UH Neurological Institute Journal

SPECIAL ISSUE

Special Issue on Neural Engineering

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FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Winter 2014 issue of the UH Neurological Institute Journal.

Through continuing collaboration with scientists at Case Western Reserve University School of Medicine and in the School of Engineering, physicians at the UH Neurological Institute test and refine the latest advances in treatment for patients with disabling neurological disorders. The Journal highlights these advances and demonstrates our interdisciplinary strengths. As an added benefit for our readers, CME credit is available for the busy practitioner interested in receiving *AMA PRA Category 1 Credits*™.

Neural engineering is the highlight of this issue, for which I have invited Anthony J. Furlan, MD, and Robert Kirsch, PhD, to serve as guest editors. The issue features five unique articles that explore the use of multi-modal data in intensive care units of the 21st century; the advances in scientific knowledge and technology that are laying the groundwork for the re-engineering of deep brain stimulation technology; a new treatment for mesial temporal lobe seizures; the promise of ever-expanding neuromodulation technology; and the use of advanced neuroimaging for mapping brain function.

All of us at the NI Journal extend our thanks to the eight contributing authors as well as to Dr. Furlan and Dr. Kirsch. We also thank our readers. Your comments and suggestions are always welcome.

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University Hospitals Neurological Institute

Recognized by U.S. News & World Report as one of the nation's finest neuroscience programs, University Hospitals Neurological Institute delivers innovative, integrated and individualized care to patients with diseases affecting the nervous system.

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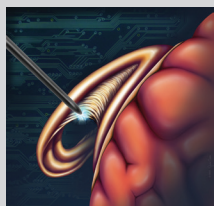
On the cover: *Low-impulse stimulation near the posterior fornix. Electrical stimulation at the intersection of the fornix and the dorsal hippocampal commissural fiber tract provides treatment for patients with mesial temporal lobe epilepsy. Read more about this topic in the article by Dominique Durand, PhD, on page 9. (Illustration by Julie Coats.)*

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TABLE OF CONTENTS

University Hospitals
Case Medical Center

SCHOOL OF MEDICINE
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The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

The ICU of the Future:
Translating Raw Data into Bedside Action

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Introduction

There is a broad consensus that health care in the 21st century will require the intensive use of information technology to acquire and manage patient data, transform the data into actionable information, and then disseminate this information so that it can be effectively used to improve patient care. Nowhere is this more evident and more important than in the intensive care unit (ICU). Critical care involves highly complex decision-making to treat vital organ system failure and prevent life-threatening deterioration. It is by nature data-intense with hundreds of changing variables confronting the clinician at the same time. In today's ICU, there are staggering amounts of data, beyond the capability of any person to absorb, integrate and act upon reliably. In short, our ability to acquire data has outstripped our ability to understand it. This is because, despite the growth of critical care, the basic approach of information management in the ICU has remained essentially unchanged over the past 40 years. Providers must navigate through a jungle of monitors, screens, software applications, and often supplemental paper charts inherent in today's cacophony of information systems.[1] Data from patient monitors and devices, which drove the growth of critical care in general and especially neurocritical care, although available visually at the bedside, is difficult to acquire in electronic (digital) format. And there is limited medical device interoperability or integration with the electronic medical record (EMR). The result is too much data and not enough information *(Figure 1)*.
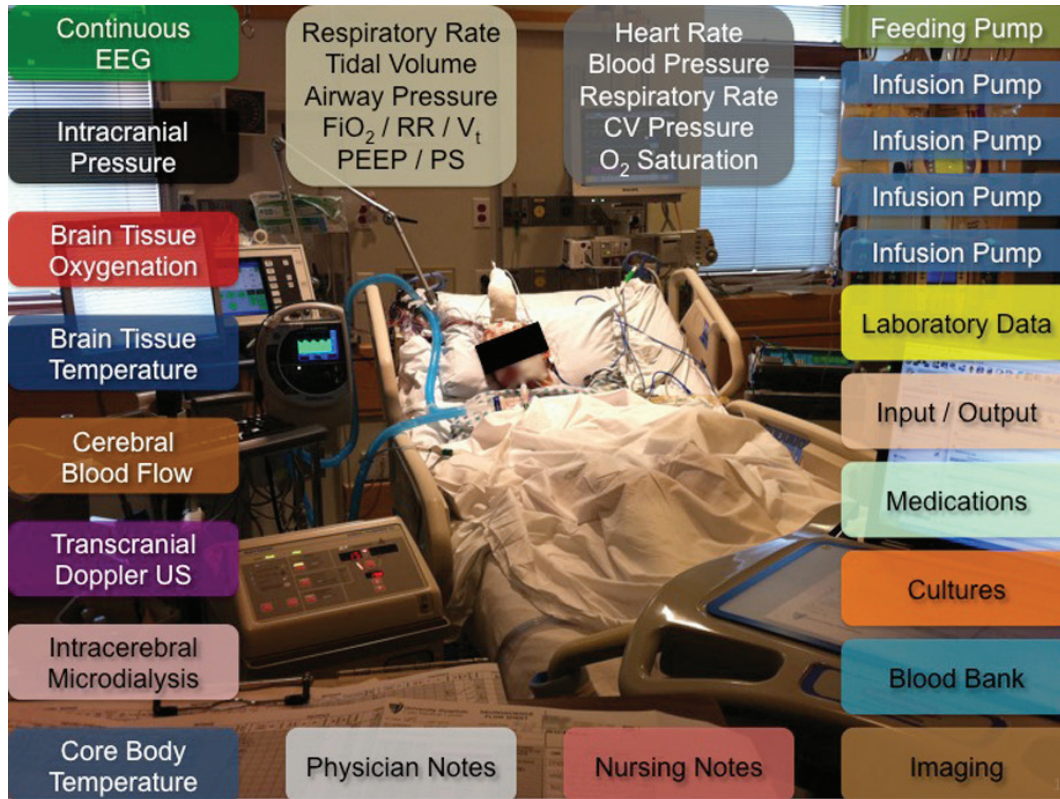
Figure 1: Multi-modal monitoring in today's neurocritical care unit.

Multi-Modal Monitoring in Today's Neurocritical Care Unit

Even when data can be viewed in real-time, standard approaches provide little insight into a patient's actual pathophysiologic state. Understanding the dynamics of critical illness requires precisely time-stamped physiologic data (sampled frequently enough to accurately recreate the detail of physiologic waveforms) integrated with clinical context. Once synchronized physiologic signals are integrated with relevant clinical observations, lab results, and imaging data and stored in a searchable database, clinicians can process the data using a wide array of analytical tools, tools that move beyond the traditional univariate, linear and reductionistic approach of breaking down the body into its component parts and addressing each one in isolation. The reality is that the body is all connected and behaves like a complex system with nonlinear and multivariate behavior. So in order to translate data into

bedside action, we need to develop models that more accurately reflect this reality. The result is a better understanding of the underlying dynamics and a more informed and personalized approach to clinical decision support. This is far beyond the capability of typical commercial monitoring or information systems today.[2] But this is the future.

Challenges on the Road to the Future

There are many challenges that need to be overcome in order to realize this vision. First, the simple ability to acquire, integrate, and time-synchronize physiologic data has been confounded by incompatibilities among monitoring equipment, proprietary limitations from industry, and the absence of standard data formatting. Part of the reason for this limited interoperability is the cost of medical device integration, stemming from, in large part, the lack of incentives for industry to use open standard interfaces that are necessary for

interoperability. In contrast to the "plug and play" world of consumer electronics, most acute care medical devices are not designed to interoperate. For example, more than 90 percent of hospitals recently surveyed by the Healthcare Information and Management Systems Society (HIMSS) use six or more types of medical devices and only about a third integrate them with one another or with their EMRs.[3] While most devices have data output ports (analog, serial, USB, and Ethernet) for data acquisition, there is no universally adopted standard that facilitates multi-modal data acquisition and synchronization in a clinical setting. The underlying critical care informatics architecture needs to be upgraded to a "plug and play" environment.

