Cortical and Putaminal Mechanisms for Self-Timed Movements

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The long-term goal of this project is to understand the real-time cortical and subcortical neuronal mechanisms for movement initiation, to help provide better signals for driving neural-based prosthetics. We have examined the neuronal activity in parietal cortex 5 and the sensorimotor putamen in awake, behaving macaque monkeys trained to make the same arm movements either as simple reactions to an abrupt visual cue, or as a 'self-timed" movements without explicit external prompting. This distinction has been suggested to be important in movement disorders such as Parkinson's disease. The equivalence of the movements *per se* was demonstrated by EMG recordings from arm and shoulder muscles. For neurons both in parietal area 5 and phasically active putaminal neurons, we found increased activity from 500-250 ms preceding the onset of EMG activity on self-timed movements, but not simple reactions. These data are consistent with a threshold mechanism, perhaps involving feedback between neocortex and basal ganglia. Moreover, in the lateral parietal area, we found that neurons showed a build-up of activity specifically before self-timed movements that -- by applying a simple threshold model -- could account for the precise time of movement over a range of nearly one second. These parietal signals, which are neither sensory nor strictly motor, could be valuable surrogates for initiating the movement of prosthetic devices.

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Implantable Biomimetic Electronics as Neural Prostheses for Lost Cognitive Function

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A multi-disciplinary project will be described that is developing a microchip-based neural prosthetic for the hippocampus, a region of the brain responsible for the formation of long-term memories, and that frequently is damaged as a result of epilepsy, stroke, and Alzheimer's disease. The essential goals of this effort include: (1) experimental study of hippocampal neuron and neural network function – what are the nonlinear dynamics that determine how the hippocampus encodes information?, (2) formulation of biologically realistic models of neural system dynamics -- can that nonlinear dynamic encoding process be described mathematically to realize a predictive model of how the hippocampus will respond to a particular event?, (3) microchip implementation of hippocampal system models -- can the mathematical model be realized as a set of electronic circuits to achieve rapid computational speed and miniaturization?, and (4) hybrid neuron-silicon interfaces -- can structural and functional connections between electronic devices and neural tissue be achieved for long-term, bi-directional communication with the brain? By integrating solutions to these component problems, the team is realizing a microchip-based model of hippocampal nonlinear dynamics that can perform the same function as a removed, damaged hippocampal region. Through bi-directional communication with other neural tissue that normally provides the inputs and outputs to/from the damaged hippocampal area, the neural model can serve as a neural prosthesis.

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Rodent Model of Deep Brain Stimulation, Behavioral and Electrophysiological approaches to Parkinson's Disease Research

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Deep brain stimulation (DBS) has been used successfully in the clinic to ameliorate Parkinson's disease (PD). However, the mechanism underlying therapeutic effects of DBS is unclear. The goal of this study is to establish rodent models of deep brain stimulation and to study the neural mechanisms of DBS using multi neuron unit recording. DBS showed beneficial effects on three PD models: treadmill locomotion, running wheel and limb use asymmetry tests. In these tests, DBS of the subthalamic nucleus (STN) significantly reversed motor deficits caused by unilateral dopamine depletion. Predominant inhibitory responses were found in the STN stimulation site during behaviorally effective DBS. On the other hand, different neural responses were observed in other basal ganglia regions. Both inhibitory and excitatory responses were observed in the substantia nigra pars reticulata, the basal ganglia output site, suggesting that responses other than uniform rate changes may be responsible for the effect of DBS. Furthermore, the percent of inhibitory responses to DBS was higher in the limb use asymmetry test than that in the treadmill locomotion test, indicating that responses to DBS are dependent on the behavioral events. In addition to the rate change, a decrease in burst firing was detected in the STN and globus pallidus immediately after DBS of the STN. These results suggest that DBS regulates information flow in the basal ganglia through a dynamic process related to ongoing behavioral context.

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Polymer-Based Microelectrode Arrays for Stimulation

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We are developing a cochlear implant that represents a significant advancement over current devices. The device integrates a high contact density, polymer-based electrode with a high-bandwidth, optical transcutaneous link and a new signal processing algorithm. The system retains phase information in the auditory signal and allows parallel, simultaneous stimulation of the auditory nerve. The polymer-based electrode utilizes liquid crystal polymer (LCP) as the base dielectric. LCP has many desirable properties for electronic medical implants, including biocompatibility, low moisture absorption and permeability, and high bulk resistivity. The material is also readily processed by injection molding and thermoforming. The array, as currently developed, utilizes thin-film metallized traces formed by laser direct write lithography and iridium oxide metallization on the stimulation sites to promote maximum charge transfer.

