DBS for Movement Disorders Outcome Optimization

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Disclosures

None

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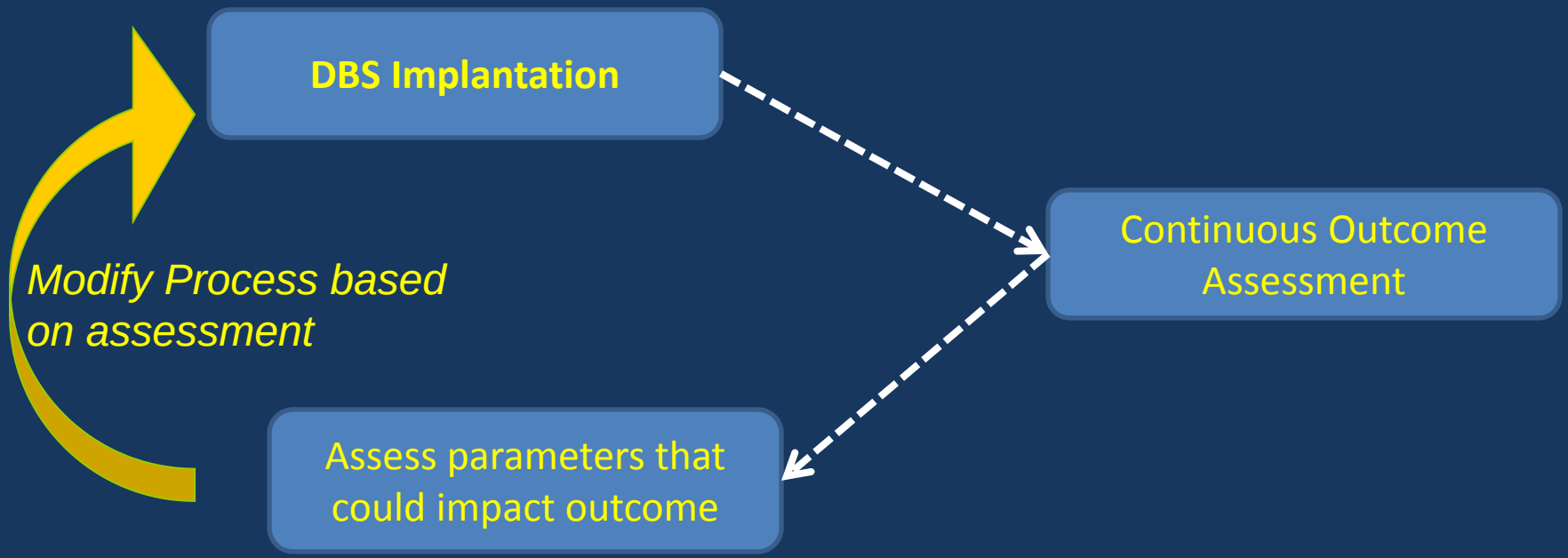
Surgical Optimization



DBS Optimization

- Understand clinical outcomes
  - Parkinson's, Dystonia, Tremor, Other
- Position DBS to optimize outcome
  - ⇧ Good
  - ⇩ Bad

Outcome-based optimization

BILATERAL EFFECTS OF UNILATERAL SUBTHALAMIC DEEP BRAIN STIMULATION ON PARKINSON'S DISEASE AT 1 YEAR

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Received, April 28, 2008.
Accepted, March 30, 2009.

OBJECTIVE: To quantify the benefit of unilateral subthalamic nucleus (STN) deep brain stimulation (DBS) on contralateral, ipsilateral, and axial symptoms of advanced Parkinson's disease.

METHODS: Thirty-seven patients received unilateral STN DBS and were rated on the Unified Parkinson's Disease Rating Scale (UPDRS) and timed tests of motor function in the "practically defined off" state at baseline and at 3, 6, and 12 months postoperatively.

RESULTS: UPDRS motor scores improved significantly at 3, 6, and 12 months relative to the preoperative baseline ($P < 0.001$, 37.1% at 1 year). There was improvement in the contralateral UPDRS subscores ($P < 0.001$, 54.6% at 1 year), and although contralateral benefit was larger on all outcome measures, ipsilateral benefit was present at 3 and 6 months on the UPDRS subscore ($P = 0.013$ and 23.5%, $P = 0.005$ and 27.7%, respectively). A trend toward ipsilateral benefit was present on the UPDRS subscore at 12 months; however, the effect was not statistically significant. Two timed tests of motor function in the upper extremities showed significant ipsilateral benefit in bradykinesia at 12 months ($P < 0.001$ and $P = 0.014$, respectively). Significant benefit was also observed in the UPDRS part 2 "off" medications and the UPDRS part 4 after unilateral STN DBS at 12 months (both $P < 0.001$).

CONCLUSION: Considering the bilateral effects and tolerability of unilateral STN DBS, unilateral stimulation followed by a contralateral procedure later, if necessary, is a reasonable option for patients with advanced Parkinson's disease, especially with prominent asymmetry.

KEY WORDS: Deep brain stimulation, Ipsilateral, Parkinson's disease, Subthalamic nucleus, Unilateral

Neurosurgery 65:302–310, 2009 DOI: 10.1227/01.NEU.0000349764.34211.74 www.neurosurgery-online.com

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has revolutionized the treatment of patients with moderate to severe idiopathic Parkinson's disease (PD) and motor complications of dopaminergic therapy, but little is known about the relative benefits of initial bilateral DBS implantation versus a unilateral or staged procedure (9, 14, 17, 18). Most of the symptomatic benefits of STN DBS influenced contralateral motor symptoms; however, axial and ipsilateral benefits, particularly in the initial months after surgery, have been observed in several small studies of unilateral STN DBS, albeit inconsistently (4, 5, 19, 26, 27, 40, 45). Although a larger motor benefit usually results from the initial implantation of bilateral electrodes, idiopathic PD is usually an asymmetric disease, and it is possible that the placement of bilateral electrodes introduces additional risk for surgical complications and cognitive, behavioral, or speech dysfunction (28, 35, 38, 41, 42, 47, 48).

Therefore, important questions regarding unilateral STN DBS should be addressed, including: 1) what is the magnitude and duration of its effects on contralateral, ipsilateral, and axial motor function; 2) how well is unilateral STN DBS tolerated; and 3) does unilateral STN DBS improve quality of life measures in

ABBREVIATIONS: DBS, deep brain stimulation; **MRI,** magnetic resonance imaging; **PD,** Parkinson disease; **STN,** subthalamic nucleus; **UPDRS,** Unified Parkinson's Disease Rating Scale

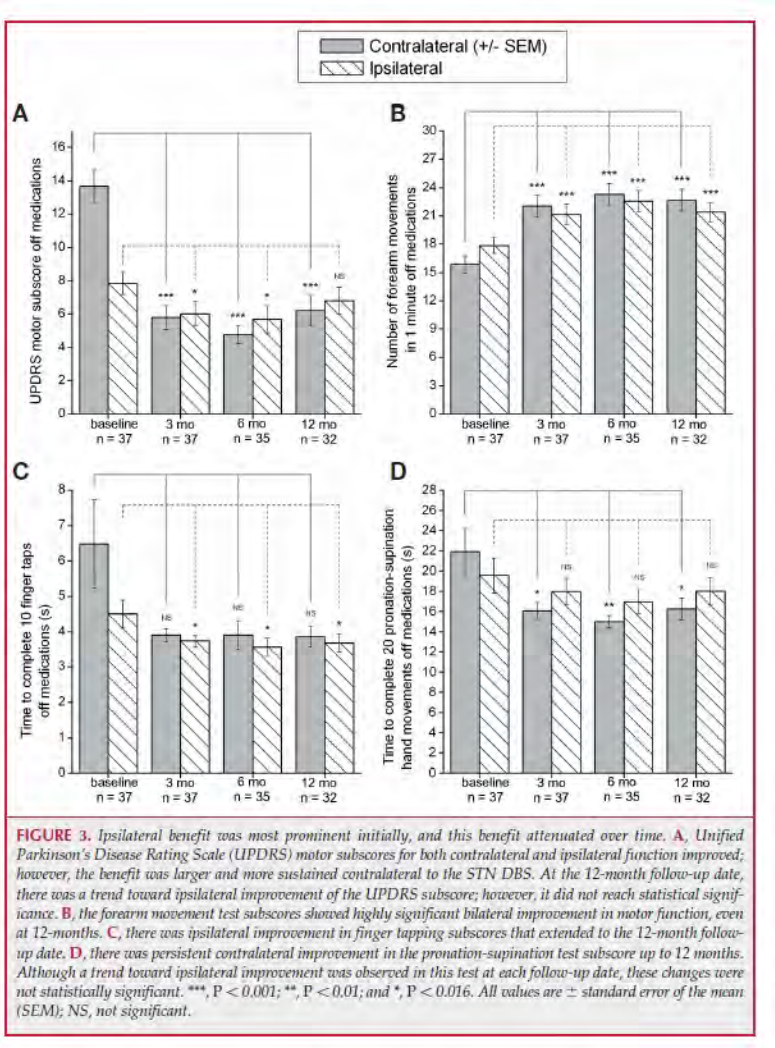


*FIGURE 3. Ipsilateral benefit was most prominent initially, and this benefit attenuated over time. A, Unified Parkinson's Disease Rating Scale (UPDRS) motor subscores for both contralateral and ipsilateral function improved; however, the benefit was larger and more sustained contralateral to the STN DBS. At the 12-month follow-up date, there was a trend toward ipsilateral improvement of the UPDRS subscore; however, it did not reach statistical significance. B, the forearm movement test subscores showed highly significant bilateral improvement in motor function, even at 12-months. C, there was ipsilateral improvement in finger tapping subscores that extended to the 12-month follow-up date. D, there was persistent contralateral improvement in the pronation-supination test subscore up to 12 months. Although a trend toward ipsilateral improvement was observed in this test at each follow-up date, these changes were not statistically significant. ***, $P < 0.001$; **, $P < 0.01$; and *, $P < 0.016$. All values are ± standard error of the mean (SEM); NS, not significant.*

How to apply this to 'next case'…….

Goal

- Identify predictors of outcome
  - Patient selection
  - Neuroanatomical target
  - Intraoperative electrophysiology
    - Neuronal
    - Local Field
    - Cortical
  - Intraoperative behavior
  - Understand functional anatomic relationships
- Use these for optimal DBS position
  - Maximum benefit with fewest trajectories

Summary of DBS Procedure

- Stage 1 Placement of DBS
  - Local anesthesia
  - Placement of Stereotactic Head frame
  - Localization MRI
  - Case planning
  - Placement of DBS
  - Survey MRI
- Stage 2 (week later) – Implant pulse generator (IPG)
  - General anesthesia
  - Same day surgery

Patient Selection

- Operating the ‘wrong’ patient results in poor outcomes

Optimal Preoperative patient

Essential Tremor

- Optimal
  - Uncomplicated action tremor
  - Unresponsive to medication
  - Patient physiologically healthy
- Suboptimal
  - Complicated tremor (dystonic, ataxic, midline)
    - Multiple sclerosis
    - Trauma
    - Ischemic injury
  - Unhealthy patient

Optimal Preoperative patient

Parkinson's Disease

- Optimal
  - Physiologically young
  - Initially responsiuve to dopaminergics
  - Tremor, dystonia, bradykinesia
  - Dyskinesias
- Suboptimal
  - Unresponsive to medication
  - Complicated Parkinson's
    - Parkinson's 'plus'
    - Gait difficulty
    - Hypophonia
    - Dementia
  - Otherwise unhealthy

Optimal Preoperative patient

Dystonia

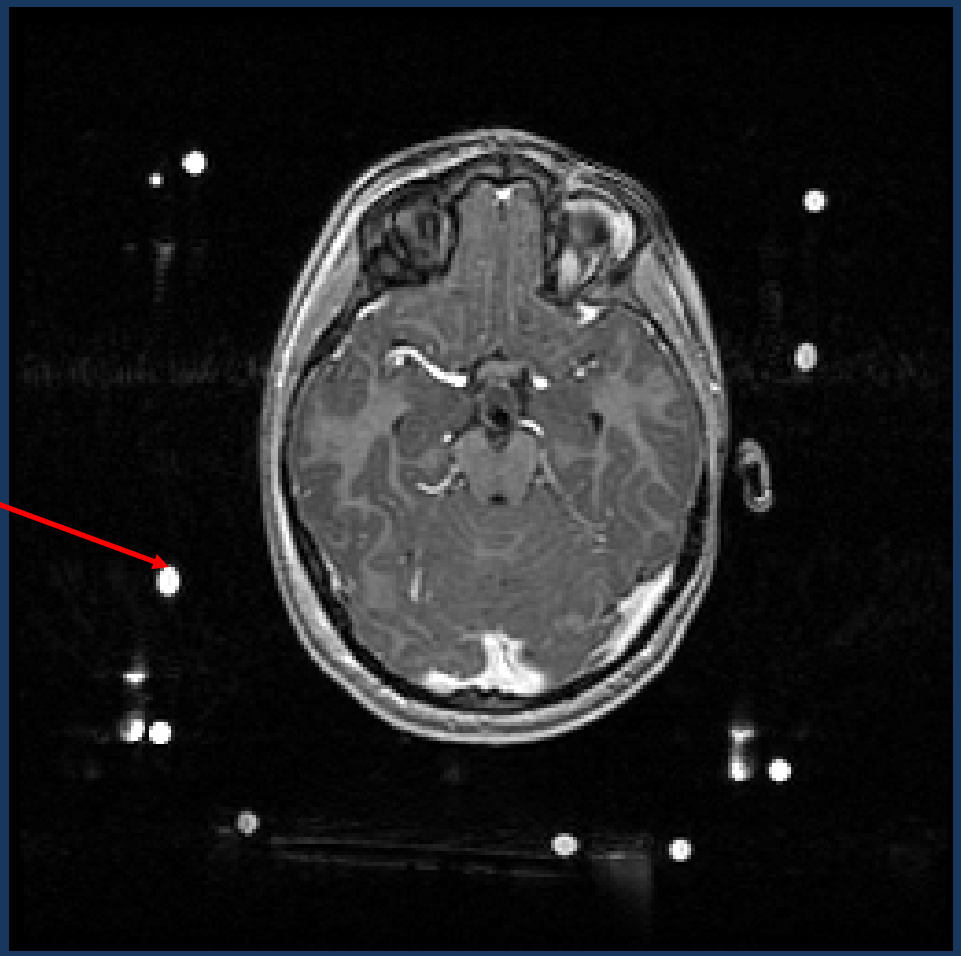
- Optimal
  - Physiologically young
  - Appendicular (arms/legs)
  - Inherited or idiopathic
- Suboptimal
  - Acquired
  - Midline
  - Otherwise unhealthy