Second, there is currently neither processing nor analysis of data. Waveforms scroll across the screen and disappear. While a few monitors can display raw trends, even basic analyses (mean, median, standard deviations) are difficult to perform at all let alone in real time, and higher-level analyses are impossible. New physiological models are now emerging, suggesting that nonlinear changes in dynamics over time may have more predictive value. Understanding this complex physiology can lead to more timely intervention and better outcomes. Techniques for the analysis of nonlinear systems have emerged from the mathematical and engineering sciences but have not been applied to physiological data in the ICU (in part because the acquisition and integration challenges have not been met). The promise of critical care informatics lies in the potential to use these advanced analytical techniques on high-resolution multi-modal physiological data in order to have a better understanding of the complex relationships between physiological parameters, improve the ability to predict future events, and thereby provide targets for individualized treatment in real time. In the future, we will use a system that doesn't simply report streams of raw data to physicians but synthesizes it to form hypotheses that best explain the observed data, a system that translates multidimensional data into actionable information and provides situational awareness to the clinician.[4]

Third, visual displays in the ICU have advanced little since bedside electronic monitors were introduced more than four decades ago. Just as pilots no longer attempt to fly complex aircraft on "needle, ball and airspeed" but rather depend on graphical displays of landscape, projected track and potential terrain/traffic conflicts, intuitive graphical display of data is essential for summarizing complex information. Graphical displays must be carefully and thoughtfully designed, however, by applying a human-systems integration approach. It is important to understand not only how information should be optimally presented to promote a better understanding of the patient's pathophysiologic state and support decision-making but also to facilitate collaboration and work-flow among the team.[5]

There are no unifying commercial off-the-shelf products that put everything together – high-resolution physiologic data acquisition, integration, processing, archiving, annotation with bedside observations for clinical applications, and visualization. Some systems have been developed in academic settings though mainly for clinical research.[6-11] For example, Moody and colleagues from Massachusetts General Hospital initially reported on their initial efforts in developing the MIMIC (Multiparameter Intelligent Monitoring for Intensive Care) database.[12] Each record included several channels of real-time waveforms (multi-lead ECGs, blood pressures) and hemodynamic parametric data as well as fluid balance, continuous and drip-medications, lab results, and clinical notes. While MIMIC II represents a major achievement, because physiological data and clinical annotations are collected separately, the two datasets are poorly synchronized. Also, physiological data and clinical annotations have different time "granularity," making it difficult to even retrospectively determine the precise timing of a clinical event. Also, because they are not open source, most of these systems are not readily available, which has resulted in considerable duplication of effort in software development for acquiring and archiving physiological data.
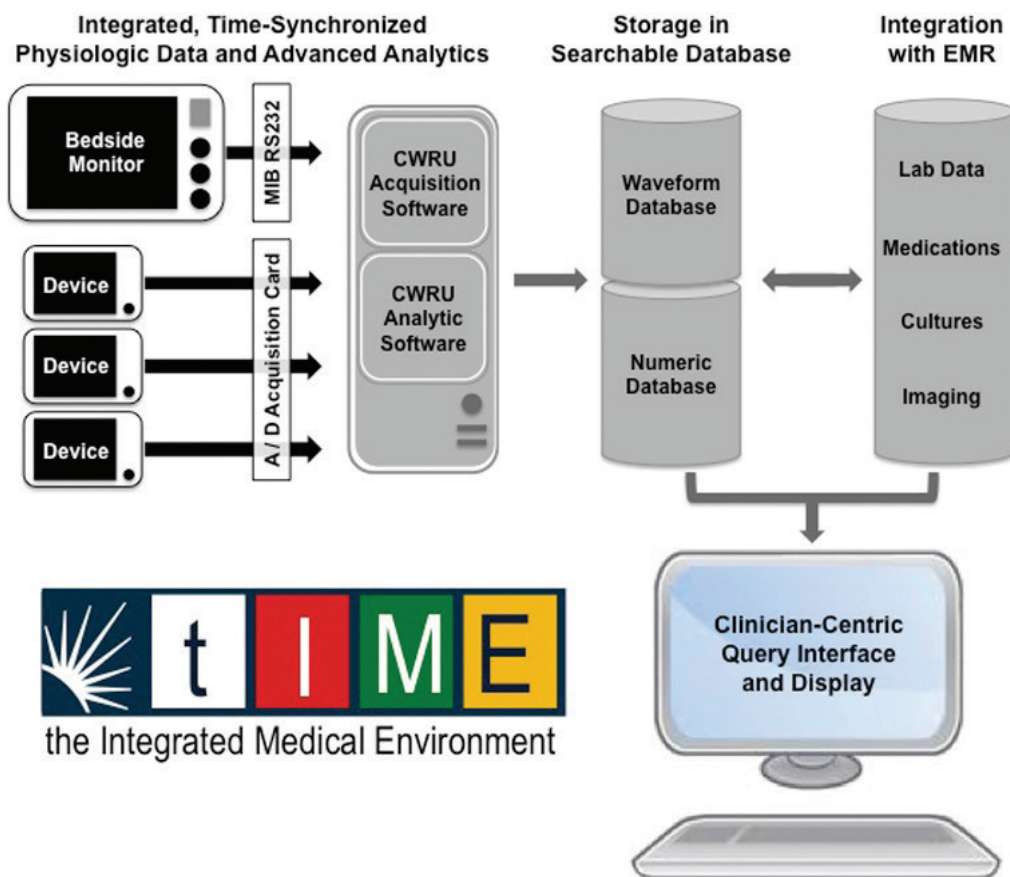
Integrated, Time-Synchronized Physiologic Data and Advanced Analytics

- Bedside Monitor → MIB RS232 → CWRU Acquisition Software
- Device → A / D Acquisition Card → CWRU Analytic Software
- Device
- Device

tIME — the Integrated Medical Environment

Storage in Searchable Database
- Waveform Database
- Numeric Database

Integration with EMR
- Lab Data
- Medications
- Cultures
- Imaging

Clinician-Centric Query Interface and Display

Figure 2: Schematic illustration of the Integrated Medical Environment™ (tIME™).

Developing the Integrated Medical Environment™ at UH Case Medical Center and Case Western Reserve University

At University Hospitals Case Medical Center and Case Western Reserve University, we have focused on overcoming these obstacles with the Integrated Medical Environment™ (tIME™) (Figure 2), a new open source architecture that we believe can provide the backbone for the ICU of the future. Specifically, tIME™ provides (1) real-time data acquisition, integration, time-synchronization, and data annotation of multi-modal physiological waveform data (both analog and digital) from a variety of medical devices and bedside monitors using custom developed parsing algorithms. Both the waveform data and the extracted parametric numeric data are displayed using real-time algorithms developed by our group and simultaneously stored in a local database for easy access, retrieval, and queries. The local database can connect and import into the hospital EMR using a secure HL7 data transfer protocol; (2) a new critical care open middleware informatics architecture that facilitates complex systems analysis methods and data mining capabilities for hypothesis generation and testing; and (3) a clinician-centric visual display and interface, to present an integrated overview of the patient state (past, present, and predicted futures) so that providers can make sensible decisions at the bedside based on all the data.

Only when all of these components work in concert will we be able to fully harness the power of information technology to improve patient outcomes in the ICU.

The goals are surely ambitious; however, they can be achieved. The transformation echoes that of pilots and their aircraft. Pilots have equally complex data streams coming from aircraft, the environment, communications and navigation systems. Flying aircraft using raw data in the absence of natural visual display (being able to see the sky, ground, and horizon) leads to disaster. Yet aircraft can now be safely flown from takeoff to touchdown relying on instrumentation alone. Safety engineers focus on transforming the data streams into visual displays that create situational awareness while those same data streams are used in control systems to support keeping the airplane upright and on track. The pilot can thus focus on making the best possible decisions in the face of ambiguous alternatives. The critical care provider and patient deserve no less.

Conclusion

Intensive care monitoring has remained essentially the same over the past 40 years. The medical industry has not incorporated many of the advances in computer science, biomedical engineering, signal processing, and mathematics that many other industries have readily embraced. Intensivists and other professionals who care for critically ill patients have traditionally relied on irregular sampling of time-averaged physiologic data. For years we have been limited by insufficient computational power, a lack of specialized software, incompatibility between monitoring equipment and systems for data collection and analysis, and limited data storage. Through advances in technology and a coordinated effort involving clinicians, engineers, computer scientists, and experts in informatics, however, we are beginning to make the goal of the Integrated Medical Environment™ achievable by combining modern signal processing, computational modeling, complex systems analysis, knowledge-based clinical reasoning, and clear, user-friendly visualization tools. The potential payoffs are huge: better understanding of critical illness, reduction in medical errors, and improvement in patient outcome.

Ultimately, we believe that this approach – translating bedside data into actionable information – will fundamentally change the way medicine is practiced. It's about tIME!

