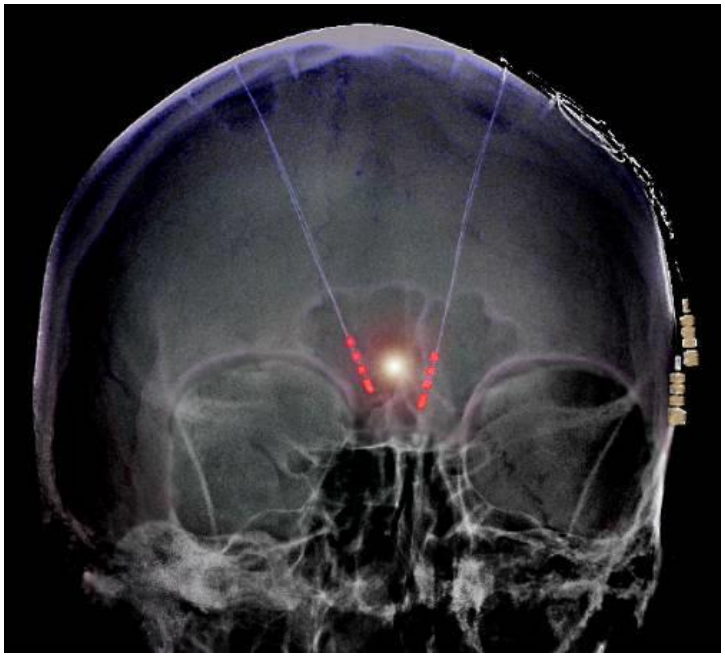
Deep Brain Stimulation and Depression: A Decade of Progress



Kevin Warren

Helen S. Mayberg, MD
Emory University

Brain & Behavior Research Foundation Webinar
January 14, 2014

Disclosures

Grant Support: NARSAD, Dana Foundation, Woodruff Fund,
Stanley Medical Research Institute,
Hope for Depression Research Foundation

Off-Label Use of Devices: DBS electrodes/pulse generators

1. Medtronic Inc. (UT, Emory)
2. St. Jude Medical, Inc (Emory)

Emory DBS study: FDA IDE: G060028 (PI: HM), G130107 (PI: HM)
Clinicaltrials.gov ID#: NCT00367003
research devices donated by SJM and Medtronic

Patent: US2005/0033379A1 (Andres Lozano, co-inventor)
issued March 2008, St. Jude Medical Inc, assignee

Consultant: St Jude Medical Inc / Neuromodulation Division

DBS Team

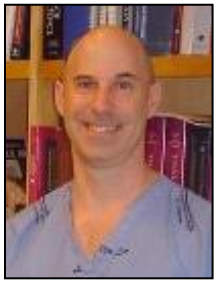
University of Toronto


A Lozano


S. Kennedy


C. Hamani

Neurosurgery


R Gross

Psychiatry and Psychophysiology


P Holtzheimer


S Garlow


P Riva Posse


A Crowell

Imaging: DTI, PET, fMRI, Modeling


K Choi


C McGrath


J Rajendra


C McIntyre

Electrophysiology


O Smart


V Tiruvadi

Animal Models


D Rainnie


T Madsen

Affective/Cog NS/Psychology


S Hamann


C Inman

Psychotherapy


L Ritschel


C Ramirez

Biostats


M Kelley

Patient Coordination


S Quinn


M Woody

Context: Proof-of-Principle Pilot Study 2005

6 month open-label, chronic, continuous DBS in 6 patients

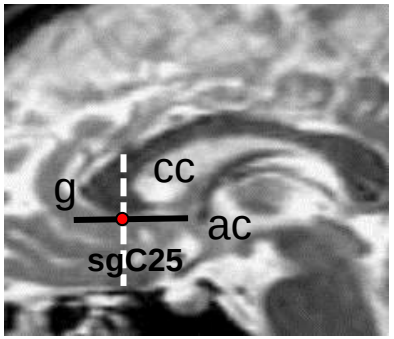
Neuron, Vol. 45, 1–10, March 3, 2005,

Deep Brain Stimulation for Treatment-Resistant Depression

Helen S. Mayberg,[1,2,*] Andres M. Lozano,[3,*]
Valerie Voon,[4] Heather E. McNeely,[5]
David Seminowicz,[6] Clement Hamani,[3]
Jason M. Schwalb,[3] and Sidney H. Kennedy[4]

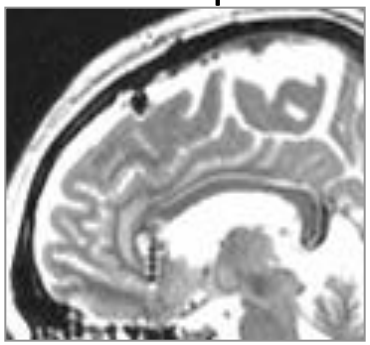
severe TRD, HDRS17>20, GAF<50
chronic: Illness duration avg 5.6 yrs
failed multiple meds, CBT, ECT
6 months open label DBS
4/6 Resp; 3/6 remission
hypothesis supported by PET Δ

Pre-op MRI



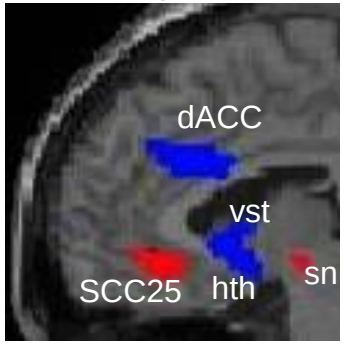
Electrode Targeting

Post-op MRI



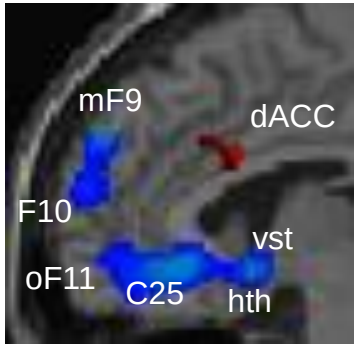
Confirm electrode placement

Pre-op PET



Pts vs Controls

Δ 6 months DBS



Responders

Funded by NARSAD, Toronto Western hospital

DBS for Depression: Motivation

- ✓ Status Quo: treatments available; not always effective
  - < 40% achieve remission with first treatment
    - no reliable biomarkers to guide treatment selection
    - relapse, recurrence common
  - ~ 10% become treatment resistant over time
    - only experimental options if fail ECT (ablation, VNS, ketamine)

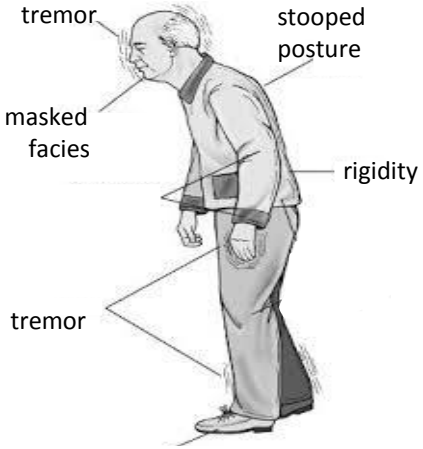
- ✓ Thinking 2001: Neuromodulation as a Potential Strategy

Scientific Facilitators ›

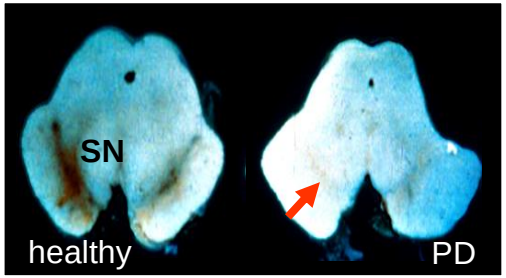
1. Advances in stereotaxic neurosurgery
2. Experience in other neurological disorders
3. Knowledge from structural/functional imaging