To date, we have fabricated high-density arrays (100 micron wide array contacts with 100 micron space separating elements) in a small footprint suitable for acute auditory stimulation in animals. We have successfully stimulated cat cochleae with LCP arrays and demonstrated more natural excitation patterns with recordings in the inferior colliculus. These results confirm the performance improvements possible using high-density arrays for cochlear implants. Testing of the array in a variety of long term soaking and other tests suggest that while the array functions successfully in acute applications, further improvements may be needed before the electrodes are suitable for chronic stimulation. Specifically, hermetic interfaces between LCP layers in the array are susceptible to ion leakage, degrading channel isolation. The thin-film stimulation interface also requires further characterization under chronic stimulus demands. We are working on methods to improve the array and we continue to explore alternative high-density array designs. These alternate designs combine new and traditional materials with advanced fabrication techniques to further the art of polymer-based arrays. We are also investigating other uses for the array technology including deep brain stimulation and neural recording applications.

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Effects of STN Stimulation on Tremor, Rigidity and Bradykinesia

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The long-term goal of this project is to quantify and compare the effects of STN stimulation and medication on the three cardinal signs of Parkinson's disease, and to determine how STN stimulation alleviates these signs. First, our recent findings demonstrate that STN stimulation dramatically increases movement speed at both the elbow and ankle joint. It does so by causing increases in the magnitude of both agonist and antagonist electromyographic bursts. However, a considerable gap remains between the agonist and antagonist burst pattern of healthy individuals and Parkinson's patients on STN stimulation and medication. Second, resting and postural tremor amplitude is reduced to healthy levels by STN stimulation. This is not the case for medication. In addition, STN stimulation modifies multiple features of tremor including the frequency, regularity, and 1-8 Hz tremor-EMG coherence. These findings lead to the conclusion that STN stimulation desynchronizes pathological oscillators. Third, ongoing investigations indicate that rigidity is reduced by STN stimulation, and this reduction is associated with changes in how STN stimulation alters flexor and extensor muscle activation. These findings are discussed in the context of both the rate model of the basal ganglia, as well as models that incorporate the frequency content of basal ganglia and cortical neural signals.

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A Multichannel, Implantable Prosthesis for Restoration of 3D Vestibular Function

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The normal vestibulo-ocular reflex (VOR) senses head rotation and generates compensatory eye rotations that stabilize images on each retina. Absence of vestibular sensation causes degraded vision during head movement, impaired postural stability and chronic disequilibrium. There are no adequate treatment options for patients disabled by this loss. An implantable, multichannel vestibular prosthesis that encodes head movement in all 3 dimensions (3D) as electrical stimuli delivered to the corresponding branches of the vestibular nerve could significantly improve quality of life for these patients. We have developed a prototype of such a device, and we have characterized an animal model of ototoxic vestibulopathy in which to test it.

We used 3D scleral coils and 3D video-oculography to examine eye movements during transient head rotations of awake chinchillas in darkness. Normal animals (N=8) exhibited responses like those of normal humans, with VOR gain (eye/head acceleration) near -1 in each canal plane. Animals treated unilaterally with ototoxic doses of gentamicin (N=8) responded like similarly treated humans, with decreased gain for head movements exciting the treated labyrinth. Single-unit recordings from vestibular nerve afferents and light microscopy have demonstrated that gentamicin causes a hair cell injury but spares viable vestibular nerve afferents that are accessible to prosthetic stimulation.

In chinchillas made vestibular-deficient through canal plugging and otolith disruption, biphasic pulse-frequency modulated current pulse trains encoding head rotation in the horizontal plane were delivered via electrodes in the horizontal semicircular canal, eliciting an apparently perfect 1D VOR (i.e., gain = -1) for modest head velocities. However, 3D analysis revealed eye movements outside the horizontal plane, indicating a need to increase electrode selectivity.

