Therapeutic applications of technology in Parkinson's disease

Lothar Krinke, PhD
VP & General Manager, Brain Modulation

Disclaimers

- I am employed by Medtronic, Inc.
- Medtronic has a financial interest in Functional Neuromodulation, a company that I will discuss today, and I am a Board of Directors' observer
- Some potential uses of DBS discussed today are under development or are in the investigational phase only, and are not currently approved for clinical use or commercialization in the US.
- DBS therapy is not for everyone. DBS Therapy requires brain surgery which could have serious or even fatal complications. Other complications can occur and may require additional surgery. Medtronic DBS Therapy may cause worsening of some symptoms. For additional safety information, please refer to Indications, Safety and Warnings at www.http://professional.medtronic.com/pt/neuro/dbs-md/ind

Brain Modulation: one aspect of functional restoration of the brain

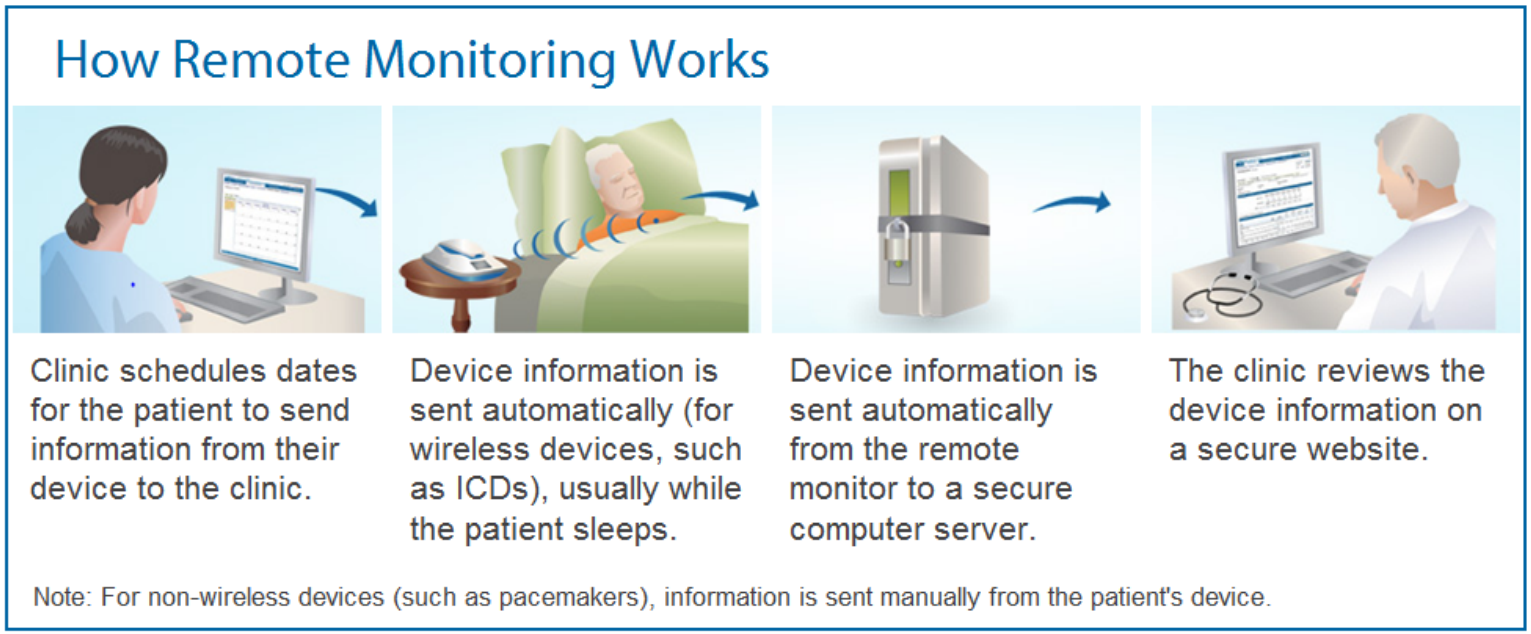
Proposed Definition

Functional brain restoration defined:

Modulation, repair or replacement of brain structures by precise delivery of stimulation, medication or cells to treat disordered brain function.

What can we learn from Cardiac Resynchronization Therapy?

- Therapy: Pacing and Shock algorithms
- Diagnosis: Fluid Status Monitoring
- Patient Management: Remote monitoring system provide fast and easy remote device follow-

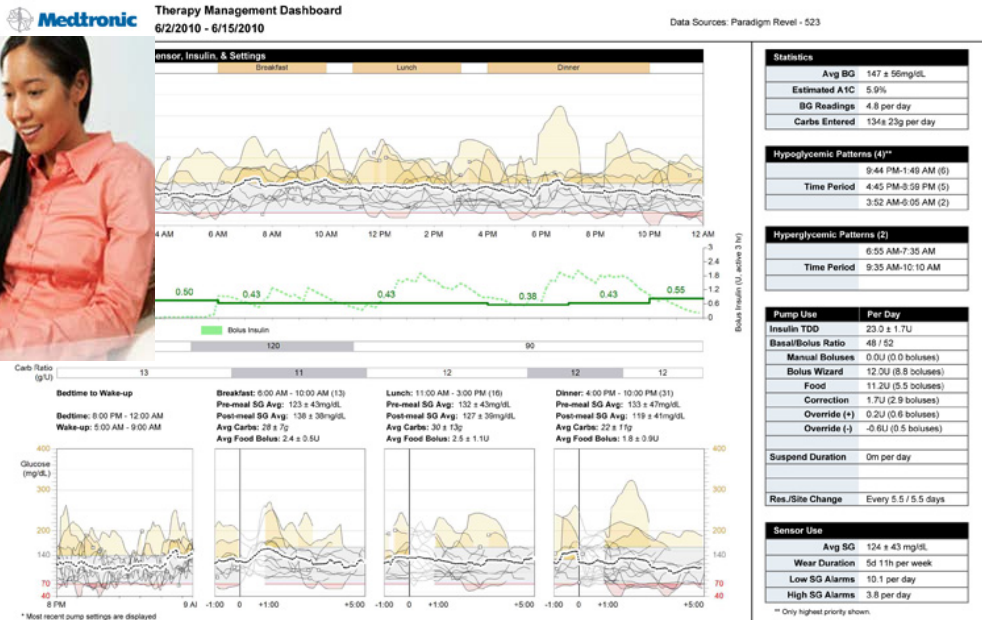


What can we learn from Diabetes?

