Inc. presented an exciting neural prosthetic being tested in humans. The Argus II implant is a 60-electrode neural device that bypasses defective photoreceptors and stimulates remaining viable retinal cells in people blinded by retinal degenerative diseases such as retinitis pigmentosa or macular degeneration. An external camera wirelessly transmits image data to the implant, which stimulates electrodes in an array on the retina to produce an image. Though that image is nowhere near as detailed as those produced in a normal functional eye, the patient can see phosphenes, spots of light, with this device, which a blind patient can use to perform visual tasks. In clinical trials otherwise blind patients using this retinal prosthesis were able to detect and identify visual percepts, both on a computer monitor and in the real world: they were able to find real world objects (a door, for example), identify direction of motion, walk along a straight line,

and even recognize letters and words on a computer screen and read magazine headlines . These very promising results have been shown over the long-term (years). In the largest and longest study of a visual prosthesis to date 30 retinally blind people were implanted with the Argus® II and their treatment followed for up to 3.2 years, during which time Argus was able to provide the patients with visual function.

To transition other neural prosthetic devices to the clinic, investigators need find ways to increase the performance of prostheses, including their robustness, to maximize the benefit-to-risk ratio, and to create better options for patients. Researchers need to map better the relationship between device performance and invasiveness—to understand the relative impact of surgical and non-surgical techniques and to grasp the overall impact of a device on a person's life. These factors will need to be weighed for each of the different modalities, EEG, epidural ECoG, subdural ECoG, and intracortical recordings among them. The goal is to develop "high-performance prostheses" that can be implanted for the long term so that the benefit of using neural prosthetic devices in humans will outweigh the risks of employing them.

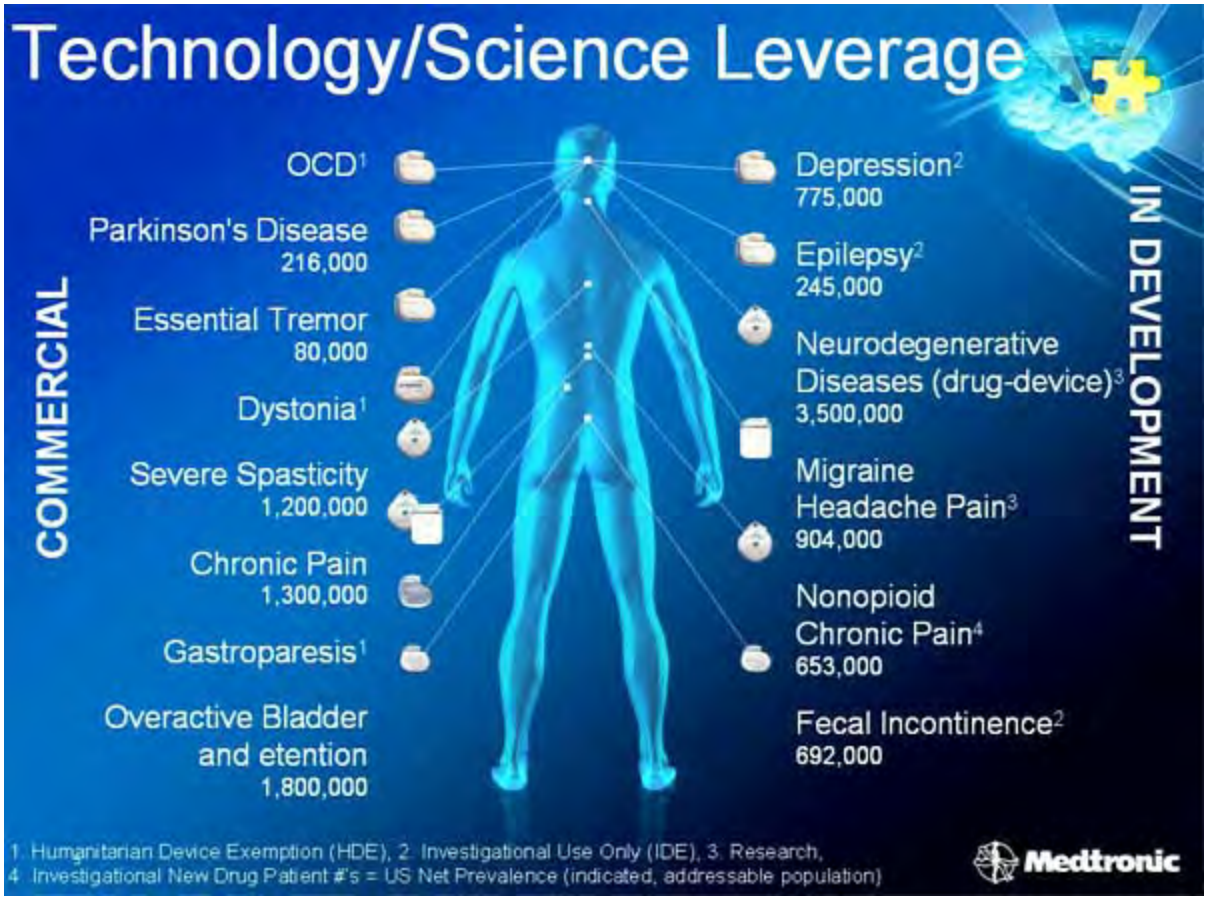
Promising New Applications of Neural Prosthetics