Drawing on these findings, we constructed a multi-channel vestibular prosthesis comprising 3 rotational accelerometers, a microcontroller, a current source, and 8 electrodes. The device, which is fully reprogrammable *in situ*, encodes 3D head rotation as pulse-frequency-modulated and/or amplitude-modulated stimulation of up to 4 vestibular nerve branches in bipolar mode or 7 branches in monopolar mode. Although not yet optimized for minimal thickness, it is thin enough (~11 mm) to be packaged for subcutaneous implantation and cranial fixation using surgical techniques comparable to those employed for cochlear implantation.

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A Human Neuro-Motor Prosthesis

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With the recent explosion of computer- and information technology several centers have focused their research on reading the brain's messages by connecting computers directly to the brain. We present our preliminary findings on BRAINGATE®, a human neuro-motor prosthesis system. The device is currently used for implantation in patients with quadriplegia under a FDA investigational device exemption. Patients selected for the study undergo a minimally-invasive neurosurgical procedure whereby a 100-electrode array is implanted with stereotactic guidance into the arm area of the dominant motor cortex. The array is wired to a percutaneous connector, which is fixated to the person's skull. Continuous extracellular recordings are obtained, decoded and converted into a universal movement output signal that can drive various output devices from computer cursor to artificial limb. Our initial findings indicate that the BRAINGATE® system is safe and provides a long-term neuro-motor prosthesis platform. Future developments might make it possible to connect the movement-control signal back into the patient's own limbs.

Nanofiber Material and Microscale Braiding Technologies for Multifunctional Neural Prosthetics

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Wiring and connectors form a major issue in almost every neuroprosthetic design. Wires' mechanical impedances, wire tangling and knotting, and the consequent stresses on neural tissues and at the joints and junctions are potentially a major source of failure and neural damage in implantable neuroprostheses. As current neuroprosthetic designs become more mainstream in clinical application, and are applied in more active individuals, the mechanical environment to which they are subject will become more challenging. Multi-electrode structures that are layered onto and conform to devices of known safety or that offer far higher mechanical compliance than presently are a very desirable addition to current approaches.

In an active collaboration of the Drexel-Materials Engineering Lab (lead by Dr Frank Ko) and our team, we have developed a braiding and weaving system suited for braiding six or more quite fragile 13-micron wires (tetrode-type wire) and other materials, such as nanofibers, into a tubular braid. This braid can be layered onto a host probe structure for recording extracellular activity in the cortex. This fabrication system is designed to be extensible, first, to more complex braiding arrangements and second, to increasing numbers of wires braided. Braiding technologies offer a range of desirable mechanical properties for the wiring, interface and probe structures. These technologies allow the development of electrode structures incorporating nanoscale and microscale materials of either biological or synthetic origin in custom-designed fibrous composites. We are exploring how this technology can be adapted and extended to a range of prosthetic interface designs.

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Intraocular Retinal Prosthesis

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A retinal prosthesis has the potential to treat blinding diseases of the outer retina, such as age-related macular degeneration and retinitis pigmentosa. At the Doheny Retina Institute-University of Southern California, an on-going clinical trial is evaluating a low-resolution device while technologies to support higher resolution implants are under development. In the clinical trial, a prototype epiretinal prosthesis was implanted in six subjects with bare or no light perception due to retinitis pigmentosa. The FDA granted an IDE and USC-IRB approved the study protocol. After obtaining informed consent, subjects were screened using visual psychophysics, electrophysiology, ophthalmic photography, and scanning laser ophthalmoscopy. Implants, developed jointly by USC and Second Sight Medical Products, Inc., consist of an extraocular microelectronic device and an intraocular electrode array, connected by a multiwire cable. The electrode array is a 4x4 grid of platinum electrodes embedded in silicone rubber. Electrodes are wirelessly activated using an external system. The external system is controlled via a computer interface or a head mounted video camera. As of August 2005, 6 subjects have been implanted for 13-41 months. Performance using the head mounted video camera suggests that patients are capable of interpreting patterned electrical stimulation. Subjects can localize the position of, or count the number of, high contrast objects with 74-99% accuracy (3 or 4 Alternative Forced Choice (AltFC)), and can discriminate simple shapes such as the orientation of a bar or an "L" (2 or 4AltFC) with 61-80% accuracy. There was no improvement in perceptual acuity when the device was electrically inactive, suggesting that electrical stimulation did not improve the health or function of the retina. Using data generated by the clinical trial, considerable progress has been made towards a higher resolution device with the development of image processing, microelectronics, and polymer based electrodes and interconnects. An image processing system has been realized that is capable of real-time implementation of image decimation and filtering (for example, edge detection). Application specific integrated circuits (ASICs) have been designed and tested to demonstrate closed loop power control and efficient microstimulation. A novel packaging process has been developed that is capable of simultaneously forming a receiver coil, interconnects, and stimulating electrodes. The high-resolution system is targeting 1000 electrodes, which simulations predict can restore face recognition and mobility to blind individuals.