- Therapy: Threshold Suspend, which automatically stops insulin delivery when sensor glucose values reach a preset low threshold.
- Diagnosis: Continuous blood glucose monitoring
- Patient Management: Patient and Physician reporting on trends

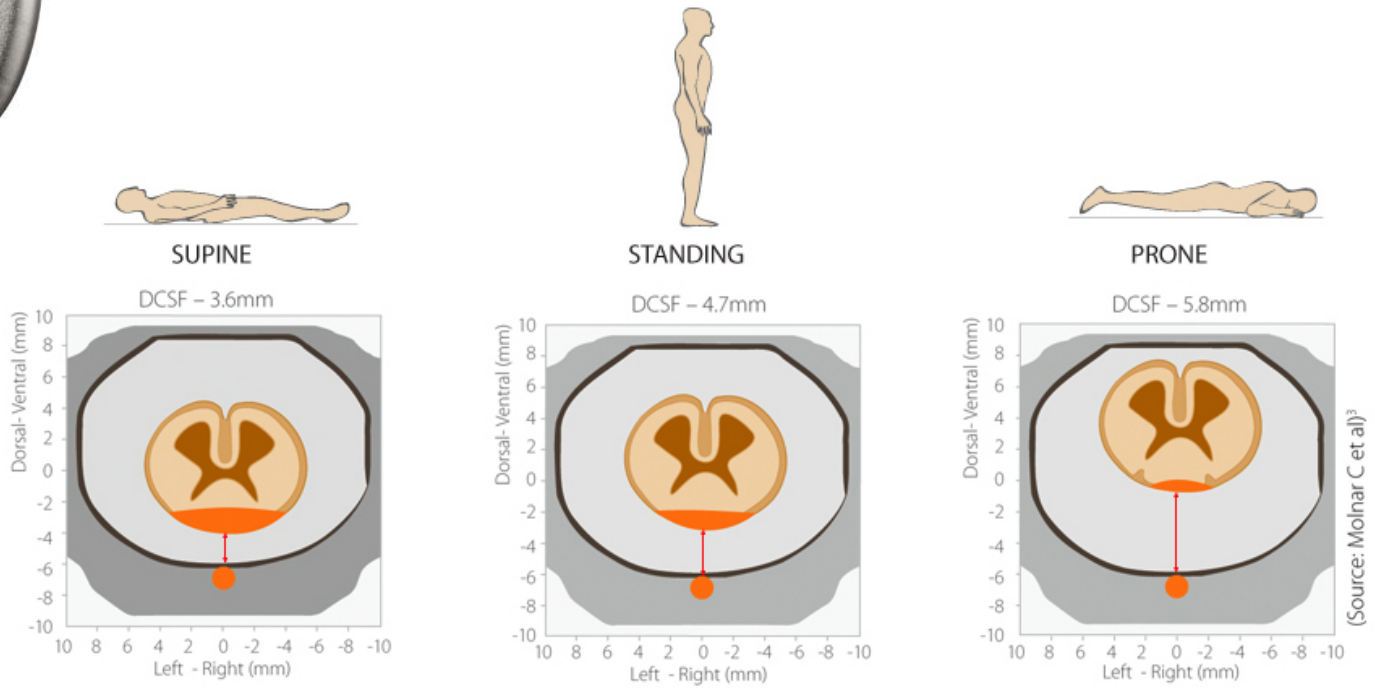
CareLink® Personal Therapy Management Software

CareLink Personal software is a convenient online tool that brings together critical information from your diabetes-monitoring devices, including Medtronic insulin pumps, continuous glucose monitoring systems, and more than 25 of the most popular blood glucose meters.



What can we learn from Pain Management?

- Therapy: Adaptive Stim automatically adjusts stimulation based on the patient's needs and preferences in different body positions
- Diagnosis: AdaptiveStim Diary provides objective data regarding patient activity



Sensors and Connected Care

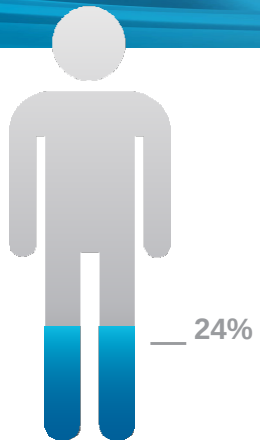
1. Patient Screening and Diagnosis
2. 24/7 patient optimized therapy
   - Responsive Therapy
   - Automatic therapy adjustment
3. Improved patient self management
4. Remote patient monitoring
5. Remote patient management
6. Automatic quantification of outcomes to prove value to payers
7. Scientific discovery
   - Large patient datasets
   - Rare events

Challenge: Many qualified DBS candidates do not have access to the therapy

Of the estimated 1,000,000+ Americans with PD

110,000

Are potential candidates for DBS Therapy



only

24%

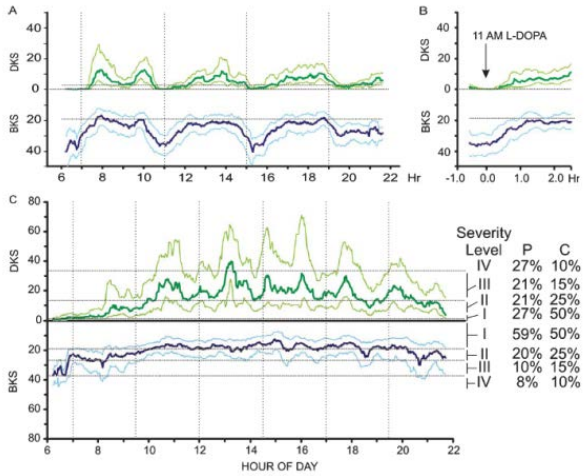
receive an implant

We are all striving for the best in patient care which involves making therapies more **accessible**.

MDT data on file PAA

Misconception: Patient is not yet a candidate for DBS or DBS may not provide the expected outcome

TECHNOLOGY SOLUTION = Quantifying symptom fluctuation for DBS application



[1]

Technology Goal

- Improve patient selection and identify “DBS-ready” patients
- Confidence in decision with objective measures
- Reduce physician burden and simplify patient follow-up

Sensor-based Quantification

Objective Assessments

Impact to Practice

- **Patient selection for DBS**
- **Therapy optimization**
- **Quantification of therapeutic benefit**

GLOBAL KINETICS CORPORATION

[1]Griffiths RI etal. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. *J Parkinsons Dis.* 2012;2(1):47-55

KITE Study

Study Title:
Evaluation of the Parkinson's KinetiGraph Data Logger (PKG) as a tool to measure motor fluctuations and support the DBS eligibility assessment of Parkinson's disease patients.

