Toward Neurotechnology Innovation: Report from the 2005 Neural Interfaces Workshop. An NIH-Sponsored Event

Joseph J. Pancrazio, PhD* ▪ Daofen Chen, PhD* ▪ Stephanie J. Fertig, BS* ▪ Roger L. Miller, PhD† ▪ Eugene Oliver, PhD* ▪ Grace C. Y. Peng, PhD‡ ▪ Nancy L. Shinowara, PhD§ ▪ Michael Weinrich, PhD§ ▪ Naomi Kleitman, PhD*

**NIH/National Institute for Neurological Disorders and Stroke, Bethesda, MD 20892; †NIH/National Institute on Deafness and Other Communication Disorders, Bethesda, MD 20892; ‡NIH/National Institute for Biomedical Imaging and Bioengineering, Bethesda, MD 20892; and §NIH/National Institute of Child Health and Human Development, National Center for Medical Rehabilitation Research, Bethesda, MD 20892, USA*

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INTRODUCTION

Neural interfaces have emerged as effective interventions to reduce the burden associated with some neurologic diseases, injuries, and disabilities. The 2005 Neural Interfaces Workshop was convened to discuss recent advances and future opportunities for neural technologies. As in 2004, the Workshop combined the 36th Annual Neural Prosthesis Workshop and the annual meeting of the National Institutes of Health's (NIH) Deep Brain Stimulation (DBS) Consortium. The NIH Neural Prosthesis research community consists of investigators supported by grants and contracts; areas of interest include functional neuromuscular stimulation (FNS), auditory prosthesis, cortical prosthesis, microelectrode array technology, and brain computer/machine interfaces. The NIH DBS Consortium is a core group of multidisciplinary researchers funded under a series of NIH-sponsored programs to advance technological innovation and elucidate the sites and mechanisms of action of DBS. The purpose of this report is to highlight scientific presentations and discussions from the meeting. The workshop was

Address correspondence and reprint requests to: Joseph J. Pancrazio, PhD, National Institutes of Health, NINDS, 6001 Executive Blvd, MSC 9525, Rockville, MD 20892, USA. Email: pancrazj@ninds.nih.gov

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organized around six plenary sessions: Progress in Deep Brain Stimulation, Novel Interface Technologies for Stimulation, Surgical Considerations for Neural Interfaces, Chronic Recording Microelectrodes, Neural Interfaces for Sensory Information, Spinal Cord Interfaces, and Future Efforts in Neural Interfaces. A highlight of the meeting was the dedicated poster sessions consisting of nearly 130 posters, where valuable discussions and new collaborations were cultivated. The Workshop agenda and abstracts are available from the National Institute for Neurological Disorders and Stroke (NINDS) Neural Prosthesis Program Web site (http://www.ninds.nih.gov/funding/research/npp/index.htm).

Dr Story Landis, director of the NINDS, welcomed the assembled audience of more than 520 engineers, basic scientists, and clinicians. In her opening comments, she recognized the investigators who started this field for their vision of recording and decoding signals from the brain and translating the resulting findings to help patients with neurologic disorders. Dr Landis also commented on the more recent findings that DBS holds potential benefits for disorders beyond Parkinson disease such as depression. In his opening comments, Mr Jeffrey Martin shared his personal experience with DBS. His insights as a patient not only affirmed the benefits of neurotechnology, but also challenged the workshop participants to continue to advance technologies and applications in DBS.

PROGRESS IN DEEP BRAIN STIMULATION

The goal of this session was to review the progress achieved within the DBS portfolio. Indeed, the investment in DBS research has spanned a diverse range of topics from how to assess and quantify efficacy of DBS in relieving movement dysfunction to the study of the psychological impact of DBS. While it is clear that significant progress has been made in recent years, a recurring point from many of the presenters was the need to gain a better understanding of the pathophysiology of movement disorders, which appear to be manifested in disruptions of normal sensorimotor network function. Two presentations focused on how to quantitatively characterize the therapeutic effects of DBS in rodents as well as in humans. Dr Jing-Yu Chang of Wake Forest University reported on his efforts to develop a rodent model of Parkinson disease to explore the therapeutic mechanisms of DBS. He described the implementation of two tests for the rodent model: a treadmill motor task for forced movement, where DBS significantly improves both stance and swing dynamics; and an asymmetry test, where DBS improves spontaneous activity involving the lesion-affected limb. Dr Daniel Corcos of the University of Illinois at Chicago presented his work concerning the effects of subthalamic nucleus (STN) stimulation on tremor, rigidity, and bradykinesia. His data quantitatively demonstrated that stimulation of the STN greatly improves the movement speed of both the elbow and ankle joints in patients with Parkinson disease, approaching performance levels of healthy individuals. The basis of this improvement appears to be through increased activation of both agonist and antagonist muscles, as indicated by concurrent electromyographic measurements.