Speakers:
Helen Mayberg, Emory University
Robert Fisher, Stanford University School of Medicine

Highlights

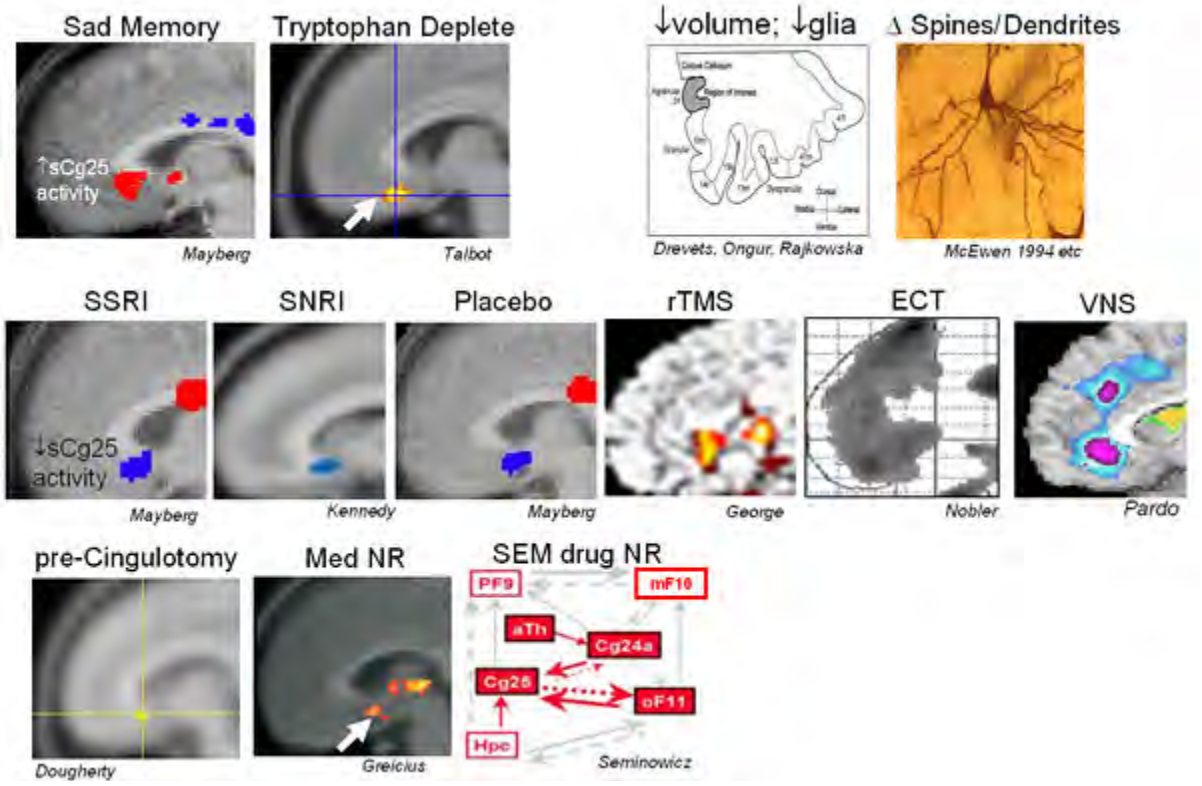
- Deep brain stimulation is a promising new therapy for epilepsy and treatment refractory depression.
- DBS of the central thalamus in a patient who was in a minimally conscious state for 6 years supported significant functional recovery.
- DBS of the subcallosal cingulate white matter was associated with 60% sustained response rate out a minimum of 3 years in a first cohort of 20 patients.