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White Matter, Low Frequency Stimulation to Control **Mesial Temporal Lobe Seizures**

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Why White Matter Tracts

Epilepsy is a disorder of the nervous system that has severe consequences for patients and generates a significant social burden. About 3 million people have been diagnosed with epilepsy, and the cost to society is about $12.5 billion a year. More must be done to enhance the treatment of these patients. Although antiepileptic drugs (AEDs) are effective at controlling seizures in most patients, neuro-ablative surgery can treat epilepsies that are refractory to conventional pharmacotherapy.[1] However, epileptic foci resection does not guarantee seizure reduction and is not appropriate for generalized, multifocal, or bilateral epilepsy. Therefore, novel electrical stimulation approaches have been developed for the treatment of epilepsy.[2-6] Mesial temporal lobe epilepsy (MTLE) is the most common type of medically intractable epilepsy, characterized by hippocampal sclerosis and localization-related symptoms.[7] For the treatment of MTLE, a strategic target for stimulation is the hippocampus. The hippocampus is actively involved in seizures among a substantial population of epilepsy patients. Its densely packed structure and substantial feedback networks cause it to have the lowest seizure threshold of any brain region.[8-13] Moreover, the hippocampus is innervated by several fiber tracts that can recruit significant portions of the structure. In particular, the ventral hippocampal commissure (VHC) can activate cells in two-thirds of the hippocampus, bilaterally in rodents *(Figure 1)*. *In vitro* studies acute in *in vivo*

Figure 1: White matter tract stimulation of the rodent hippocampi through the ventral hippocampal commissure (VHC). The tract consists of the CA3 cell axons connecting the two hippocampi bilaterally. A dorsal tract (DHC) connects the hippocampi through the entorhinal cortex (EC) but is much smaller. The human DHC is sizable and can be targeted.
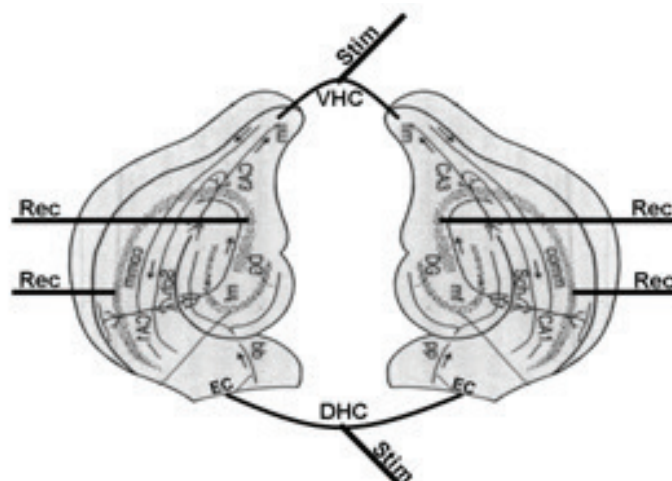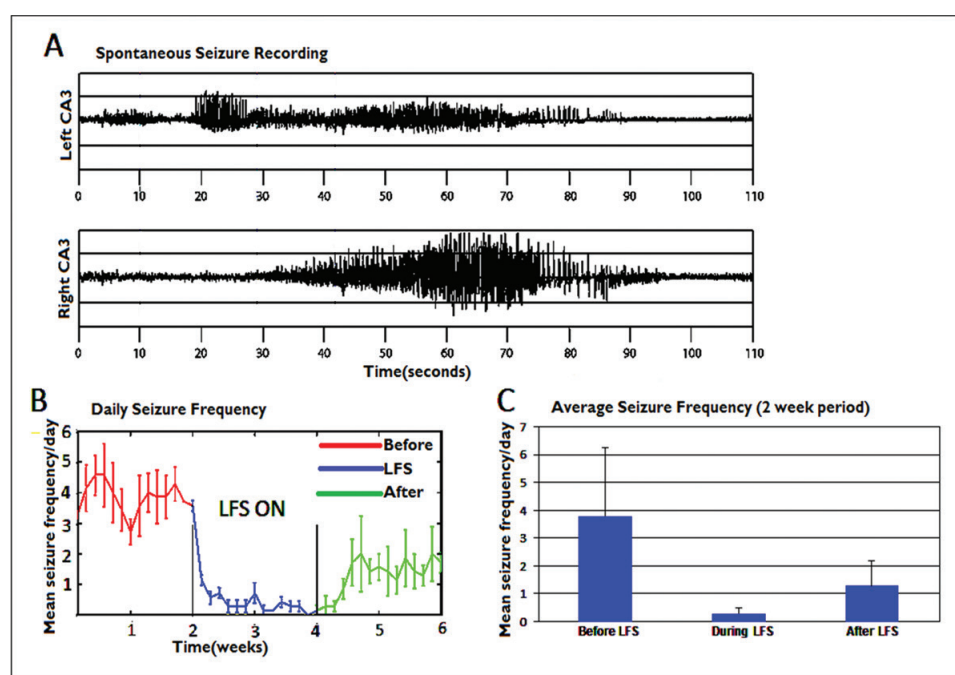
Figure 2: (A) An example of rat *in vivo* hippocampal recordings showing seizure activity. (B and C) Stimulation of the ventral hippocampal commissure. Low frequency stimulation (LFS-ON) produced a 90 percent decrease in seizure frequency.[16]

and chronic studies with a rat spontaneous seizure model have a near 90 percent reduction in seizure frequency with low frequency (1 Hz) stimulation (LFS) of this tract *(Figure 2)*.[14-16] Following stimulation, the seizure frequency was still decreased by 50 percent (after-effect). These results suggest the possibility that white matter tract stimulation could be of interest in human patients with mesial temporal lobe epilepsy (MTLE).

DBS in Patients with MTLE

Although several studies have shown that electrical stimulation of the brain can reduce clinical symptoms in epileptic patients,[17-21] the mechanisms are still unknown and the efficacy is limited. Recent technological development has led to several new studies investigating the feasibility of open loop and/or closed loop feedback to decrease the seizure frequency in patients.[5,22] Closed-loop stimulation is applied to the seizure focus, typically a grey matter target to disrupt the seizure activity following detection.

The idea of targeting a fiber bundle instead of grey matter comes from the fact that tract stimulation can affect a large portion of the brain rather than target specific, localized nuclei. Since seizure detection can take time (several seconds), local electrical stimulation may not prevent seizure propagation. White matter tract stimulation could prevent the propagation and the generation of seizures. To test this idea in human patients, a clinical study was carried out by stimulating the dorsal hippocampal commissure (DHC) fibers with electrodes located within the DHC fiber tract as it intersects with the fornix *(Figure 3)*.[23] In the human brain, the VHC is vestigial but the DHC is a sizable tract.[24-25] Eight patients were implanted with depth electrodes in the DHC without any complication. During video EEG monitoring of the study patients, the DHC was stimulated to activate the cortico-cortical evoked potentials in the temporal structures. Stimulation of the DHC showed robust activation of the three hippocampal electrodes (lateral, medial, and temporal) bilaterally.[26] LFS was applied in four-hour sessions (one to three sessions/patient at 5 Hz, current 8 mA, pulse width 0.2 ms) during the patients' evaluation period in the epilepsy monitoring unit. No complications were noted, and hourly mini-mental status examinations during stimulation showed no deviation from the baseline. LFS resulted in a significant reduction of hippocampal interictal epileptiform discharges ($P = 0.001$, generalized estimating equations [GEE]-Identity Link Function).

Seizure likelihood was reduced by 87 percent in one to two days following each four-hour LFS session (P = 0.001, GEE-Logit Link Function), without changes in anti-epileptic medication.[23] These results are in strong agreement with animal experiments.

Why Low Frequency

Low frequency electrical stimulation has been used successfully to suppress seizure activity in both animals and human patients. Jerger and Schiff showed that stimulation of the Schaffer collaterals and mossy fibers, at frequencies of 1.0 and 1.3 Hz, were able to entrain interictal spike generation and suppress seizure activity.[27] They suggest that frequency-dependent inhibition in the CA1 region is the mechanism responsible for this effect. Another study showed that low frequency stimulus trains were able to greatly suppress the after-discharge duration of seizures generated through the kindling process.[28] Goodman and Berger suggested that the suppression effect is caused by an increase in after-discharge threshold following low frequency stimulation.[29] They also suggested that long-term depression (LTD) is not the likely mechanism of action due to the short duration of the low frequency stimulus train. Yet, Albensi and colleagues applied 1 Hz stimulation (30-minute duration) to the Schaeffer collaterals in rat hippocampal slices treated with 200 µM bicuculline.[30] The 1 Hz stimulus train gradually suppressed seizure activity with suppression lasting 20 minutes after the stimulation was stopped; the authors suggested that synaptic depression was involved. Schiller and Bankirer also showed that LFS can suppress seizure activity in *in vitro* brain slices and attributed the effect to excitatory synaptic depression.[31]