Study Objective:
To evaluate whether the GKC algorithm can differentiate DBS ready from DBS not-ready patients as assessed during the visit at the clinical site by the DBS specialist

Study Design:
Prospective, dual-center, non-interventional, post-market release clinical study

Primary endpoint:
Percentage of agreement on DBS eligibility classification between DBS specialists assessment and GKC assessment

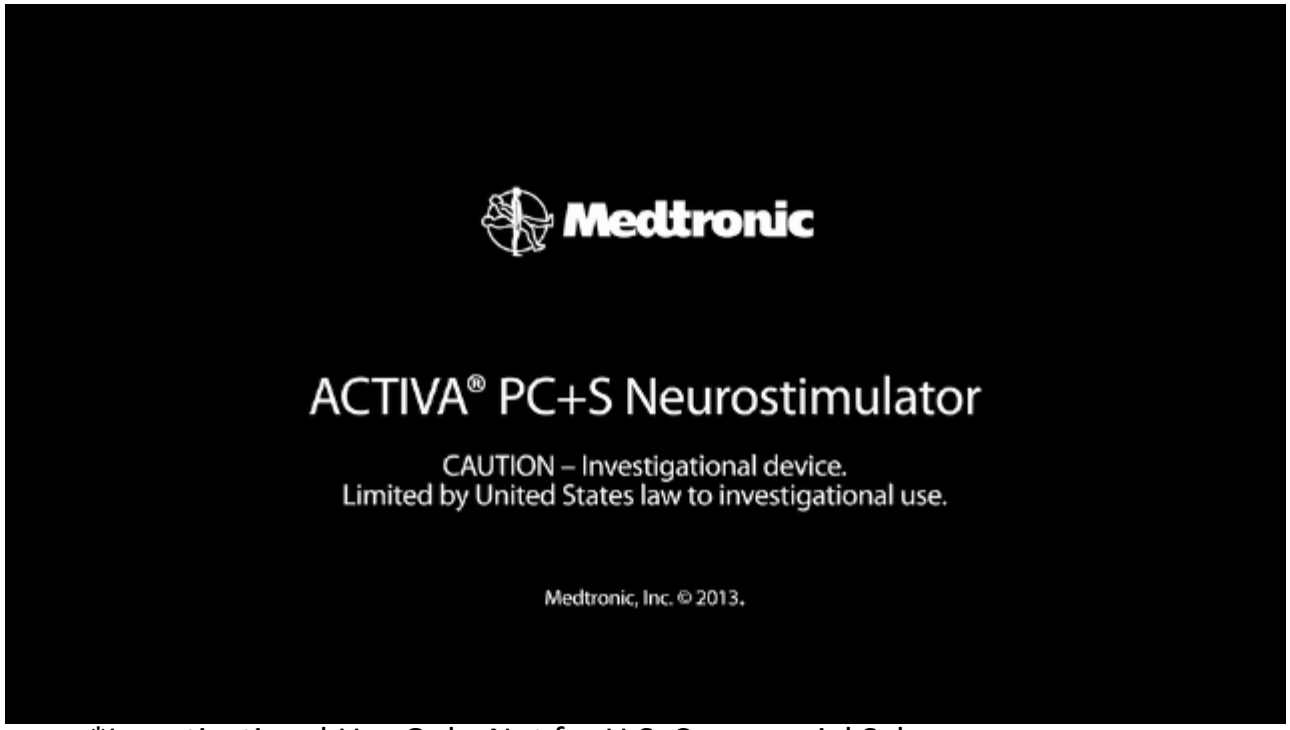
Sites: Prof. Moro (Grenoble, France) and Prof. Volkmann (Würzburg, Germany)

Patients: 36 evaluable patients

Device:
- PKG Data logger (PKG) is a CE mark device.
- Manufactured by Global Kinetics Corporation (GKC).

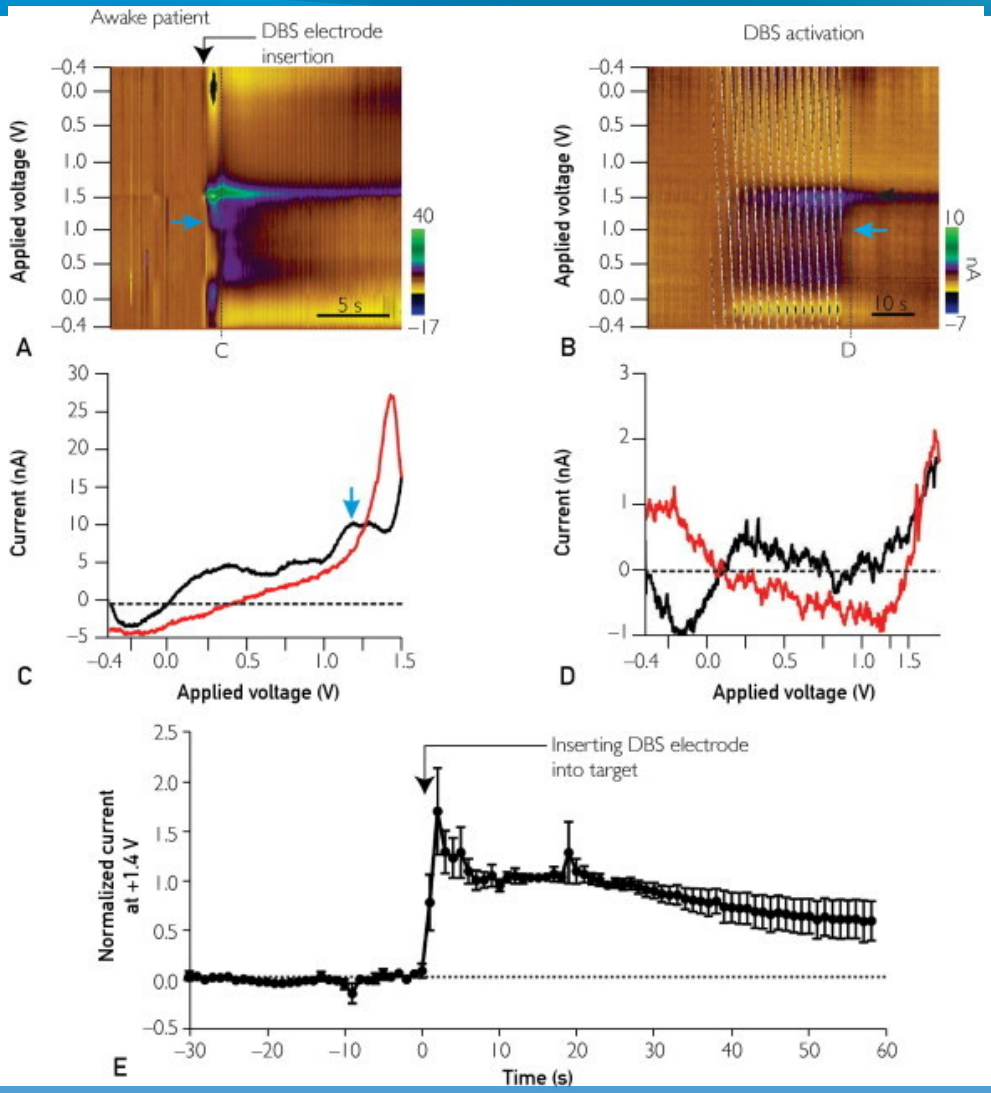
Brain sensing

Animation of brain activity sensing built into a commercial Activa DBS system (like a CRDM device that measures electrophysiology)*