Dr Dieter Jaeger of Emory University addressed issues regarding the mechanisms of DBS action. His group used anesthetized rats where antidromic stimulation of the STN produced a dampening of the electroencephalographic potentials, consistent with the observed therapeutic effect of DBS. Dr Robert Turner of the University of California, San Francisco, argued that a comprehensive understanding of the effects of DBS requires detailed information simultaneous recordings using microelectrode arrays. By monitoring multiple locations simultaneously, he demonstrated that DBS alters pallidal somatic activity to abolish oscillatory and burst discharges characteristic of Parkinson disease. Dr Turner's observations suggest that STN DBS affects motor cortical activity through antidromic stimulation.

Initiation of movement, which is often internal and self-timed, is difficult for individuals suffering from Parkinson disease. Dr John Assad of Harvard Medical School described his work investigating cortical and subcortical structures in movement initiation. Multisite recordings in behaving macaques, self-timed movements, but not reaction movements triggered through training, were found to be preceded by increased activity in the parietal cortex and sensorimotor putamen hundreds of milliseconds before movements were initiated. These results have

implications for the design of neural prostheses, where systems using control signals derived from brain structures involved in self-timed movements may prove most effective.

Dr Marjan Jahanashi of the University of London presented her work characterizing the effects of STN DBS on mood and cognition. Overall, STN DBS produces few adverse effects on cognition and some improvements on mood. One of the problems identified with DBS was the negative impact on verbal fluency, possibly due to the spreading of electrical stimulation beyond localized pathologic regions. During a brief platform presentation, Dr Jeffrey Wertheimer of Wayne State University presented survey results consistent with the positive effects of DBS, with the important caveat that DBS can negatively impact verbal fluency.

Dr Jerrold Vitek of the Cleveland Clinic discussed current clinical challenges for DBS in movement disorders. He highlighted numerous issues that may contribute to the inconsistency in the benefit derived from DBS. Among those issues that involve scientific design, it appears that the substantial methodological differences in many DBS studies often make interpretations complicated. For example, outcome measures and the duration of postoperative follow-up are not standardized, and electrode lead locations are not consistently reported. Future clinical opportunities may involve earlier interventions with DBS, although the risk–benefit profile is unclear. Dr Vitek also raised a series of current technological limitations including the inability for high-resolution imaging following surgery due to electrode materials, the lack of telemetry for the implantable pulse generators (IPGs), and the need for extended battery life or rechargeable battery systems. Among the recommendations were to expand the capabilities of IPGs to enable the evaluation of novel stimulation waveforms and to explore the possibility of "smart stimulators" that have the capacity for dynamic internal adjustments. Dr Vitek also suggested that the DBS field needs well-controlled clinical trials for generation of class I evidence,[1] although there appears to be a lack of consensus as to how best to design trials. Nevertheless, it is apparent that the DBS community can work together to develop consensus standards for conducting and reporting data from studies across the spectrum of clinical and translational arenas. These standards could include characterization of electrode lead placement and stimulation paradigms, and incorporation of both motor and nonmotor outcome measures with protocols for follow-up. With regard to gaining a more comprehensive understanding of both the pathophysiology of movement disorders and the basis of DBS action, the ability to stimulate and monitor neuronal activity from multiple regions of the brain simultaneously and generate network-level representations may prove invaluable.

[1]Evidence provided by well-designed, randomized, controlled clinical trials including overviews (meta-analyses) of such trials.