In human patients with epilepsy, low frequency electrical stimulation at 0.5 Hz (square wave biphasic, 2 – 4 mA) delivered to different ictal onset zones each day in 30-minute intervals was able to reduce seizure frequency.[32] Stimulation of the caudate nucleus at 4 – 8 Hz in 57 patients suffering from intractable epilepsy also reduced the seizure frequency. The mechanisms were attributed to the possible activation of inhibitory responses in the network.[33] Activation of the ictal zones in patients with intractable epilepsy showed a small but detectable decrease in seizure frequency.[34] Possible mechanisms suggested by the authors include the induction of LTD and activities by GABA-benzodiazepine and local opioid systems.[34] Therefore, the literature strongly suggests that low frequency can reduce excitability but with unclear mechanisms.
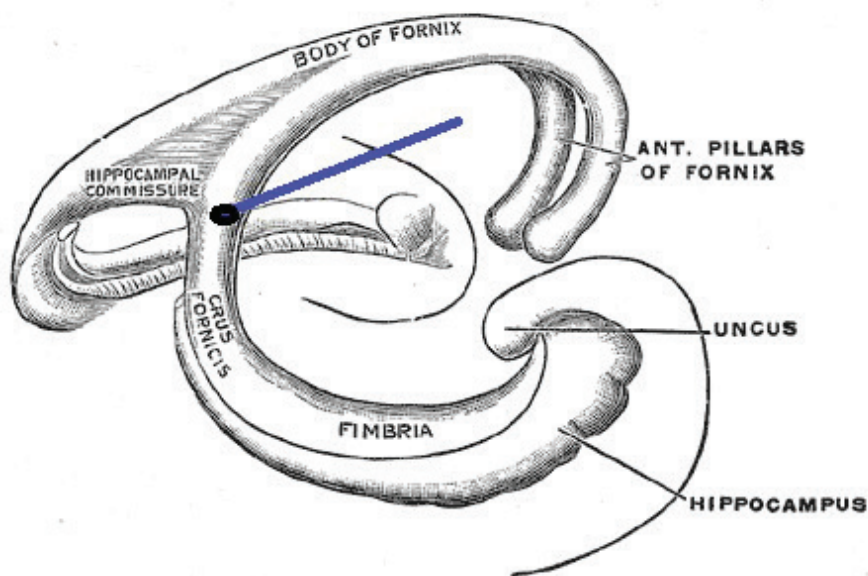

Figure 3: Electrical stimulation in human patients with mesial temporal lobe epilepsy. An electrode is placed at the intersection of the fornix and the dorsal hippocampal commissural fiber tract.

Mechanisms of LFS-induced Seizure Reduction

To study the mechanisms of the suppression effect, a novel *in vitro* seizure model consisting of bilateral hippocampi connected by the VHC fiber tract was developed.[14] Epileptiform activity is generated in this model using 4-aminopyridine (4-AP) and consists of high frequency seizure-like events as well as periodic low frequency interictal events.[35] Utilizing this model, we have shown that LFS of the VHC at 1 Hz can reduce bilateral epileptiform activity completely, as measured by (1) total seizure time, (2) seizure duration, (3) seizures per minute, and (4) power in the ictal as well as (5) interictal spectra. Electrophysiological analysis including field potentials and intracellular recordings shows that this effect is due to a stimulus-induced long-lasting hyperpolarization that prevents epileptiform activity from occurring during the interstimulus intervals. In particular, electrical stimulation can trigger (1) the $GABA_B$ slow IPSP and (2) the medium and slow after-hyperpolarization (m/sAHP), each of which is around one second in duration. We have studied the efficacy of the LFS paradigm under conditions of long-lasting hyperpolarization block with (1) $GABA_B$ antagonism by 450 µM 2-OH-saclofen and (2) m/sAHP antagonism with 10 µM clotrimazole.[35] The LFS efficacy was measured in three distinct seizure models where long-lasting hyperpolarization is preserved, including (1) 4-AP, which blocks Kv channels; (2) 100 µM bicuculline methiodide (BMI), an antagonist of the $GABA_A$ fast IPSP; and (3) low-magnesium artificial cerebrospinal fluid, which enhances glutamatergic activity. *In vitro* results show the LFS paradigm is robust in chemical models of epilepsy with distinct mechanisms of action but that its efficacy is significantly decreased in chemical models of epilepsy where long-lasting hyperpolarization is inhibited. Utilizing intracellular recording techniques, our experiments indicate that interstimulus hyperpolarization amplitude is significantly diminished when using these antagonists of $GABA_B$ and m/sAHP, concurrent with the decrease in LFS efficacy. These data suggest that long-lasting hyperpolarization mediated by inhibitory neurons is involved in the mechanism of seizure reduction by the LFS paradigm.[35]
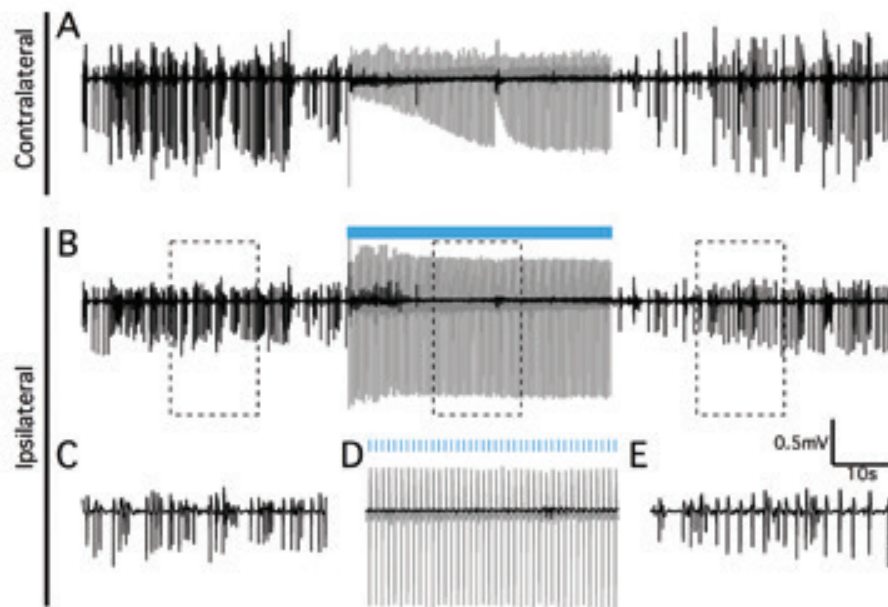

Figure 4. (A) *In vivo* low frequency optogenetic stimulation. Bilateral neural activity before, during, and after 1 Hz optical stimulation with blue light in the THY1promoter mouse. (B) Neural activity in the VGAT-promoter mouse. Epileptiform activity is induced with 4-AP injected directly in the cortex and, in both cases, low frequency stimulation can suppress abnormal seizure activity.

Leveraging Optogenetics to Determine Which Cells Are Involved in the Suppression

To determine which cells are responsible for the suppression effect, we used two transgenic cells lines: (1) the THY1-ChR2-YFP expressing channel Rodhopsin in both excitatory and inhibitory neurons and (2) VGAT-ChR2-YFP expression ChR2 only in GABA cells.

An optical fiber was inserted into the brain and reached the surface of the left hippocampus with a specific angle so that the blue laser could illuminate the CA3 region where the tungsten electrode was placed *(Figure 4A)*. Neural activity was recorded for 10 minutes as the baseline of the normal neural activity. 4-AP was then injected into the left CA3 (AP -1.7, ML +2.0, DV -2.0) to induce seizures. 40 mM 4-AP was injected (1 ul) every 10 minutes until the seizures became continuous (status epilepticus).

A 5ms blue laser pulse was used to suppress seizures. The laser pulse was applied at 1 Hz, and the power density was measured to be approximately 11 mW/mm^2. Seizures were recorded for two minutes during the baseline, and then optical stimulation at 1 Hz was applied for two minutes. The power of the neural activity before and during optical stimulation was calculated for comparison.

Optical stimulation with 1 Hz could suppress seizures bilaterally *(Figure 4)*. The laser was only applied on the epileptic focus, but suppression happened bilaterally. In both the ipsilateral and contralateral sites, the amplitude of seizures decreased for the first 20 seconds and was later completely suppressed. Following stimulation, seizure activity returned gradually with a similar pattern as before stimulation. By calculating the power of neural activity before and during the stimulation, we concluded that seizures were suppressed by 92.9 percent during stimulation and 13.8 percent after stimulation in the ipsilateral site. Seizure activity was suppressed by 97.1 percent during stimulation and 16.6 percent after stimulation in the contralateral site. Similar preliminary results were obtained in the VGAT line in which only GABA cells express ChR2, suggesting that the GABERergic neurons are involved in the suppression effect.

Conclusion

Intractable mesial temporal lobe epilepsy is a clearly significant problem, and stimulation methods are currently in development to address it. In particular, the near 90 percent seizure frequency reduction obtained on our recently published chronic animal preparation and human study is very encouraging.[16,23] The fact that we now understand some of the cellular mechanisms involved in the suppression effect and that we have identified some of the cells responsible suggests that improvement could still be made to ensure that patients with intractable epilepsy can become seizure-free in the near future.

Dominique Durand, PhD, is a consultant for Lake Biosciences, though this relationship has not affected the content of this article and the CME Program has determined there is no conflict of interest.