In his keynote address **Apostolos Georgopoulos** of University of Minnesota Medical School encouraged conference attendees to open up the field of neural prosthetics by using brain signals not only to control prosthetic devices or communicate directly with the external world, but also to diagnose illnesses that would affect neural signals, and perhaps even to treat human diseases. After all, these diagnostic and therapeutic applications use the same kind of information, namely the variation over time of the electromagnetic signals that result from synaptic or spike activity, as communication and prosthesis applications do. It should therefore not require a great deal of change to the field to attempt to extend the use of neural information to the whole range of problems it could be deployed to solve.



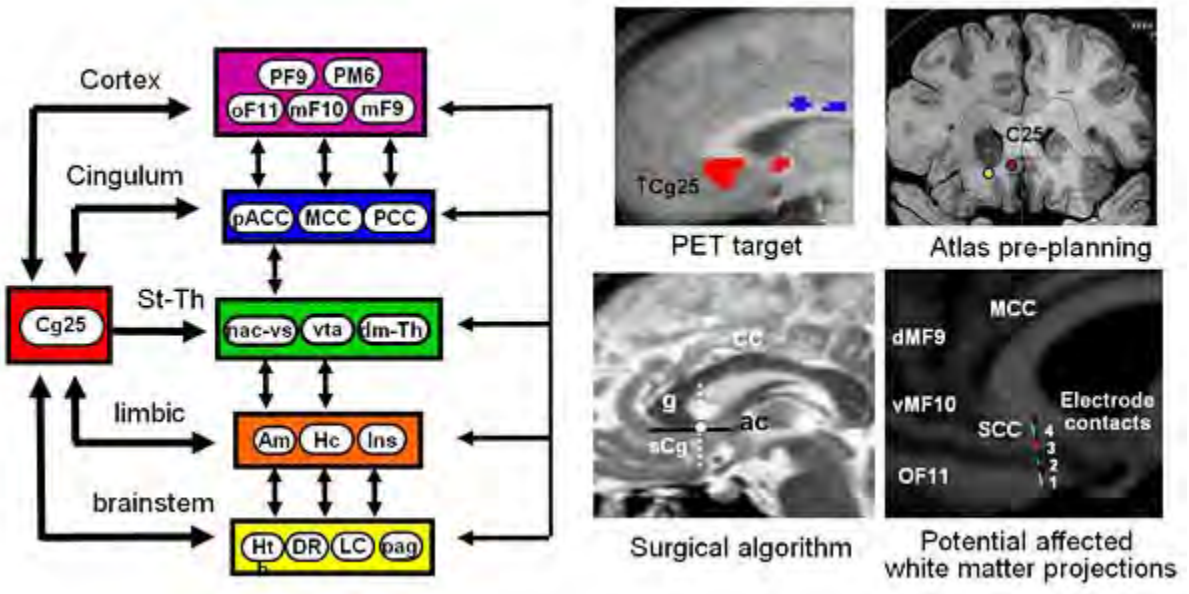
Current (left) and future (right) uses of Medtronic neural prosthetic devices. (Courtesy of Timothy Denison)

But how can researchers use neural prosthetics to treat disorders including not only neurodegenerative diseases and paralysis, but also including less typical targets such as depression and epilepsy? One promising possibility is deep brain stimulation (DBS), for which electrodes are implanted deep within the brain to stimulate brain regions directly. An extension wire connects the stimulating leads to a pulse generator usually implanted under the skin of the chest, and a hand-held external magnet activates the pulse generator to deliver the stimulation. In 1997 the FDA approved 1-electrode location DBS as a treatment for intractable motor disorders (such as essential tremor disorder or refractory Parkinson's Disease), and in 2002 they approved bilateral implantation DBS treatments. The success of DBS for movement disorders and its reversibility, adjustability, and relatively safe side-effect profile render DBS an attractive treatment candidate. These features, in conjunction with the known relationship between the overlapping dysfunction of neural circuits mediating movement and certain psychiatric disorders, have prompted researchers to investigate DBS as a treatment for psychiatric disorders such as obsessive compulsive disorder and treatment-resistant depression (TRD), and other neurological disorders including epilepsy .