NOVEL INTERFACE TECHNOLOGIES FOR STIMULATION

Several presentations focused on the development of novel stimulation technologies that could impact both the DBS and neural prosthetics fields. Future DBS systems with greater precision of current delivery may reduce side-effects such as the negative effects on speech fluency. Dr Jit Muthuswamy of Arizona State University is developing DBS microelectrode technology coupled to microactuators to enable precise and robust electrode placement. With the actuators and electrodes embedded in the same architecture, it is anticipated that the time required for surgery could be significantly reduced and it would be possible to easily adjust insertion depth post surgery. Dr Jun Li of the NASA Ames Research Center presented early work on the development of a nanoelectrode array for assessing cellular physiology. The chip under development utilizes aligned carbon nanofibers to perform electrochemical recording through amperometry, as well as cell stimulation and recording. The ability to deliver more precise and complex stimulation patterns may be enhanced through the use of high-density arrays. Mr Scott Corbett of Advanced Cochlear Systems presented work on the implementation of a next-generation cochlear prosthetic stimulation array based on the use of liquid crystal polymers (LCPs) as a dielectric material. The advantages of using LCPs include ease of manufacturability through injection molding and biocompatibility. Furthermore, the weakest link for current high-density arrays is the packaging/interconnect interface between

wires and thin-film lithography-based arrays; using LCPs may result in a more durable polymer-based planar circuit technology.

FUTURE OPPORTUNITIES FOR DEEP BRAIN STIMULATION

Deep brain stimulation is being used in a number of therapeutic applications beyond the treatment of Parkinson disease. Dr Steven Shapiro of Virginia Commonwealth University discussed the application of DBS to a disorder of newborn infants, kernicterus, which is produced by excessive jaundice and manifested as a static, secondary dystonia associated with deafness. The main point of the presentation was that potential future applications for DBS may include the pediatric population, for which the technological requirements for long-term implanted systems may be different from those established for Parkinson disease, a disorder associated with adult and aged populations. In addition, the combination of DBS and cochlear prosthetics for children suffering from the effects of kernicterus raises the question of how to design and manage multiple neural interface technologies within a single patient for long periods of time.

SURGICAL CONSIDERATIONS FOR NEURAL INTERFACES

Two neurosurgeons integrally involved in the application of neural prostheses addressed surgical considerations for neural interfaces. Dr Gerhard Friehs of Brown University described the ongoing pilot human trial with the Cyberkinetics BrainGate system. Cyberkinetics, which has completed 1 year of study with its first patient subject, described a plan to eventually develop a wireless implementation of the BrainGate system. Dr Michael Keith of Case Western Reserve University (CWRU) discussed surgical considerations for FNS systems, particularly for restoration of upper limb function. He emphasized the importance of the partnership that has been nurtured at CWRU, which focuses on the collaboration of neurosurgeons and engineers, nurses and students, all working toward common goals. Dr Keith conveyed that the capability provided by FNS is only one of several factors in the decision of a paralyzed individual to opt for the technology. The long time course for surgery and rehabilitation is an important issue and has driven the development of implanted systems that are readily implantable and upgradeable. Progress at CWRU regarding minimization of the number of wire leads, reduction in size, and improved power efficiency was outlined. Dr Keith offered the vision of a neural interfaces "intranet" where multiple implanted devices communicate and share resources, such as power, to address the deficits of multiple physiologic systems affected during paralysis.

An important discussion concerning the utility of brain machine interfaces occurred with Mr Laszlo Nagy, a high-level quadriplegic with an implanted respiratory pacemaker that has freed him from use of a ventilator. Mr Nagy communicated key patient concerns, including the invasiveness of some surgical solutions, saying he would choose to use speech recognition software over an implanted microchip to operate a computer. In response to the question of what capability he *would* require before he would be willing to pursue an implanted microelectrode array technology such as a brain machine interface, Mr Nagy indicated that he would insist on restoration of a substantial function, such as the capability to use his own limb to feed himself.

CHRONIC RECORDING MICROELECTRODES

Progress reports were offered by Dr Kensall Wise of the University of Michigan and Dr Florian Solzbacher of the University of Utah, whose groups are each working on chronic electrode recording systems under contract with NINDS. Their goal is to develop microelectrode arrays that will be capable of robust recordings for periods as long as 6 months to be demonstrated in nonhuman primates. Both groups have identified the external tethering of the implanted microelectrode arrays as a critical issue impeding long-term functionality. Therefore, both groups are developing microelectrode array systems that incorporate onboard amplification, spike detection, as well as wireless transmission of both power and data. The first performance phase of these two contractual efforts will be completed in March–May 2006, when the performers will be required to demonstrate recording capability of the wireless systems for at least 2 weeks in the nonhuman primate model.