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The Computational Future of **Deep Brain Stimulation**

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Deep Brain Stimulation

Deep brain stimulation (DBS) is a powerful clinical technology, positively impacting the lives of tens of thousands of patients worldwide. DBS has FDA-approval for the treatment of Parkinson disease (PD), essential tremor (ET), dystonia, and obsessive-compulsive disorder (OCD).[1-4] In addition, numerous clinical trials to evaluate its efficacy for other disorders, notably epilepsy and treatment-refractory depression (TRD), are currently underway or recently completed.[5-8] However, for all of the clinical successes of DBS, numerous questions remain on its therapeutic mechanisms of action and effects on the nervous system.[9]

The clinical outcomes achieved with DBS are a testament to the efficacy of the existing device technology, surgical implantation techniques, and clinical programming strategies. For example, DBS for movement disorders can provide greater than 50 percent improvement in clinical ratings of motor symptoms in appropriately selected patients.[10] Unfortunately, DBS typically requires highly trained and experienced clinical oversight to achieve maximal therapeutic benefit in each patient.[11] In turn, an important and necessary step forward for wider scale use of this medical technology is the development of assistive technologies that optimize the clinical implementation of DBS.

Optimization of DBS technology, from both an engineering and clinical perspective, will require improved scientific understanding of the effects and therapeutic mechanisms of electrical stimulation of the brain. The fundamental purpose of DBS is to modulate pathological neural activity with applied electric fields. However, the clinical staff that typically implements DBS technology does not necessarily have a quantitative understanding of the neural response to adjustment of the various stimulation parameters. Fortunately, guidelines do exist for general stimulation parameter settings that are typically effective,[12] but it is infeasible to clinically evaluate each of the thousands of individual stimulation parameter combinations that may be useful to a given patient. As a result, the therapeutic benefit currently achievable with DBS is strongly dependent on the surgical placement accuracy of the DBS electrode and the intuitive skill of the clinician performing the stimulation parameter selection.

Computational modeling is playing an important role in new developments to improve both electrode placement and stimulation parameter selection in DBS patients. Stereotactic neurosurgical navigation has a long history of relying on computational models to help identify target coordinates in the brain for electrode placement based on the patient's medical imaging and intraoperative neurophysiological data.[13] Recently, software technologies have been designed to assist clinicians in identifying therapeutic stimulation parameter settings customized to each patient.[14]

Movement disorder symptoms like tremor respond quickly to the onset of stimulation, providing the clinician with feedback on the effectiveness of a given setting. However, application of DBS technology to disorders such as epilepsy, dystonia, depression, and obsessive-compulsive disorder are more problematic because the beneficial effects of stimulation can take days to weeks to manifest. This delay makes stimulation parameter selection during a short clinical visit difficult, and this problem is compounded by the somewhat limited scientific guidelines on optimal stimulation paradigms for these different disorders. Therefore, synergistic combination of clinical experience and scientific knowledge is needed to enable more efficacious application of DBS technology to patients.

Patient-Specific DBS Models

Computational modeling of DBS has established itself as a useful tool for investigating both mechanisms of action and techniques to optimize clinical application of the technology. Much of this field has focused on the creation and use of patient-specific DBS models as well as the corresponding electric field generated by the human DBS electrode (cylindrical electrode contact, 1.5 mm in height and 1.27 mm in diameter). The last decade has seen these models evolve from point source electrodes in an infinite homogeneous medium, to clinical electrodes in a human brain, to detailed representations of the electrode-tissue interface.[15-17] The electric field predictions from modern DBS models have been validated against experimental measurements in the brains of nonhuman primates and electrophysiological measurements in human patients.[17,18]

Patient-specific DBS models have had their greatest impact in analysis of the anatomical and electrical target

of the stimulation. DBS surgical targeting traditionally focused on electrode placement within the confines of subcortical gray matter nuclei, following the assumption that stimulation of the cell bodies of the neurons in the given nucleus was responsible for therapeutic benefit. However, numerous theoretical and experimental studies have shown that the primary effect of DBS is to stimulate axons that surround the electrode.[19-21] These axons may be associated with the implanted nucleus (i.e., axonal projections originating from the nucleus) or any other axon projecting to or passing by the nucleus. In the case of subthalamic DBS for PD, patient-specific models have demonstrated that activation of the white matter dorsal to the subthalamic nucleus (STN) is most associated with therapeutic benefit.[22,23] Further, when this region is explicitly targeted via surgical electrode placement, or stimulation parameter selection, outcomes improve relative to stimulation concentrated on the STN itself.[14,24]

Clinical Application of DBS Models

A clinical limitation associated with bilateral subthalamic DBS has been declining cognitive function. It is hypothesized that this side effect results from spread of current to nonmotor regions of the STN.[25,26] Frankemolle and colleagues prospectively assessed 10 PD patients, implanted with subthalamic DBS systems, during either clinically determined stimulation settings or settings derived from their patient-specific DBS model *(Figure 1A)*.[14] The clinical settings for each patient were defined via standard clinical practice (which did not include the use of DBS visualization software) and were stable for at least six months prior to study participation. Blinded to the clinical settings, patient-specific DBS models were used to define settings that minimized current spread to nonmotor areas of the STN. This process relied on a target stimulation volume *(Figure 1B)* derived from the results of Butson and colleagues.[23] Randomized and blinded clinical comparisons with quantitative outcome measures showed that the model defined *(Figure 1C)* or clinically defined *(Figure 1D)* parameter settings were equally effective in improving motor scores on the traditional clinical rating scale (UPDRS-III), both achieving an average OFF MEDS, ON DBS improvement of 46 percent. However, the model settings provided a 67 percent average reduction in power consumption because of the more focused stimulation delivery. When patients were simultaneously tested with the combination of a working memory (n-back) and motor (force-tracking) task
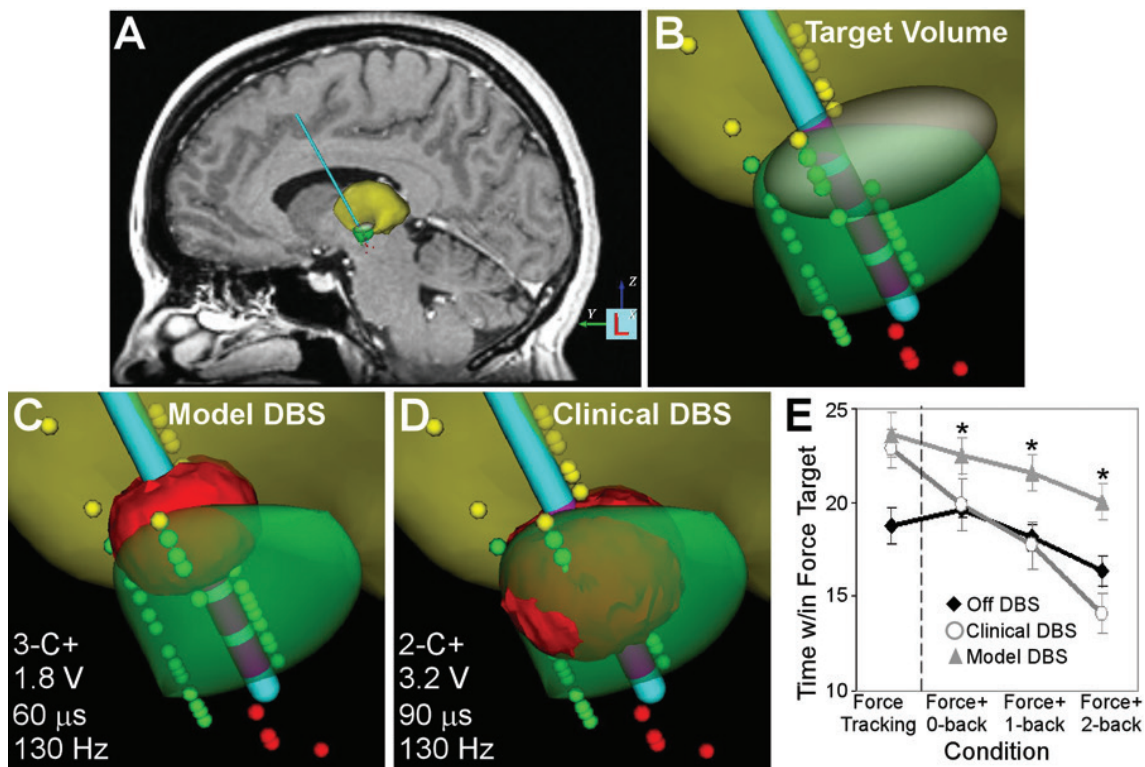
Figure 1: Patient-specific deep brain stimulation (DBS) models. A. Example patient model based on MRI data (blue shaft = DBS electrode; yellow volume = thalamus; green volume = subthalamic nucleus. B. The target stimulation volume for subthalamic DBS is shown in gray. The dots represent the stereotactic location of intraoperative microelectrode recordings (yellow dots = thalamic neurons; green dots = subthalamic nucleus neurons). C. Model-defined stimulation parameter settings and stimulation volume (red volume) defined to match the target volume. D. Settings defined by traditional clinical practice and the resulting stimulation volume. E. Experimental comparison of force-tracking and force-tracking with the n-back working memory task under the different DBS conditions. Model-defined DBS settings generated significantly better results than clinically defined DBS settings during the dual-task experiments.[14]