Optimal Neuroanatomical target

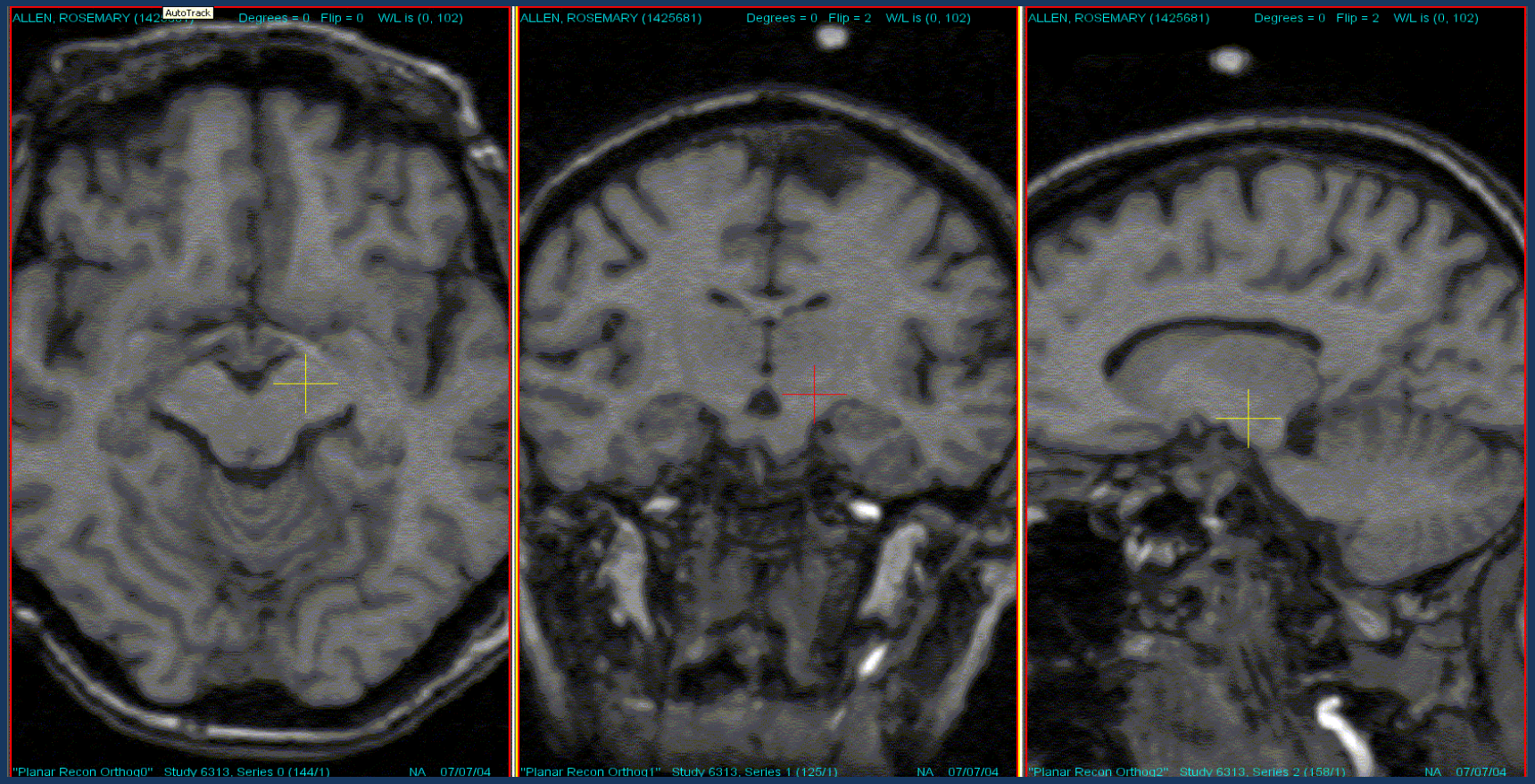
- Parkinson's: STN
- Tremor: VIM
- Dystonia: GPi

Head Frame System

Local Anesthesia



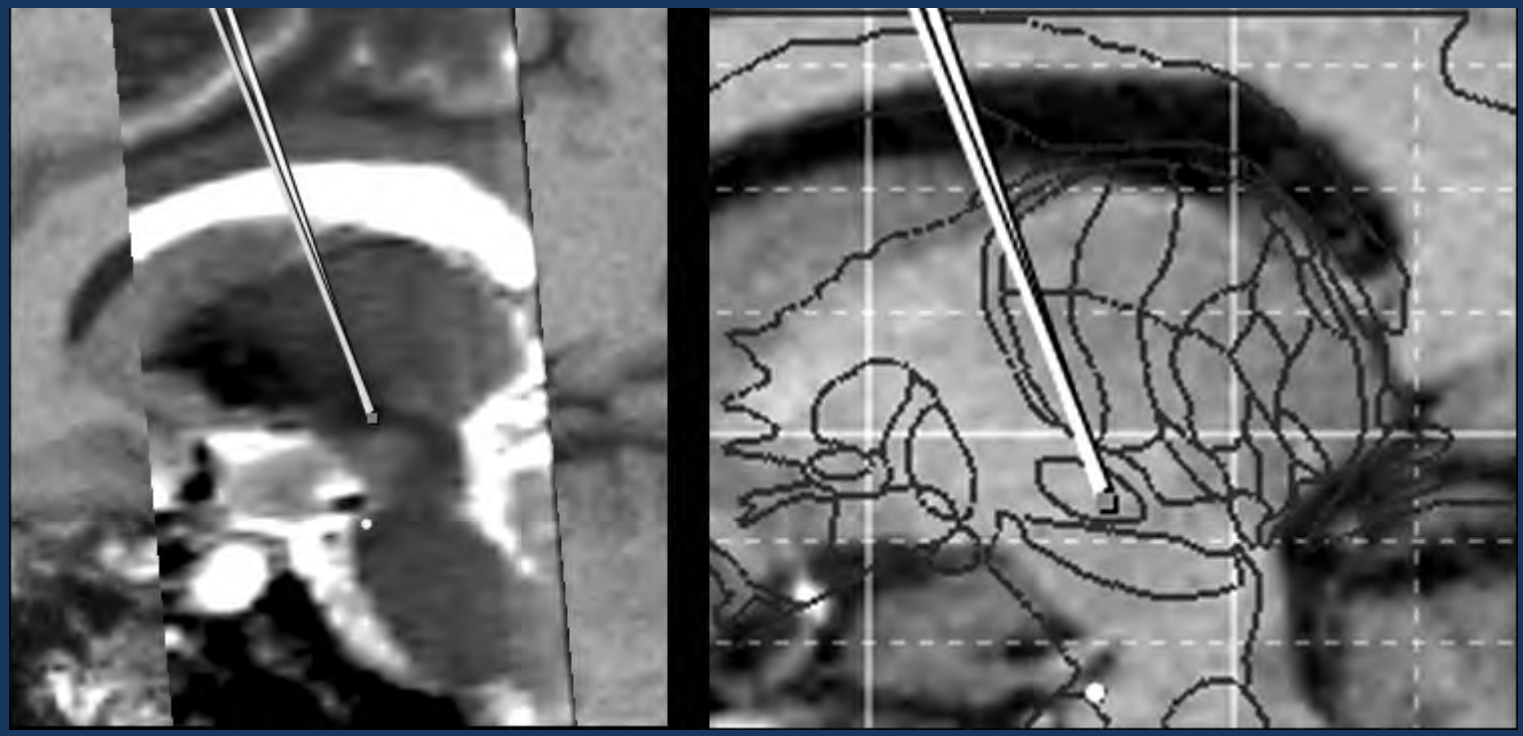
MRI-based brain targeting



Bottom of left STN

ACPC: X=-12.5, Y=-4, Z=-5

Sagittal STN Electrode Graphic



Optimal Electrophysiology

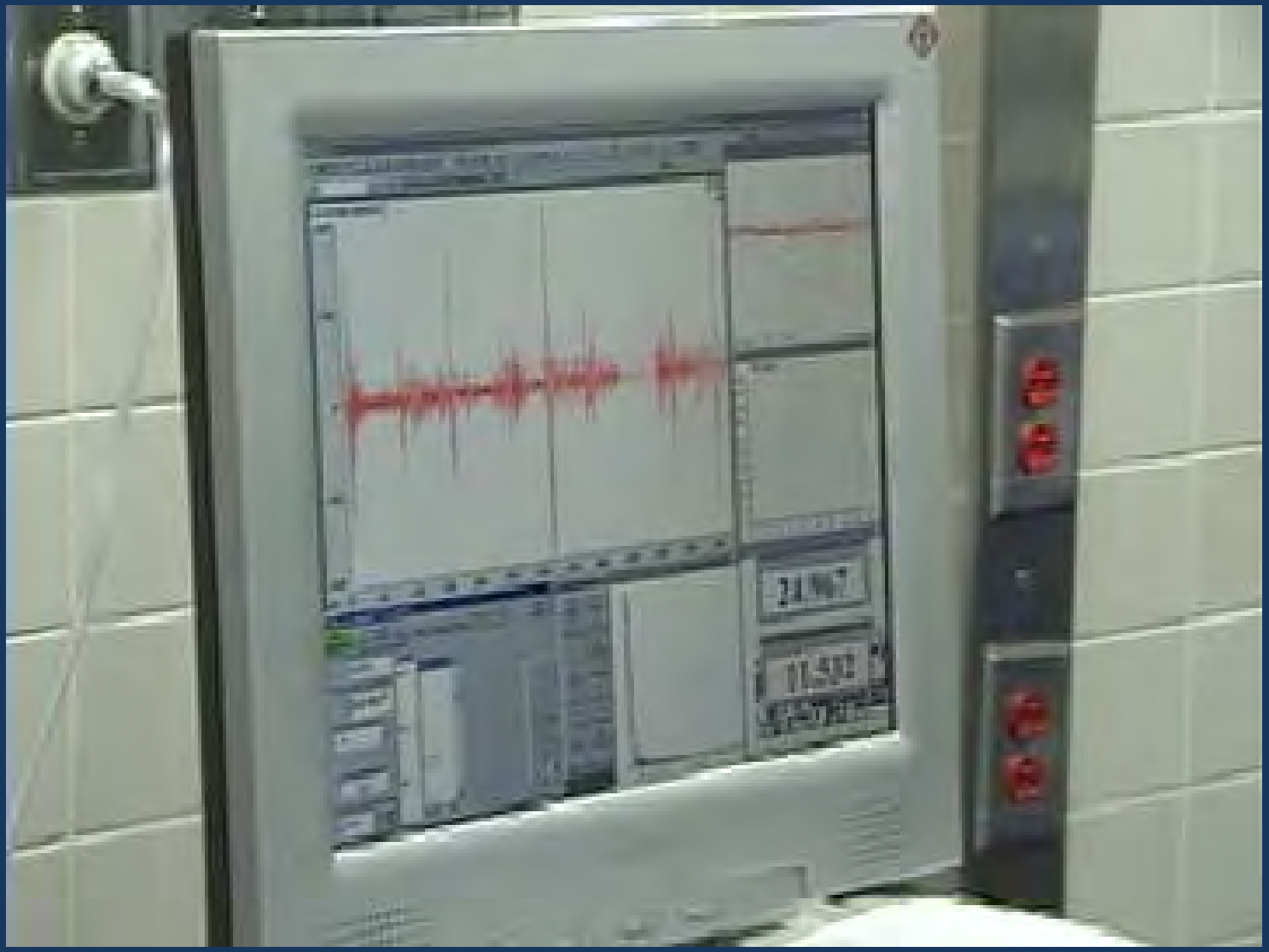
Single Neuron Recording

- Characteristic neuronal firing
- Characteristic electrophysiological trajectory