Critical role of subcallosal cingulate: converging evidence. (Courtesy of Helen Mayberg)

Depression is a highly prevalent and debilitating disorder and available treatments are not always effective. Presenters indicated that less than 40% of patients achieve remission with the first treatment, and approximately 10% suffer from treatment resistant depression for which multiple medications, psychotherapy and electroconvulsive therapy fail. Made possible by advances in neuroimaging and stereotactic neurosurgery to locate therapy target areas precisely, neuromodulation with DBS is a new treatment strategy for patients with TRD. **Helen Mayberg** from Emory University School of Medicine explained that converging neuroimaging evidence implicates the subcallosal (ventral) cingulate (Brodmann area 25), located deep to the frontal cortex, as a region critical to depression within a limbic-cortical dysregulation model of the disease's cause. Coordinating the modulation of dysfunctional limbic-cortical pathways in this distributed network is thought to be crucial for illness remission. Therefore, proof-of-concept testing of DBS as a treatment for TRD targeted the subcallosal cingulate, metabolically overactive in TRD, for DBS.



Modulating depression networks with DBS where the goal is to block aberrant SCC25 activity with 2°

effect on connections. (Courtesy of Helen Mayberg)

Mayberg and colleagues found that 6 months of chronic DBS of white matter tracts adjacent to the subgenual cingulate gyrus (the region mentioned above) was associated with significant clinical response (evident after 3 months) in 4 of 6 TRD patients. And symptom improvement was accompanied by reduced local cerebral blood flow changes in limbic and cortical areas downstream as measured by PET scans. DBS decreased the overactivity in area 25 and improved patients' symptoms, an important result . When Mayberg's group expanded the study to include more patients (the original 6 plus 14 new subjects) in an open trial with 1 year follow-up, they found similar and sustained improvement with chronic DBS and replication of PET scan changes in limbic and cortical areas. Chronic DBS appears to be a relatively safe (serious adverse events were sparse and there were no permanent deficits), well tolerated, and long-lasting (now more than 3 years) treatment for TRD. To take this treatment to full clinical application, researchers will need to conduct double-blind placebo-controlled clinical studies, to refine the 'dose' by determining whether continuous, cycled, or directed stimulation works best, to compare this target region in the brain to other targets in the circuit, to search for predictors of response using clinical and imaging data, and to develop better animal models to explore the underlying mechanism of depression.

DBS is also a promising new therapy for epilepsy. Available surgery and medications cannot adequately control seizures in one-third of all people with the disease, but one day DBS may be able to interrupt, prevent, or cure epileptic seizures. So far DBS has shown some ability to interrupt and prevent seizures, but whether the procedure can be optimized to cure seizures effectively remains to be seen. But optimizing the technique may not be a trivial task. Scientists have already adjusted the timing of treatment by either cycling DBS treatment or stimulating seizure foci in response to seizure detection. They have also tested the stimulation of different brain regions, including the cerebellum, caudate, brainstem, hippocampus, hypothalamus, subthalamus, centromedian thalamus, anterior thalamus, and cortical seizure focus. Since the hippocampus is perhaps the most common area involved in epilepsy, researchers anticipated the best results from DBS of this region. In a double blind, multiple cross-over, randomized controlled study, 4 patients with refractory mesial temporal lobe epilepsy were implanted with a stimulating electrode in the left hippocampus. According to **Robert Fisher** from Stanford University Medical School, DBS treatment with this electrode caused a moderate reduction in seizures (15%), some positive trends and long-term benefits, and no adverse effects, but these effects were of limited impact. Moving to a different region of the brain, in the SANTE (stimulation of the anterior nucleus of thalamus for epilepsy) trial, researchers implanted 110 sufferers of frequent and unmanageable partial-onset seizures with DBS electrodes bilaterally in anterior thalamic nuclei. DBS was generally well tolerated, and over a 3-month blinded phase there were fewer seizures in the stimulated group (40% reduction) than in the control group (15% reduction), severe seizures and injuries were reduced, and improvement in seizure frequency increased over the next two years, with 14% becoming seizure-free for 6 months.

Despite this success scientists still do not know the precise mechanisms of DBS efficacy, but they suspect those mechanisms are complex and involve more than just one pathway to achieve the clinical effects observed. DBS using high-frequency pulses (≥100 Hz) is thought to have complex effects that include a blocking effect on the stimulated area's ability to receive or transmit signals, mimicking the effect of tissue lesions, but without actually destroying tissue. Even if the process of stimulation is optimized successfully, more work is needed to make the DBS device smaller and wireless, with a longer-life battery, better voltage steering, continuous readout, and a closed loop system. Better rehabilitation programs will also need to accompany DBS treatment as the technology makes the transition to clinical use.