(i.e., dual-task), cognitive-motor performance was significantly better with the model settings than the clinical settings *(Figure 1E)*. These results suggest that the cognitive-motor declines associated with bilateral stimulation can be mitigated by minimizing current spread into the nonmotor regions of STN. Further, overall improvement in motor function does not have to be compromised to limit cognitive-motor declines as long as stimulation is focused on the appropriate target volume.[14]

Conclusion

DBS is a powerful clinical technology that allows for customization of the therapy to the individual patient needs over time via alteration of the stimulation parameters. Furthermore, DBS does not destroy tissue, allowing patients to potentially benefit from emerging restorative therapies. However, defining the optimal surgical placement for the DBS electrode and programming DBS devices for maximal clinical benefit can be a difficult and time-consuming process. In addition, current DBS electrode designs and stimulation pulsing paradigms were derived empirically and are probably not optimal. Computational modeling represents a useful technique to analyze current DBS practice and enable the creation of virtual testing grounds for the evaluation of future innovations. For example, new DBS technical developments in current-controlled stimulation, current steering between electrodes, stimulus waveform shape, temporal patterning of stimuli, and electrode contact design have been vetted in computational models and are beginning to enter clinical testing.[27-31] In turn, advances in scientific knowledge and technology are laying the groundwork for the re-engineering of DBS technology to better serve clinicians and patients.

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The Promise of **Neuromodulation**

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For most of human history, surgical intervention to improve the workings of the nervous system has been limited to crude lesioning operations. Even after the circuits involved in many disease processes were understood, neurosurgical intervention was still quite limited. However, over the past five decades, there has been a remarkable growth in our ability to use precisely targeted implantable devices to restore brain health. The ability to intervene in the function of the nervous system without permanently altering its structure is known as neuromodulation, and in the relatively short period of its availability, it has profoundly affected our ability to improve the lives of patients with many chronic and debilitating neurological conditions. Initially grounded in attempts to treat chronic pain, the spectrum of neurological disorders improved by neuromodulation technology is constantly expanding.

Spinal Cord Stimulation

Spinal cord stimulation (SCS) refers to the use of electrodes placed on the surface of the covering of the spinal cord to modulate spinal pathways for the treatment of neuropathic pain and other conditions. The very first spinal cord stimulator device was designed and tested in 1966 by neurosurgeon Norman Shealy and engineer Thomas Mortimer at what was then the Western Reserve University School of Medicine and University Hospitals of Cleveland.[1,2] Since then, the technology has been FDA-approved for failed back surgery syndrome and complex regional pain syndrome and has brought relief to thousands of patients with pain refractory to all other treatments. Applications for the technology continue to be expanded and refined.[3] SCS shows great promise in patients with angina pectoris and may improve exercise tolerance and quality of life.[4] It appears poised to offer similar relief to patients with severe peripheral vascular disease, diabetic neuropathy, and cancer pain.[5,6] Using similar principles, stimulation of peripheral/cranial nerves and the brain have also been shown to be helpful for chronic pain.[7,8]

Deep Brain Stimulation

Deep brain stimulation (DBS) refers to the implantation of electrodes into the substance of the brain in order to modify its activity through electrical stimulation. The technology was originally developed for the treatment of chronic pain but was found to be extremely effective in the treatment of movement disorders like Parkinson disease and essential tremor.[9] Recent studies have demonstrated effectiveness in patients with medically refractory depression and obsessive-compulsive disorder.[10,11] University Hospitals was the site of the first randomized controlled trial showing efficacy for DBS in Tourette's disease.[12] The advantage of DBS over pharmacologic therapies for these disorders is that medications will act wherever their target receptor or neurotransmitter is found, which can lead to unwanted effects. DBS, by contrast, can be precisely targeted, and the electrical field generated by stimulation can be shaped to ensure that no unnecessary structures are stimulated, minimizing side effects. As improvements in functional neuroimaging techniques lead to a better understanding of which brain networks are affected in different disorders, indications for DBS continue to expand at a rapid pace. For example, recent studies of DBS show promise for medically refractory epilepsy,[13,14] obesity,[15,16] aggression,[17,18] and minimally conscious states.[19] DBS also appears to offer the ability to influence pathways important for learning and memory.[20] An active area of investigation in our laboratory is the use of DBS to mitigate the deleterious cognitive effects of traumatic brain injury.

Technologies that alter the function of the nervous system through stimulation are only part of the story of neuromodulation: it is also possible to decode signals from within the nervous system to then decode intended movement for brain-computer interface. A recent demonstration of this emerging ability came in 2006 when a description of the first patient in the BrainGate trial was published. This report, published in the journal Nature,[21] described the implantation of a sensor array into the brain of a patient who had become quadriplegic three years earlier. The array was implanted into the area of the brain that had previously been responsible for moving the contralateral hand, and the patient was asked to visualize performing specific hand movements with his paralyzed limb. Once the electrical activity corresponding to those movements had been analyzed, the patient was able to control a computer cursor and even a robotic arm directly via the activity of his brain. The Department of Biomedical Engineering at Case Western Reserve University has done substantial work modeling how neuronal activity translates into movement, with the goal of eventually using electrodes implanted into the nerves and muscles of the arm to bring the patient's paralyzed limb back under his or her own control.[22,23] The technology has continued to advance, leading to the pilot phase of BrainGate [2,24] which will take place in part at University Hospitals Case Medical Center.

As remarkable as all of this may seem, it still does not do justice to the full range and potential of neuromodulation technologies. Targeted drug delivery pumps provide medication directly to the spinal column, where it can produce clinical benefit without side effects. Trials of gene therapy and stem cells offer early promise that the changes that occur in Parkinson disease and Alzheimer disease may be prevented or even reversed. Our ability to more precisely localize specific functions within the brain has taken a major step forward with the refinement of implantable electrodes for epilepsy monitoring, and modeling research in both animals and humans is teaching us how to maximize the therapeutic effects of stimulation once the appropriate target site is chosen. Progress on the materials and information technology has meant that implantable hardware continues to get smaller, even as its functional capacity expands, with new features such as rechargeable batteries and MRI compatibility helping to minimize the need for replacement or removal surgeries. Finally, advances in neuroimaging modalities are allowing for an ever more complex understanding of the circuitry within the brain, raising the possibility of stimulation systems that can exert an excitatory or inhibitory effect on more than one area within the brain for the synergistic treatment of disorders not currently manageable with a single stimulator. While we cannot specifically predict what new applications await us in the coming years, we can confidently state that neuromodulation technologies will continue to revolutionize the way we treat injuries and diseases of the nervous system.

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Advanced Neuroimaging –
Mapping Brain Function for Targeted Neuromodulation

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Deep Brain Stimulation – The Prototype Neuromodulation System

Deep brain stimulation (DBS) is the canonical application of neuromodulation technology used today. Like many aspects of functional neurosurgery, it has roots that date back long before it was commonly available, and its success has been rapidly catalyzed by periodic transformative evolutions of brain imaging technology. As early as the 1960s, Hassler used high frequency brain stimulation in the thalamus intraoperatively while determining the best site for thalamotomy and found that it relieved Parkinson tremor.[1] Subsequently, in 1973, Irving Cooper first deployed an implantable brain neurostimulator in patients with cerebral palsy and spasticity.[2] In the early 1970s, computed tomography was developed and the first human full-body magnetic resonance imaging (MRI) scan was performed in 1977; the first commercially available scanners were available in 1983. This advent of three-dimensional (3-D) brain imaging allowed for the necessary accuracy for a successful proliferation of targeted brain neuromodulation. Concurrently, Mahlon Delong and others were using neurophysiology in animal models to develop an understanding of basal ganglia and thalamocortical circuit function, which has provided a rational basis for where to intervene with neuromodulation for the treatment of movement disorders.[3,4]

While the earlier attempts at brain neuromodulation in the 1970s had never really caught on, now armed with advanced neuroimaging and understanding of the neurophysiology of these critical brain circuits, Alim Benabid reported success with using a Medtronic quadrapolar electrode in the ventral intermediate nucleus of the thalamus to control tremor.[5] It was not long before DBS had proven efficacy in many of these nodes within the basal ganglia for several different movement disorders.[6,7] In 1997, the FDA approved DBS to be used in the thalamus for tremor associated with essential tremor and Parkinson disease (PD). In 2002, approval came for DBS of the subthalamic nucleus and internal segment of the globus pallidus (GP) for PD. In 2003, the FDA granted a humanitarian device exemption for dystonia, and, in 2009, the first neuropsychiatric application was approved as a humanitarian device exemption for obsessive compulsive disorder.

