Cell

Studying Circuits with Therapy in Mind

Prostheses: Hopes and Hurdles

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Recent advances in basic research and clinical trials have poised motor and visual prostheses to help restore movement and sight. Together with cochlear implants and deep brain stimulators already in use for improving audition and reducing tremor, neural prostheses offer a new avenue of therapy. Progress will continue to depend on deeper scientific understanding of the underlying neural circuits and how they process information. One limitation to sustained progress relates to the inability to measure activity from millions of identified neurons simultaneously. New methods are needed, as highlighted by President Obama's BRAIN Initiative. Less appreciated is the critical need for new conceptual frameworks for information processing. Without these, it is unclear whether the "big data" produced by new measurements will result in deeper scientific understanding. Emerging frameworks include those based on dynamical systems, dimensionality reduction, recurrent neural networks, and machine learning and should increase the performance of prostheses. Another limitation relates to "writing" information into the brain. While optogenetics has revolutionized neuroscience by enabling the modulation of cell-type-specific and projection-targeted neurons, the ability to create naturalistic patterns of activity across millions of specific neurons is still needed. Altering neural activity in this way (along various "meaningful dimensions") should allow neural prostheses to deliver better sensory signals.

Deconstructing Disease and Treatment

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Catalyzed by 20 years of advances in neuroimaging methods, there has been a fundamental shift in the biological constructs of neuropsychiatric disorders, with a growing emphasis on systems-level network models. Highlighting this paradigm shift is deep brain stimulation: focal modulation of specific neural circuits using implanted electrodes that is being applied to a growing number of intractable conditions such as depression. While efficacy testing of deep brain stimulation for any particular disorder will likely continue through conventional clinical trials, the unique potential to simultaneously deconstruct disease pathophysiology and treatment mechanisms through these studies is an opportunity we cannot afford to miss. To understand, optimize, and improve these emerging treatment strategies, we can directly leverage next-generation tools using complementary and synergetic human and animal studies. In patients, we can now track immediate, short-term, and long-term cellular changes in real time at the site of stimulation, complementing studies using structural and functional imaging (PET, EEG, DTI, MRI). Such approaches provide critical foundation for explicit reverse-translational experiments in animals with multiunit electrophysiological recordings in relevant neural circuits using homologous stimulation targets and parameters. Truly bidirectional studies between patients and animals should streamline progress across research fields and ultimately improve treatments. But, such progress can only occur in an environment that facilitates well-funded multidisciplinary team science.

Toward Selectivity and Refinement

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Think of your central heating being on all of the time, winter or summer. Now imagine the fuel supplied to be the same for every house, big or small. That is the state of current electrical brain stimulation therapies in Parkinson's disease. Patients undergo fixed, continuous, regular high-frequency stimulation of key brain targets through an implanted pacemaker irrespective of their current state. Just as modern central heating tracks temperature using a thermostat, we should identify the core brain circuit changes underpinning symptoms and continually monitor these to optimally control stimulation. Understanding these circuit changes may also tell us with what pattern to best stimulate for any given symptom complex. We are just beginning to understand the aberrant circuit dynamics in Parkinson's disease sufficiently well to explore such closed loop and intelligently patterned stimulation regimes. But we must also make stimulation more selective in space. Electrodes with finer resolution and steerable fields are in development, and the ultimate in cell-type-specific control is potentially achievable through techniques like optogenetics and pharmacogenetics. There are, however, major obstacles to be overcome before cell-type-specific treatments can be realized in patients. Meanwhile, electrical stimulation represents a tractable means by which to interact with brain circuits that can still be substantially improved, with significant near-term gains for patients.