Cortical Effects of STN Stimulation: An Intracellular Study in Anesthetized Rats

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Deep brain stimulation in the subthalamic nucleus has been found to be an effective treatment of Parkinson's' disease, most notably by effectively suppressing tremor. This effect is widely believed to be due to an alteration in the output activity of basal ganglia nuclei by manipulating the subthalmo-pallidal pathway with DBS. However, the effects of STN – DBS on pallidal activity are complex, and both increases and decreases in pallidal firing have been observed.

Another important candidate for the therapeutic effect of STN – DBS is given by the antidromic stimulation of cortical efferents to the STN. In this study we investigate the antidromic cortical stimulation occurring with STN – DBS in an anesthetized rodent preparation. Bipolar stimulation electrodes (Rhodes) were lowered into the STN using electrophysiological guidance and histological verification. These electrodes are scaled with respect to Human DBS electrodes such that a similar geometry of stimulated areas in the rat STN is achieved. We used cortical EEG recordings as well as intracellular single cell recordings to characterize the effect of STN – DBS at frequencies from 80 to 150 Hz and intensities from 50 to 300 μA. Intracellular striatal and extracellular pallidal recordings were also obtained in some animals. The results show robust antidromic cortical activation with STN – DBS. On the macroscopic level these effects included a positive EEG potential deflection following each stimulus, as well as a dampening of global cortical bursting behavior in ketamine anesthesia. On the single-cell level, some cortical neurons showed stimulus-locked antidromic spiking, while other cells were predominantly inhibited.

The intracellular depolarization during global cortical up- states was reduced during DBS stimulation. These results suggest a complex cortical network activation induced by antidromic activation, which includes the activation of inhibitory cortical networks. The observed dampening of global cortical synchrony in ketamine anesthesia suggests that antidromic effects of DBS are suited to break synchronized cortical activity patterns that may underlie the generation of tremor.

Overall, the observed strong antidromic effects of STN –DBS suggest that this pathway makes an important contribution to the therapeutic effects of STN – DBS in Parkinson's disease.

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Impact of Deep Brain Stimulation of the Subthalamic Nucleus on Cognition, Mood, and Behaviour in Parkinson's Disease

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves the motor symptoms of Parkinson's disease (PD). The main effects of DBS of the STN on cognition, mood and behaviour in PD, can be summarized as follows:

1. In carefully screened and selected PD patients, DBS of the STN does not produce any global adverse effects on cognition.
2. When cognitive decline is documented following DBS surgery, the age of the patients, their pre-operative cognitive status and level of dopaminergic medication, the precise location of the implanted electrodes and the pulse width used for stimulation appear to be the key factors.
3. With STN stimulation impairment in specific tasks such as verbal fluency, the Stroop, and random number generation which require response selection through suppression of inappropriate/ habitual responses, has been observed.
4. With imaging, the changes in verbal fluency, Stroop and random number generation have been shown to be associated with altered processing in striato-frontal networks . For example, we have demonstrated that during fast paced random number generation, compared to when the stimulators are off, DBS of the STN is associated with increased non-randomness of the output, reduced rCBF in the left prefrontal cortex and the right anterior cingulate, and increased rCBF in the right internal pallidum, and negative pallidal-prefrontal/cingulate coupling.
5. When the STN stimulation is switched on, PD patients report a greater sense of well-being, for example feeling more relaxed, content, and attentive and less fatigued than when the stimulators are switched off.
6. DBS of the STN has also been shown to produce a variety of behavioural effects ranging from euphoria/mania to apathy, hallucination, aggression, and improvement of obsessive-compulsive behaviour. Some of these effects are transient and only present in the immediate post-operative phase; others more longer-lasting. A number of cases of post-surgical depression and suicide have been documented, possibly as a result of a complex interaction between biological and psychosocial factors.
7. For the majority of operated patients, significant improvement of anxiety, depression and quality of life has also been reported, probably as a reaction to the major improvement of the motor symptoms and reduced disability.