Neuroimaging Transforming Neuromodulation – Benefits and New Challenges

Thus far, imaging technologies have made a significant impact on the successful emergence of neuromodulation technologies. However, this impact has mostly been achieved by producing more reliable results by allowing better visualization of brain anatomy for more precise surgical planning. There are still many limitations.

(1) Some of the target nuclei, such as the subthalamic nucleus, are not fully visualized on MRI at 3 Tesla.

(2) We do not know precisely the relationship between anatomical structure and function or how excitability of brain tissue may vary from individual to individual with electrical stimulation.

(3) There is often significant brain-shift during surgery so that preoperative MRI may only provide an estimate of a stereotactic trajectory as it relates to brain anatomy.

As a result, careful microelectrode physiological mapping is often used intraoperatively to confirm the boundaries of the target with micron-level accuracy followed by careful testing of stimulation on test trajectories as well and with the DBS electrode to evaluate stimulation thresholds for benefit and side effects and assure that there is a significant "therapeutic window" between the two. Now, new technology is emerging to use intraoperative MRI, which should minimize errors related to number 3 above (brain-shift) but doesn't address issues related to number 1 or 2 or allow for clinical stimulation testing to confirm and refine the target based on outcome prior to outpatient programming.

Neuroimaging is again beginning to impact the future of neuromodulation through the use of functional imaging modalities to create a rational basis for neurological and neuropsychiatric applications in other disease states. Animal models have served us well, but there are not good animal models for many neuropsychiatric disorders and, even in disorders such as PD, many clinical features are not seen in animal models and therefore may only be evaluated in humans. Further, most of these diseases are themselves heterogeneous with different genetic or other etiological associations. They may have a different constellation of symptoms and subtypes and, at a systems level, may have different patterns of dysfunction. Functional neuroimaging is starting to reveal some of these differences and may be a key technology for potentially discerning if a patient is a target for neuromodulation and what target and type of neuromodulation he or she may likely benefit from.

Challenges Posed By Neuromodulation Technologies

When assessing how neuromodulation is working, we are challenged by problems posed by the fact that we are stimulating in 3-D space, with dense complicated regional anatomy, and there is variability of the patient's anatomy and the lead location within it as well as the shape, direction, and extent of spread of electrical current. Furthermore, while our current DBS systems are relatively simple and the essential features of the stimulus waveform and modes of stimulation are not much changed from the original models approved in 1997, each lead still has more than 1.5 million unique programming settings. This variation creates an information management problem but one that may be overcome with advanced, therapy-specific, medical informatics and computer modeling of stimulation effects.

Neuroimaging Modalities for Brain Mapping

Positron emissions tomography (PET), though one of the older functional imaging technologies, has several advantages. It is quantitative, where functional MRI (fMRI) is not, and has a diverse expanding array of ligands that produce estimations of brain metabolism, blood flow, and neurotransmitter function. Amyloid ligands are now available providing noninvasive insight into neuropathology and further development of other proteins including tau will likely continue to improve our ability to use PET to image neurodegenerative disease. Drawbacks of PET imaging include its poor spatial resolution and reliance on radiopharmaceuticals. Blood oxygen dependent fMRI has a much higher spatial resolution and can be paired easily with other MRI sequences to give a multimodal assessment at one time. One of these – diffusion tensor imaging (DTI) – produces an image of anatomical connectivity in the brain. Neuron axons have lower thresholds for activation from neurostimulation than the soma. DTI essentially produces a patient-specific data set of axonal pathways in the brain, thus producing critical information for the understanding of neuromodulation effects on the brain.

Imaging Brain Function in Movement Disorders

PET studies have been useful in producing quantitative metrics of brain function as it relates to specific disease states. David Eidelberg has described many disease or symptom-specific network covariance patterns using resting-state PET and a principle component analysis. He has found reliable networks for a PD-specific network as well as specific patterns for atypical parkinsonism, including progressive supranuclear palsy; multiple systems atrophy; cognitive change associated with PD, Huntington disease, and Alzheimer disease; dystonia; Tourette syndrome; and tremor.[8-10] These network patterns have been shown to correlate with disease severity and improve with treatment. The approach may be useful for neuromodulation by assisting in separating patients into phenotypes that are likely or unlikely to be responsive to neuromodulation. Further, disease-specific network activity may provide a useful objective imaging biomarker of disease severity. As an example of this approach applied to DBS, Eidelberg's group showed PD patients had improved PD-specific network activity, including improved metabolism in the premotor cortex and cerebellum after GP DBS.[11]

Another important approach is to use functional imaging to look at neural function during a task to yield insight into how motor control is generated differently or how sensory/proprioceptive information may be abnormally integrated in motor planning. These studies, by nature, cannot occur at rest and must be carefully controlled within the limitations of the imaging environment. As an example of this approach, we examined sensorimotor integration in 10 PD patients and 10 age-matched controls by using a task that uses a vibratory stimulus to create a controlled illusion of wrist movement (kinesthetic illusion).[12] Doing so revealed a pattern of decreased activity in the prefrontal cortex, putamen, and caudate and is consistent with the loss of dopamine that normally regulates the basal ganglia-thalamocortical motor loop *(Figure 1)*.
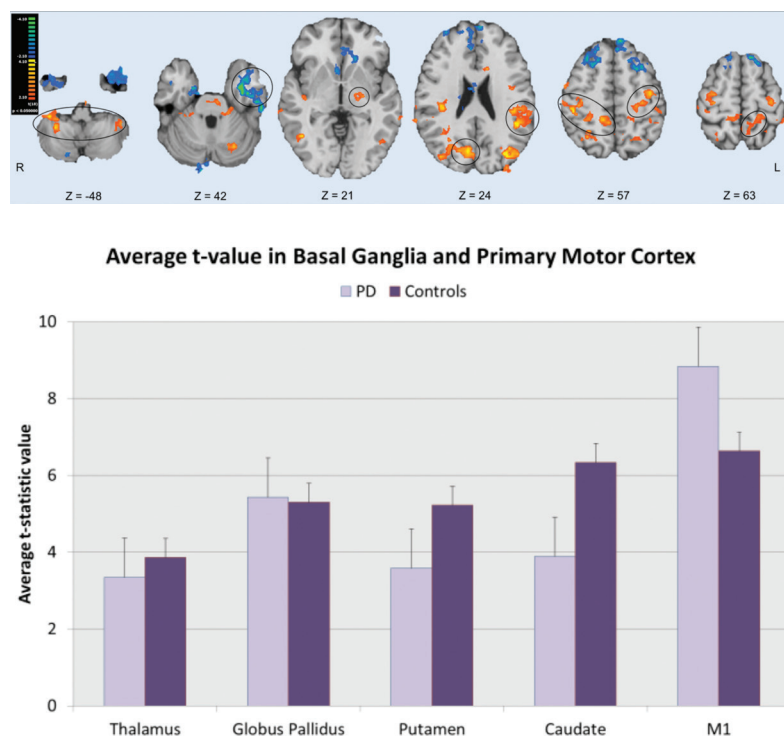

Figure 1: (A) The contralateral sensorimotor cortex and subcortical structures in controls and PD subjects were activated. A random effects group comparison (PD vs. controls) showed the PD group had decreased activity in the bilateral prefrontal cortex (BA 8, 9, 10) and temporal lobe (BA 20, 21, 22, 35, 37). Increased activity was noted in the bilateral cerebellum, lateral premotor (BA 6), visual association areas (BA 19), insular (BA 13), contralateral GPi, anterior cingulate (BA 24), S2 (BA 39, 40), primary motor cortex (M1) (BA 4), superior parietal lobule (BA 5, 7) ipsilateral precuneus (BA 31), S1 (BA 2, 3). The subcortical structures were segmented, and the average t-value in each area was compared between the groups using a one-sample t-test. (B) Reduced activation of the putamen and caudate and increased activation of M1 were found.

Further, we saw increased activity in the cerebellum, ipsilateral S1, and contralateral M1, which most likely reflects compensatory mechanisms in response to reduced activity in the cerebellar-thalamocortical motor loop. Approaches such as this one may be useful in understanding the systems-level circuit dysfunction underlying different clinical issues in patients with neurological disorders and present opportunities to define new targets for neuromodulation.