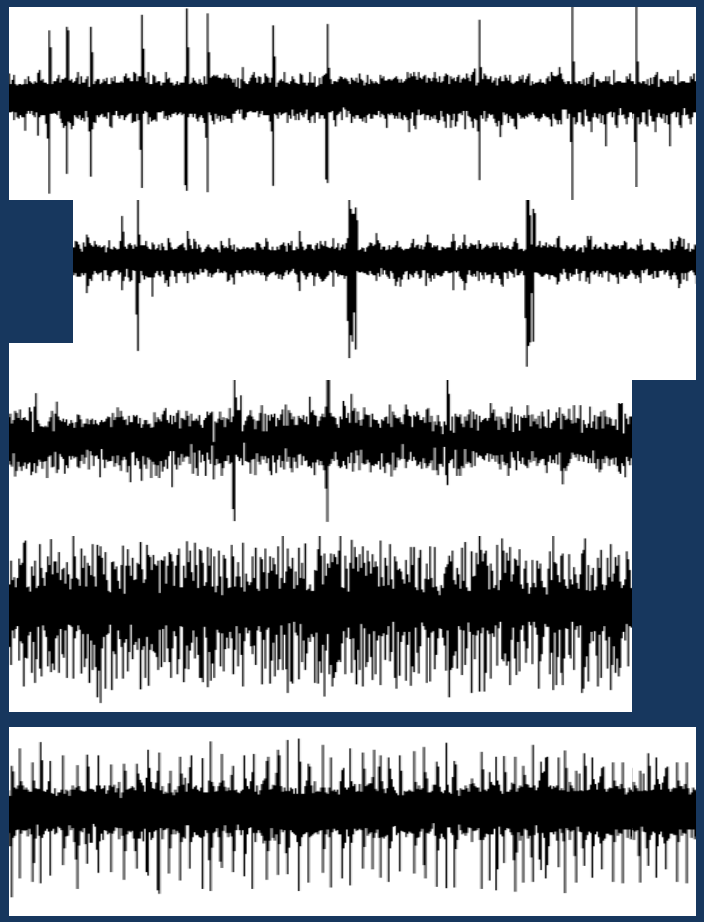
Microelectrode Neuron Recording

Computer-based recording

Capture and store brain activity for later analysis



Guide trajectory by neuronal activity



Anterior / Reticular Nucleus

Anterior / Reticular Nucleus

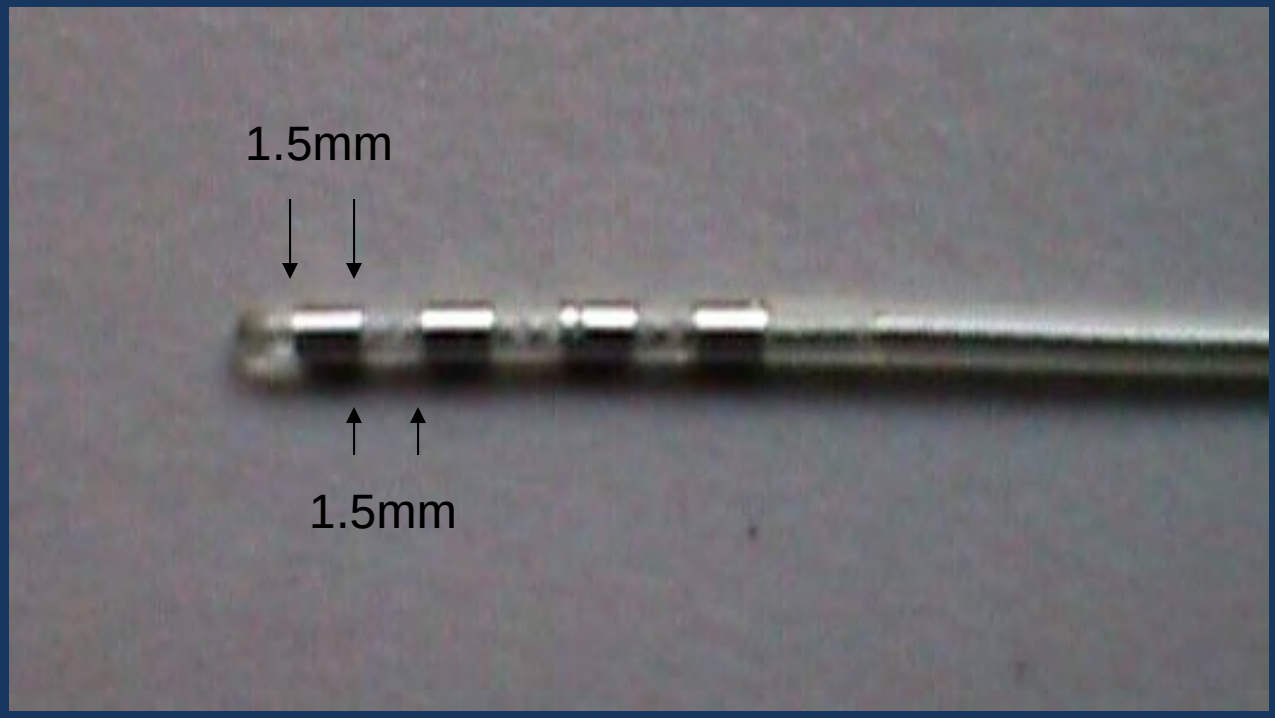
Zona Incerta / Forel's Fields

Subthalamic Nucleus

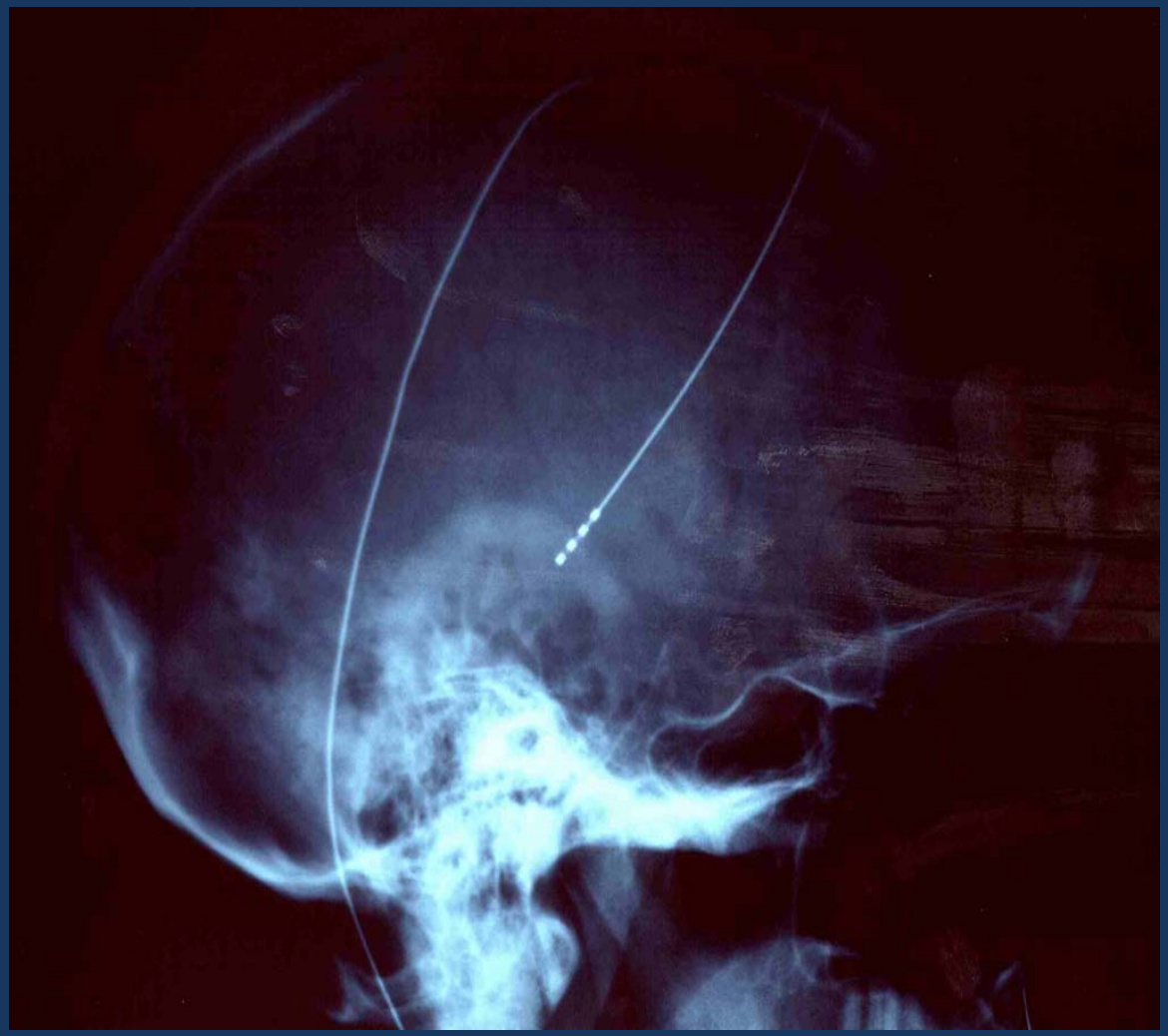
Substantia Nigra pars reticulata

Representative samples of neuronal recordings encountered targeting the subthalamic nucleus. Each sample is one second in length.

DBS Electrode



Postoperative Xray



Intraoperative Behavior

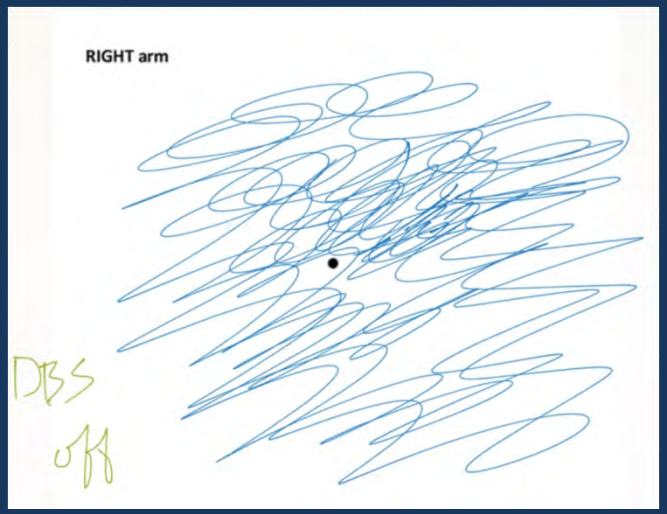
- Optimize intraoperatve stimulation results
- Presumed to mimic postoperative results

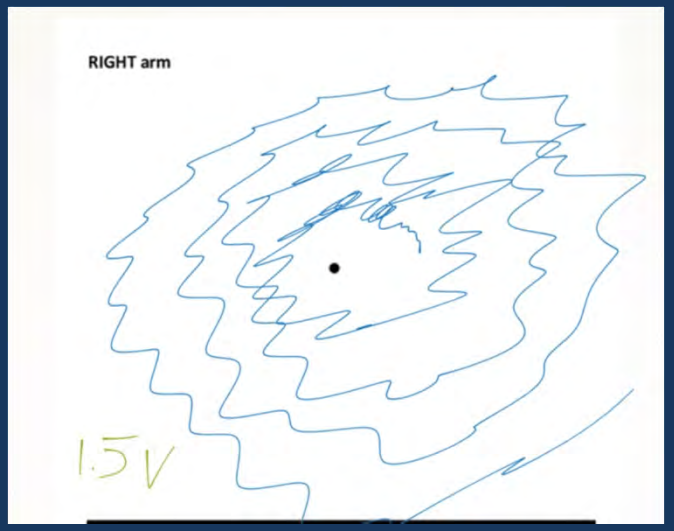
Optimal Behavioral Results

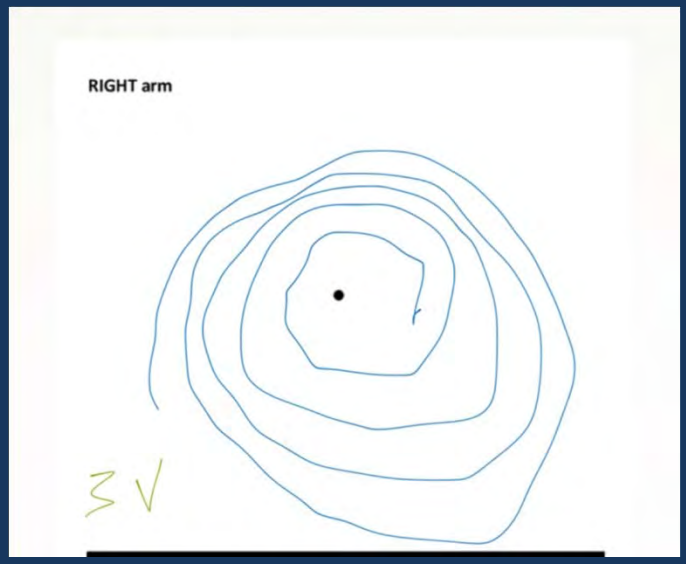
- Essential Tremor (VIM)
  - Optimize Good
    - Stop tremor
  - Minimize bad responses
    - Slowed speech
    - Paresthesias

Intraoperative Behavior Testing

Tremor







Optimal Behavioral Results

- Parkinson's Disease (STN)
  - Optimize Good
    - Loosen hand/arm
    - Stop Tremor
  - Minimize bad responses
    - Corticospinal contractions
    - Slowed speech
    - Paresthesias
    - Diplopia

Optimal Behavioral Results

- Dystonmia(GPi)
  - Optimize Good
    - Loosen affected side
  - Minimize bad responses
    - Corticospinal contractions
    - No effect

When Recording and Behavior Aren't Enough?

- Functional relationships between stim sites
- Cortical responses to stimulation

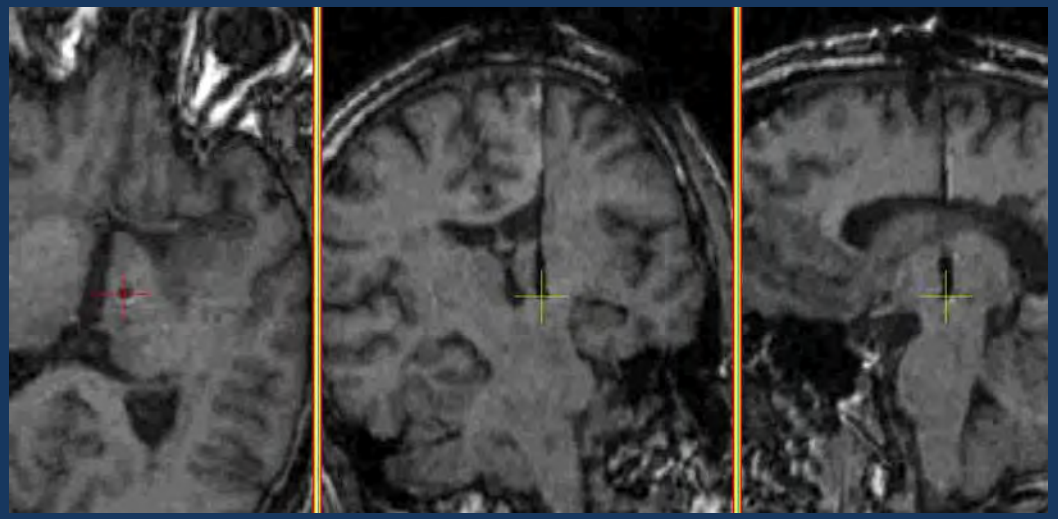
Functional Relationships

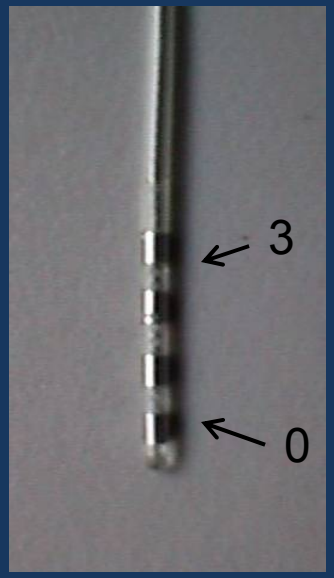
Map intraoperative observations to outcome

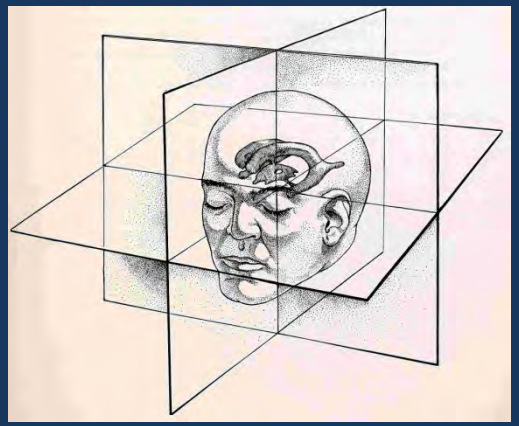
- Topography of good outcome
- Topography of bad outcome

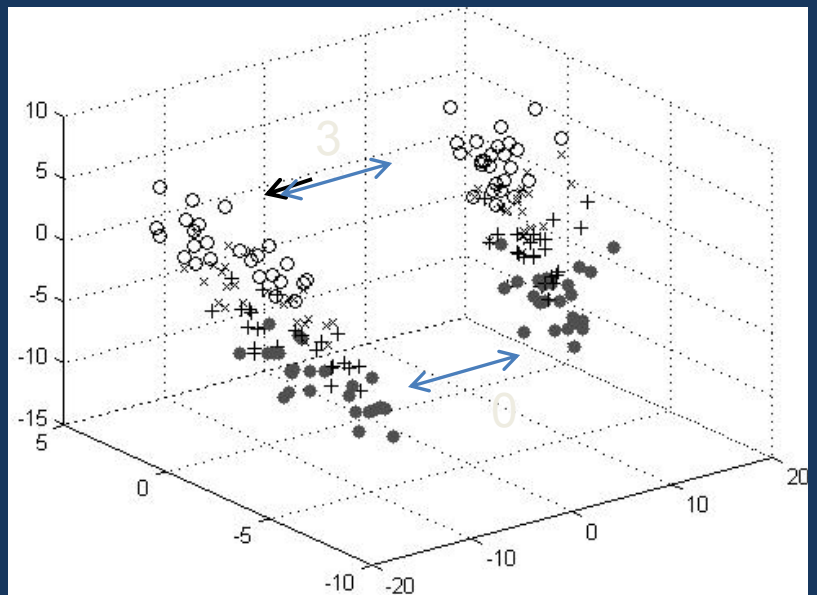
Mapping effects to location

- Volumetric post-op MRI
- DBS electrode location
- Record each contact location as X,Y,Z coordinates in ACPC space
- Reference parameter to the location of the active contact (cathode)

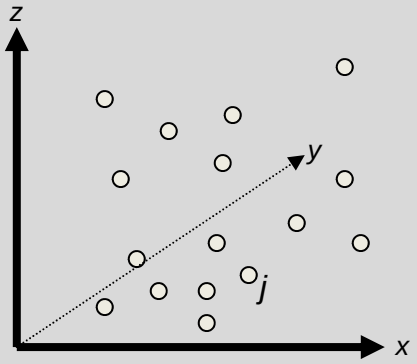




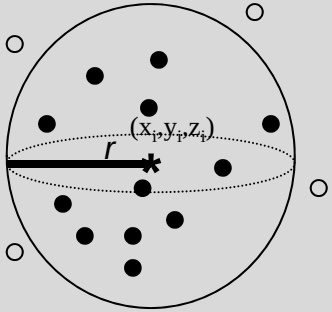




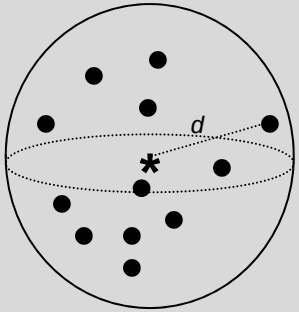
Map Effect to Location



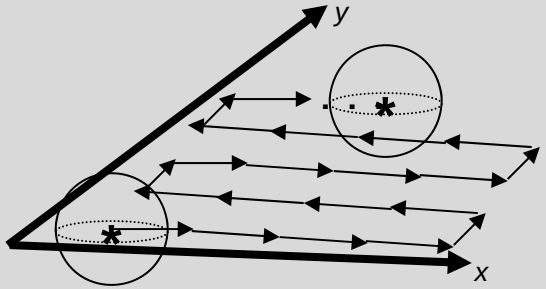
A. Contact locations (x_j,y_j,z_j) in AC-PC space



B. Define "neighborhood" sphere of radius *r;* at point of interest (*), (x_i,y_i,z_i) . Contact locations are included (●) or excluded (o).