The above effects of DBS of the STN on cognition, mood and behaviour will be illustrated with examples from our own work as well as the literature.

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Optical Stimulation of Neural Tissue In Vivo

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A novel method for damage-free, artifact-free stimulation of neural tissue using pulsed, low-energy infrared laser light is presented. Optical stimulation elicits compound nerve and muscle potentials similar to responses obtained with conventional electrical neural stimulation in a rat sciatic nerve model. Stimulation and damage thresholds were determined as a function of wavelength using a tunable free electron laser source (λ = 2–10 μm) and a solid state Holmium:YAG laser (λ = 2.12μm). Threshold radiant exposure required for stimulation varies with wavelength from 0.312 J/cm^2 (λ = 3μm) to 1.22 J/cm^2 (λ = 2.1μm). Histological analysis indicates no discernable thermal damage with supra-threshold stimulation. The largest damage/stimulation threshold ratios (>6) were at wavelengths corresponding to valleys in the IR spectrum of soft tissue absorption (4 and 2.1 μm). Furthermore, optical stimulation can be used to generate a spatially selective response in small fascicles of the sciatic nerve that has significant advantages (e.g. non-contact, spatial resolution, lack of stimulation artifact) over conventional electrical methods in diagnostic and therapeutic procedures in neuroscience, neurology and neurosurgery.

Nanoelectrode Array for Neural Electrophysiology Using Carbon Nanofibers

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Carbon nanofibers (CNFs) or carbon nanotubes (CNTs) can serve as an ideal electrical-neural interface based on their unique physical, chemical, and electronic properties. Such vertically aligned nanostructures can be precisely grown on underlying electronic circuits using techniques compatible with Si processes. They can be fabricated as nanoelectrode arrays on a multiplex microchip in an "array-in-array" format for neural electrophysiology. The chip contains multiple individually addressable nanoelectrode arrays that are designated with three functions, including: (1) electrical stimulation, (2) electrical recording, and (3) electrochemical recording. The electrodes for the former two functions are configured as a forest-like CNF array, which exhibits extremely low impedance due to the large surface area of the three-dimensional structure. The impedance can be further reduced by coating with a conformal polypyrrole film, which also improves the biocompatibility. The electrodes for electrochemical recording is designed such that the CNFs are embedded in a dielectric material (such as SiO_2) with only the tips exposed, which forms an inlaid nanodisk electrode array. The nanodisk electrode array demonstrates ultra-sensitive electroanalysis properties with the detection limits in the nanomolar range and potentially an extremely high temporal resolution. These properties are ideal for capturing neural signaling events facilitated through electrochemically active neurotransmitters such as dopamine. The feasibility of the multiplex CNF arrays as implantable electrodes has been investigated using in-vitro cell culture experiments. The neuron-like PC12 cell line derived from a rat pheochromocytoma has shown to form a distinct monolayer when cultured on CNF arrays coated with a thin layer of collagen. This closed-loop integrated microchip with real-time feedback of neurological processes upon electrical stimulation can be used to improve implantable devices currently employed for deep brain stimulation treatment of neurological disorders.

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Intraspinal Microstimulation for Restoring Limb Movements After Spinal Cord Injury

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We are investigating the feasibility of using intraspinal microstimulation (ISMS) as a new functional electrical stimulation (FES) approach for restoring standing and stepping after spinal cord injury (SCI). We have suggested the use of ISMS for a number of reasons: The spinal cord is distant from contracting muscles, thus minimizing complications due to movement of the target tissue. The lumbosacral region of the cord, which contains the cell bodies of motoneurons innervating lower extremity muscles as well as elements of the spinal locomotor circuitry, is ~5 cm long in humans; therefore, all the microwires needed to restore leg function can be implanted in this localized region. By stimulating directly within the cord, inherent spinal networks involved in generating synergistic movements may be activated, thereby simplifying the control paradigms involved in stimulating and coordinating the activation of a multitude of muscles involved in standing and stepping.