Translating the Tool to the Treatment – How Functional Imaging is Revolutionizing the Future of Neuromodulation

Great examples of how neuroimaging has been used to find, define, and validate targets for neuromodulation in the emerging applications for neuropsychiatric disorders now exist. Helen Mayberg's group has built a case for the subgenual cingulate (BA25) to play a critical role in the genesis of depression using a series of PET studies. Liotti and colleagues showed that normal volunteers had hypermetabolism in CA25 during a transient state of sadness.[13] Depressed patients also had hypermetabolism of the same area that was reduced with successful treatment composed of antidepressants, cognitive behavioral therapy, and anterior cingulotomy.[13-15] This converging evidence led Mayberg and Lozano to propose a clinical trial of DBS of CA25, which thus far has had positive results.[16]

The fact that many, if not all, neurological and neuropsychiatric disorders for which we may consider neuromodulation are heterogeneous is cause for a role of functional imaging. Just as functional imaging has been useful in finding targets for neuromodulation, it can be used to follow up on patients after surgery and reveal predictive features of responders and nonresponders. There may be clues on preoperative scans, and on postoperative scans there may be changes that correlate with outcome that may be related to variable lead placement.

Another direct application of neuroimaging to improve neuromodulation comes from the use of DTI to image axonal tracts in the brain. This process may relate to benefits or side effects of stimulation and, in any neuromodulation application, both have to be taken into account to explain outcomes. Because of some limitations in how we can spread electrical current with

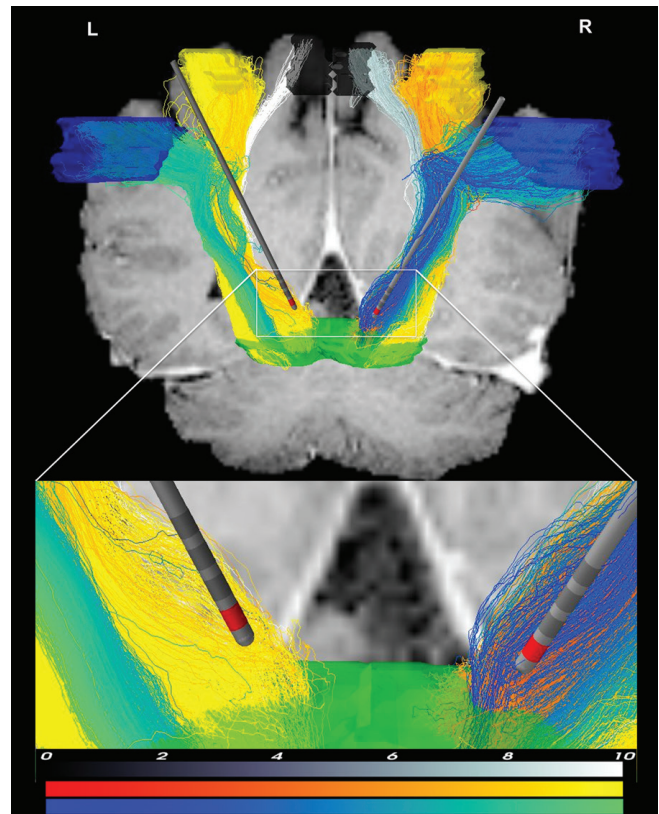Figure 2: The image displays probabilistic fiber tracts for a single subject overlaid on the subject's own MRI. Fibers were tracted from the face (blue/green), hand (red/yellow), and foot (black/white) areas in the primary motor cortex to the diencephalon (green). The color bars indicate the distances in millimeters for each set of tracts. The postoperative location of the leads is overlaid in grey.

Distance vs Stimulation Threshold for Face Side Effects

Legend:
- ◆ Face
- ■ Hand
- ▲ Foot
- — Face
- — Hand
- — Foot

Y-axis: Mean distance of the closest 10% of tracts (mm)

X-axis: Stimulation threshold (V)

Regression equations on chart:
$y = 0.7265x + 1.7437$, $R^2 = 0.2036$
$y = 0.805x + 0.4704$, $R^2 = 0.3039$
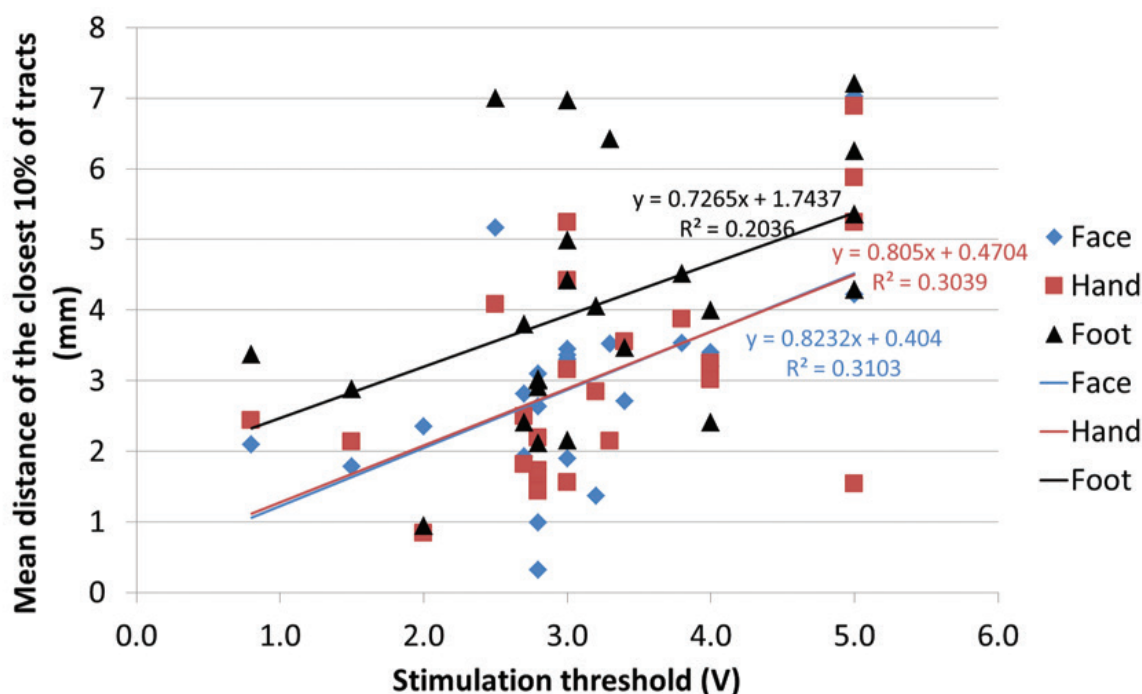$y = 0.8232x + 0.404$, $R^2 = 0.3103$

Figure 3: The stimulation thresholds for motor side effects recorded at monopolar review plotted against the distance of the closest 10 percent of the diffusion tensor imaging fiber tracts for each area of the primary motor cortex (face, hand, and foot in the left and right hemispheres).

a neurostimulator, the relationship between structures related to benefit, side effects, and stimulation parameters is not trivial. For example, a structure that causes side effects not only impairs function when directly stimulated but also limits the ability to spread current to neighboring beneficial target regions because it limits the amplitude of current that can be used without side effects.

For stimulation in the basal ganglia for movement disorders, all of our targets share a border with the corticospinal tract passing through the internal capsule. We conducted a study using DTI to reconstruct the internal capsule from seeds placed in face, hand, and leg areas of the primary motor cortex. In doing so, we were able to track the path of the corticospinal axons and segment them somatotopically *(Figure 2)*. The Euclidian

distance from a DBS contact placed in the neighboring subthalamic nucleus to the closest internal capsule streamline was calculated and correlated against clinically measured thresholds for stimulation side effects from that contact related to face, arm, or leg somatotopy *(Figure 3)*. The highest incidence of capsule-related threshold effects were found in the face and, as seen in the correlation analysis, 30 percent of the variance was explained by this relationship. We know clinically that there are some patients who are not found to have significant side effect thresholds with acute stimulation but, over weeks to months, lower thresholds are revealed with chronic stimulation. One can now use this analysis to predict when unintended stimulation side effects may be likely and potentially avoid such problems by using DTI analysis.

Conclusion

In summary, the fields of neuroimaging and neuromodulation are evolving quickly, and imaging advances have been critical to the success of neuromodulation technology. New imaging technology has refined visualization of anatomical targets and now provides an understanding of the brain-circuit dysfunction underlying many of these disorders that may make them amenable to neuromodulation.

Benjamin Walter, MD, is a consultant for Teva Pharmaceutical Industries Ltd. and US WorldMeds, LLC, and a speaker for Teva Pharmaceutical Industries Ltd.; US WorldMeds, LLC; and UCB, Inc. These relationships have not affected the content of this article and the CME Program has determined there is no conflict of interest.

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• Describe why white matter tract stimulation is preferable to grey matter stimulation.

• Discuss deep brain stimulation and its therapeutic mechanisms of action and effects on the nervous system.

• Identify potential new applications of neuromodulation technology.

• Recognize the limitations of imaging technologies that have made a significant impact on the successful emergence of neuromodulation.

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