Neural Interfaces Workshop 2006

Approximately 500 attendees gathered at the Bethesda North Marriott Hotel and Conference Center on August 21-23, 2006. Consistent with the prior two years, the Workshop combined the Annual Neural Prosthesis Workshop and the annual meeting of the National Institutes of Health's (NIH) Deep Brain Stimulation (DBS) Consortium.

Support for the Workshop came from the following Institutes within the NIH: the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and the National Institute on Deafness and Other Communication Disorders (NIDCD).

The Workshop was organized around seven plenary sessions: Neural Function in Parkinson's Disease: Implications for DBS, New Clinical applications for DBS, Tissue/Device Interface, Progress in Functional Neuromuscular Stimulation, Progress in Electrode Technologies, Tactile and Proprioceptive Feedback, and Advances in Cochlear Prostheses. In addition, the Workshop included three panel discussions: Neural Function in Parkinson's Disease: Implications for DBS, Optimizing DBS Implantation and Targeting, and Functional Neuromuscular Stimulation Approaches to Standing and Walking. The Workshop attendees contributed 127 posters, which provided a valuable forum for discussions and cultivation on new collaborations. While most of the attendees were from the US, there were attendees from Sweden, Australia, Canada, Germany, the Netherlands, and Israel. Overall student attendance to the Workshop was relatively high; approximately 23% of the participants identified themselves as students. The Workshop agenda and abstracts are available from the NINDS Neural Prosthesis Program web-site.

Dr. Story Landis, Director of the NINDS, welcomed the multidisciplinary audience of engineers, basic scientists, and clinicians. She remarked that while the cochlear prosthesis has become a reality, other neural prosthetic applications, such as functional neuromuscular stimulation, are not yet fully mature technologies. Dr. Landis recognized the importance of early adopters that enable device improvement, but also mentioned that investigators must seriously consider when the time is right to advance devices to clinical testing.

The main goals of the first plenary session, entitled "Neural Function in Parkinson's Disease (PD): Implications for Deep Brain Stimulation" and moderated by Dr. Eugene Oliver of NINDS, were to address how the growing body of knowledge concerning the pathophysiology of PD affect the implementation of DBS, what is the basis for DBS efficacy, and what DBS has taught us about the pathophysiology of PD. Dr. Joel Perlmutter, Washington University, reported on a clinical study of patients with bilateral subthalamic nucleus (STN) DBS for PD. A cognitive side-effect of DBS was identified in this study: bilateral STN DBS produced an impairment of spatial delayed recall and response inhibition, but only when these tasks were set to a difficult level, indicating that stimulation programming may be enhanced by incorporation of cognitive tests. Dr. Perlmutter also presented an examination of the net effects of DBS on blood flow response in patients indicating increased blood flow in pallidum and thalamus whereas flow decreased in several cortical regions. These findings are consistent with stimulation leading to increased output activity from the STN.

Dr. Mark Bevan, Northwestern University, discussed the mechanisms underlying the pathophysiological activity in PD and how high frequency stimulation (HFS) at the STN provides therapy. Electrophysiological studies implemented with two-photon microscopy suggest that HFS may exert therapeutic effects by disrupting pathological synaptic integration in the STN and causing STN axons to discharge at higher frequencies associated with voluntary movement.

Dr. Cameron McIntyre, Cleveland Clinic Foundation, presented his groups efforts to couple results from functional imaging, neurophysiology, and neuroanatomy to create a theoretical framework that quantitatively models the effects of DBS and provides a virtual test bed for examination of new stimulation paradigms. Consistent with the other speakers, the modeling work suggested that the STN and GPi fiber activation were related to therapeutic efficacy. Dr. McIntyre's work suggests with identification of a target volume of tissue, one could reverse engineer the design of the DBS electrodes with respect to contact size and shape or perform current steering between contacts to optimally modulate the target region.

Dr. Jeffrey Wertheimer, Wayne State University, moderated a panel discussion concerning patient perspectives on DBS. Ms. Margaret Tuchman, President of the Parkinson Alliance, and Dr. David Heydrick, Parkinson's Action Network, provided invaluable insight into the DBS experience for the scientists, engineers, and clinicians, and identified several topics that warrant consideration. Chief among their concerns was the lack of widespread expertise in DBS programming. The panelists agreed that algorithm development to facilitate the determination of optimal parameters for DBS would be a significant advance, and may also diminish the often observed deleterious side-effect of speech dysfunction. In addition, recommendations from the panelists and moderator included the implementation of DBS systems with rechargeable batteries and development of closed loop systems that provide DBS on demand.