*Investigational Use Only, Not for U.S. Commercial Sale

VIM DBS induces adenosine release in ET patients

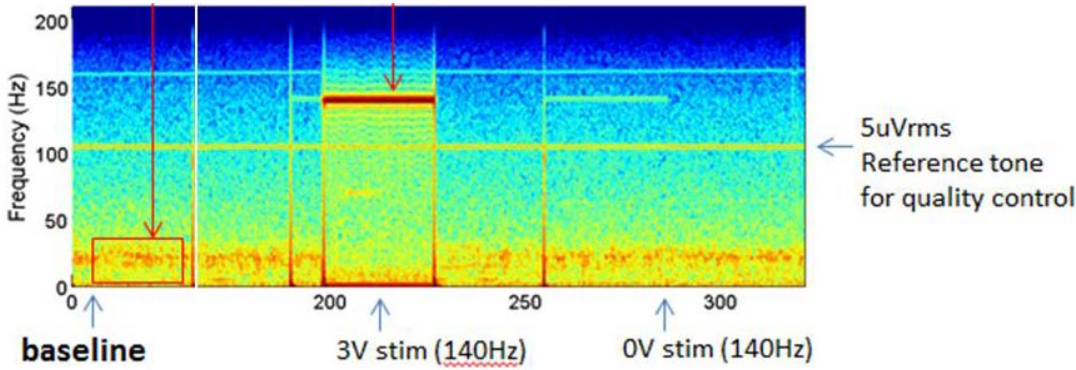


Chang SY et al. Wireless fast-scan cyclic voltammetry to monitor adenosine in patients with essential tremor during deep brain stimulation. Mayo Clin Proc. 2012 Aug;87(8):760-5.

TECHNOLOGY SOLUTION = Medtronic Integrated technology

Physiological Brain Modulation enabled by sensing technology and algorithms – Activa PC+S

Biomarker identification through sensing and closed loop systems are expected to reduce patient management burden and may lead to automated programming



Data file courtesy of Bronte-Stewart, Stanford; interpretation by Medtronic.

Why sensing?

- Basic understanding of Neuroscience
- Serendipitous discovery
- Monitoring of disease progression and therapy effectiveness
- Programming guidance
- Automated Programming
- Patient personalized stimulation

Sensing Research Status:

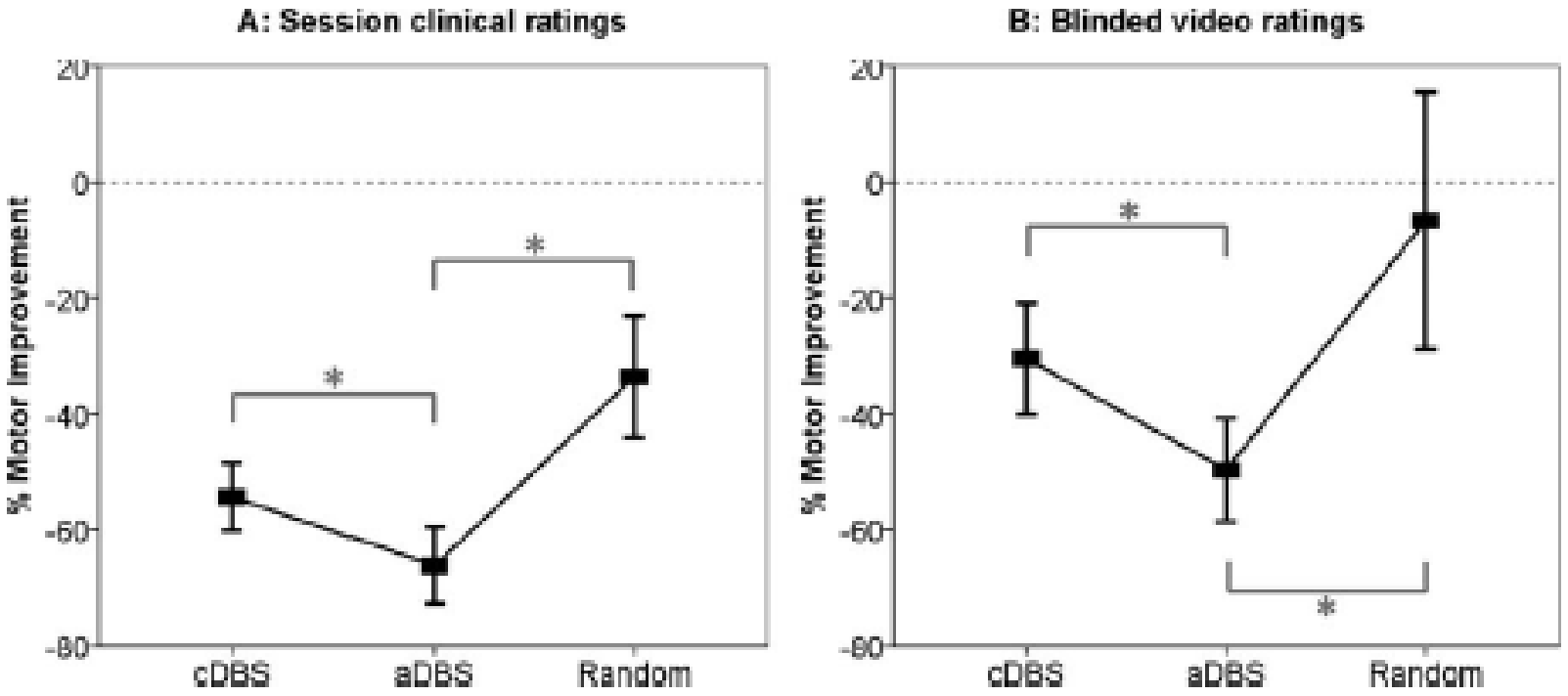
- A number of physician-sponsored studies ongoing globally
- Numerous devices implanted across a range of disease states/conditions
- Several manuscripts in progress

Potential long-term impact:

Closed-loop stimulation to deliver patient personalized stimulation

Disclosure: Innovations discussed are in development or investigational only and not approved by the FDA.