C. Values (ΔTr, ΔRg, and $\Delta TLMS$) for each included point (●) are averaged with weight (1/d), and attributed to point of interest (*).

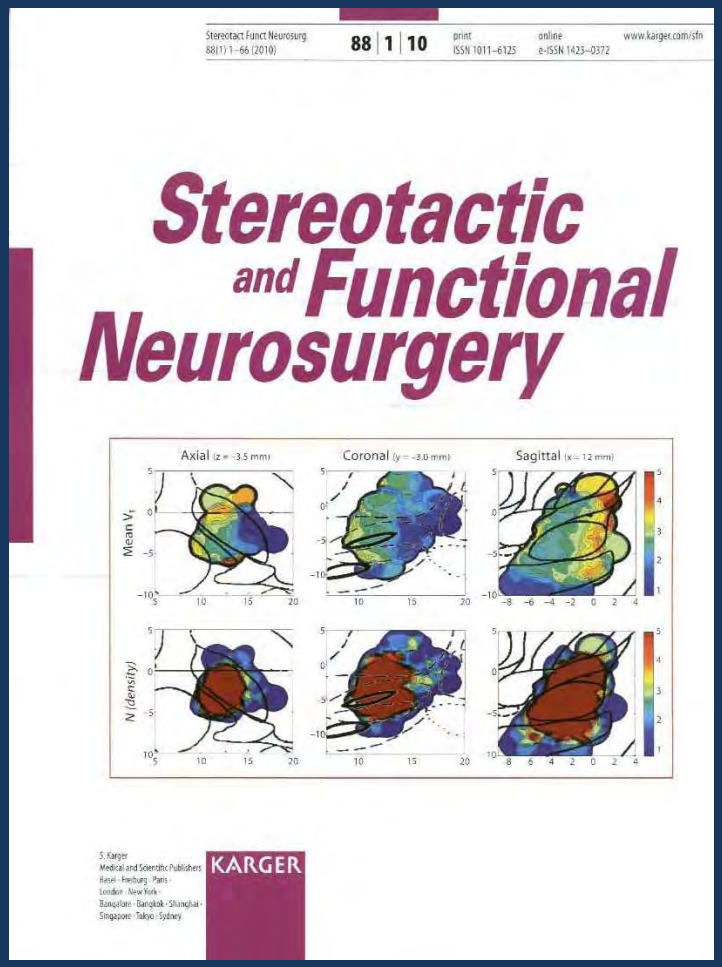


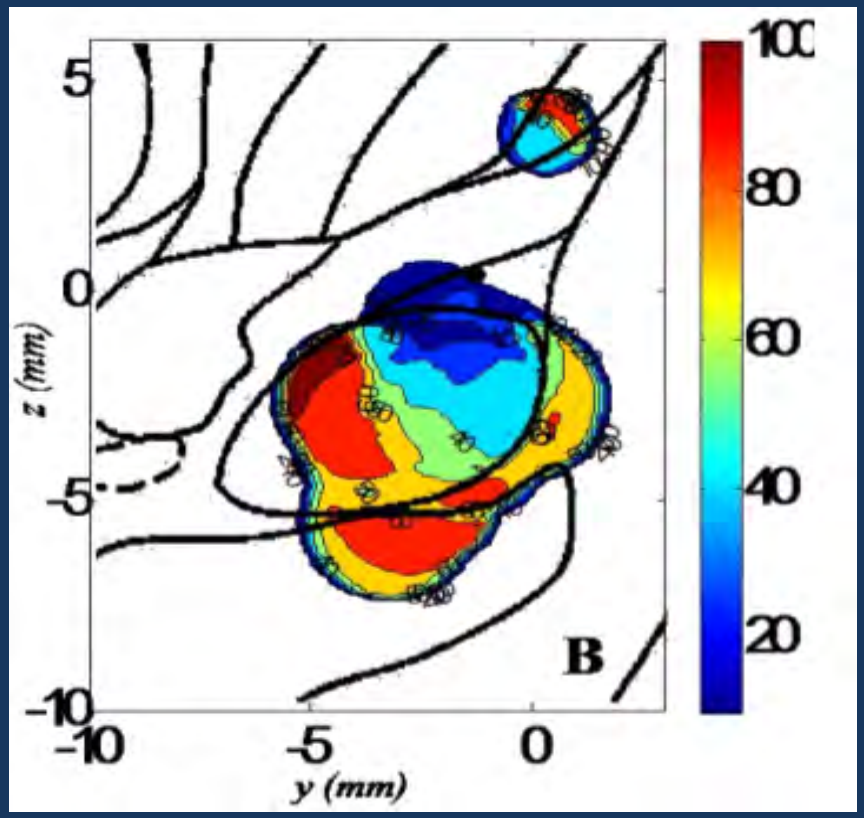
D. Sphere "roves" through a 150x150 point grid, defining values for each point of interest, in a selected plane of interest. 2D grid is rendered with countour lines.

Topography of Stimuation Effects

- Adverse effects
  - Motor
  - Sensory
  - Other
- Beneficial effects
  - Tremor control
  - Reduction in rigidity
  - Reduction in Dystonia
  - Controlled Dyskinesia

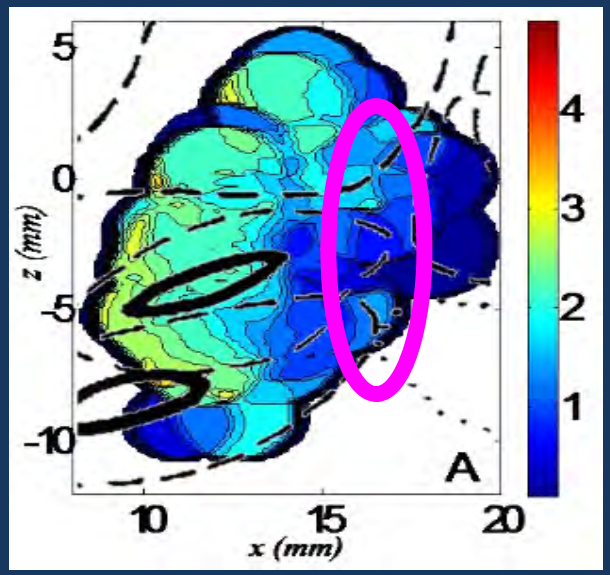
Outcome related to DBS Location (Shenai et al, 2010)





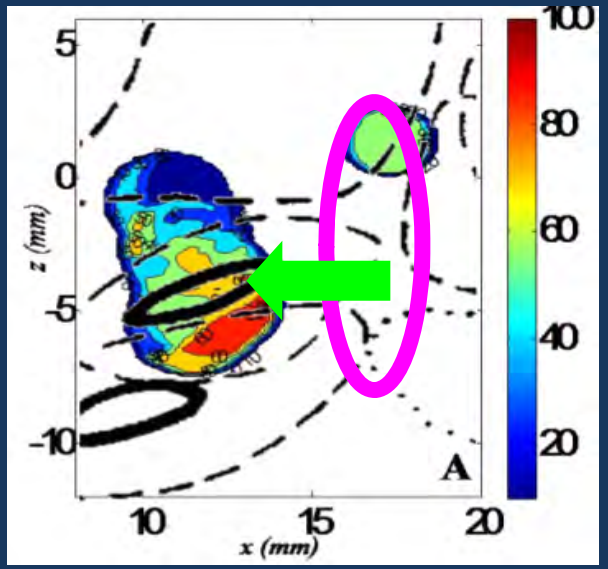
Outcome data applied to case at hand

Motor Effect Threshold



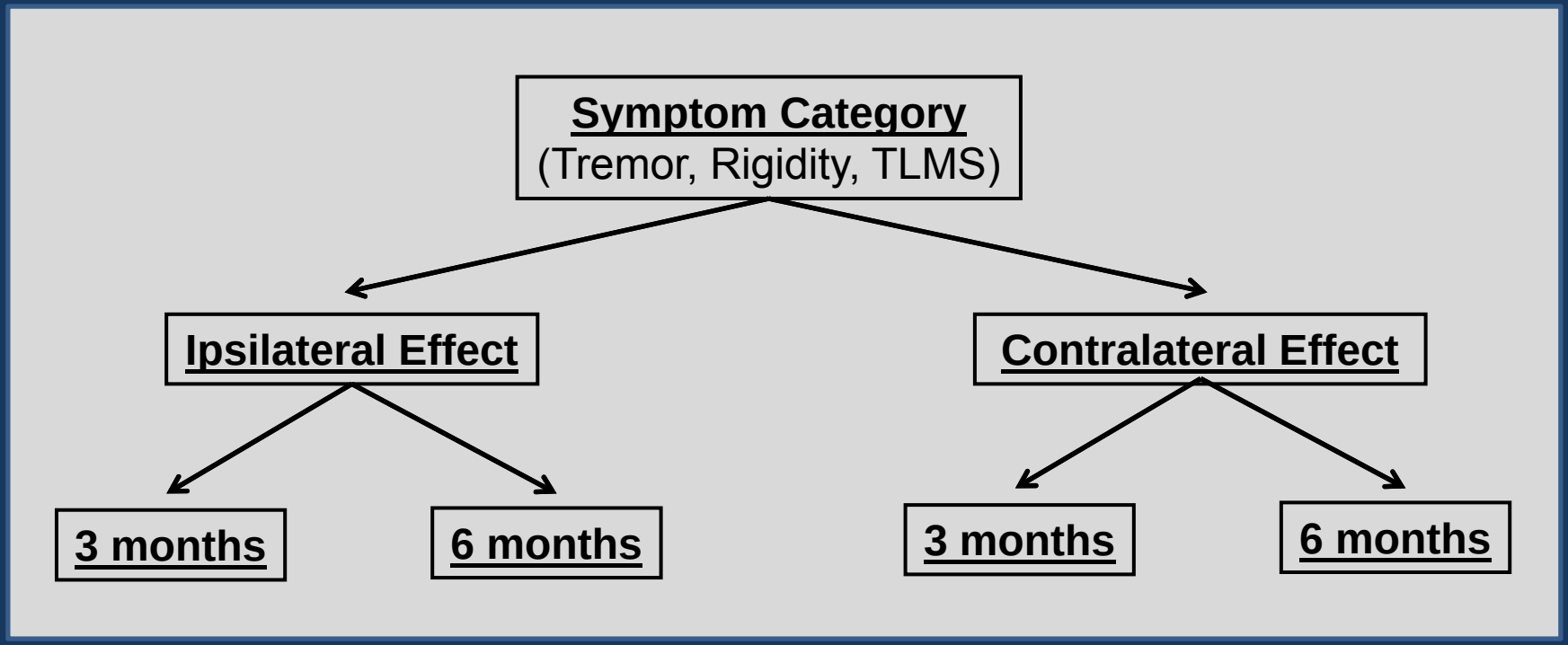
Threshold for motor side effects

Percent improvement

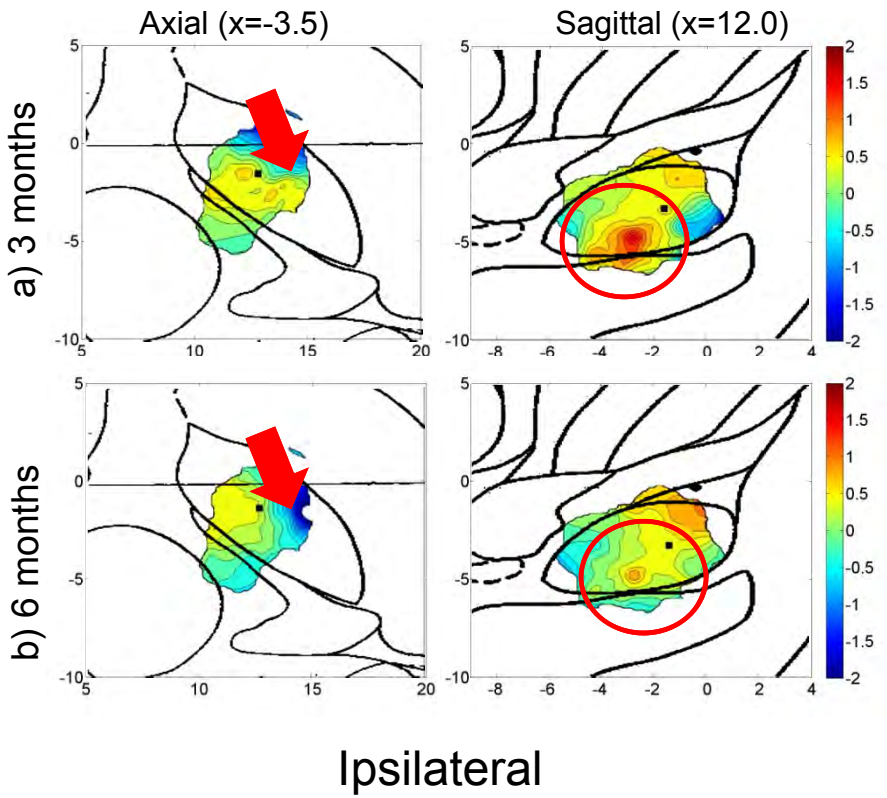


Topography of optimal clinical results

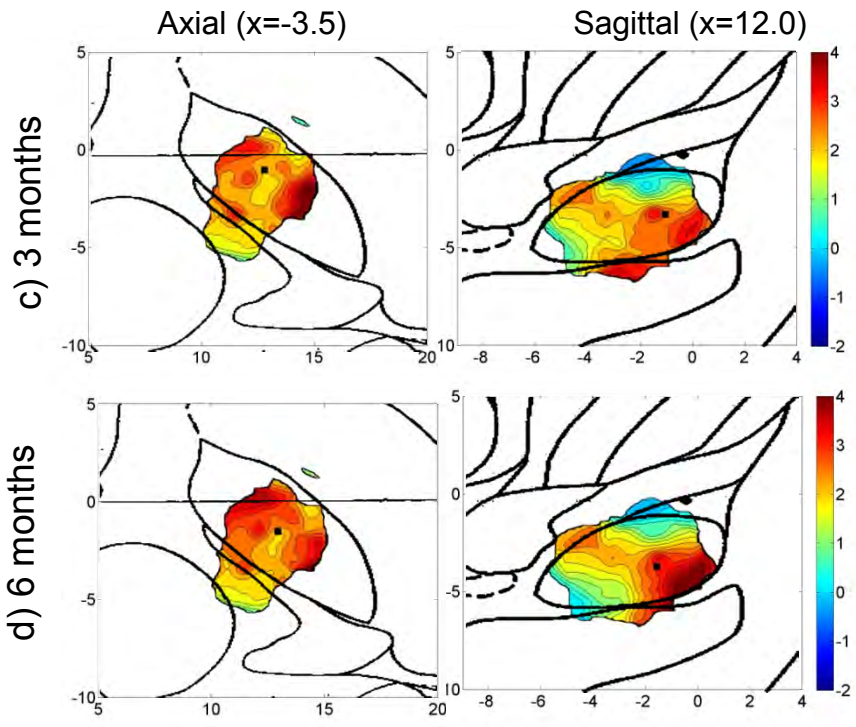
Laterality and functional topography vs. time