Previous experiments demonstrated that ISMS through microwires chronically implanted in the ventral horn generates functional limb movements in awake, spinally intact cats. The wires remained securely in place for long periods of time (i.e., 6 months), and did not cause neural damage. Other than mild gliosis associated with the initial placement of the microwires, no signs of inflammatory responses due to chronic mechanical irritation were seen. Stimulation through individual microwires in the ventral horn generated selective single joint and coordinated multi-joint flexor, extensor, forward, or backward movements. The extensor and backward synergies were powerful enough to carry the weight of the hindquarters, which suggested that standing and forward propulsion after SCI could be achieved by using only a few microwires.

In this talk, I will present our results from using ISMS in adult cats with *chronic SCI* due to a complete low-thoracic transection of the cord, to produce functional movements of the hindlimbs. Stimulation through individual microwires in the ventral horn generated predictable and graded responses, similar to those evoked in intact animals. By coordinating the stimuli through as few as 4 microwires in each side of the cord that evoked whole-limb synergies, near normal weight-bearing stepping was generated in the paralyzed hindlimbs. The evoked stepping was kinematically stable and fatigue-resistant. The fatigue-resistance of ISMS-evoked responses suggested that ISMS may recruit motor units in their normal physiological order. To address this question, acute experiments in rats were conducted with the aim of determining the muscle fibers activated by ISMS compared to those activated by peripheral stimulation in the quadriceps muscle group. More than 60% of the fibers activated by ISMS were type I and IIA (slow and fast-fatigue resistant, respectively) while more than 85% of those activated by epineural stimulation were type IIB and D (fast-fatiguable). These results showed that ISMS does indeed recruit motor units in near normal physiological order and suggested that long-term ISMS may maintain the “normal” composition of muscle fiber-types following SCI.

Taken collectively, our findings to date demonstrate that ISMS may be an efficient FES approach for restoring standing and walking after SCI. It could also be used in conjunction with other SCI interventions such as regeneration, pharmacology, and locomotor training therapy.

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Deep Brain Stimulation Using Microactuated Microprobes

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The efficacy of the DBS therapy is significantly reduced due to difficulties in precisely localizing the stimulation microelectrodes. In addition, lengthy surgical sessions under anesthesia that include electrophysiological observations and radiological methods are often necessary to confirm the microelectrode location. The overall goal of this proposed project is to develop a microactuated microelectrode technology that will enable precise positioning and movement of microelectrodes in behaving animals after implantation for deep brain stimulation. The proposed technology will provide an unprecedented ability to monitor single neuronal electrical activity and behavioral correlates to stimulation in unanesthetized animals while the stimulation electrode is being moved towards the desired target structure.

Specifically, we propose to develop a thermal micro actuator and associated microelectrode technology for precise positioning and optimal stimulation of the nigro-striatal bundle in behaving rat models of Parkinson's disease. The key technological barriers that must be overcome are (i). Developing micro actuator technologies with enough translation capability to interrogate deep brain structures in rodents with sufficient precision in displacement (ii). Development and optimization of an integrated stimulation and recording capability in the nigro-striatal bundle using an array of micro actuated microelectrodes. The proposed technology will be tested and validated in rodent models of Parkinson's disease. Successful development of this technology will make microelectrode implantation for deep brain stimulation precise leading to safe and an efficient therapy with shorter surgical times.

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Computing with Neural Ensembles

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I will review a series of recent experiments demonstrating the possibility of using real-time computational models to investigate how ensembles of neurons encode motor information. These experiments have revealed that brain-machine interfaces can be used not only to study fundamental aspects of neural ensemble physiology, but they can also serve as an experimental paradigm aimed at testing the design of modern neuroprosthetic devices. I will also describe evidence indicating that continuous operation of a closed-loop brain machine interface, which utilizes a robotic arm as its main actuator, can induce significant changes in the physiological properties of neurons located in multiple motor and sensory cortical areas. This raises the hypothesis of whether the properties of a robot arm, or any other tool, can be assimilated by neuronal representations as if they were simple extensions of the subject's own body.