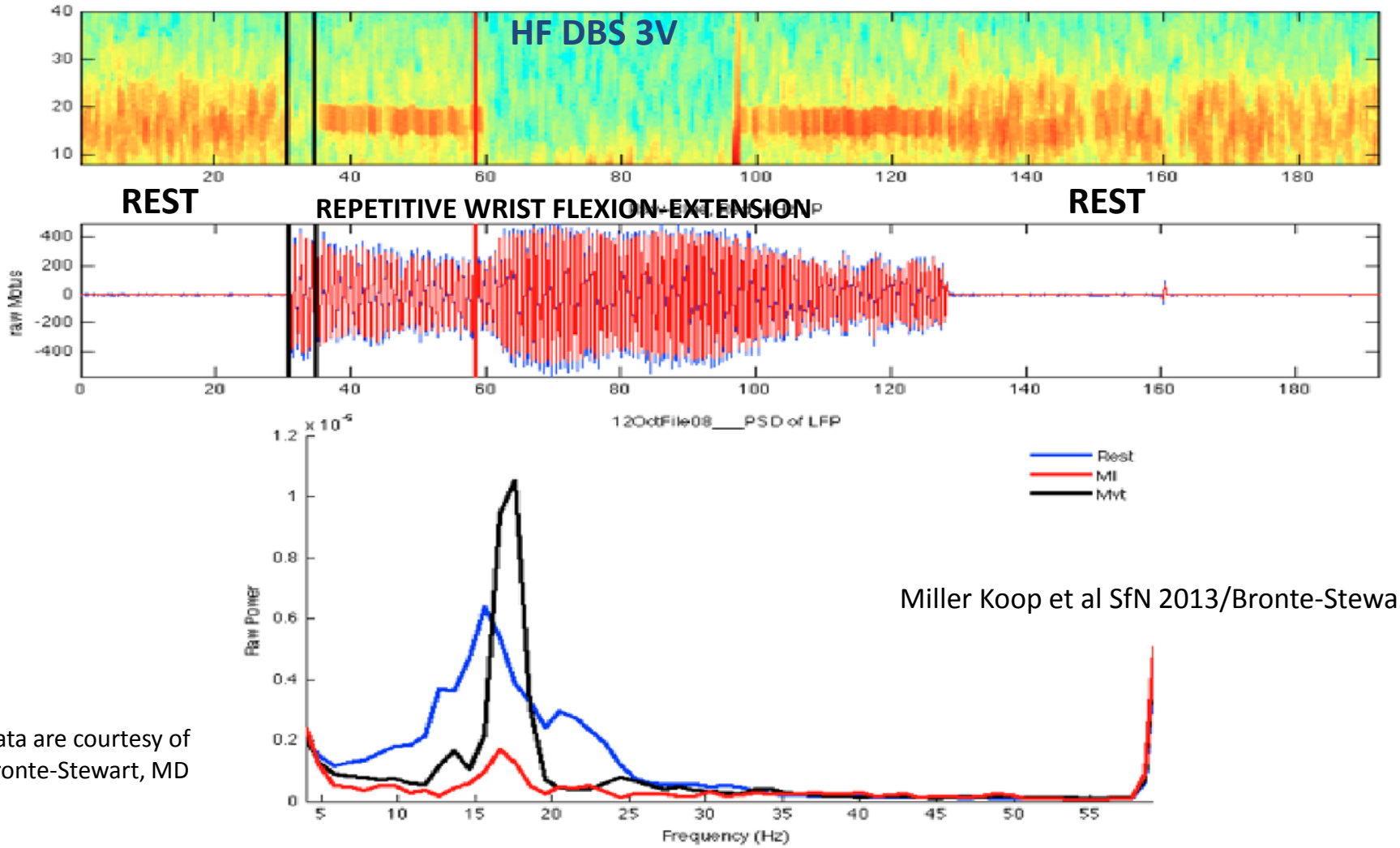
Initial efforts towards closed loop systems based on LFP sensor



Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Annals of neurology.* 2013;74(3):449-457.

Disclosure: Innovations discussed are in development or investigational only and not approved by the FDA.

Synchronized LFPs and kinematic recordings during continuous wrist flexion-extension before and during HF DBS using a wearable angular velocity sensor