Prototype Neurological Disorder

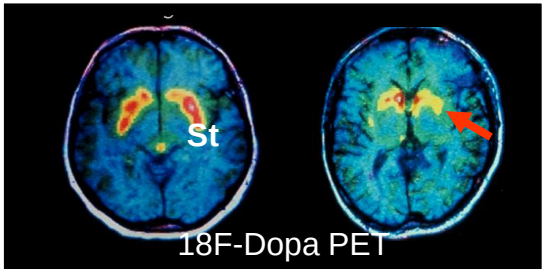
DBS for Parkinson's Disease



Diagnosis
Syndrome → Pathology

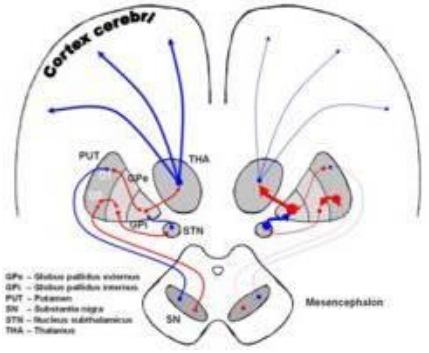


Treatment
Pathology→ Chemistry



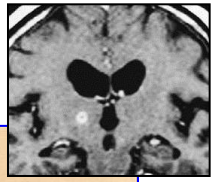
Rx
L-dopa
1963

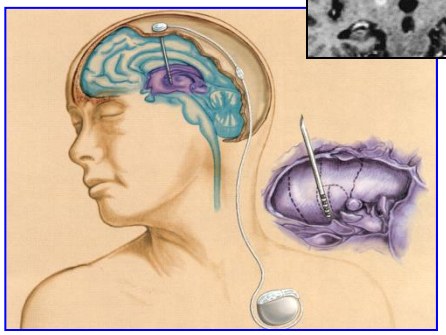
Define
Circuits



Delong, Alexander, Strick 1986

Circuit
Lesions





Benabid et al. Appl Neurophysiol 1987

Circuit
Tuning

Hi freq
130Hz
DBS

STN DBS. Courtesy Andres Lozano U Toronto

FDA approved 1997 ET, PD 2002
>100,000 pts implanted.
No Δ basic technology in 25 yrs

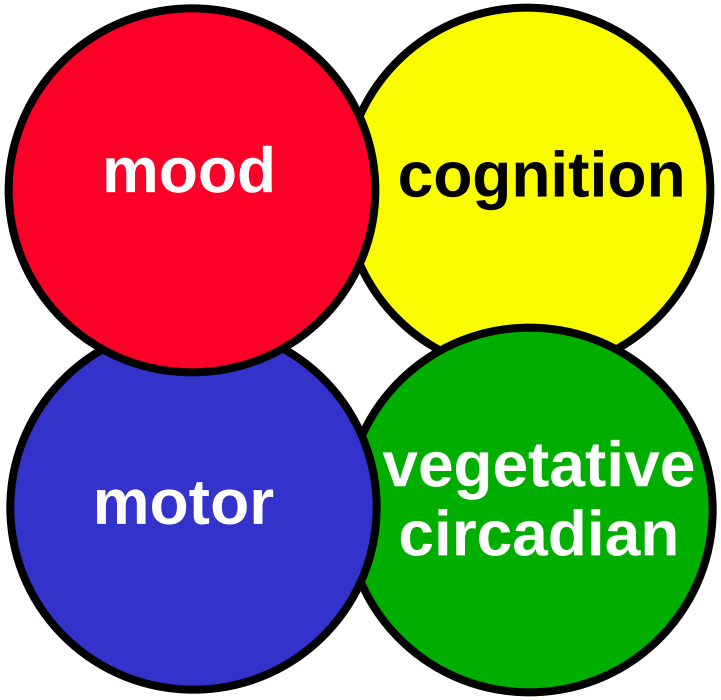
Can we Treat Depression Like PD?

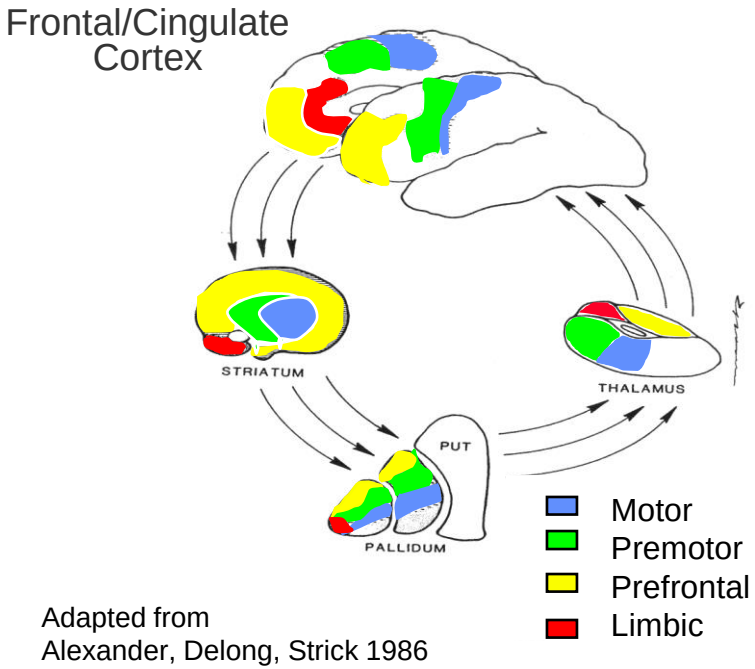
Critical Questions:

- Is there an “illness” circuit
- What changes are necessary/sufficient?
- Where should we stimulate?
- Which patients?

Defining Depression Circuits

Deconstruct syndrome into component dimensions





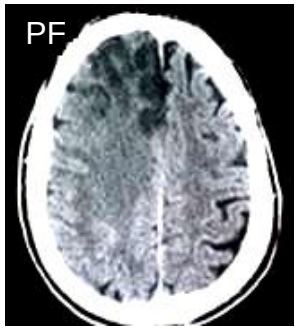
Adapted from
Alexander, Delong, Strick 1986

Approach: Symptoms map to distinct pathways.
Treatment impacts some or all subcircuits

Step 1: Define candidate regions in circuit

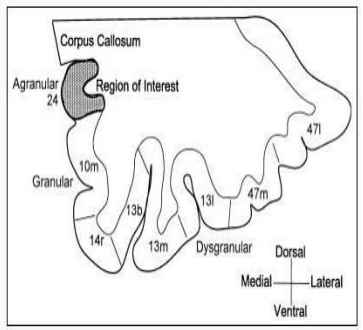
Imaging studies of structure and function