Dr. Warren Grill, Duke University, led a panel discussion concerning the optimization of DBS implantation and targeting. Dr. Jens Volkmann, Christian-Albrechts University, pointed out that placement of the electrode at the border or inside the STN appears to improve clinical efficacy, whereas placing the electrode above the STN is less efficient. Dr. Jean Saint-Cyr, Toronto Western Research Institute, discussed the differences in targeting methods used both in the United States and abroad. Dr. Saint-Cyr concluded by recognizing that advances in technology to refine placement of electrodes to the micron dimension will have limited impact, given the size of electrode contacts and current spread. Dr. Peter Konrad, Vanderbilt University, discussed the need to confirm placement of the implanted electrode since spatial deviations on the order of 1 mm will have a huge impact on efficacy and documentation will allow for more precise future use. He also made it clear that programming cannot substitute for poorly placed electrode leads.

Dr. Joseph J. Pancrazio, NINDS, moderated the plenary session entitled "New Applications for Deep Brain Stimulation" which focused on three relatively new clinical indications for which DBS is being considered and/or explored. Dr. Helen Mayberg, Emory University, described the body of evidence pointing towards area 25 as a target for DBS in pharmacological treatment resistant depression. In a pilot study, four of the six patients who received DBS implantation to target this area are in remission. Dr. Nicholas Schiff, Cornell University, presented work indicating that the activation of the human central paramedian thalamus is involved in attention,

and that the function of this region may be impaired in patients who suffered traumatic brain injury (TBI) and are categorized as minimally conscious. Dr. Schiff presented findings demonstrating that thalamic stimulation in monkeys promotes sustained attention, raising the possibility of thalamic stimulation for treatment of a subset of TBI patients. Dr. Roger Kurlan, University of Rochester, provided a survey of progress and issues concerning the use of DBS for treatment of Tourette's Disorder (TD). Among the principle issues is the lack of a well-described anatomical target, the self-injurious behavior associated with TD which increases the likelihood of breaking electrode leads or damaging the stimulator, and complications that include fatigue and decreased concentration.

A special report was given on the development of an Open Architecture Research Interface for Cochlear Implants by Dr. Philip Loizou, University of Texas at Dallas. This is a new NIDCD contract-supported project to develop a portable research device that can interface with the implanted portion of a cochlear implant. The hardware platform will be a personal digital assistant, which is inexpensive and readily available to the research community. Once the project has been completed, the software will be made available to the research community.

The plenary session entitled "Tissue/Device Interface", which was moderated by Dr. Joseph Pancrazio, NINDS, focused on recent experiments to characterize the damage associated with implantation and use of DBS electrodes in the human brain and what we know about the response of the central nervous system to implanted materials. Dr. William Shain, Wadsworth Center, presented data from post-mortem analyses of an implanted Parkinsonian brain showing a significant sheath containing astrocytes, microglia, and vascular elements surrounding the DBS electrode shaft. To develop comprehensive analysis of brain tissue after DBS, Dr. Shain recognized the need for development of standard operating protocols for tissue handling and the potential utility of a tissue repository. Dr. Patrick Tresco, University of Utah, described his histological work with microelectrode arrays indicating that tissue immediately surrounding the implanted shaft. The findings showed that after 12 weeks implantation in the rat cortex, macrophages and astrocytes are elevated within 100 microns of the shaft whereas the number of neurons is significantly reduced, which may have implications for the loss of signal integrity with time.

On the second day, Ms. Jennifer French, Neurotech Network, who has C6-7 incomplete spinal cord injury, provided a user perspective on implanted functional neuromuscular stimulation (FNS) systems. Ms. French, who has had an implanted lower extremity system for 7 years, delivered her presentation while standing at the podium, where she challenged the audience to explore the needs of the people living with the disability. Ms. French pointed out that device capability is one of several factors that patients consider, along with portability, durability, and the number surgeries required to implement the technology.