Ethical Issues

Speakers:
Martha J. Farah, University of Pennsylvania
Joseph J. Fins, Weill Cornell Medical College
Kristen A. Bowsher, US Food and Drug Administration

Highlights

- A patient in a persistent vegetative state had a differential pattern of cortical activation recorded using fMRI that was indistinguishable from that of healthy subjects doing the same imagery tasks.
- Despite vegetative state, one patient could reliably respond to yes and no questions using a mental imagery technique.
- The use of neural prosthetics raises unique regulatory and ethical questions.

There are unique regulatory and ethical problems associated with using neural prosthetics in humans. Broader social and contextual issues must be taken into account when using neuroprosthetic devices to facilitate communication and interaction with others, like how clinicians, caregivers and the legal system will interpret a patient's machine-assisted communication. **Joseph Fins** of Weill Cornell Medical College highlighted how imperfect channels of communication and ambiguous outputs from prosthetic devices based on translated neural signals can have an impact on a patient's rights, if for example a patient's responses to questions based on imperfectly translated neural signals contradict their verbal responses made before they were unable to move or communicate.

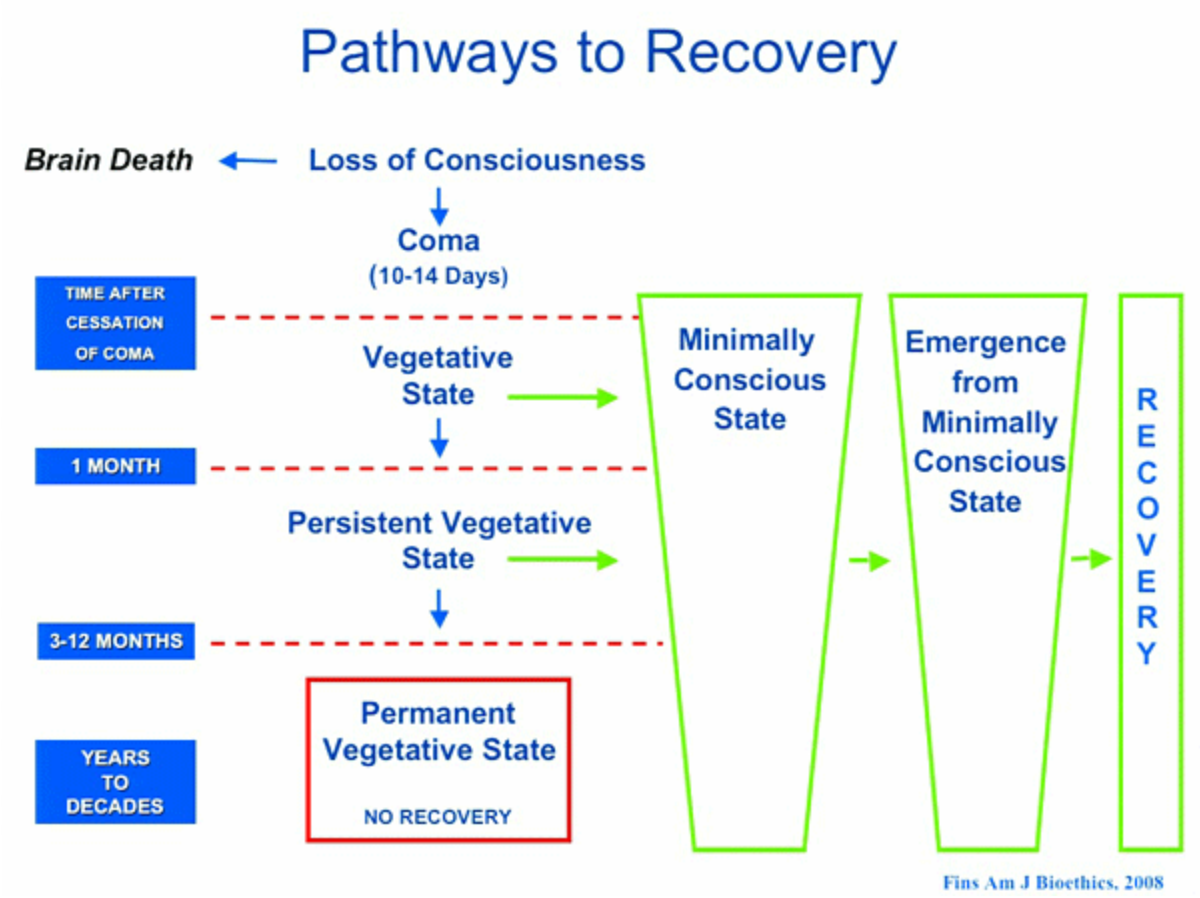


Diagram outlining possible outcomes for individuals after they lose consciousness. (Courtesy of Joseph Fins)