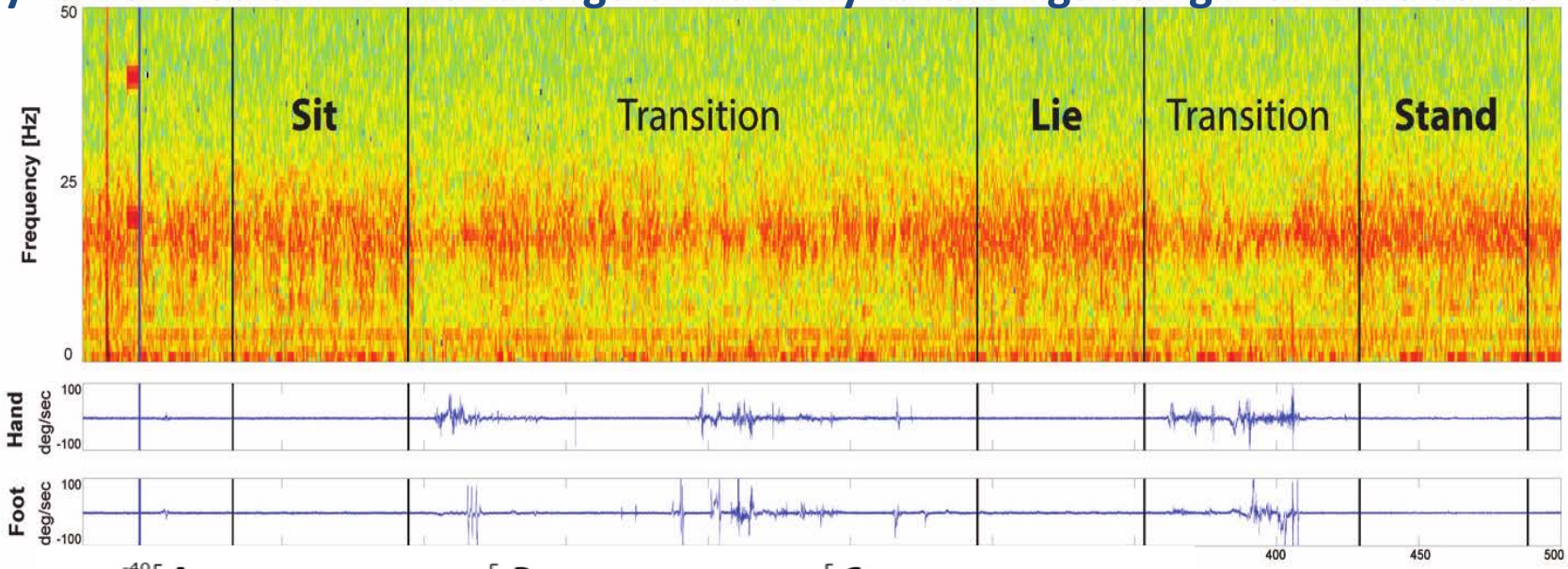


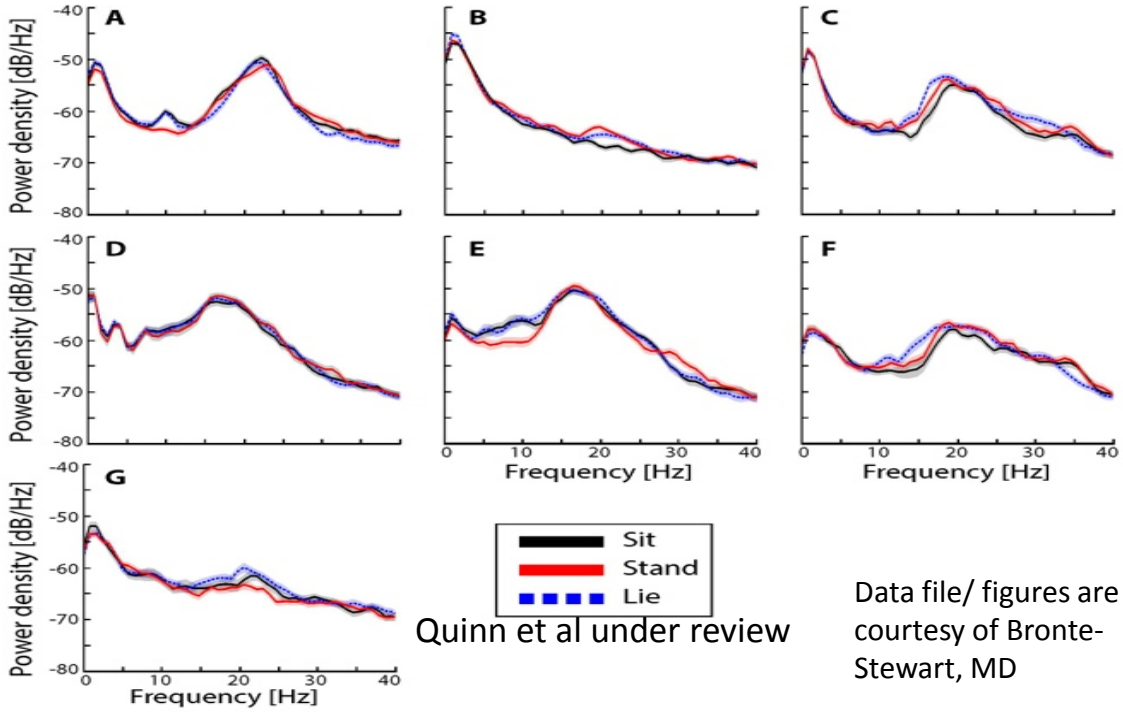
Miller Koop et al SfN 2013/Bronte-Stewart Lab

Data are courtesy of Bronte-Stewart, MD

Disclosure: Innovations discussed are in development or investigational only and not approved by the FDA.

Synchronized STN LFP and angular velocity recordings using wearable sensors





Quinn et al under review

Continuous > 8 min neural and kinematic recordings from a sensing neurostimulator in freely moving PD people. Wearable sensors detect when person moving or stationary

Data file/ figures are courtesy of Bronte-Stewart, MD

Disclosure: Innovations discussed are in development or investigational only and not approved by the FDA.

Novel Pulses: From High Frequency Stimulation to Novel Patterns

Today: High frequency continuous stimulation

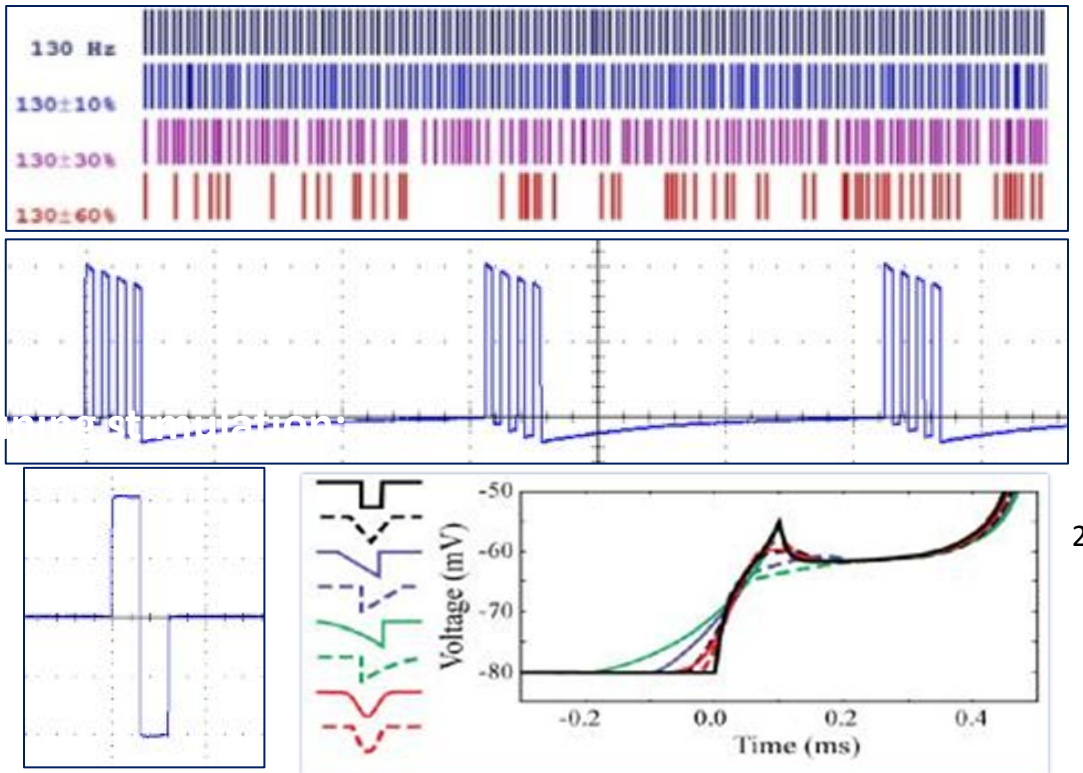
Tomorrow: Temporal or Waveform modulation to potentially improve therapy outcomes

Temporal modulation, e.g.:

- Pseudorandom
- Burst
- Stochastic

Waveform modulation, e.g.:

- Square-biphasic
- Non-square
- Arbitrary



1

2

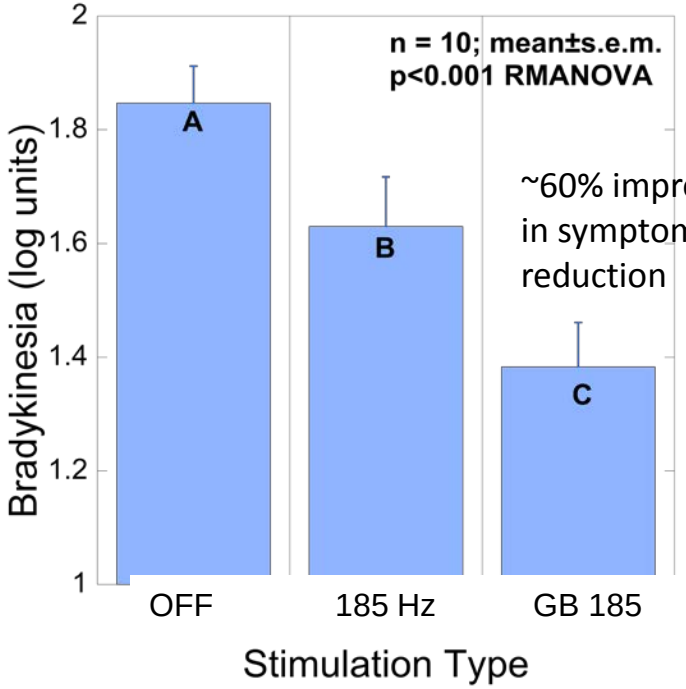
[1] J Neurophysiol. 2010 Aug;104(2):911-21. doi: 10.1152/jn.00103.2010. Epub 2010 May 26. Deep brain stimulation alleviates parkinsonian bradykinesia by regularizing pallidal activity. Dorval AD1, Kuncel AM, Birdno MJ, Turner DA, Grill WM.

[2] J Neural Eng. 2010 Dec;7(6):066008. doi: 10.1088/1741-2560/7/6/066008. Epub 2010 Nov 17. Evaluation of novel stimulus waveforms for deep brain stimulation. Foutz TJ1, McIntyre CC.

Disclosure: Innovations discussed are in development or investigational only and not approved by the FDA.

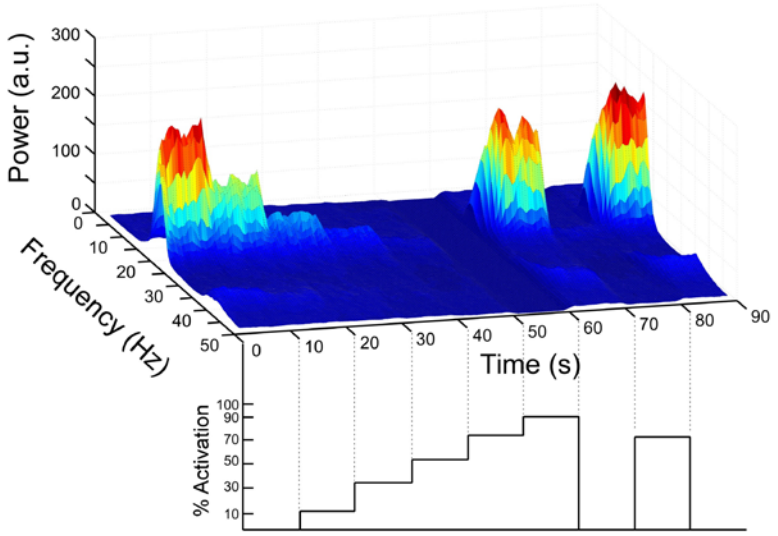
Novel Pulses: Feasibility data from Duke

Improve Efficacy and Reveal Mechanisms



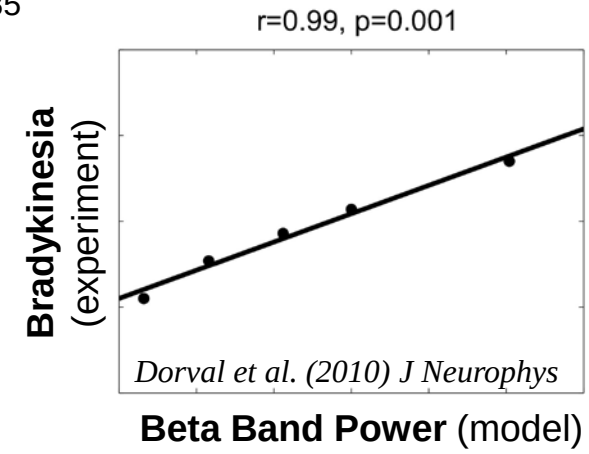
~60% improvement in symptom reduction

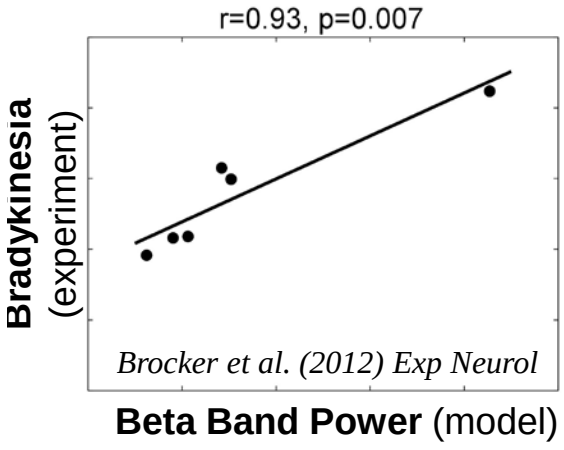
DBS Suppresses Abnormal Neural Oscillations



Strong correlation between symptom reduction and suppression of oscillatory activity across patterns of DBS

Data file courtesy of Warren Grill, Ph.D.





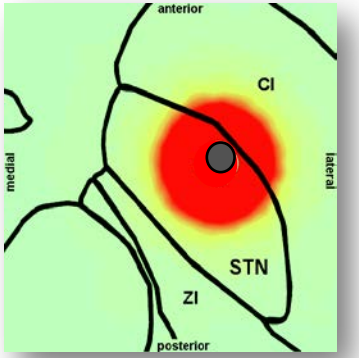
Warren Grill
Duke University

Brocker, D, Swan, B et al. Improved Efficacy of Temporally Non-Regular Deep Brain Stimulation in Parkinson's Disease. Exp Neurol.2013 January; 239: 60-67.

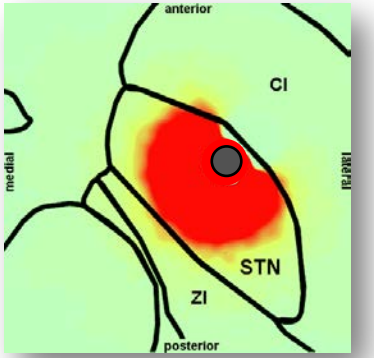
Technology Solution = Anatomical field shaping

Potentially better patient outcomes from personalized stimulation

Traditional DBS
Circumferential Stimulation



Future DBS
Field Shaping



Current spreads into adjacent structures especially if lead position is not perfect	Current can be moved away from adjacent structures and focused on target structures
• Side effects limit amount of stimulation that can be applied[1]	• Potential for higher stimulation with fewer side effects[2], leading to better therapy
• Limited data available from lead in final placement	• Potential to augment interoperative data with directionally-sensed LFP

Disclosure: Innovations discussed are in development or investigational only and not approved by the FDA.