Neurotransmitter-Based Neural Interfaces

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Retinal degenerative diseases such as age-related macular degeneration are associated with dysfunction and deterioration of the rod and cone photoreceptors. In the normally functioning retina, postsynaptic membrane receptor proteins of retinal neurons proximal to the rods and cones mediate the transmission of visual signals at multiple types of chemical synapses, by undergoing activation in response to neurotransmitter binding at the receptor's ligand-binding site(s). There is reason to believe that in certain cases, these proximal retinal neurons remain functional despite the disease-induced loss of rod and cone visual signaling. Thus, a possible approach to restoring vision in patients with photoreceptor degenerative disease is to construct neurotransmitter-mimicking molecular structures that can attach to, and in light-dependent fashion activate, postsynaptic membrane receptors of inner retinal neurons. This presentation will describe: (1) results from initial studies to prepare and (in model cell systems) test prototype structures that incorporate an agonist of the $GABA_C$ receptor, a postsynaptic receptor found in retina and other CNS tissue; (2) challenges in neurophysiology, chemistry and molecular/ structural biology that must be addressed to develop this vision-related neural interface; and (3) the potential use of postsynaptic receptor-functionalizing structures as a therapy for other CNS degenerative diseases.

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Floating Light Activated Micro-Electrical Simulators

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One of the limitations of neural stimulation is the mechanical stress and resulting trauma caused by the movement of the interconnects to the stimulating electrode. Remotely activated floating micro-stimulators are one possible method of eliminating the interconnects. As a method of energy transfer to the micro-stimulator, we use a laser beam at near infrared (NIR) wavelengths in this project. The two major questions addressed are: 1. How small can a floating stimulator be made without sacrificing the stimulation strength? 2. How deep can it be implanted into the CNS and still be activated without exceeding the NIR safety exposure limits on the surface?

To investigate these questions, first we have developed a finite element model of a floating micro-stimulator with bipolar contacts and studied the effects of various parameters on the stimulation strength, such as the separation between the contacts and the device size. The computer simulations indicated that the size of the device can be reduced down to 200 micrometer without compromising the stimulation strength in the vicinity of the contacts.

Secondly, we have fabricated silicon PIN photodiodes with various sizes and sputter coated the contacts with titanium nitride (TiN). The voltage generated by an individual diode in a volume conductor was tested experimentally by placing it in a diluted saline solution and activating with a NIR laser beam. A representative voltage seen in the volume conductor was an exponentially decaying function with a peak amplitude of approximately 200mV.

Next, the devices were tested in a rat sciatic nerve for their stimulation strength at various implantation depths. The micro-stimulators were fixed in the middle of a 1 mm wide conduit and placed underneath the tibial branch of the sciatic nerve after making a small slit with a 26g needle in the perineurium. The laser beam was aimed at the active area of the micro-stimulator. The thickness of the tissue above the micro-stimulator thus the distance that the laser beam traveled was varied by changing the height of the conduit. The NIR threshold for activation was measured for increasing pulse widths and the strength-duration curve was obtained for various thicknesses of the neural tissue. The initial tests with suboptimal devices demonstrated that implantation depths of at least 1.5 mm is feasible.

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A next generation chronically implantable wireless neural interface

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Next generation neuroprosthetics require chronically implantable, wireless neural recording arrays. We have developed a neural interface design based on the well established Utah Electrode Array (UEA). The UEA is a silicon based 10x10 array of penetrating electrodes, connected to 100 wires and a percutaneous connector. The new neural interface consists of a signal processor, a power recovery module with inductive coupling, SMD components and a modified version of the UEA. We developed the first ever 100 channel low noise, low power amplifier IC with integrated spike detection, AD converter, power recovery module and RF communication.

A new biocompatible hybrid assembly technology was developed. The IC is flip chip bonded using biocompatible AuSn/Au reflow soldering. A biocompatible under-bump-metallization was used consisting of a sputtered thin film sequence of Pt/TiW/Pt/Au (TiW) with respective thicknesses of 240/150/250/200/100 nm. The top TiW serves as wetting stop on leads. Wetting experiments were performed on dummy chips in preparation of the bump deposition. AuSn bumps were deposited on the Al pads of the IC chip.