Focal Strokes



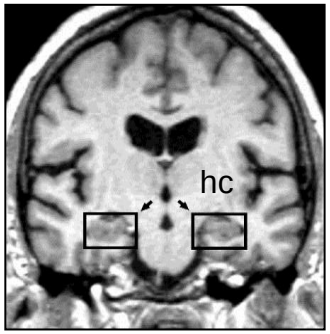
Robinson 1983

↓ MRI volume, Glia



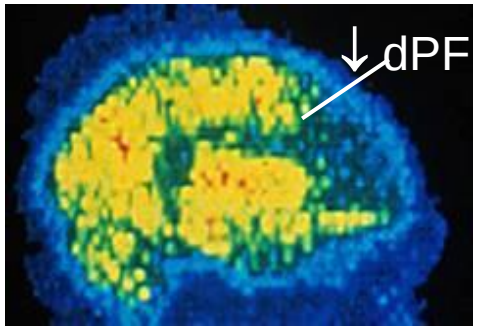
Drevets 97; Ongur 98

↓ MRI volume



Sheline, 1999

Variability

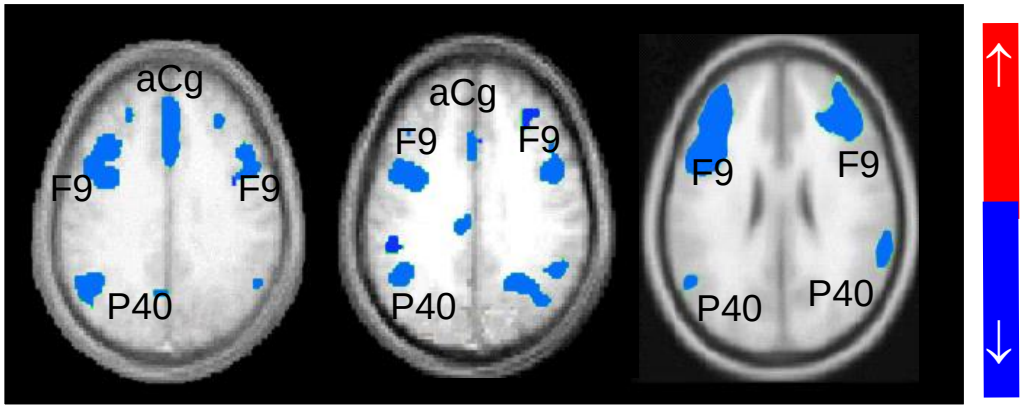


Baxter AmJP 1985

Parkinson's

Unipolar

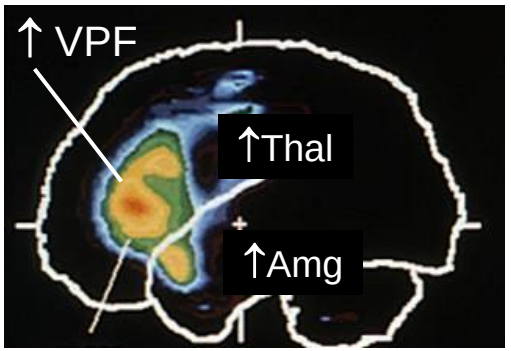
Bipolar



Mayberg et al. AJP 1988
Starkstein Brain 1989
Ann Neurol 1990
Neurol 1992

J Nuc Med 1994
NeurReport 1997
J NPCNS 1997
Am J Psych 1999

Baxter et al. 1985
Kruger et al. 2003



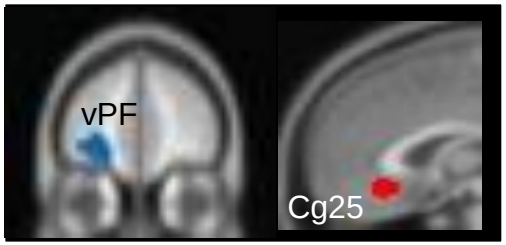
Drevets JNS 1992

Early clues to possible subtypes?

Step 2: What regions change with treatment?

treatment specific effects

CBT



↓ *ruminative thought*
↑*emotional awareness*

Emotion Regulation
Self-awareness
Insight

Is one node, compartment, or behavior most critical?

Cognition
attention-appraisal-action

PF9/46 PM6 Par40 hc
MCC PCC

mF9/10 pACC24 oF11

na-vst thal amg mb-sn

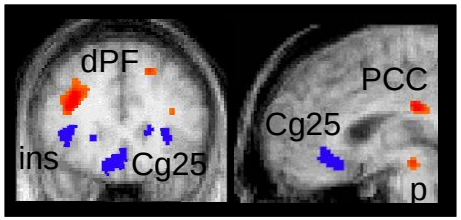
Mood state

Salience
Motivation

sACC25
a-ins hth bstem

Interoception
drive-autonomic-circadian

MEDS



Δ *limbic tone, emotion reactivity*

Mayberg J Neuropsych Clin NS 1997
Mayberg, Br Med Bul 2003, Psych Annals 2006
Goldapple et al Arch GP 2004, Kennedy et al AJP 2007
McGrath et al JAMA Psych 2013

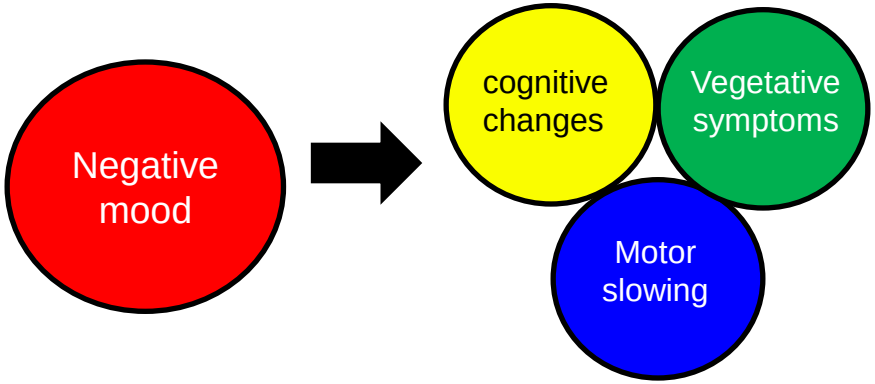
Step 3: What are core clinical features are key?

"It is a positive and active anguish, a sort of psychical neuralgia wholly unknown to normal life." — William James 1902

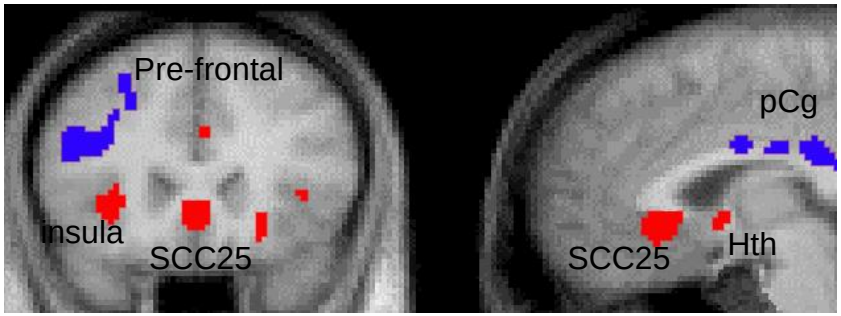
"Psychic energy throttled back close to zero. Nearly immobilized, a trance of supreme discomfort." — William Styron 1991

"A gnawing agony; a painful self-loathing that consumes all your energy and attention…" — Toronto DBS #7

Hypothesis



Map Negative Mood Directly

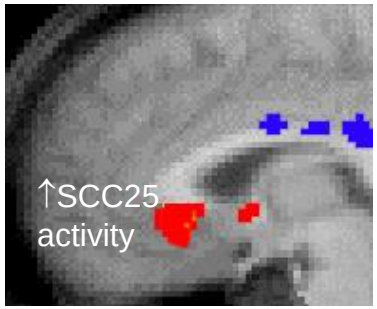


Personal sad memory CBF PET

Step 4: Isolate necessary and sufficient regions

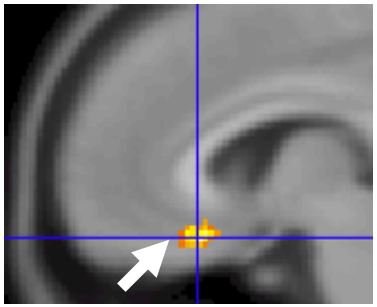
Converging findings in the subcallosal cingulate SCC25

Sad Memory



Mayberg

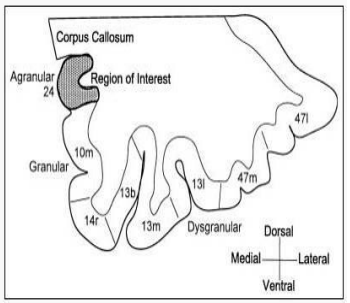
Tryptophan Deplete



Talbot

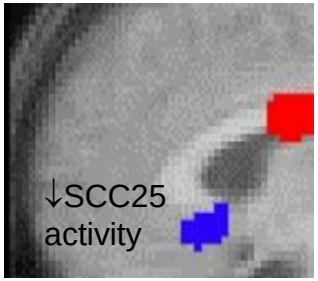
Increased sCg25 with induced depressed mood