Tremor



Ipsilateral

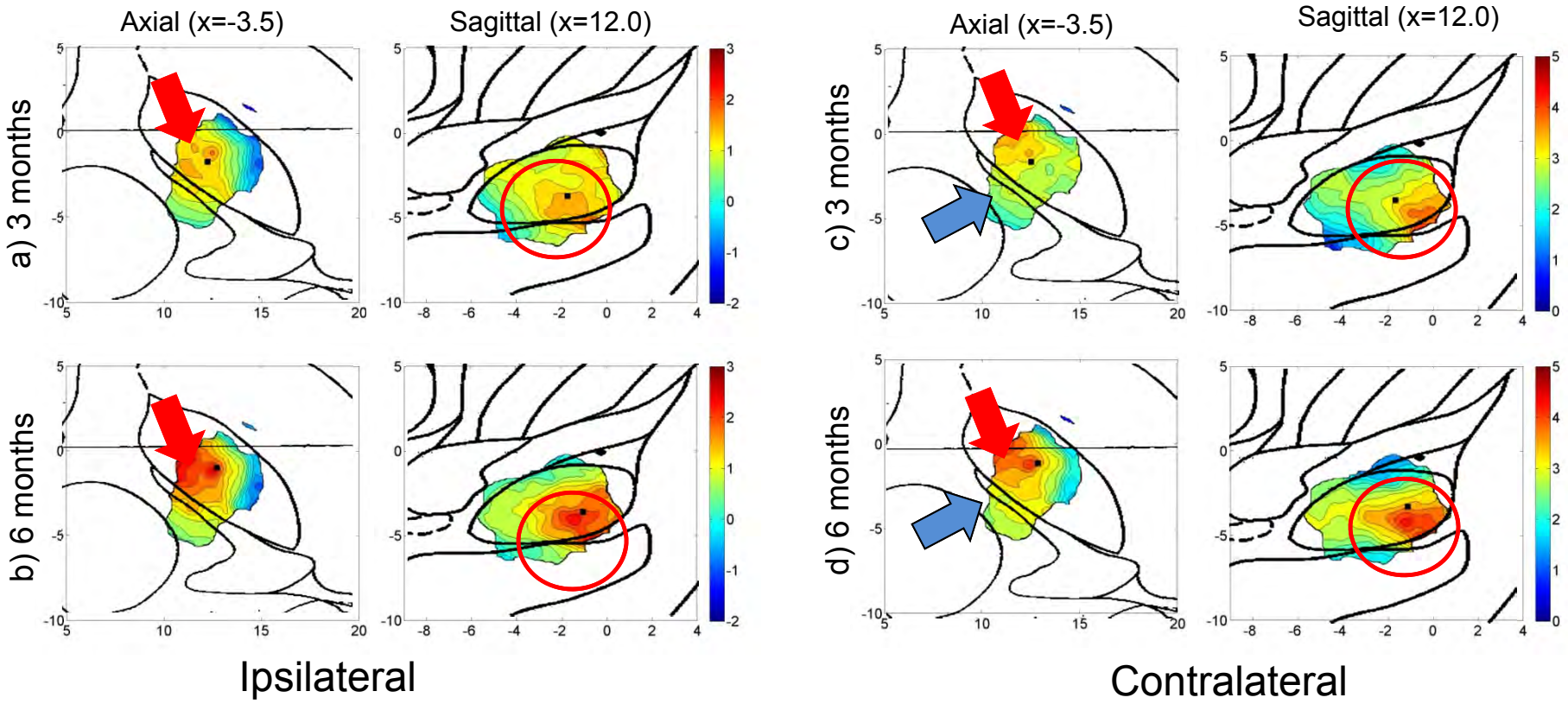


Contralateral

Ipsilateral Effect:
Shift of efficacy *away* form lateral and ventral positions.

Contralateral Effect:
Minimal change in effective electrodes over time.

Rigidity



Ipsilateral Effect:

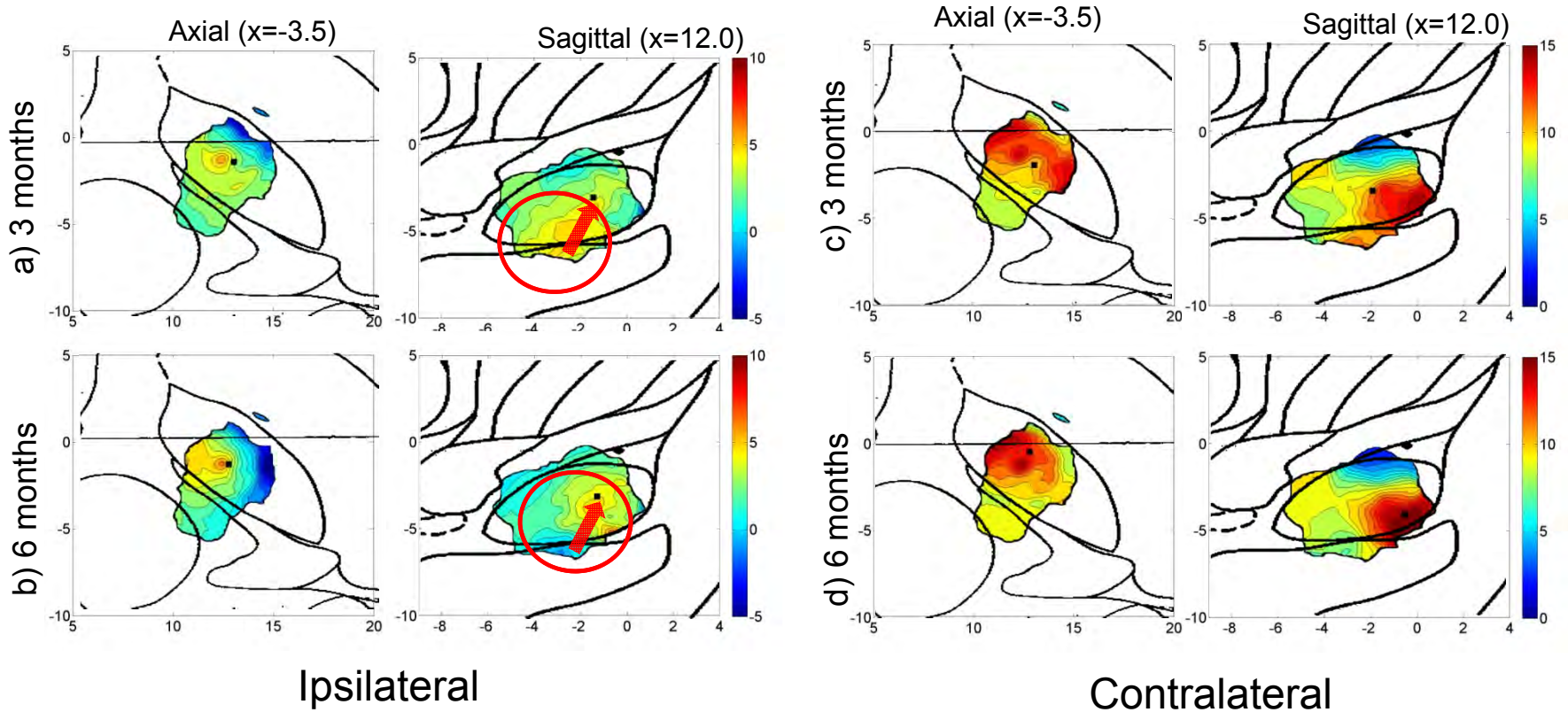
Concentration of efficacy in medial/ventral locations

Contralateral Effect:

-Concentration of efficacy in medial/ventral locations

- Extension of efficacy to more posterior locations

Total Score



Ipsilateral Effect:
Shift of efficacy towards more dorsal positions

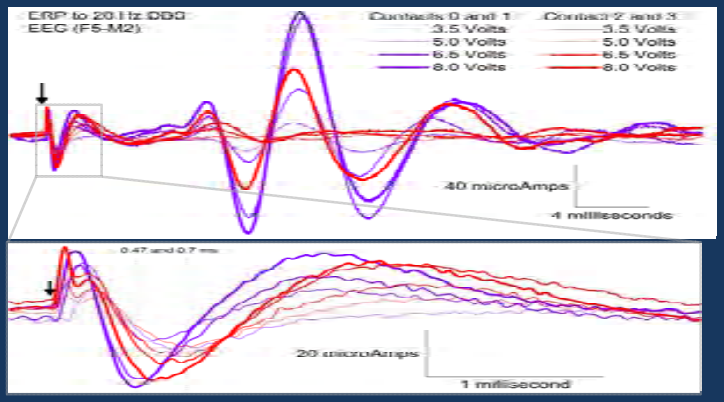
Contralateral Effect:
Minimal shifts in efficacy

Other Proxies for Outcome

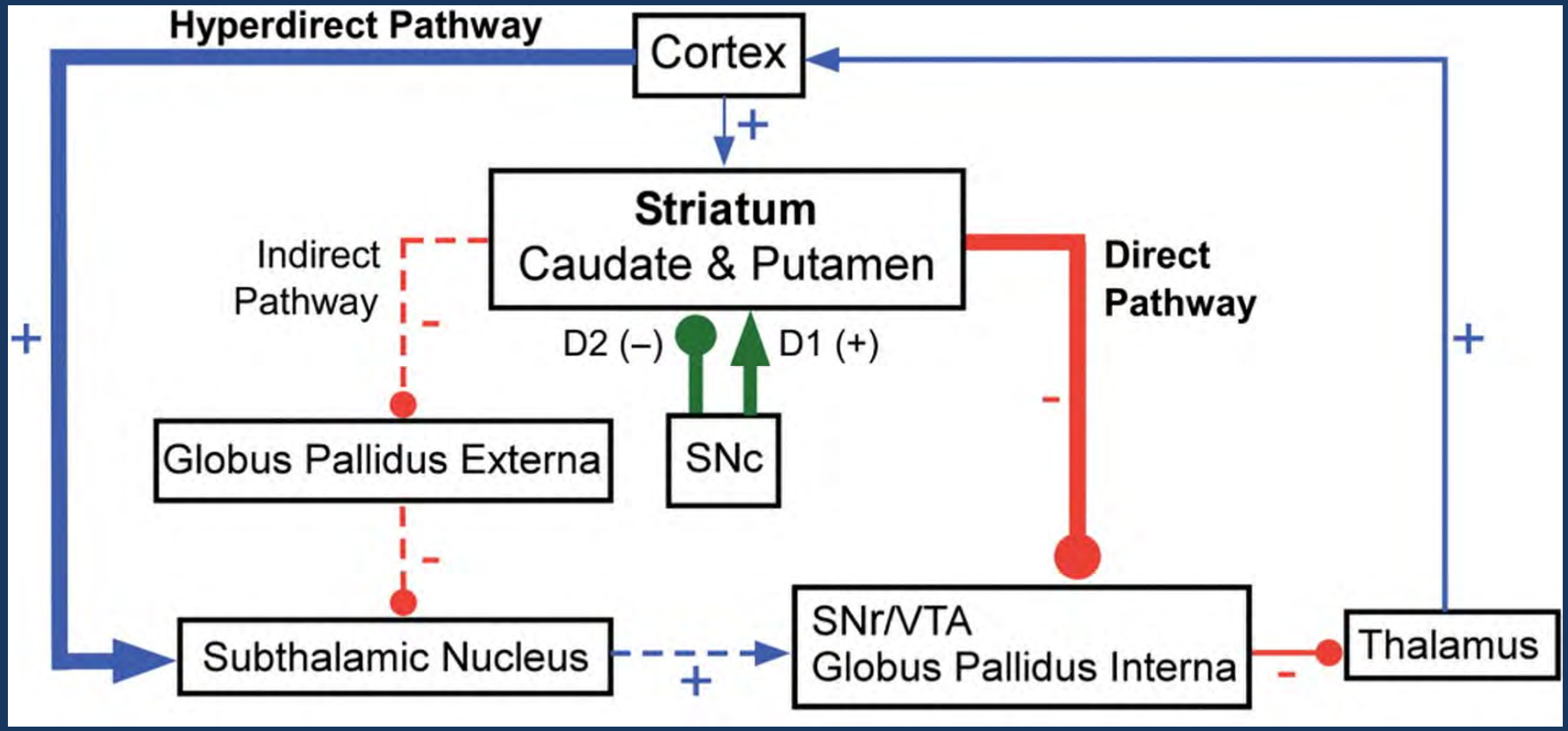
- Other neuronal circuitry?
- Proxies under under anesthesia?
- Non-behavioral markers
  - Depression
  - OCD
  - Cognitive DBS

Cortical ERP's as Biomarkers

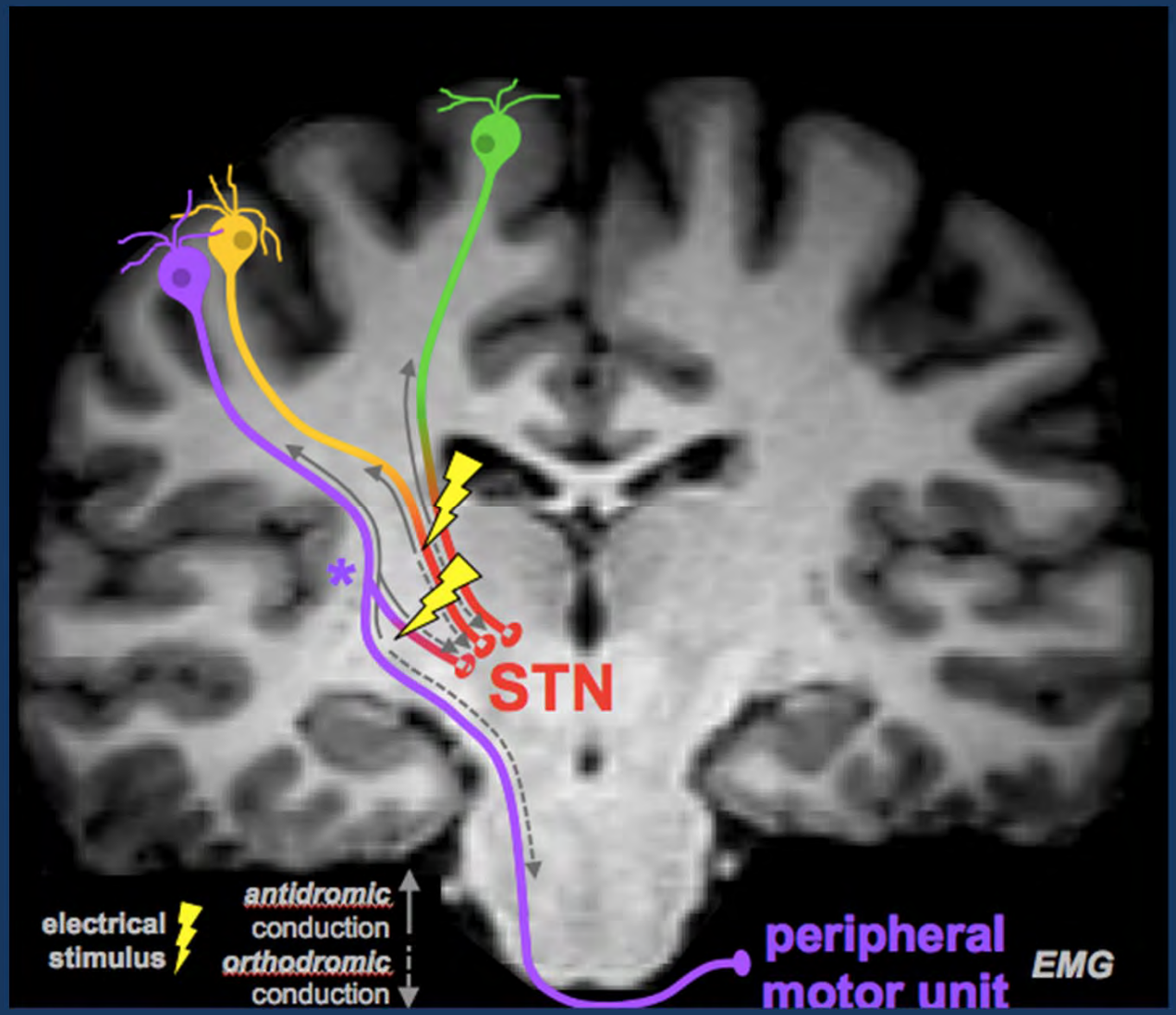
- Does subcortical stimulation produce identifiable cortical potentials?
- Do these potentials relate to clinical outcome?