Thalamic DBS and functional neuroimaging have been used as communication prostheses for people with disorders of consciousness such as permanent/persistent vegetative state (PVS) or minimally conscious state (MCS). PVS patients are 'awake'—their eyes open spontaneously and they exhibit sleep-wake cycles measured by EEG, startle responses, and preserved but inconsistent reflexive behavior to noxious, threat, tactile, and olfactory stimuli—but they are *not aware* of themselves, others, or their environment. Nor do they have elaborative, voluntary responses. Overall they are in a state of 'wakeful unresponsiveness'. MCS patients are awake and *minimally aware* in that they have episodic and intermittent moments of consciousness (as indicated by non-reflexive responsiveness or purposeful behavior), and important neural networks are functionally integrated and intact.

According to Fins, DBS of the central thalamus in a patient who was in a MCS for 6 years after severe traumatic brain injury modulated behavioral responsiveness and supported significant functional recovery. Further, fMRI revealed that a patient who met the criteria for PVS was able to reliably imagine playing tennis or moving around her home on demand, as indicated by her differential pattern of cortical activation that was indistinguishable from that of healthy subjects asked to do the same tasks. Building on this work, researchers toggled 'yes' and 'no' answers to "imagine playing tennis" and "imagine waking through your home." Of the 54 patients tested with severe traumatic brain injury in a PVS or MCS, 5 could voluntarily and reliably modulate their brain activity on command using mental imagery, and one, previously thought to be in a PVS, could reliably respond to 'yes' and 'no' questions using this mental imagery technique. These results question what it means to be "conscious," and they challenge the practice of early discontinuation of treatment for patients who show only unpredictable, inconsistent interactive behaviors.

In a recent case, a MCS patient could intermittently behaviorally respond and could make 'facially plausible' yes or no answers, but, when asked if he wanted to die, he had no response. He had, however, made verbal statements prior to his head injury that he did not want to be kept alive in such a state. 'No response' could mean a number of different things in this case: Perhaps he could not initiate a query, he was not paying attention, his response speed was too low, or he was weighing his choices. In this case, the California Supreme Court determined that it was and that his feeding tube could not be removed. So he was kept alive based on his non-response. Thus, prosthetic tools meant to provide patients with autonomy and the opportunity to communicate might inadvertently undermine their self-determination, and paradoxically, as Fins put it, "a prosthetic (device) for communication could undermine the patient's own voice."

Ethical issues in the short term (in the next 10 years) include pressure to try out neural prosthetic devices for other indications, like neural enhancement, and issues surrounding how to carry out and to fund translational work and clinical trials. The scientific community needs to enlist corporate and political assistance to determine how to handle funding, potential conflicts of interest, intellectual property law, and the regulation of devices that emerge from the research. For progress to occur researchers also need to account for people's aversion to the crossing of the blood brain barrier as well as for any general cultural resistance to technologies that appear to infringe on the individuality or independence of thought.

Martha Farah of the University of Pennsylvania predicted some of the ethical issues scientists might encounter as neural prosthetics become a clinical commonplace: If, in the next 10 to 30 years, neural prosthetics become consumer products that enhance brain function and memory and even perform complex calculations, the field will grapple with the effects of the high price tag that would accompany these technologies. Issues of access would dominate ethical discussions as researchers and regulators consider whether there will be a social class differentiation between people who can afford implants and those who cannot. Other ethical concerns might include issues around the acceptance of BCIs for less than dire conditions, the control of inputs and outputs (patients' autonomy, involuntary treatment, hackers, etc.), the choice of which applications to develop (e.g., games vs. treatment for rare diseases), and the possibility of neural enhancement, either cosmetic or therapeutic.

In the long-term, scientists will need to consider the range of social ramifications that could result from widespread, secure, reliable, and seamless integration of neural prosthetics. As the evidence presented at this conference indicates, a functional, reliable machine interface with the brain is on the horizon as is the fundamental neuroscientific research to ground therapeutic applications of such an interface. Scientists might, therefore, need to deal with the spectrum of social, scientific, and cultural consequences of neural prosthetics sooner rather than later.

Open Questions

What needs to be done to get neural prosthetics working seamlessly and efficiently in humans?

When is it appropriate to test the neural prosthetic technology developed in non-human animals in the laboratory in human subjects?

Where is the funding going to come from to propel basic neural prosthetic research forward and drive the migration of research from the laboratory to human use?

How can investigators make use of the best motor-related signals to control prosthetic device actions?

What neural signals should researchers be decoding for use with neural prosthetics?