↓volume; ↓glia



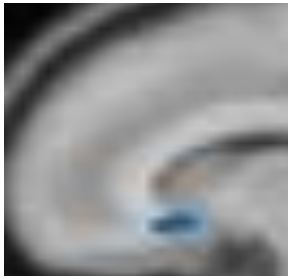
Drevets, Ongur, Rajkowska

SSRI



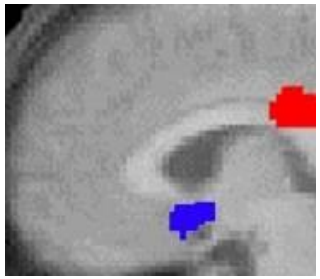
Mayberg

SNRI



Kennedy

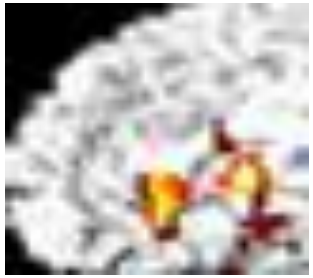
Placebo



Mayberg

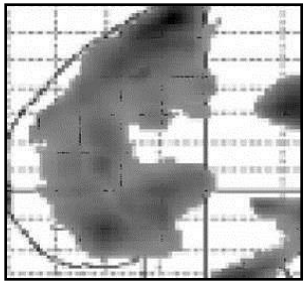
Decreased SCC25 with diverse successful treatments

rTMS



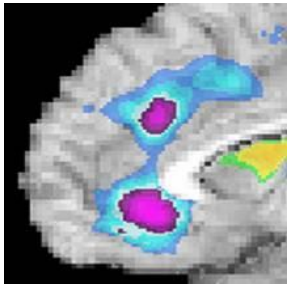
George

ECT



Nobler

VNS



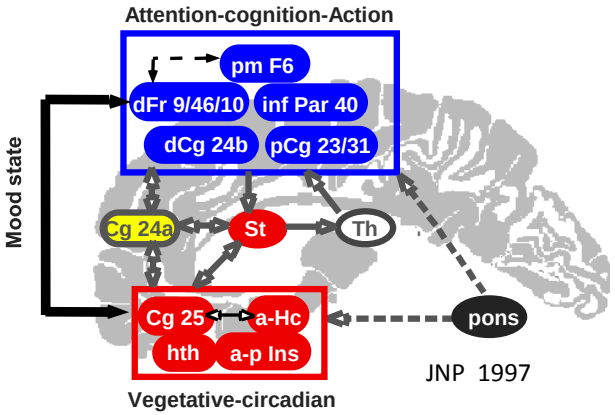
Pardo

Hypothesis: TRD=dysregulated SCC25. Target this critical hub

Back to the Beginning: Area 25 DBS for TRD

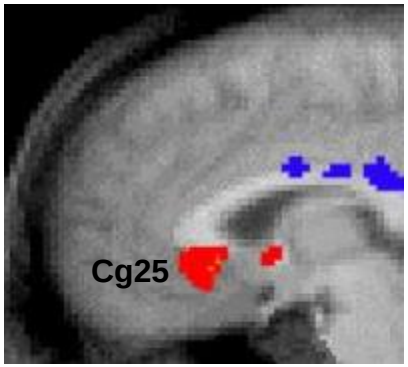
Pt #1 May 13, 2003 Toronto

Depression Circuit Model



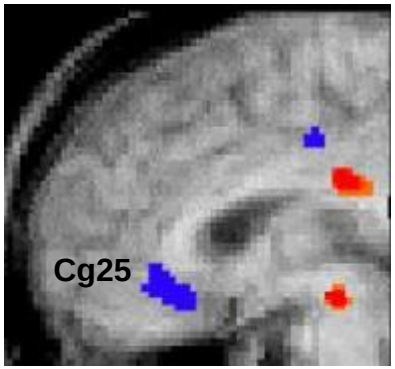
JNP 1997

CBF PET



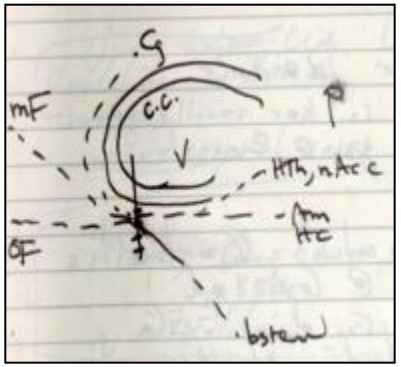
Transient Sadness
Activation of SCC25

FDG PET

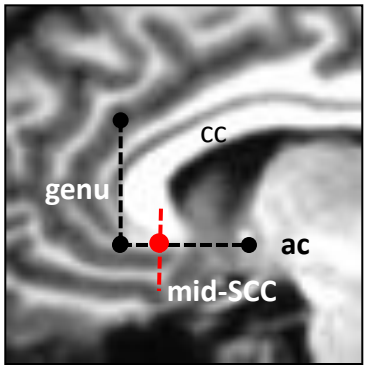


Dep Recovery w/ meds
reduced SCC25 activity

Path Connections

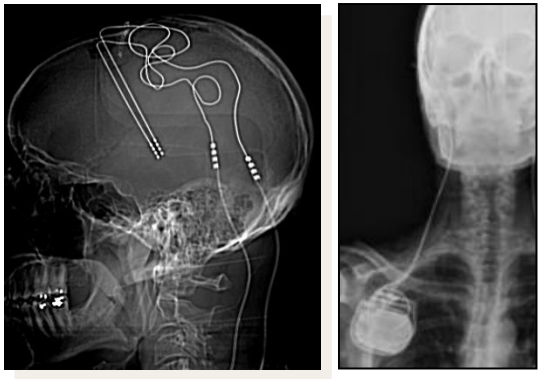


Impacted fibers based
On tract tracing studies



Anatomical Target
Stereotactic MRI

Surgical Implantation
While Awake



Bilateral Leads+ IPG
Parameters 130Hz/90usec/~6mA

Eligible Patients
MDD only GAF<50
Episode >1 yr, Ham17>20
Failed 4 meds, ECT, PsyTx
No medical/psych
comorbidity

Toronto: Continued Proof-of-Principle Testing

Unblinded, safety and efficacy testing of chronic stimulation

PRIORITY COMMUNICATION

Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression

Andres M. Lozano, Helen S. Mayberg, Peter Giacobbe, Clement Hamani, R. Cameron Craddock, and Sydney H. Kennedy

BIOL PSYCHIATRY 2008;64:461–467

2008

AJP in Advance. Published February 1, 2011 (doi: 10.1176/appi.ajp.2010.10081187)

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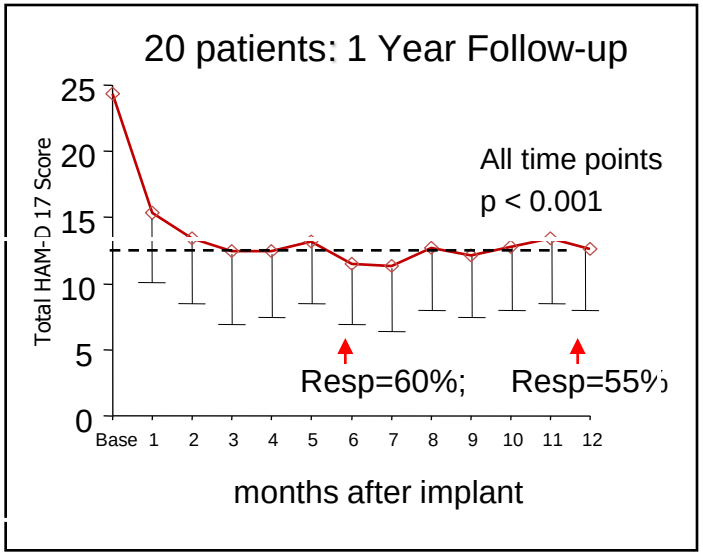
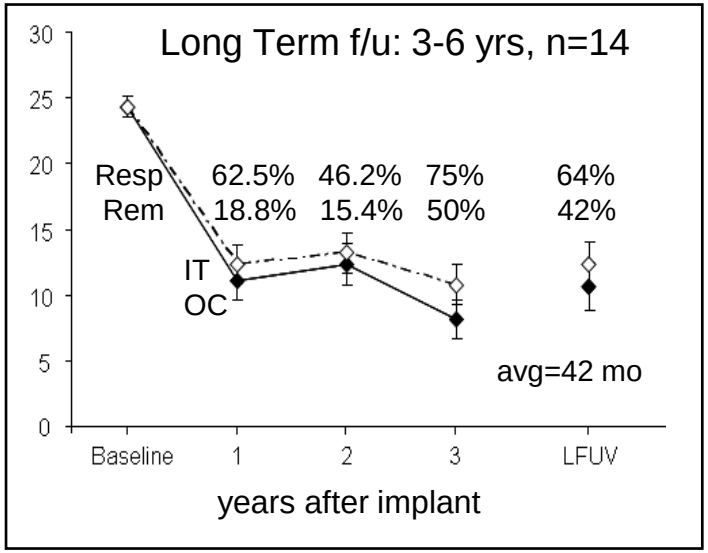
Article

Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years

2011





Emerging Questions

- Predictors
  - ✓ Who are the right Patients?
  - ✓ Can surgery, parameters be further optimized?
- What does DBS do?
  - ✓ ↓negative mood or ↑positive mood?
  - ✓ Mood PLUS motivation, vegetative features, cognition?
  - ✓ Do different brain target differentially affect different symptoms?
  - ✓ Can rehabilitation enhance DBS effects; facilitate plasticity?
- Basic Mechanisms
  - ✓ What regions/pathways/cell types are most critical
  - ✓ reverse-engineering to animal models
  - ✓ Real-time readouts (brain radio, actigraphy)
  - ✓ platform for non-invasive alternatives?