NEURAL INTERFACES FOR SENSORY INFORMATION

Presentations summarized ongoing work for three neural prostheses at very different stages of development. Dr Patricia Leake of the University of California, San Francisco, offered insights on the use of cochlear implants taken from studies performed with animal models. Neurophysiology data taken from the inferior colliculus were reviewed to illustrate the influence of the duration of deafness and the stage of development on neural afferents from the implanted cochlea. Dr Leake also presented anatomical data supporting a trophic role arising from electrical stimulation that promotes survival of auditory neurons. Drs Mark Humayan and James Weiland of the University of California, Los Angeles, described progress from clinical studies with an intraocular retinal prosthesis. An investigational device exemption was granted by the FDA for their study protocol, and videotaped demonstrations of patient tests were shown. The present device utilizes 16 platinum electrodes and provides cues that allow patients to discriminate visual object shape and motion with accuracies up to 80%. Dr Charles Della Santina of the Johns Hopkins University presented his work on electrical stimulation of the vestibular nerve. Using an animal model of vestibular deficiency, he showed that stimulation with frequency-modulated bipolar pulses delivered through an electrode placed in a single horizontal canal could induce compensatory vestibular–ocular reflex movement in the horizontal plane. Control over the spread of these stimulating currents into other branches of the vestibular nerve is an area of ongoing refinement. Future plans were presented for a multichannel prototype that might be mounted on the head to encode three axes of rotation through electrical stimulation of the vestibular nerve.

SPINAL CORD INTERFACES

Two presentations focused on technology and application of neural interfaces for the spinal cord. Dr Mesut Sahin of the New Jersey Institute of Technology described a novel approach to interfacing with neural tissue, such as the spinal cord, which eliminates mechanical tethering associated with interconnects. His group has developed a photodiode-based stimulator that converts incident near infrared wavelength light to an electrical stimulus. Preliminary data using a rat sciatic nerve model suggest that the stimulator may operate at depths of 1.5 mm from the laser source. Dr Vivian Mushahwar of the University of Alberta presented exciting work demonstrating the utility of intraspinal microstimulation via implanted microwires to enable functional movements of hind limbs of adult cats with chronic spinal cord injury. Two-thirds of the implanted microwire arrays remained intact for periods reaching 6 months with little or no indication of tissue damage. Coordinated intraspinal microstimulation of motor neuron cell bodies in the ventral horn produced fatigue-resistant stepping movements, consistent with the predominate recruitment of type I or IIa fibers. In contrast, peripheral nerve stimulation showed preferential recruitment of type IIB and D fibers, which are subject to rapid fatigue, suggesting an advantage of intraspinal microstimulation over cuff-based peripheral nerve stimulation to restore limb movement. The relative success of intraspinal stimulation for restoration of locomotion may not translate easily to other systems such as micturition. Brief presentations by two groups working under NINDS contract to develop intraspinal stimulators for bladder and sphincter activity reported some progress in obtaining coordinated motor responses, but major technical difficulties with electrode placement and stability. Differences in electrode placement of only tens of microns may determine success or failure in this application, whereas other ongoing efforts in peripheral nerve stimulation appear more promising at the present time.

FUTURE EFFORTS IN NEURAL INTERFACES

This session consisted of multiple forward-looking presentations that considered the potential impact of new emerging technologies on the future of neural interfaces research. Dr Simon Giszter of Drexel University, working in collaboration with Dr Frank Ko, described a newly developed braiding and weaving system capable of weaving micron dimension wires and nanofibers, producing a wide range of geometries and mechanical properties. With incorporation of electrically

conductive substrates into the weave, novel electrode probe designs may be implemented.

Dr Miguel Nicolelis of Duke University presented three novel paradigms to explore the future of neural interfaces research. In the first paradigm, Dr Nicolelis has applied a multielectrode recording array approach to a dopamine transporter knockout mouse model that exhibits reversible parkinsonian characteristics via blockade of dopamine synthesis. Based on the analysis of firing patterns from hundreds of neurons recorded from the arrays implanted in the dorsolateral striatum and motor cortex in knockout mice, phase locking in local field potentials was found, an observation consistent with the notion of abnormal network synchrony as a contributing factor to Parkinson disorders. Their experiments also have shown that the synchronization could be disrupted through vagal nerve stimulation. A second paradigm presented by Dr Nicolelis involved studies in which implanted monkeys were provided with vibrotactile input as haptic feedback. Application of microstimulation at the thalamic and cortical levels was found to produce effects that were proportional to joint movements and kinematics. The third paradigm he presented was related to development of bipedal locomotion using an animal model. Their most recent data have shown that visual and tactile feedback in monkeys was proportional to the velocity of the treadmill. In summary, these paradigms illustrate the utility of the multineuronal recording approach to address basic and translational questions of the central control of motor function in health and disease states.