Indirect and 'Hyperdirect' Circuits



Axonal connections between cortex and subcortical structures

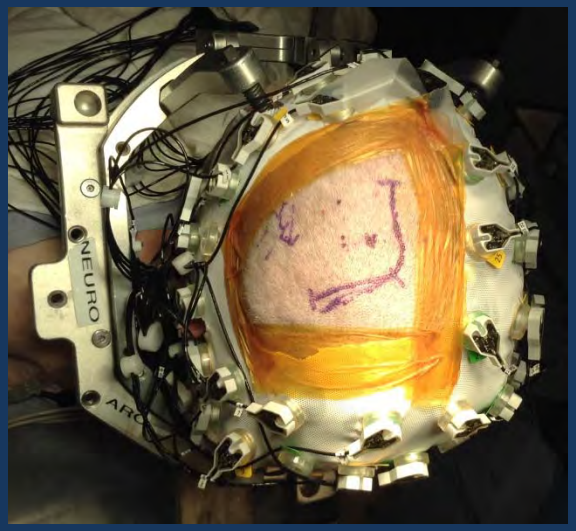


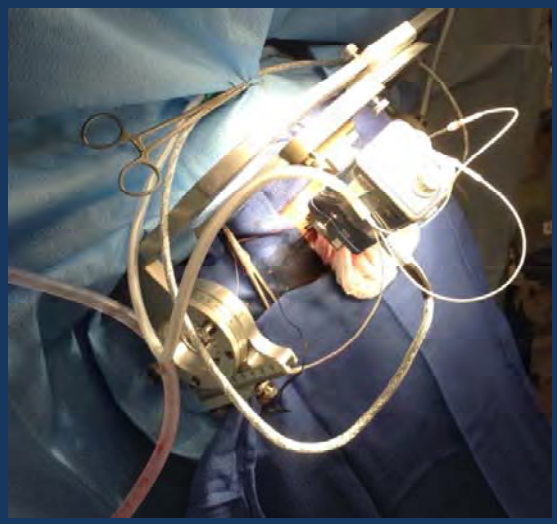
ERPs to VIM/STN DBS for ET and PD

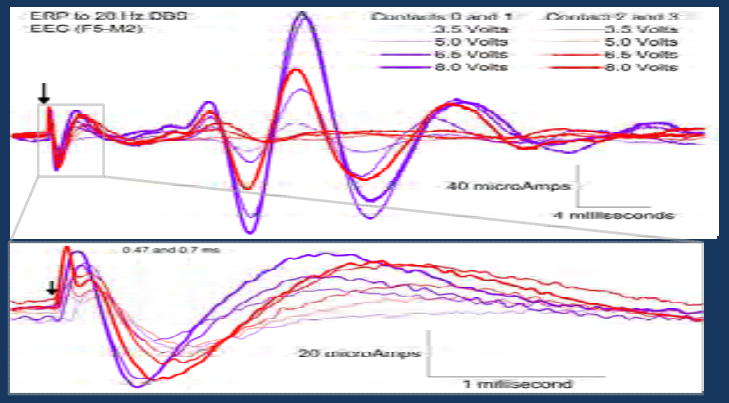
- Subjects undergoing DBS for clinical care (IRB).
- Event related potentials to 20 Hertz immediately after DBS electrode placement in OR

Walker HC et al, Mov Disorder. 2012
Walker HC et al, Mov Disorder. 2012
NIH R01 Submission