We have developed a coil stack for inductive power coupling consisting of two Polyimide based electroplated Au coils with 60 turns, each (lead width 15 µm, lead height 10 µm, spacing 15 µm). The coils are glued with a Low-temperature-co-fired-ceramics (LTCC) ferrite platelet to the back of the IC using a 20 µm thick epoxy resin. The coils can be operated as single coils or switched in parallel or series to compensate for varying parasitic capacitances and voltage gain. The coils are connected to the IC using a customized ceramic spacer with an SMD 0402 footprint through a re-routing plane on the UEA. Sn solder is used to contact SMDs and spacer. For protection of the solder connections a polymer underfiller (NAMICS U8433) was used and tested in buffer solution. Alternatively, a 100 µm thick Su/Sn solder ring can be used for mechanical and chemical protection of the interconnect.

The process and assembly makes use of the most biocompatible combination of materials, takes into account process compatibility, electrochemical effects and stability in electrolytic environments. The amplifier is fully functional and first in-vitro system results are expected for the third quarter 2005

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Effects of Pallidal and STN DBS on Single Neuron Activity in the Primate Globus Pallidus and Motor Cortex

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Multiple lines of evidence position the motor cortices as an important link between focal nigrostriatal pathology within the basal ganglia and the systemic expression of parkinsonian symptoms. A full understanding of the mechanisms of action of therapeutic DBS will require not only detailed information about the local effects of DBS on neuronal elements near the site of stimulation, but also a clear picture of how those local effects are translated into a global reduction in parkinsonian symptoms. Work in my lab seeks to address the latter question by recording neuronal activity in the motor cortices during DBS in normal and MPTP-treated parkinsonian animals. In this talk I will first outline techniques we have developed to perform multi-electrode extracellular recording unhindered by the electrical artifacts associated with stimulation at high frequencies and currents. I will then show how these methods have allowed us to confirm and expand upon recent observations that DBS induces a sustained complex temporal locking of pallidal spike activity during pallidal and STN stimulation. This locking abolishes much of the oscillatory and burst discharge that is characteristic of the parkinsonian pallidum. Finally, I will summarize results from recent motor cortical recordings during DBS of GPi or STN. The effects of DBS vary widely between neurons, perhaps correlating with cell subtypes within cortex. GPi DBS at levels that reduce arm rigidity and increase mobility in an MPTP-treated animal is accompanied by reduced cortical responsiveness to muscle stretch, perhaps reflecting a DBS-induced reduction in the long-latency stretch reflex. Not surprisingly, STN DBS activates some cortical neurons antidromically, thereby providing an alternative pathway by which STN DBS can affect motor cortical function. Additional work is required to deepen our understanding of the abnormalities in cortical function associated with parkinsonism and of how those abnormalities are altered during therapeutic DBS.

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Advances in Neural Interfaces From In Vitro Models

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In vitro models offer many significant advantages over in vivo models for helping researchers better understand the interface between electrodes and brain tissue. Most of these are the advantages that in vitro systems offer biologists in all areas, including reduced expense, rapid results, ease of manipulation of experimental variables and biochemical environment, ease of establishing controls, and visual access to the preparation. Obvious applications are establishment of biocompatility, testing of biomarkers and pharmacological interventions, and investigating fundamental neural phenomena. The ability to record and stimulate with electrode arrays offers potential for understanding neural network behavior and understanding neural coding. Work devoted to developing in vitro media has led to advances in media for limiting brain damage upon injury. Much of the work needed to realize the great potential for stem cell interventions will be done with in vitro preparations. Iin vitro preparations have helped in instrumentation development, including hardware and software to support large numbers of electrodes and in optical recording technologies.

This talk argues that much progress has been made, to the point of commercial offerings, in the ability to make electrode arrays and record signals from cultured cells and brain slices. However, out ability to analyze huge quantities of multichannel information is lagging. Insights from in vitro work are likely to inform in vivo scientists, and vice versa, in the areas of information handling and analysis, instrumentation (e.g. stimulation and artifact rejection circuits), and in surface control of cellular interactions. In vitro work has been hampered by lack of an external reference system, such as exists for in vivo recordings from visual or motor cortices, to help organize responses; however, this has led researchers to be more creative in statistical analyses and stimulation paradigms that may be of use to in vivo workers.

The future certainly holds promise for the integration of three dimensional culture techniques that more faithfully represent the natural environment and which hold promise as useful models for prosthetics and other medical science investigations of the brain. Difficulties to be overcome include choice of scaffolding, providing a vasculature or perfusion to perform transport of nutrients, gases and waste products; and technologies for visualizing and acquiring electrical signals from these cultures.

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