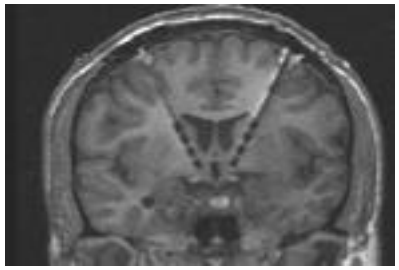
Other Brain Targets Under Study

Same/different: circuit? 1° target symptoms? best pts?

Biological Psychiatry Feb 2009

Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Treatment-Resistant Depression

Donald A. Malone Jr., Darin D. Dougherty, Ali R. Rezai, Linda L. Carpenter, Gerhard M. Friehs, Emad N. Eskandar, Scott L. Rauch, Steven A. Rasmussen, Andre G. Machado, Cynthia S. Kubu, Audrey R. Tyrka, Lawrence H. Price, Paul H. Stypulkowski, Jonathon E. Giftakis, Mark T. Rise, Paul F. Malloy, Stephen P. Salloway, and Benjamin D. Greenberg

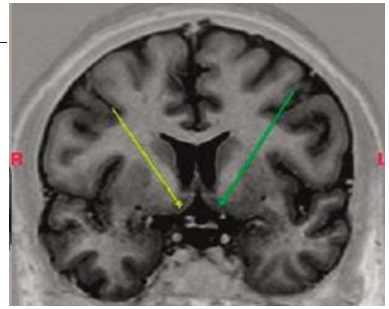


15 MDD (1BP1), 3 sites; 6 months open; 40% Resp Final H24=17.5; 53% R last f/u

Biological Psychiatry (2010) epub Dec 2009

Nucleus Accumbens Deep Brain Stimulation Decreases Ratings of Depression and Anxiety in Treatment-Resistant Depression

Bettina H. Bewernick, René Hurlemann, Andreas Matusch, Sarah Kayser, Christiane Grubert, Barbara Hadrysiewicz, Nikolai Axmacher, Matthias Lemke, Deirdre Cooper-Mahkorn, Michael X. Cohen, Holger Brockmann, Doris Lenartz, Volker Sturm, and Thomas E. Schlaepfer

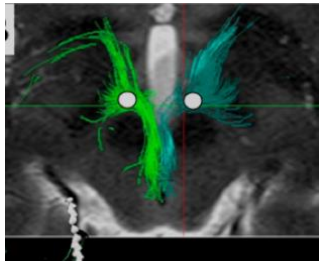


10 MDD; 1 year open; 50% Resp; Final H28=15

Biological Psychiatry (2013) epub Apr 2013

Rapid Effects of Deep Brain Stimulation for Treatment-Resistant Major Depression

Thomas E. Schlaepfer, Bettina H. Bewernick, Sarah Kayser, Burkhard Mädler, and Volker A. Coenen



7 MDD, 12 wk-33 wks open; 6/7 Responders at 12 wks MADRAS=14.6; 4 of 6 in remission

Emory Studies: Replication, Extension

Arch Gen Psychiatry. 2012;69(2):150-158. doi:10.1001/archgenpsychiatry.2011.1456

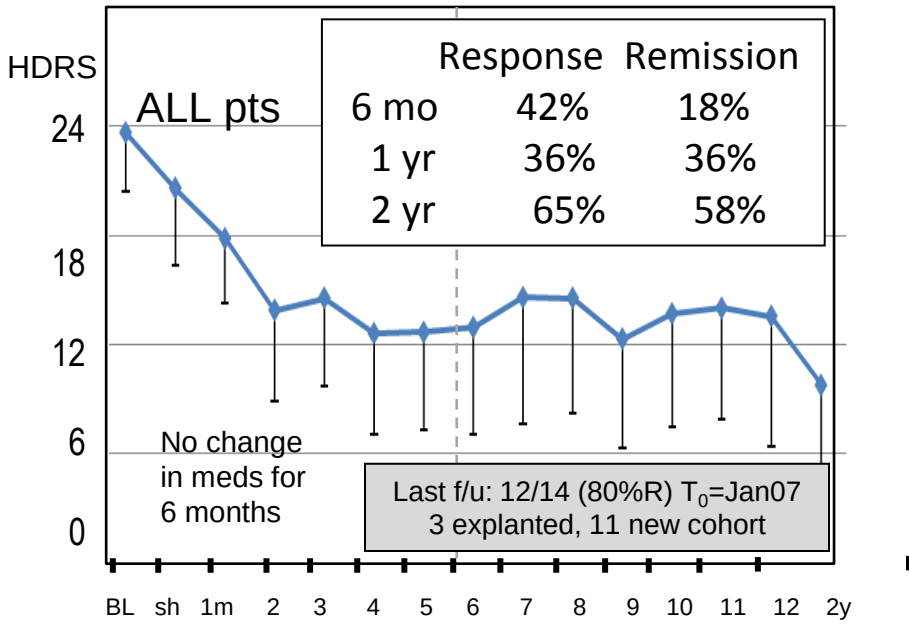
Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Unipolar and Bipolar Depression

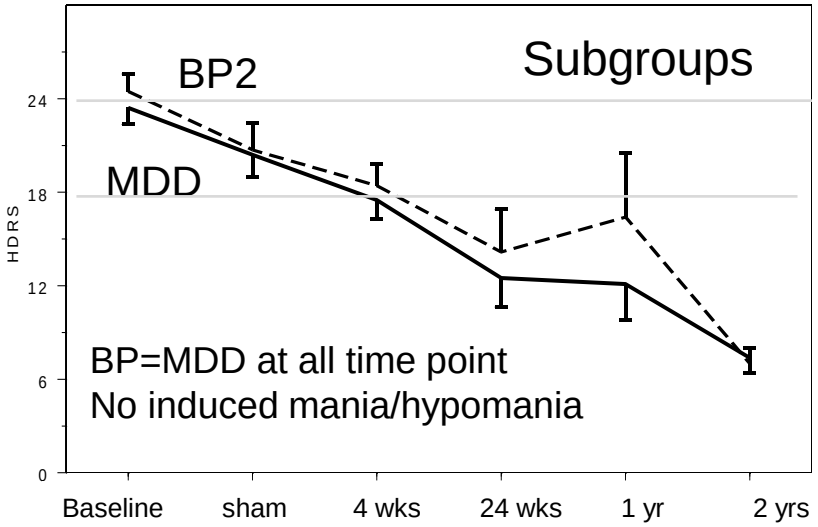
Paul E. Holtzheimer, MD; Mary E. Kelley, PhD; Robert E. Gross, MD, PhD; Megan M. Filkowski, BA; Steven J. Garlow, MD, PhD; Andrea Barrocas, MA; Dylan Wint, MD; Margaret C. Craighead, BA; Julie Kozarsky, BA; Ronald Chismar, RN; Jared L. Moreines, BS; Klaus Mewes, PhD; Patricio Riva Posse, MD; David A. Gutman, MD, PhD; Helen S. Mayberg, MD

10UP/7BP2; 10W/7M; age 42±9, MDE 5.3+4y
Meds stable, 1 mo placebo, 6 mo open DBS
First patient Jan 12, 2007

- time course, remission rate, similar to Toronto
- modest sham effect; carryover from OR?
- Continued improvement over time
- if Remitter, no spont relapses, more resilient?