Dr Theodore Berger of the University of Southern California presented his work in the development of biomimetic electronic devices for cognitive function. This work is centered on the development of novel mathematical models that encode the nonlinear dynamics of hippocampal neuronal networks. By integrating the modeling approach with electrode array recordings from hippocampal slices, Dr Berger's group was able to demonstrate replication of some of the hippocampal functions by substituting the CA3 region of the hippocampus with a microchip implementation of the predictive mathematical models. Moving beyond "slice computation," Dr Berger's team is beginning to translate these methods to ensemble encoding studies in the whole brain, developing multi-input mathematical models that incorporate neuronal dynamics from pairs of synaptically connected cells. The result will be a microchip that captures the three-dimensional neuronal behavior of a particular hippocampal region. Although in its infancy, this pioneering work challenges the notion that the only foreseeable means of treating individuals with damaged regions of the brain would be through cell-based and/or pharmacologic interventions. At a minimum, this biomimetic neural engineering highlights the strong potential that computational methods and models may have on enhancing the development of neural interface systems.

Two presentations offered alternative ways of stimulating neural tissues. Dr Duco Jansen of Vanderbilt University showed preliminary data indicating that it is possible to activate neural structure with low-level, pulsed infrared laser light. This system has the ability of applying a wide range of wavelengths for depth penetration in tissue to target nerve fascicles. The underlying mechanism of this effect is unclear, although it may involve photothermal effects evidenced by localized elevations in temperature. Dr David Pepperberg of the University of Illinois at Chicago described efforts to construct neurotransmitter-mimicking molecular structures that tether and control the dynamics of the neurotransmitter γ-amino butyric acid (GABA) for neural prosthetic applications. Through tethering with azobenzene molecules, GABA could interact with postsynaptic receptors to elicit channel opening. Dr Pepperberg's group is exploring the potential utility of this approach to create synthetic photosensors to stimulate inner retinal neurons via the GABA type C receptor.

Dr Bruce Wheeler of the University of Illinois at Urbana reviewed advances in neural interfaces from studies using *in vitro* models. His group and others have developed reproducible patterns of neurons on two-dimensional architectures bearing microelectrode contacts for stimulation and recording. Dr Wheeler emphasized the value of *in vitro* approaches to address fundamental and applied aspects of neuro-electronic interfaces. For example, the controlled architecture and accessibility of *in vitro* systems allow quantitative modeling and experimental work to evaluate effectiveness of electrode with recessed vs. protruding geometries. Dr Wheeler pointed out

that not all *in vitro* models are equal; there are significant limitations in the use of transformed cell lines that typically fail to exhibit robust synaptic connectivity. Lastly, Dr Wheeler discussed the development of three-dimensional *in vitro* culture models through which the space around the electrode can be engineered and further studied.

During a panel discussion led by Dr Warren Grill of Duke University, several goals and challenges were identified for future consideration relative to neural prosthetics. A major research and development goal is the implementation of a neuromotor prosthesis that would enable a paralyzed individual to control the movement of their own limb through volition. Achieving this goal would involve the combination of next generation FNS or intraspinal stimulation technologies coupled with robust and reliable brain machine interfaces that extract volitional signals. As implied by Mr Nagy, metrics of success must include activities of daily living. It was noted during the panel discussion that a critical technology gap exists in the delivery of sensation to paralyzed individuals. In addition to returning the perception of sensation, sensory feedback would be anticipated to provide a performance benefit for neural prostheses for upper limb control.

In closing, two important questions were raised during the panel discussion: 1) What can be learned from the success in cochlear prosthetics for future research and development of neural prosthetics in other areas? 2) With adoption of any new technology, what failures should be anticipated as preludes to success? Mr Geoffrey Thrope of NDI Medical offered perspectives from the private sector on how to achieve commercial success for neural prosthetics. His insights were derived from his previous marketing experience of the NeuroControl Freehand system, a surgically implanted device designed to restore hand function in people with quadriplegia by neuromuscular stimulation of forearm and hand muscles. In short, while end users of the Freehand technology considered the system a success and reimbursement from insurance companies was generally accepted, the sales volume did not meet the expectations of the financial backers. Mr Thrope's plans for the next generation of the product, Freehand II, incorporate smaller yet fully implantable technology that will decrease the duration and complexity of the implant surgery. Moreover, expectations and commercial measures of success will be consistent with those derived from other successful neural technologies, such as the cochlear prosthesis and implanted devices for bladder stimulation.

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