What movement parameters make the best control for a continuous motor prosthesis?

What is the benefit-to-risk ratio for different BCI techniques? What is the relationship between device performance and invasiveness, and how do different device modalities (e.g., EEG, epidural ECoG, subdural ECoG, intracortical recordings) differ in these measures?

What are potential applications of neural prosthetics, not only to control assistive or communicative devices, but also to diagnose or treat diseases? Which diseases are most amenable to neural prosthetic therapy?

What are the underlying mechanisms of action of deep brain stimulation (DBS)?

Why does the benefit of DBS therapy increase over time? What are predictors of response to DBS?

What are the best anatomical targets and stimulation parameters (cycling, continuous, or responsive stimulation) for

different disorders?

Does DBS have long-term problems/adverse effects, such as withdrawal, kindling? How can DBS be made safe for MRI or combined with other therapies?

What are the goals of treatment with neural prosthetics? What do patients want to achieve with neural prosthetic devices?

How should imperfect channels of communication and ambiguous outputs with prosthetic devices be dealt with when answering important medical questions about, for example, whether patients want to live or whether they feel pain? What happens if a patient's answers undermine the wishes he or she made clear when fully communicative? How should researchers interpret ambiguous or incomplete responses from patients communicating via neural prosthetics?

What is the future of neural prosthetics? Should they be used for cognitive enhancement? What are the possible social ramifications of cosmetic or medical use of neural prosthetics?

Media


Audio

A History of Prosthetics

Andrew B. Schwartz (University of Pittsburgh)


Slides & Audio

Factors Affecting Cursor Control by Small Ensembles of Motor Cortex Neurons

Marc H. Schieber (University of Rochester)


Audio

Panel Discussion: Translating Basic Research into Effective BCI

Moderator: Robert J. Greenberg (Second Sight Medical Products, Inc.)


Slides & Audio

Toward High-performance Cortically-controlled Prostheses

Krishna V. Shenoy (Stanford University)


Slides & Audio

Controlling Brain Circuits with Light

Edward S. Boyden III (Massachusetts Institute of Technology)

Slides & Audio

Advanced Implantable Microelectrode Technologies for High-fidelity, Multi-modal Neural Interfaces

Takashi Kozai for Daryl Kipke (University of Michigan)

Slides & Audio

Lessons from Chronic Histological Studies

Patrick Tresco (University of Utah)

Slides & Audio

Brain Computer Interfaces: Theory vs. Reality

Jonathan R. Wolpaw (Wadsworth Center, NY State Department of Health)

Slides & Audio

Electrocorticographic Brain Computer Interfaces

Daniel Moran (Washington University)

Audio

Panel Discussion: How to Engineer an Effective Neural Interface? Pros and Cons of Current Devices and Materials

Moderator: Krishna V. Shenoy (Stanford University)

Slides & Audio

Research in Human Electrocorticography and Neuroprosthetic Implications

Eric C. Leuthardt (Washington University School of Medicine)

Slides & Audio

Interfacing Brain to Machine for Restoration and Enhancement of Human Functionality

Philip Kennedy (Neural Signals, Inc.)

Slides & Audio

Clinical Translation of a Motor System Neuroprosthesis

P. Hunter Peckham (Case Western Reserve University)

Slides & Audio

Brain–Computer Interfaces in Paralysis: Applications in Locked-in Syndrome, Chronic Stroke, and Emotional Disorders

Niels Birbaumer (University of Tübingen)

Slides & Audio

Targets for Neural Prosthetic Interventions in Spinal Cord Injury

Jacqueline C. Bresnahan (University of California, San Francisco)

Slides & Audio

The Development of Deep Brain Stimulation for Treatment Resistant Depression

Helen Mayberg (Emory University)

Slides & Audio

Brain Stimulation for Epilepsy

Robert Fisher (Stanford University Medical Center)

Slides & Audio

An Overview of FDA Medical Device Regulation

Kristen A. Bowsher (US Food & Drug Administration)

Slides & Audio

When Ethics Become Prosthetic: Bringing Context to the Neural Interface

Joseph J. Fins (Weill Cornell Medical College)

Resources

Web Sites

BrainGate

Second Sight Medical Products

Neural Signals Inc.