Therapy for the Periphery

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The power of optogenetics to improve our understanding of neural circuits is clear. Applying optogenetic techniques to humans, however, remains a goal that is yet to be realized. In my laboratory, we have used optogenetics to manipulate activity in selected neurons of the peripheral nervous system, motivated by the desire to use optogenetics to excite muscle in cases of paralysis, inhibit motor neurons to reduce spasticity, and control nociceptors to treat neuropathic pain. Others have demonstrated that optogenetics can be applied to control neuronal activity in nonhuman primates or have used optogenetics in rodent models to partially restore vision. Translating these exciting results into optogenetic therapies for humans will require successfully overcoming a set of challenges. These include the identification of important disease states that are not adequately addressed by electrical stimulation, pharmacology, or other therapies, demonstration of a potent therapeutic effect of optogenetics in an animal model of the disease state, development and demonstration of safe and effective gene therapy techniques that can transduce selected neurons in humans, development and evaluation of devices to deliver light to transduced neurons in humans, and, finally, management of a clinical trial to evaluate the safety and efficacy of the optogenetic treatment. Meeting these challenges will be difficult but will allow us to harness the power of optogenetics to improve human health.

Prostheses in Sight

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New technologies come along every few years. Sometimes they are a fad, and sometimes they let us move forward in big leaps. Here, I'd like to give an example about how a specific technology—optogenetics—made a real leap possible. The example involves a treatment we're developing for restoring sight for patients with retinal degenerative diseases. Patients with these diseases need a way to get visual information to their brains. This is a two-step process. First, the information needs to be converted into the retina's neural code. Second, the code needs to be transmitted to the brain. My lab works on neural coding and had addressed the first step: converting visual images of arbitrary complexity such as faces and landscapes in real time into the retina's code. But how could we get the coded signals to the brain? Electrodes don't offer a good solution because they're too coarse: the retina's code has single-cell resolution, and electrodes would force us to blur this as each electrode stimulates 50–100 cells. This is where optogenetics came in: the resolution it provides matches the resolution of the code, and when we put the two together, we had a very effective solution. We converted the solution into a prosthetic system that can make completely blind retinas in animals behave very much like normal ones, and we're now starting to bring it through the FDA and into clinical trials.

Coping with Background Noise

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UCL

I've just read about Google's acquisition of DeepMind, and I was impressed, but not surprised, at the humility of Demis Hassabis, the founder of the $400,000,000 AI company. He emphasizes how difficult it is to understand the human brain. This is in stark contrast to my own field, human brain stimulation. There are many claims, based on small effects under laboratory conditions, that brain stimulation can improve memory, mathematical cognition, creativity, language, or performance in athletes or military personnel. In some cases, there seems to be a lack of understanding of the conceptual and technical gulf between these lab results and what to expect in the real-world setting. Overblown statements also don't help. Human brain stimulation has proven its worth in the treatment of depression and neurodegenerative disorders, but success in other fields has so far been limited. There are dangers in not being grounded in reality; for those who can't see these patterns, I'd recommend Carl Djerassi's novel "Cantor's Dilemma" as a good fictionalization of the issues and the cost of not confronting them. The success of transcranial magnetic stimulation in depression shows that brain stimulation can make a serious contribution to health, and it may be the case that other forms of stimulation will be useful for other conditions. But, unless we take a step back now, we are in danger of spreading false hope and of masking real potential in the low signal-to-noise environment created by shouting before there is much to say.

Ear and Brain

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USC

Recent outcomes with auditory prostheses present a unique opportunity for understanding brain mechanisms of speech and music. Both cochlear implants and auditory brainstem implants provide excellent speech recognition but poor music recognition. The outcomes across patients are highly variable, ranging from no speech recognition to the ability to converse by telephone. Children born deaf have shown variable degrees of speech recognition with a cochlear implant. These differences across the types of implants—sound type (speech vs. music), previous sound experience (congenital vs. acquired), and developmental age (adult vs. child)—offer unique opportunities for understanding cortical mechanisms for processing auditory patterns. Recent advances in brain imaging and connectivity will allow us to track the changes in brain pathways that occur when adults learn to adapt to a distorted pattern of neural information provided by auditory prosthesis. We will also be able to track the development of auditory pattern recognition in congenitally deaf children and to understand differences in brain processing between patients with good and poor outcomes. Such new knowledge should provide insight on how the brain adapts to new or distorted patterns of sensory information. The combination of new prostheses and new imaging provides leverage toward better understanding the dynamic synergy between ear and brain.