Cortical ERP's as Outcome Proxy

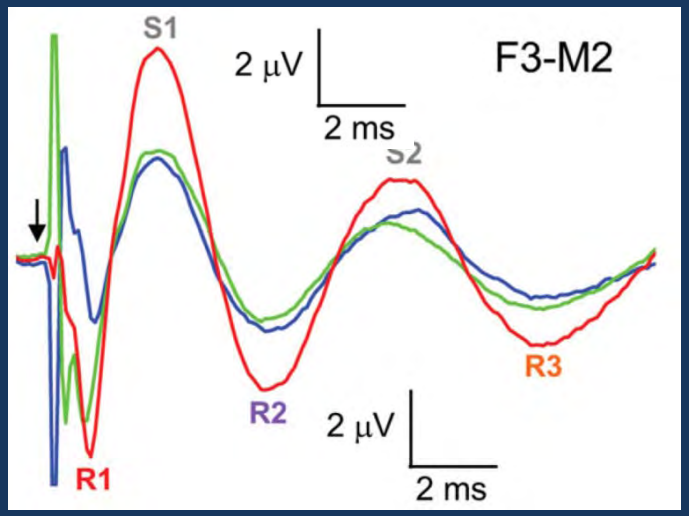


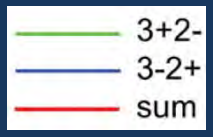


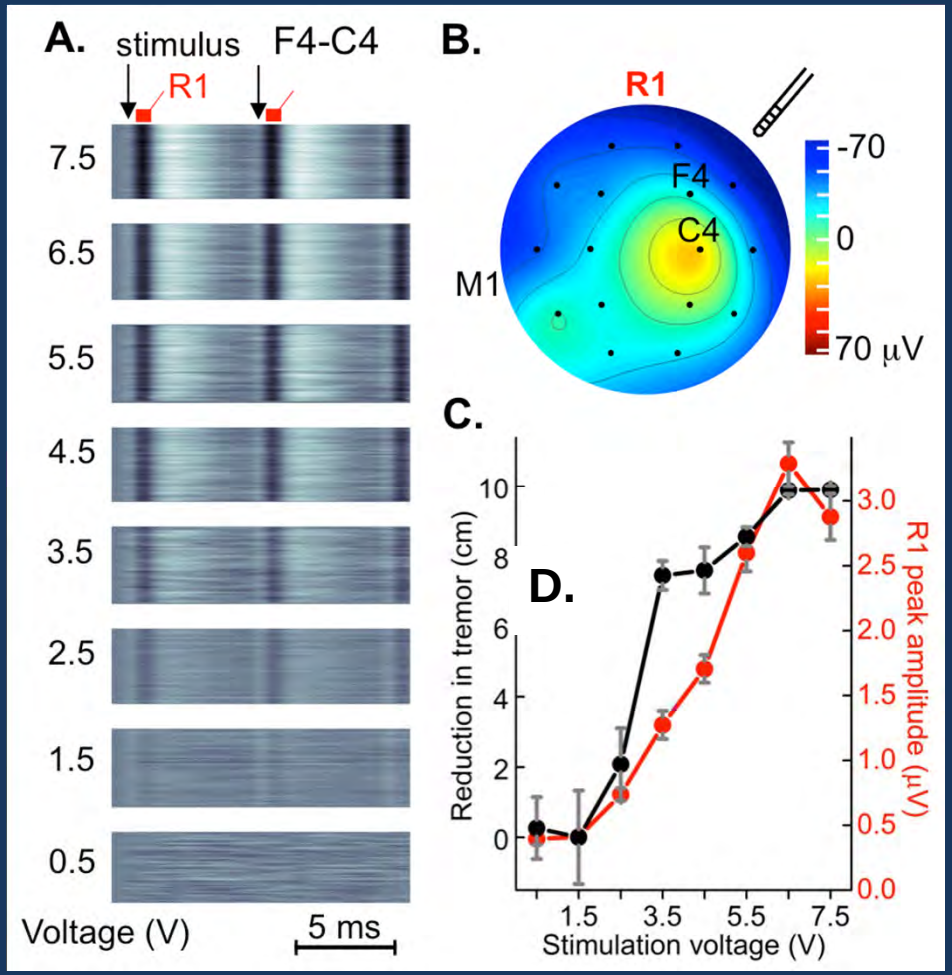


Cortical activity during (VIM) DBS for ET

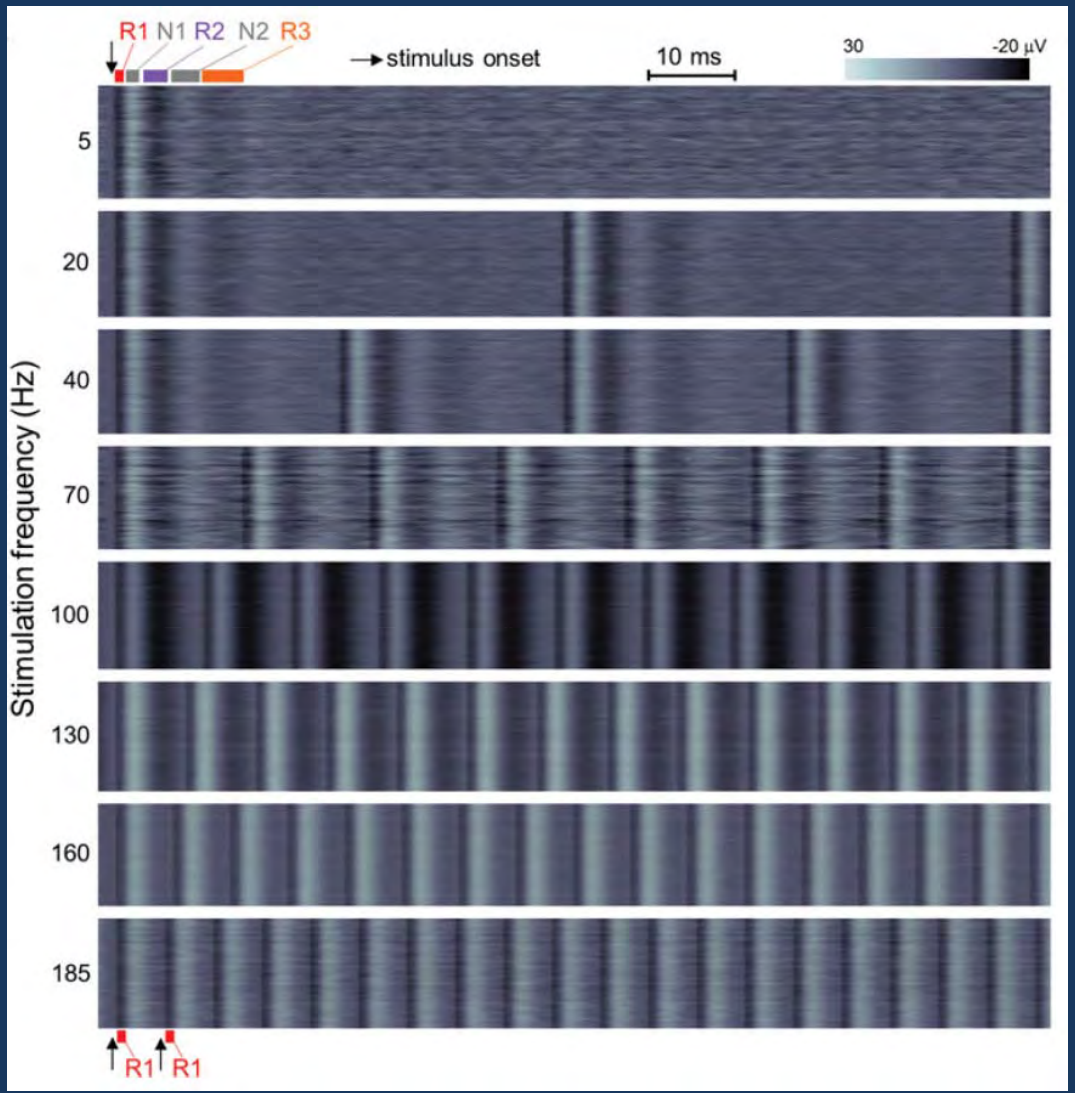
VIM DBS for ET (20 Hz)
EEG: F3-M2



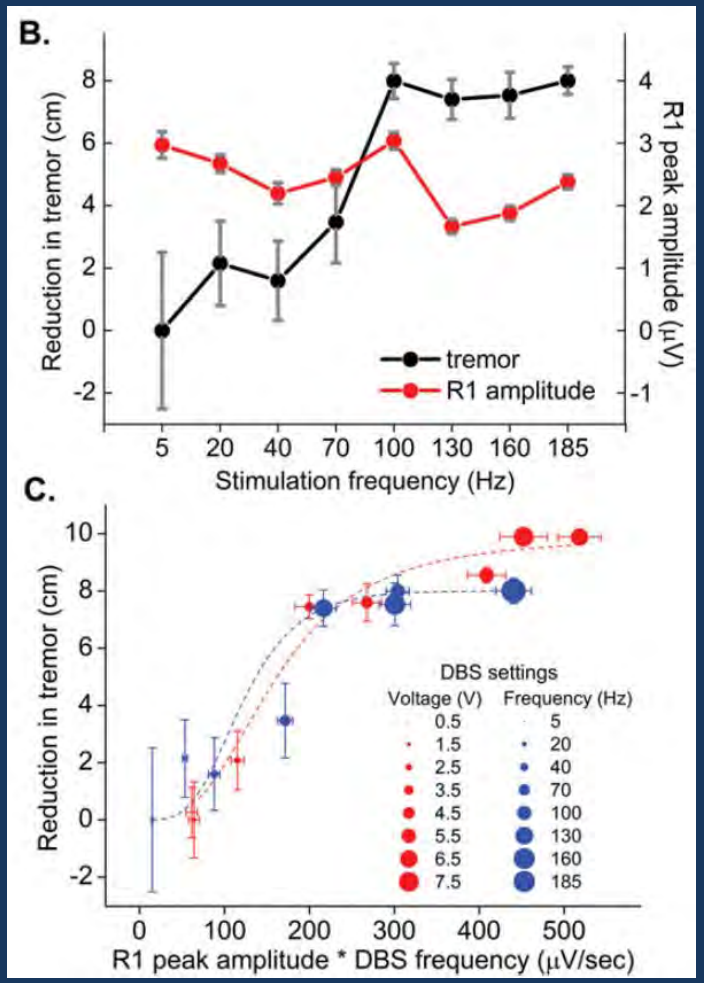




Cortical activity during (VIM) DBS for ET

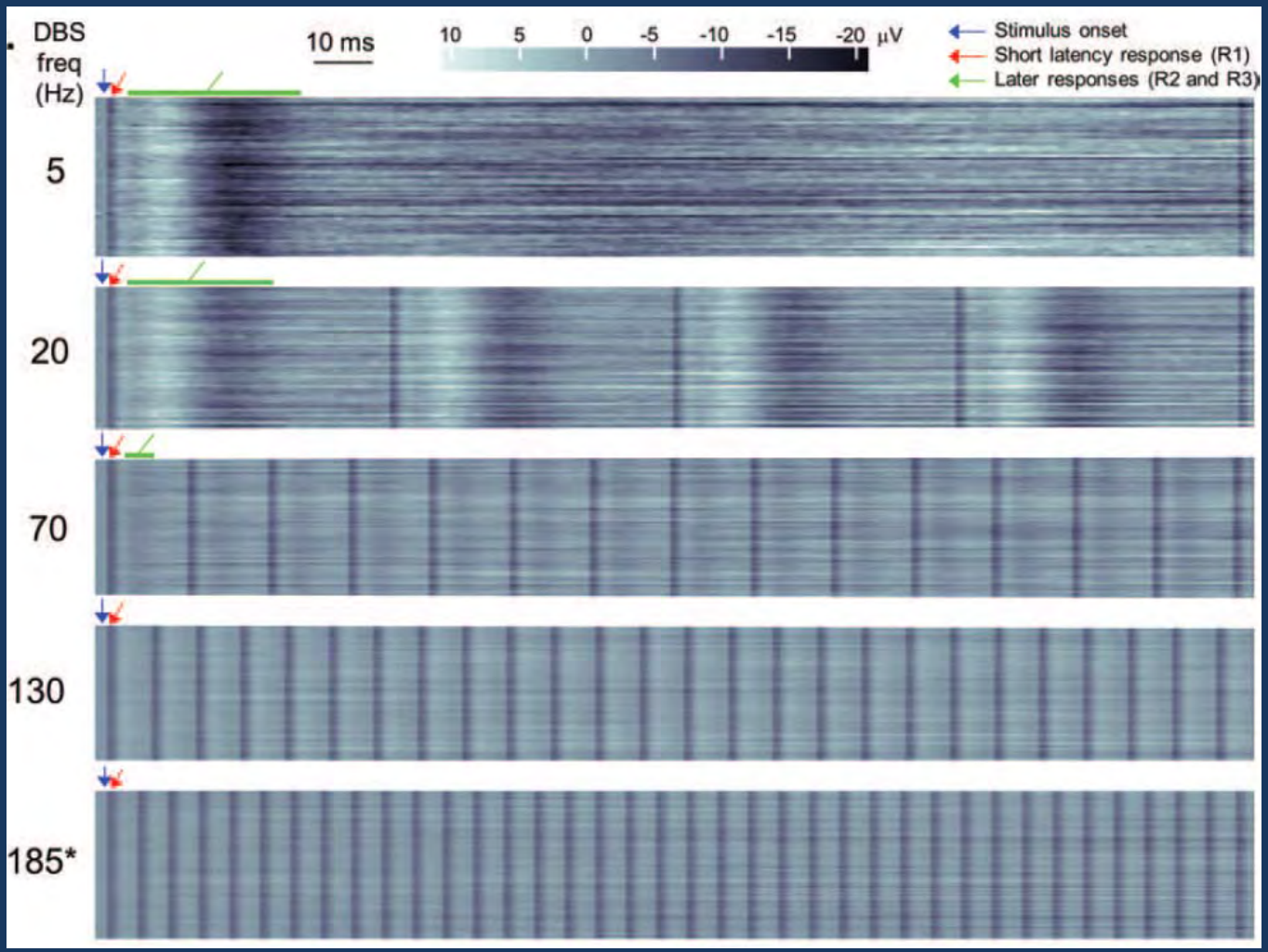


EEG: F3-M2



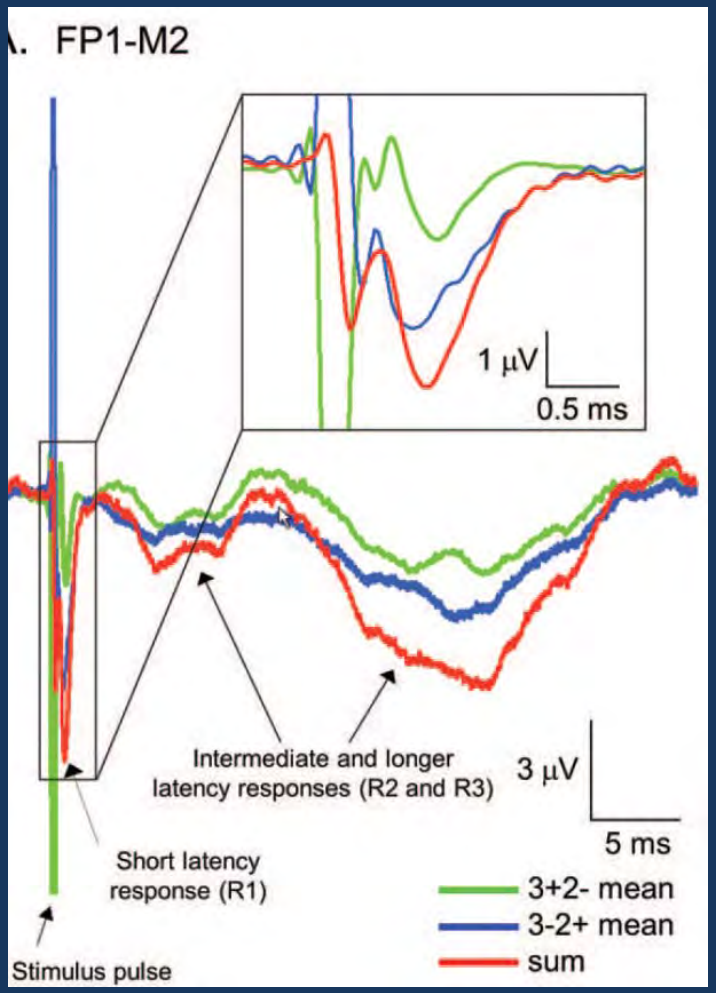
from Walker HC et al, *Mov Disorder.* 2012; 27(11)

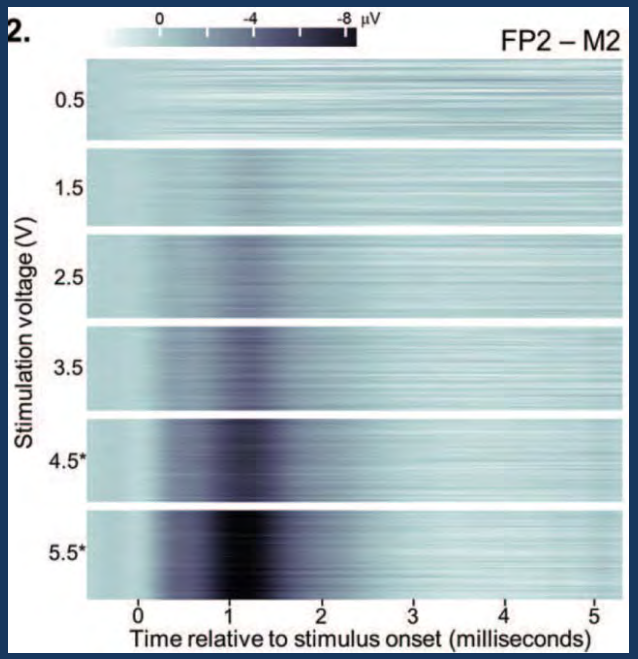
Regularization of cortical activity during STN DBS for PD

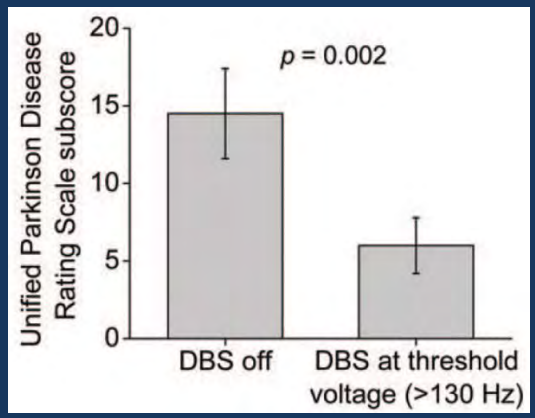


from Walker HC et al, *Mov Disorder.* 2012; 27(7)

Regularization of cortical activity during STN DBS for PD



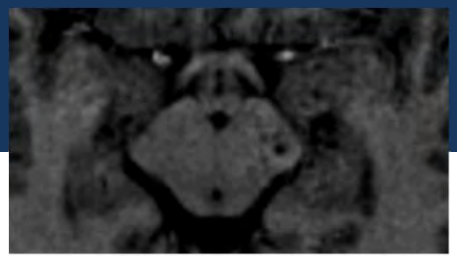




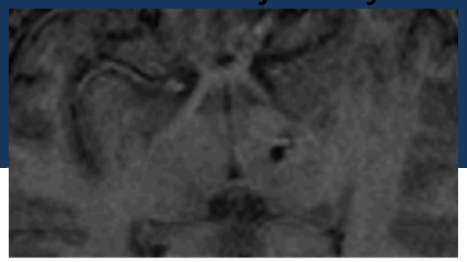
from Walker HC et al, *Mov Disorder.* 2012; 27(7)