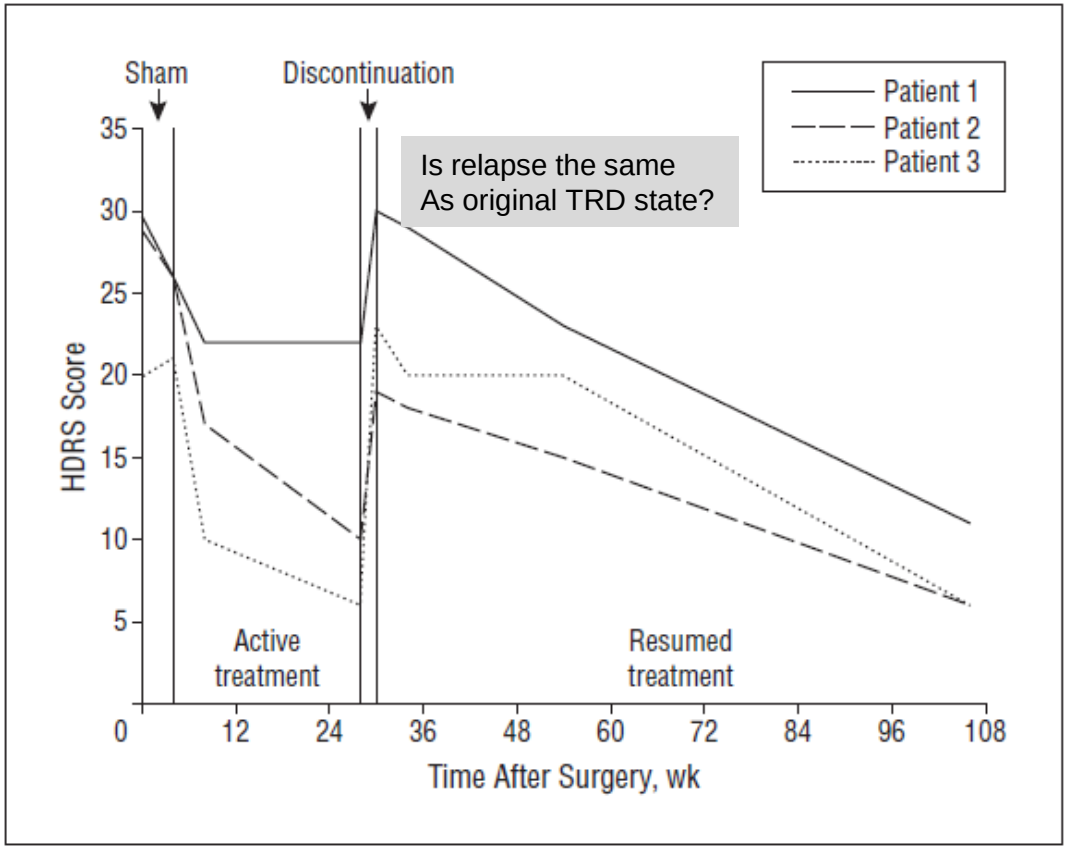
Spain n=8 62% 1 yr
SJM pilot n=21 48% 6 mo (3 centers)
case reports (Argentina, GR, Calgary)





Funding: Dana, Stanley, Woodruff Found'n , Emory Hosp
Devices donated by St. Jude Medical , IDE: G060028/S002

Is Recovery Stable Without Continued DBS?



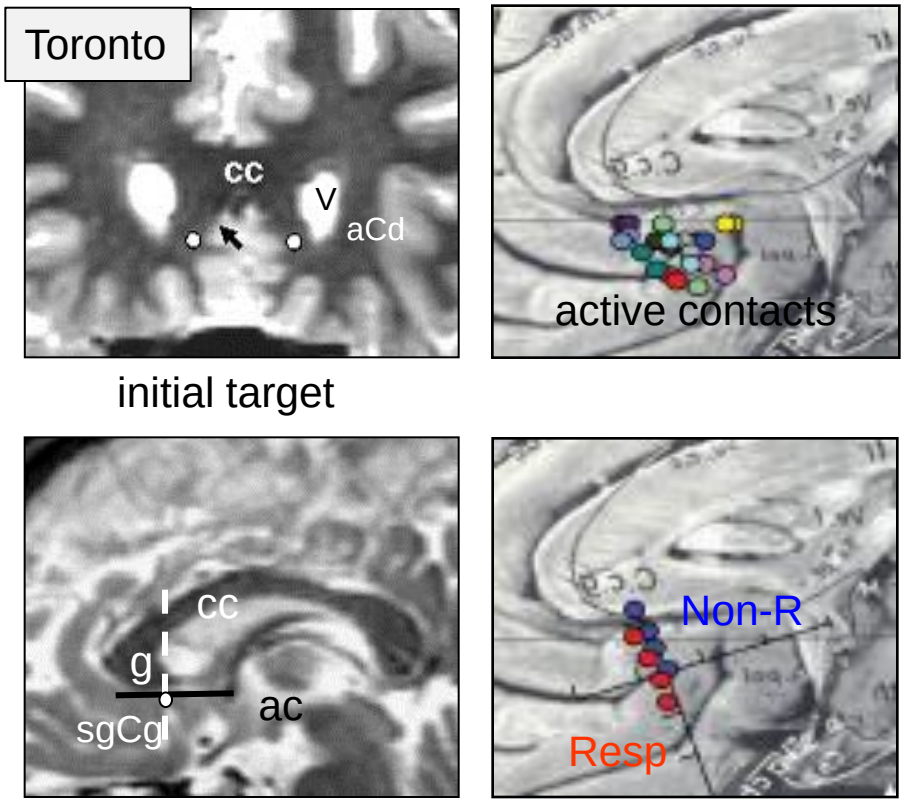
Reproducible loss of effect over 2 wks; further confirmed with battery depletion
No evidence of 'plasticity' although not tested to see if rescued with other Tx
Rate of deterioration may vary for different DBS targets.
Opportunity: time course of relapse suggests cycling of stimulation possible

Holtzheimer et al. Arch Gen Psych 2012

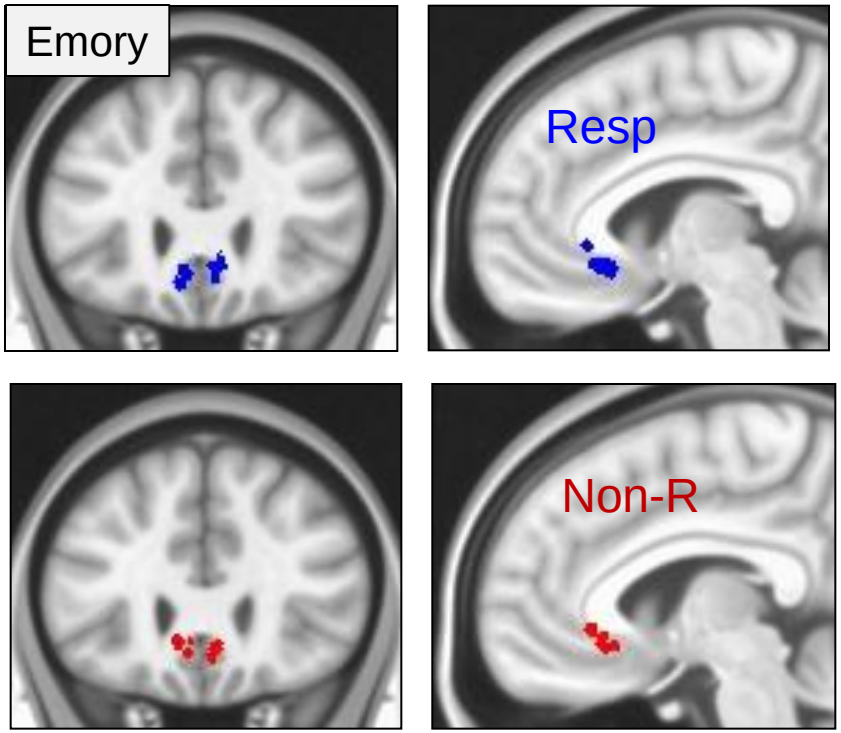
Potential Sources of Response Variability

Patient selection, surgical precision

Evaluation of electrode placement



Standardized to Mean %genu-AC



Standardized to AC-PC mean MNI space

Simple localization uninformative.
What are we missing?