Following the user perspectives on FNS, the plenary session entitled "Progress in Functional Neuromuscular Stimulation" was moderated by Dr. Nancy L. Shinowara of NICHD and highlighted different approaches toward goals for enabling voluntary neuromuscular control by individuals with paralysis. Dr. Robert Kirsch, Case Western Reserve University, presented an overview of collaborative research using electrical stimulation in human patients to restore lost function due to paralysis. By making use of a computational modeling framework, they have

developed a “Dynamic Arm Simulator” which allows for the evaluation of candidate control paradigms for paralyzed individuals, and future plans include using this simulation tool in studies with participants in the BrainGate trial (see Special Report below). Dr. Gerald Loeb from the University of Southern California presented progress on a different technology for FNS through the use of wireless, injectable stimulators called BIONs. He noted the use of BIONs in several clinical trials that are focused on preventing or reversing disuse atrophy, a significant clinical concern for paralyzed individuals. Dr. Loeb and colleagues have also developed a computer environment and are testing the ability of subjects to learn to control these simulations when presented as 3D animations in a virtual reality environment.

A special report entitled “BrainGate Trial Update: Spinal Cord Injury, Stroke and ALS” was presented by Dr. John Donoghue, Brown University and Cyberkinetics Neurotechnology Systems Inc, and Dr. Leigh Hochberg, Providence Veteran’s Administration Medical Center. They reported that the preliminary clinical experience with the implanted sensor have not shown any unanticipated adverse device effects in four patients with tetraplegia, three with incomplete spinal cord injury or stroke, and one individual with ALS. Their preliminary findings of repeatable volitional control and real time neural control over a computer cursor are considered supportive of the clinical feasibility of an implanted neuroprosthetic device.

The Panel Discussion on "Functional Neuromuscular Stimulation (FNS) Approaches to Standing and Walking," moderated by Dr. Naomi Kleitman, NINDS, encompassed both stimulation system development and clinical testing of FNS systems. Speakers were challenged to discuss the strengths and weaknesses of the relevant technologies, how success is evaluated, and challenges for the next 5-10 years. Dr. Patrick Jacobs, Florida International University, described the wide range of physiological as well as functional systems that FNS exercise can improve in people with SCI. The goal Dr. Jacobs emphasized was to address realistic expectations and alternative means to train users in order to maximize the commitment to long-term use that would allow these benefits can be realized. Dr. Ronald Triolo, Case Western Reserve University, described intramuscular or epimesial stimulation systems that have been tested in 15 subjects over the past decade. Future Improvements to the system should include minimizing external components and the need for assistance, as well as developing means to make predictive adjustments to improve activation, stability and address muscle fatigue. Dr. Richard Normann, University of Utah, described new studies of stimulation to achieve guided, graceful movement in anesthetized cats using Utah slant-electrodes. Goals for this system include developing multi-electrode stimulation parameters that increase resistance to fatigue. Finally, Dr. Vivian Mushahwar, University of Alberta, described a system for intraspinal stimulation of the lumbar enlargement of the spinal cord that allows for a more normal muscle recruitment pattern than other systems achieve. Despite concerns about system inconsistency, awake paralyzed cats were shown standing and supporting their weight, as well as stepping with this intraspinal stimulation system.

Dr. Grace Peng, NIBIB, moderated the session entitled “Progress in Electrode Technologies”, which highlighted the development of three electrode architecture approaches. Dr. Richard Andersen, California Institute of Technology, described the development of floating microwire electrodes for deep recordings in the parietal reach region of the brain, silicon probes which are integrated with parylene cables, and a smart MEMS recording system which moves the

electrodes to re-isolate the cell and optimize the signal. The latter system utilizes smart algorithms to control the microdrives with micron precision. Dr. Dominique Durand, Case Western Reserve University, described the development of Flat Interface Nerve Electrodes (FINE) that re-shape peripheral nerves into a flat configuration to increase the circumference and surface area for stimulation. He employed finite element modeling methods to model the stimulation and recording of selective fascicles. Dr. Daryl Kipke, University of Michigan, described the development of advanced microscale devices for chronic neural interfaces and the re-establishment of the National Center for Neural Communication Technology (CNCT). He described a biology-centered device design approach that considers tissue response in the development of polymer neural probes and open architecture probes. He also described the CNCT as a national resource to develop and provide long-term electrical and chemical interfaces driven by multiple collaborating groups to serve the larger user community.