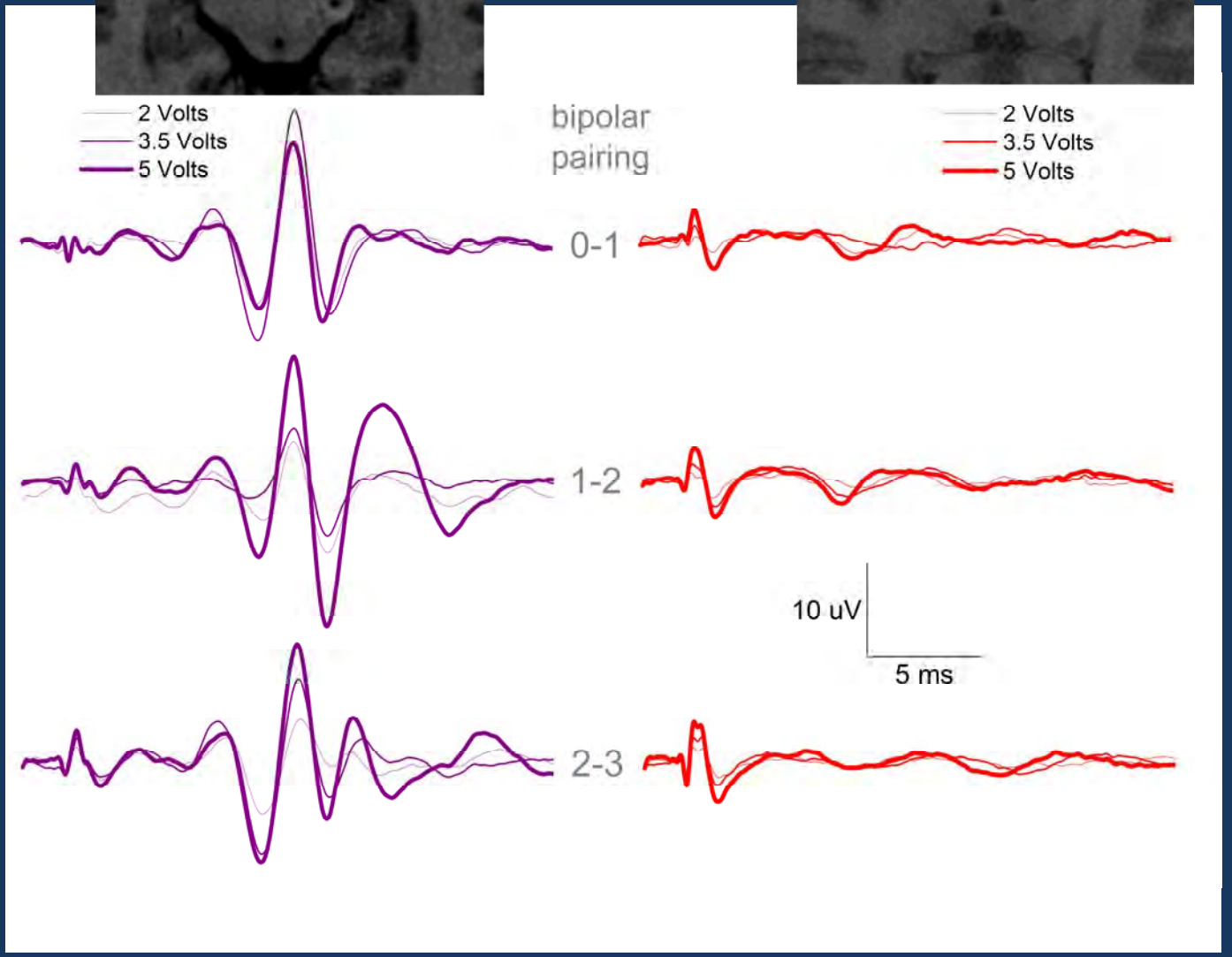
Proximity to CST

Initial Trajectory

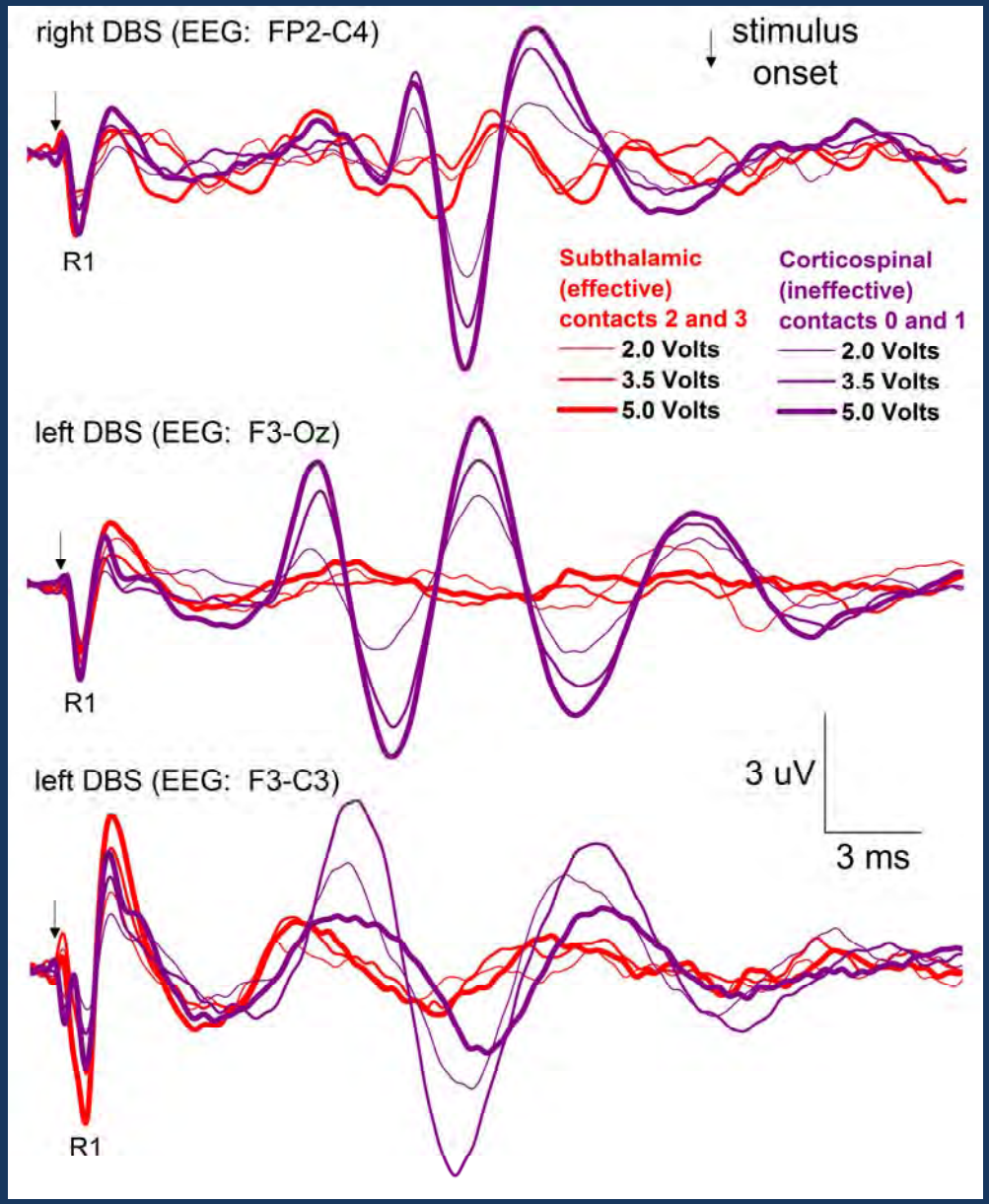


Final Trajectory

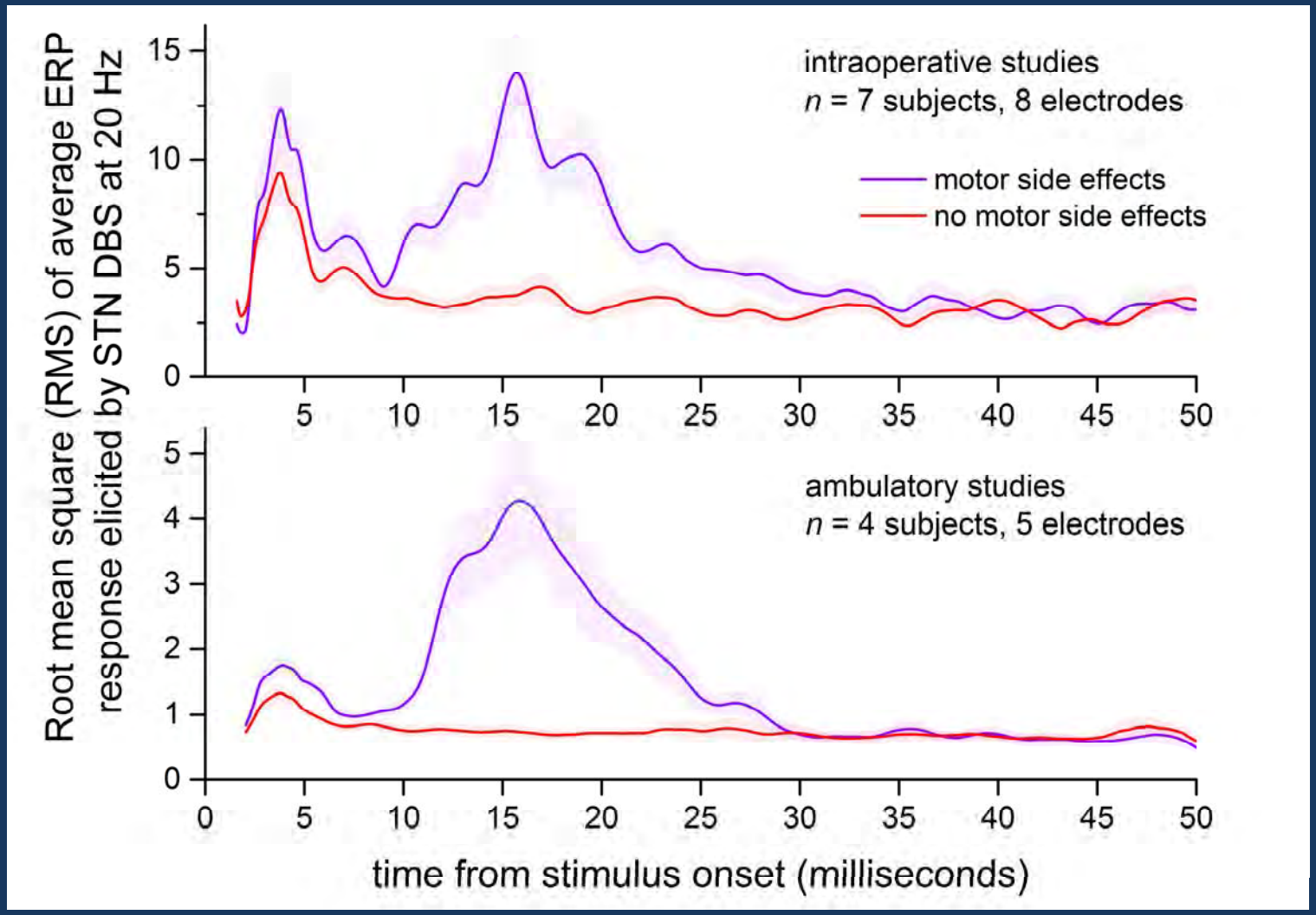




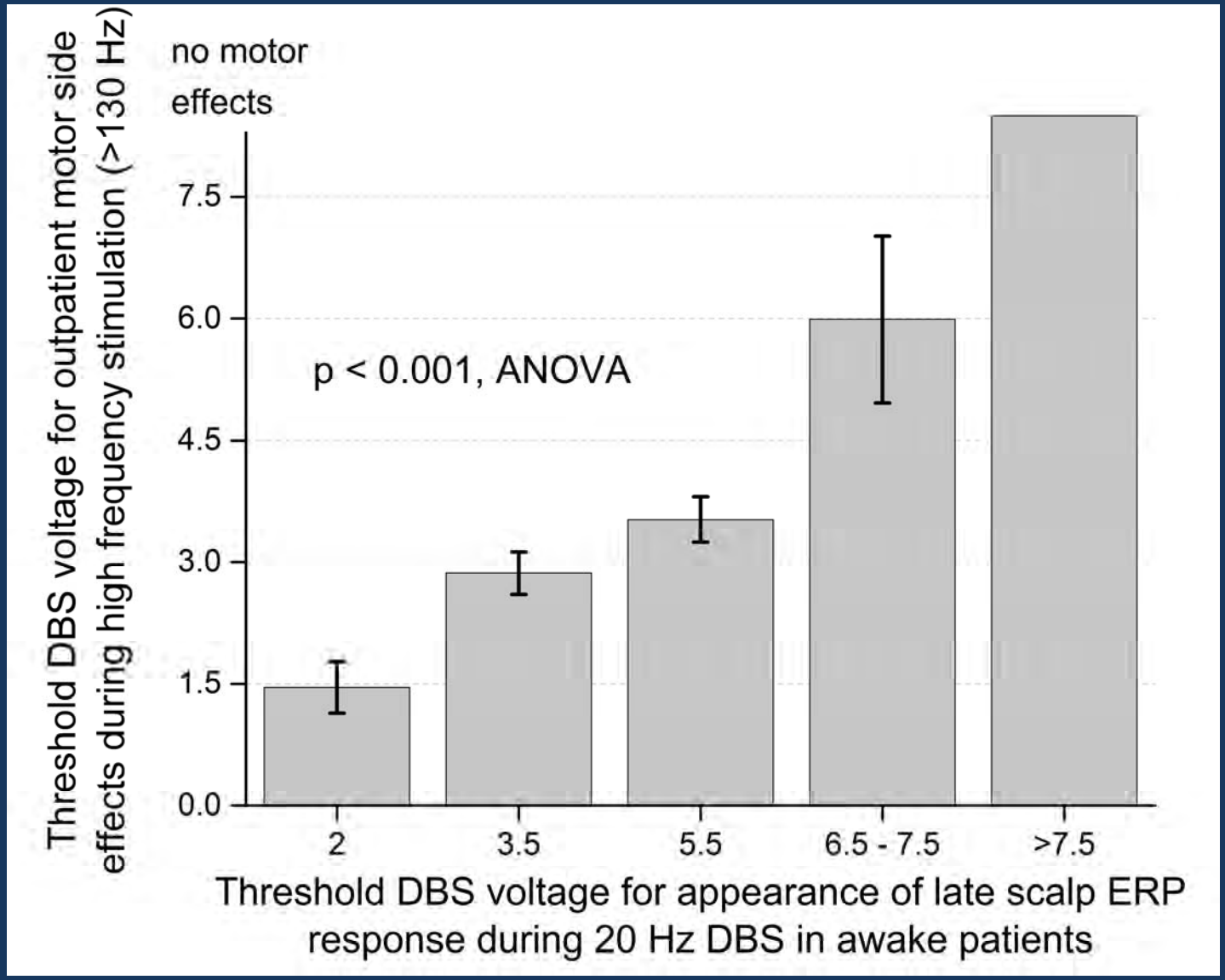
Cortical response vs. clinical effectiveness



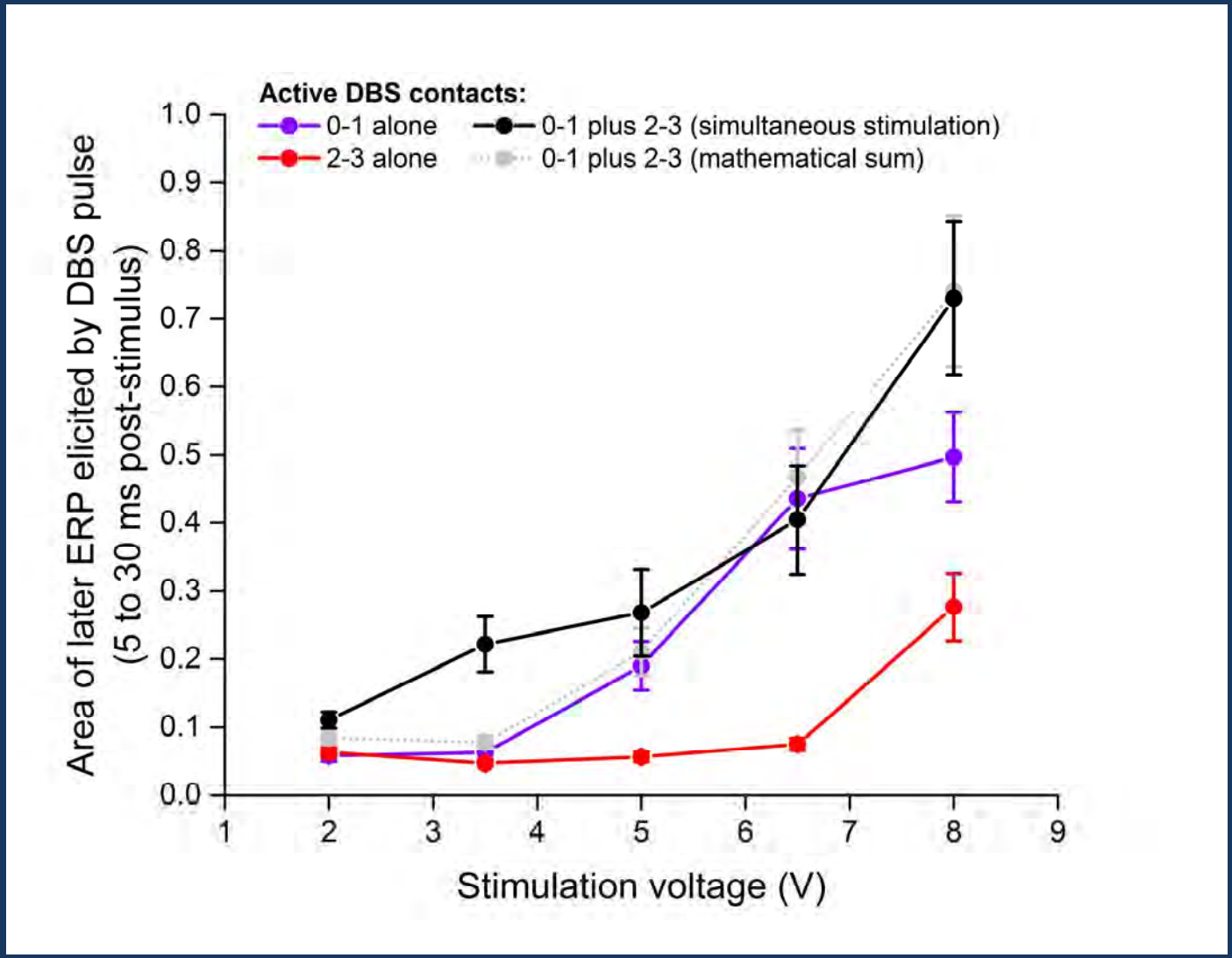
RMS of STN DBS-elicited ERP Intra vs. Postop



Intraop ERPs predict threshold for outpatient CST effects



STN and CST stimulation activates distinct populations of neurons



Cortical ERP

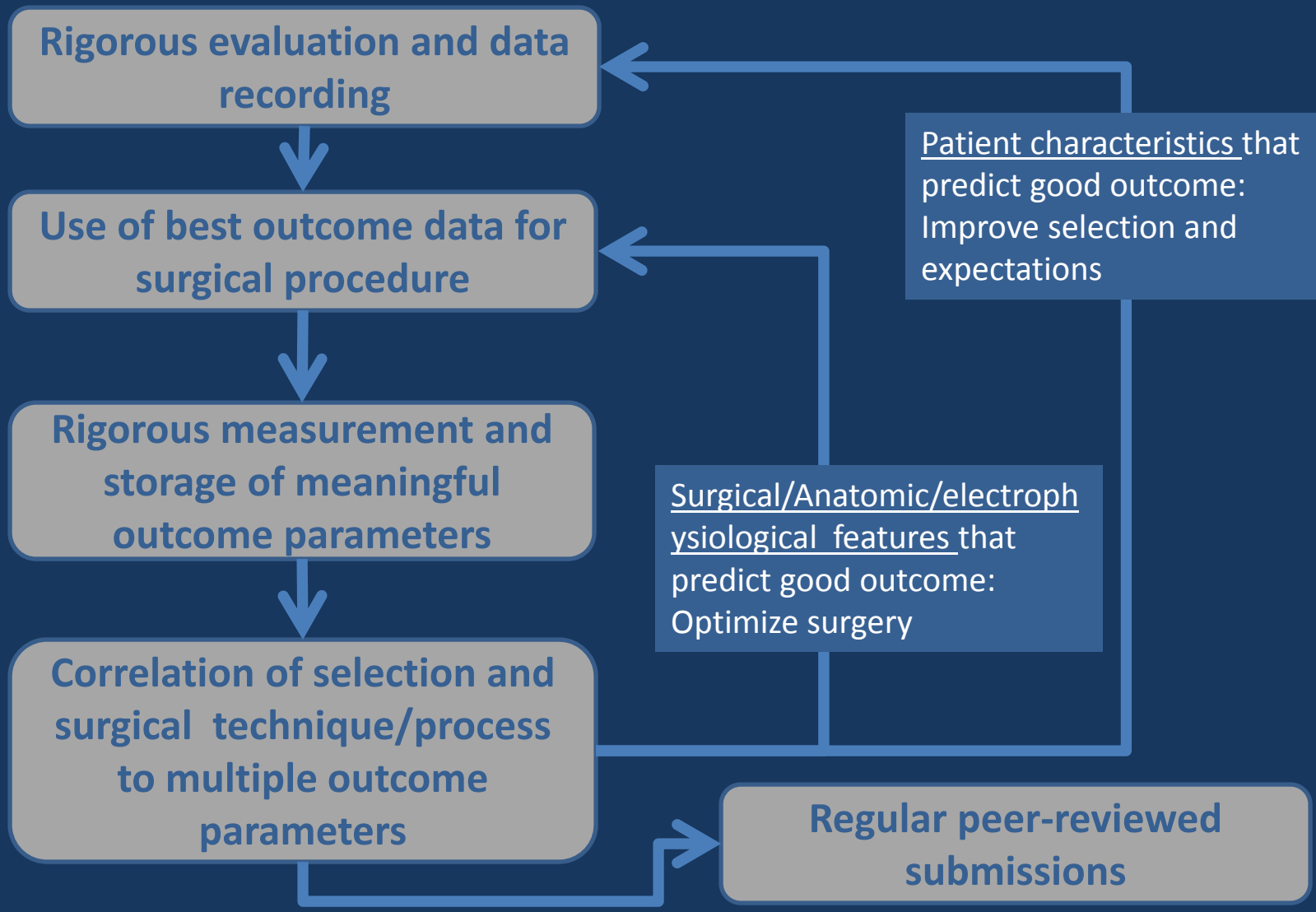
- ERPs can be measured intra- and postop
- ERPs appear to bio biomarkers for intraop prediction of certain clinical effects
- Prospective studies for further validation

Conclusion
Multiparameter Optimization

- Imaging is a rough guide to optimal DBS location
- Intra-op behavior reasonable proxy for outcome, esp with tremor
- Functional topographic relationships can guide surgeon to more efficacious location
- DBS-induced ERPs may provide a proxy for outcome, further refining DBS location
  - Anesthetized patient
  - Affective DBS

DBS Value: Outcome Optimization

PEOPLE not TECHNOLOGY



DBS Optimization

Discussion