International Functional Electrical Stimulation Society

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Organizers

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Richard Andersen is the James G. Boswell Professor of Neuroscience at the California Institute of Technology Andersen studies the neurobiological underpinnings of brain processes including the senses of sight, hearing, balance and touch, the neural mechanisms of action, and the development of neural prosthetics. Andersen obtained a PhD in Physiology from the University of California, San Francisco with thesis advisor Michael Merzenich, and was a Postdoctoral Fellow with Vernon Mountcastle at the Johns Hopkins Medical School. He was Assistant and Associate Professor at the Salk Institute, Associate and Full Professor in the Department of Brain and Cognitive Sciences at

MIT and is currently the James G. Boswell Professor of Neuroscience in the Biology Division at Caltech.

Andersen is a Member of the National Academy of Sciences, Member of the Institute of Medicine of the National Academies, Fellow of the American Academy of Arts and Sciences, Fellow of the American Association for the Advancement of Science, Associate of the Neuroscience Research Program, and Member of the International Neuropsychological Symposium.

P. Hunter Peckham, PhD

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P. Hunter Peckham is the Donnell Professor of Biomedical Engineering and Orthopaedics, the Director of Orthopaedic Research at MetroHealth Medical Center, the director for the Center of Excellence in FES (functional electrical stimulation), and a member of the Board of Directors of NeuroControl Corporation. Before his more than 35 years as an employee of Case Western Reserve, Peckham spent time as a PhD student there, earning his degree in 1972. And, before that, he received his MS in Engineering from Case Institute of Technology and his BS in Mechanical Engineering from Clarkson College of Technology.

His current research focuses on the use of functional electrical stimulation to restore hand and arm control in individuals paralyzed by nervous system damage or disease, and he is known worldwide for helping paralyzed individuals regain lost abilities through the use of his innovative technologies. Peckham holds eight patents, has authored hundreds of articles and was elected to the prestigious National Academy of Engineering in 2002. Over his career he has been honored by his peers and dozens of organizations for his achievements, including his election as Fellow of the American Institute of Medical and Biological Engineering.

Andrew Schwartz, PhD

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Andrew Schwartz received his PhD from the University of Minnesota in 1984 with a thesis entitled "Activity in the Deep Cerebellar Nuclei During Normal and Perturbed Locomotion." He then went on to a postdoctoral fellowship at the Johns Hopkins School of Medicine where he worked with Apostolos Georgopoulos. While there, Schwartz was instrumental in developing the basis for three-dimensional trajectory representation in the motor cortex. In 1988, Schwartz began his independent research career at the Barrow Neurological Institute in Phoenix. There, he developed a paradigm to explore the continuous cortical signals generated throughout volitional arm movements. After developing the ability to capture a high fidelity representation of movement intention from the motor cortex, Schwartz teamed up with engineering colleagues at Arizona State University to develop cortical neural prosthetics. Schwartz moved from the Barrow Neurological Institute to the Neurosciences Institute in San Diego in 1995 and then to the University of Pittsburgh in 2002. In addition to the prosthetics work, he has continued to utilize the neural trajectory representation to better understand the transformation from intended to actual movement using motor illusions in a virtual reality environment.

Keynote Speaker

Apostolos Georgopoulos, MD, PhD

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Apostolos P. Georgopoulos studied Medicine and Physiology at the University of Athens in Greece where he obtained his MD and PhD degrees. He was trained in neurophysiology by Vernon B. Mountcastle at Johns Hopkins and, after a brief return to Athens, he came back to Johns Hopkins. He ascended the faculty ranks and promoted to Professor of Neuroscience in 1986. He was a member of the Philip Bard Laboratories of Neurophysiology at the Department of Neuroscience until 1991 when he moved to Minnesota as the American Legion Brain Sciences Chair at the Minneapolis Veterans Affairs Medical Center and the University of Minnesota.

He is currently a Regents Professor of Neuroscience, a McKnight Presidential Chair in Cognitive Neuroscience, the American Legion Brain Sciences Chair, the Director of the Center for Cognitive Sciences and a Professor of Neuroscience, Neurology, and Psychiatry at the University of Minnesota. His research focuses on magnetoencephalography of brain function, neural mechanisms of cognitive processes, the neurophysiology of motor control and cognition, and functional MRI of motor and cognitive processes.

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Heather A. Berlin, PhD, MPH is an assistant professor of Psychiatry at Mount Sinai School of Medicine. She received her doctorate from the University of Oxford, Master of Public Health from Harvard University, and Master's in Psychology from the New School for Social Research. Her research aims to discover and further delineate brain–behavior relationships that can contribute to the prevention and treatment of psychiatric disorders and to our understanding of the neural basis of consciousness and dynamic unconscious processes.

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Grant Support

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The project described is supported by Award Number R13NS071862 from the National Institute of Neurological Disorders and Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.