Hamani et al J Neurosurg 20009

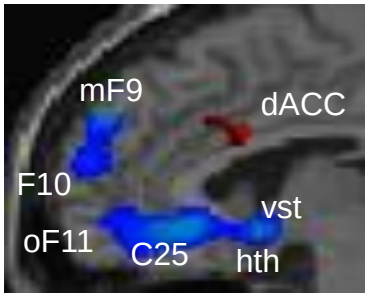
K Choi et al. unpublished

Deconstruct the DBS Target ‘Circuit’

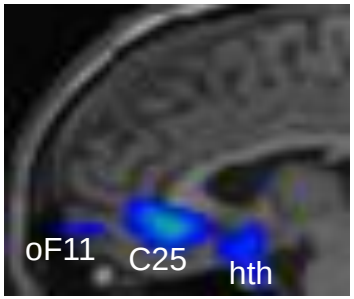
mapping white matter tracts to identify critical SCC connections

Clues
from initial PET:
local + remote
Changes

Neuron 2005



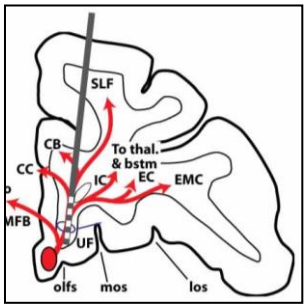
Responders

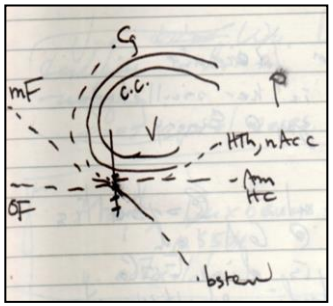


Non-Responders

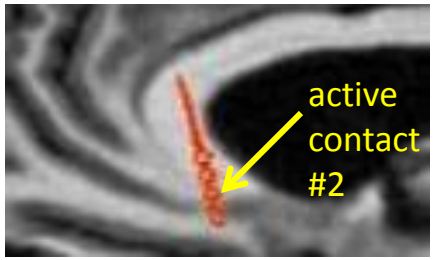
Known
Fiber tracts
Nonhuman
Primate studies

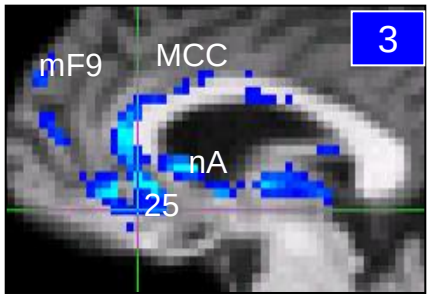
Lehman et al JNS 2012

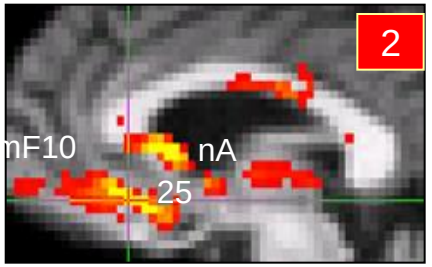




Approach:
Single Subject
Contact Tract Maps



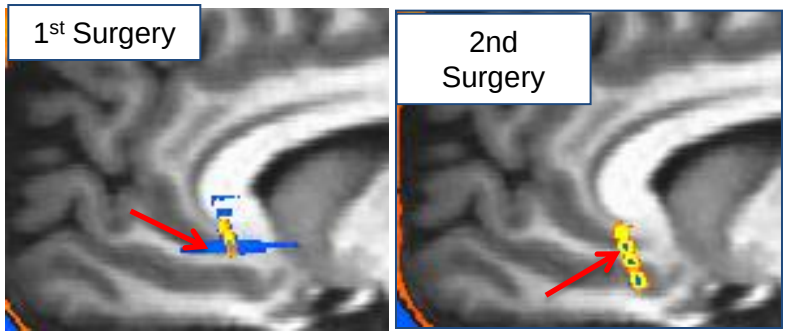




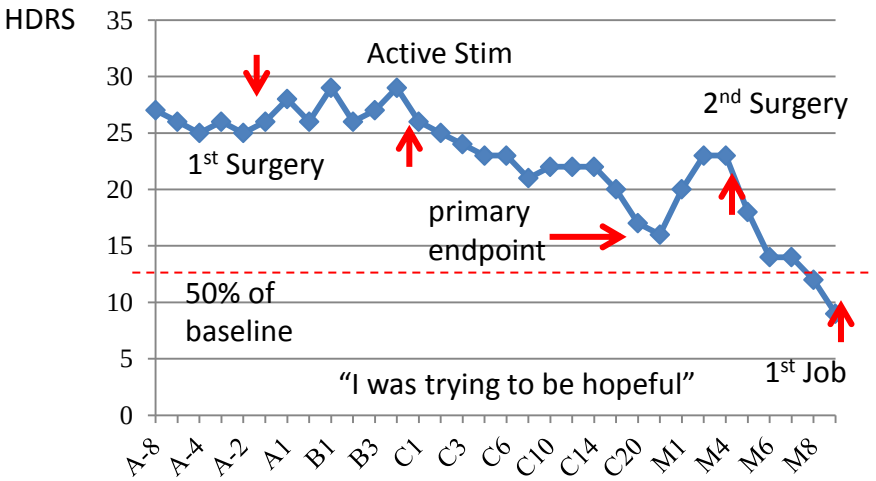
targeting optimal pathways relevant to placement and programming

Test of Concept

Surgical revision in a 6 month non-responder

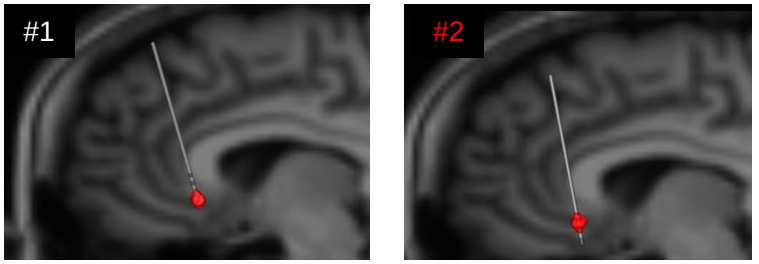


Anatomical Assessment: Lead too shallow
Clinical Decision: Surgical Revision.

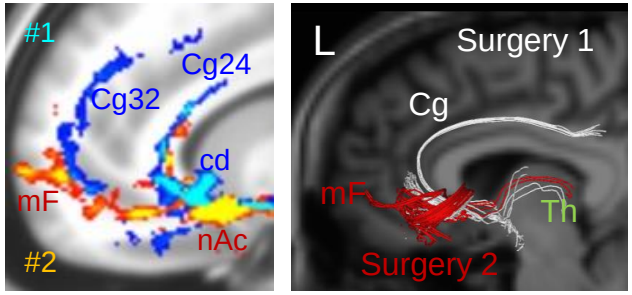


Initial 6 mo. slow, unsustained response
6 mo. post 2nd surgery: remission, 8 mo 1st job

What was changed?