1. Burdick AP, Fernandez HH, Okun MS, Chi YY, Jacobson C, Foote KD. Relationship between higher rates of adverse events in deep brain stimulation using standardized prospective recording and patient outcomes. *Neurosurgical focus.* 2010;29(2):E4
2. Martens HC, Toader E, Decre MM, et al. Spatial steering of deep brain stimulation volumes using a novel lead design. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology.* 2011;122(3):558-566.

TECHNOLOGY SOLUTION = Auto optimization of programming

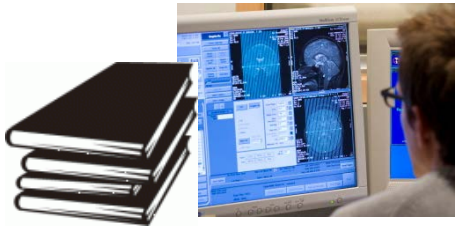
Tools provided to today's optometrist:

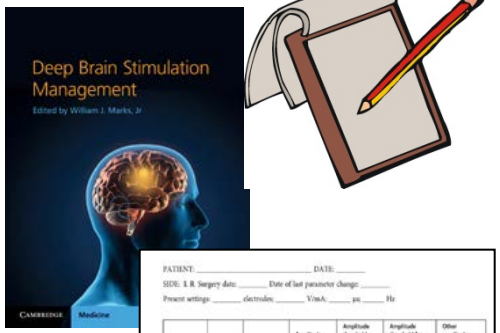
Automated starting point

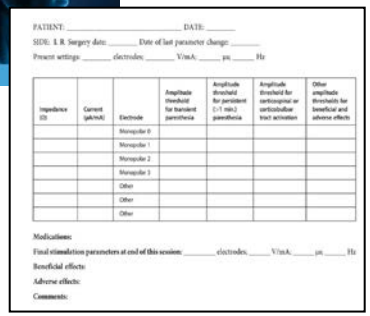
Patient exam, "subjective refraction"

Effective prescription

Tools provided to today's neurologist:



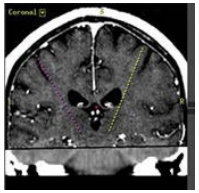




Manual protocol

Can we make an "autorefractor" for the neurologist?

Software identifies lead location in patient's brain



Predict the tissue stimulated by a given DBS setting

Assign a "score" based on tissue stimulated (target vs side-effect)

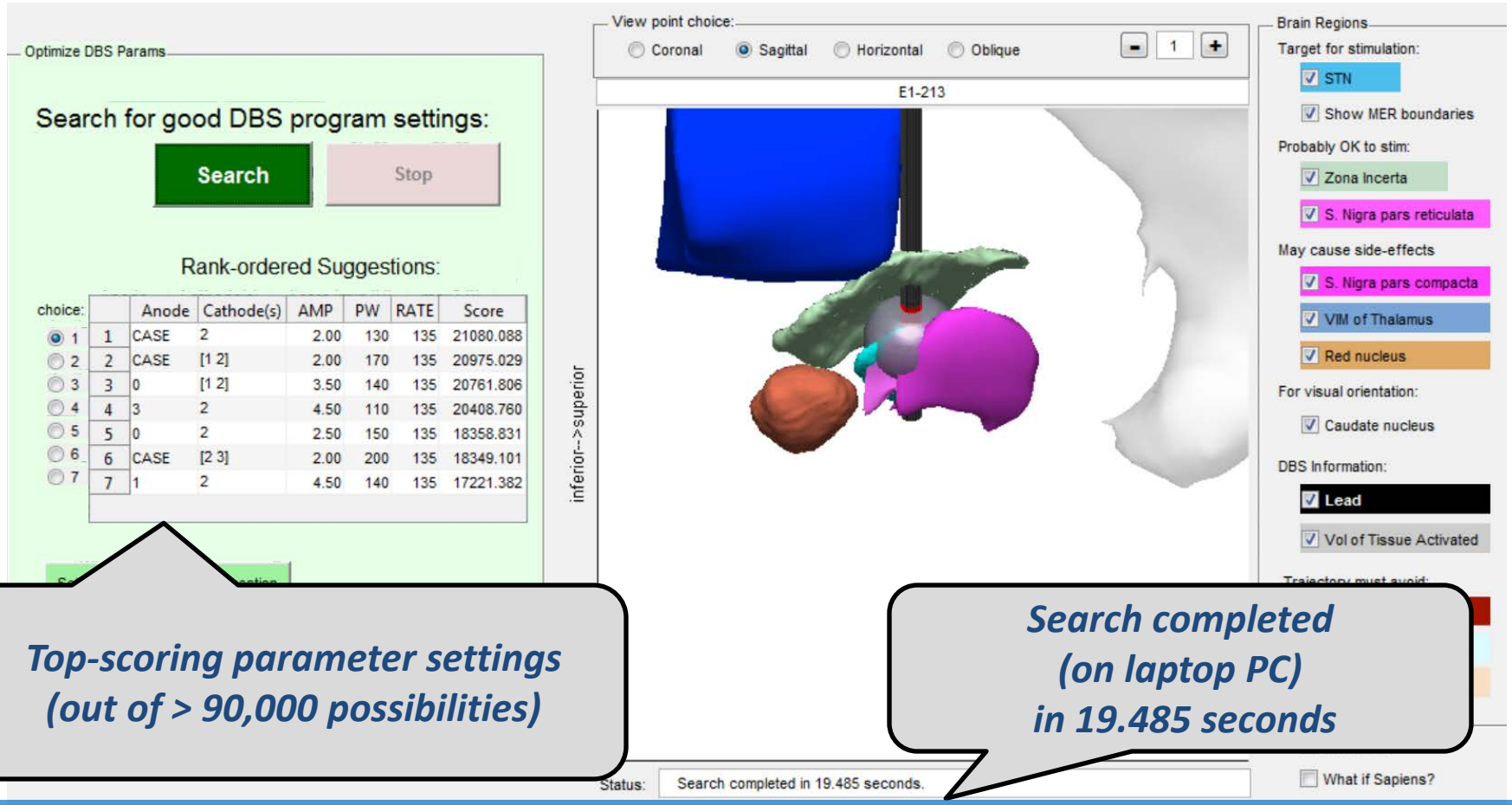
Conduct smart search to find highest scoring DBS settings

Automated starting point tailored to this patient

Disclosure: Innovations discussed are in development or investigational only and not approved by the FDA.

TECHNOLOGY SOLUTION = Auto optimization of programming

Given patient's anatomy and lead location,
prototype algorithm suggests DBS parameter settings:



Top-scoring parameter settings (out of > 90,000 possibilities)

Search completed (on laptop PC) in 19.485 seconds

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