The plenary session entitled "Tactile and Proprioceptive Feedback", moderated by Dr. Joseph Pancrazio, NINDS, addressed the importance of sensory feedback to the future of neural prosthesis. Dr. John Chapin, SUNY Brooklyn, described his efforts to determine the effectiveness of microstimulation of the somatosensory pathways to mimic tactile sensation. His findings suggest that the response to electrical stimulation in the thalamus is dose-dependent and is more specific than mechanical stimulation. In addition, there is an important spatiotemporal aspect of the tactile information encoding, which necessitates the use of multiple electrodes to provide tactile feedback. Dr. Richard Stein, University of Alberta, presented his efforts to explore the encoding of kinematic information at the spinal cord to predict where the lower limb is in space during walking. Using single unit recordings via microelectrode arrays implanted in the cat L6 and L7 dorsal root ganglia, the data suggest that the firing rates of a few, selected cells predict foot position remarkably well.

Dr. Roger Miller of NIDCD led the Advances in Cochlear Prostheses plenary session, which focused on novel designs that might be used in future cochlear prostheses. Dr. Paul Abbas, University of Iowa, presented a detailed report, "Effects of Remaining Hair Cells on Cochlear Implant Function." This was the final report from a four-year study on masking between acoustic and electrical activation of auditory nerve activity in ears with substantial residual hearing. Dr. John Middlebrooks, University of Michigan, reported on hearing restoration through direct stimulation of the auditory nerve via multichannel electrode array penetrating directly into the nerve. Very promising results have been achieved in these animal studies, indicating that focal stimulation can be achieved with low currents and a broad range of frequencies can be activated by varying the electrode's location within the auditory nerve. Dr. Ben Bonham, University of California at San Francisco, also presented the final report from a four year study. This project evaluated novel intracochlear electrode designs and a range of bipolar stimulating electrode geometries to selectively stimulate small regions of the auditory nerve. A shared report was given by Dr. Douglas McCreery, Huntington Medical Research Institutes, and Dr. Robert Shannon, House Ear Institute, to describe the latest results from an auditory brainstem implant that utilized stimulating electrodes placed on the surface of this nucleus and penetrating into the nucleus at different depths. This implant is designed to selectively stimulate neurons of varying best frequencies for patients requiring acoustic tumor removal during treatment for type 2 neurofibromatosis.

Dr. Karl Deisseroth, Stanford University, presented a special report entitled “Molecular, Optics-Based High-Speed Neural Interfaces” that offer the promise of mapping, interrogating, and controlling neural circuits to restore function. He is exploring the genetic engineering of channelrhodopsin-2, a light activated cation channel into mammalian neurons, to achieve a means of stimulating individual neurons. While clinical application for neural stimulation requires targeted genetic engineering of the channel protein to selected sites and application of light to that region and is therefore many years away, there may be more near term uses for this approach to understanding the basis of DBS in animal models.

The Workshop’s final session on therapeutic and regenerative effects of stimulation, moderated by Dr. Daofen Chen, NINDS, addressed the use of electrical stimulation to induce or facilitate brain plasticity. Dr. Robert Shepherd, University of Melbourne, reported promising findings on the effects of "re-afferentation" of a silenced auditory pathway using electrical stimulation of the auditory nerve via a cochlear implant, combined with exogenous delivery of neurotrophins following a sensorinual hearing loss. Dr. Gottfried Schlaug, Harvard Medical School, presented his work on a new non-invasive stimulation approach, i.e. transcranial direct current stimulation, to enhance or interfere with motor learning tasks. Preliminary findings indicate a therapeutic effect by stimulation in post-stroke recovery through modulating the abnormal interhemispheric inhibition by either upregulating excitability in the lesioned hemisphere or by downregulating excitability in the intact hemisphere. Finally, results from studies using a novel recurrent brain-computer interface were presented by Dr. Andrew Jackson, University of Washington. Using this new experimental paradigm in freely moving monkeys, they have demonstrated effects of long-term re-organization of motor cortical output induced by real-time brain activity triggered functional electrical stimulation.

Planning is currently underway for a Neural Interfaces Conference which is tentatively scheduled for Spring, 2008.