Finite Element Modeling + Voltage Fields
Using anatomy + DTI (TAM)



Voltage Fields Full Modeling

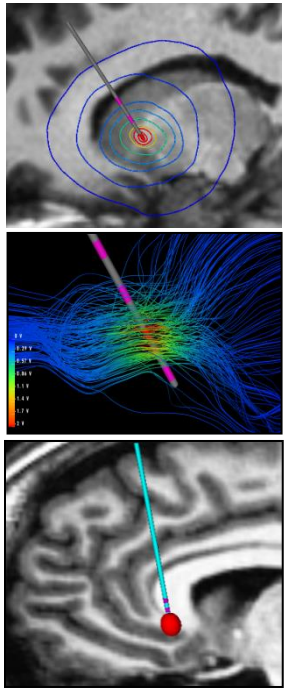
SCC is a hub for 3 sets of tracts
Hypothesis: Combination of all three needed to achieve full clinical response

TAM method: Lujan et al. Brain Stimulation 2013

Defining the Optimal Response 'Pathways'

tractography maps common to all 6 month responders

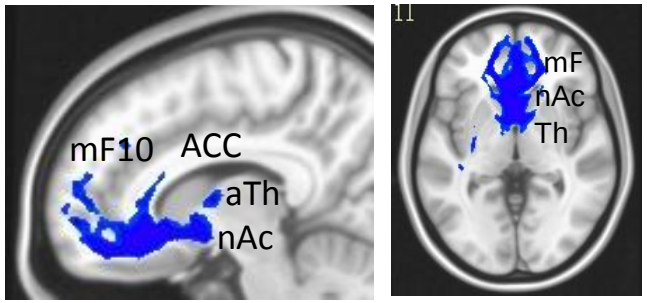
Voltage Field Modeling (TAM)



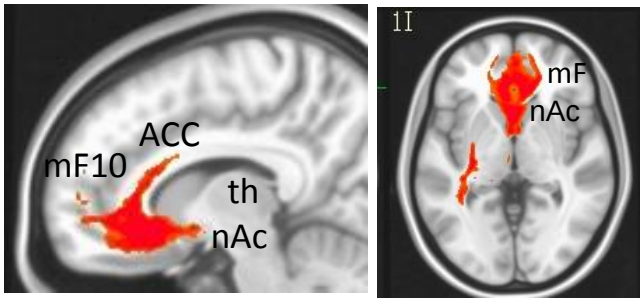
Butson & McIntyre
Brain Stim 2008

TAM-seed Probablistic Tractography

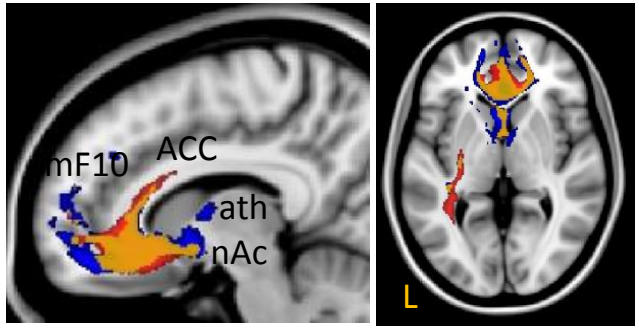
6m R
N=6



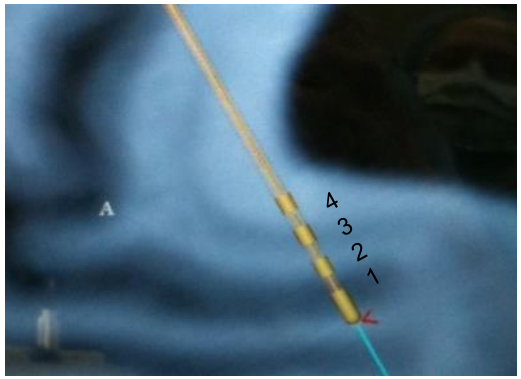
6m NR
N=9

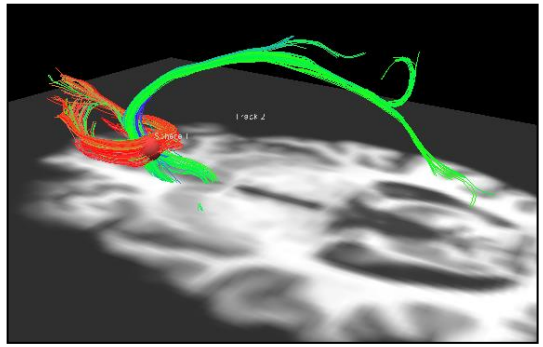


Overlap



NOW: Prospective Pre-surgical Planning of Optimal Contact

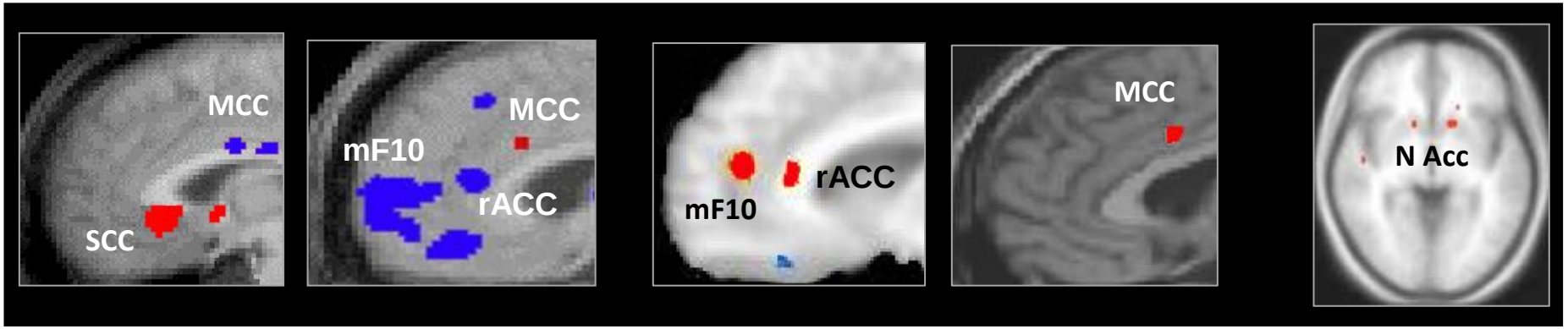




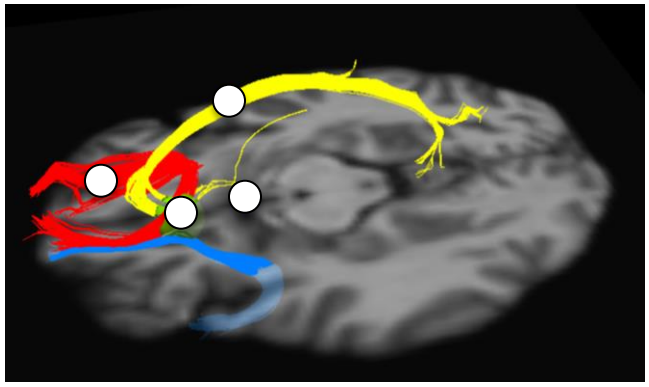
Unpublished
Riva Posse and Choi et al
Biol Psych in review

Behaviors Impacted by Network Dysfunction

Potential biomarkers of DBS effects over time?



Negative Feelings Tearful, sadness (emotion)	Vulnerability Rem MDD w/ emotional Stress	Emotional Self-relevance (insight, bias)	body awareness HR, BP, GSR (int eroception)	Amphetamine Induced euphoria (reward)



Goals

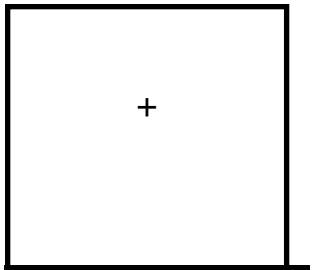
1. ID biomarkers of 1° pathways
2. Develop/Monitor real-time Δ w/DBS
3. Target for time course mech'n studies

Example: What is Basal State of SCC neurons?

microelectrode unit recording during implantation

Passive viewing scenes

2 seconds

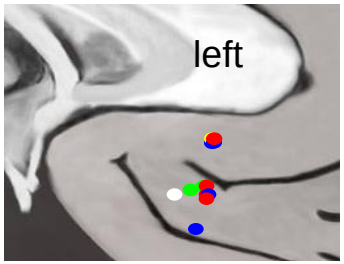


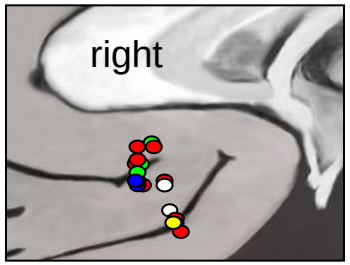
happy

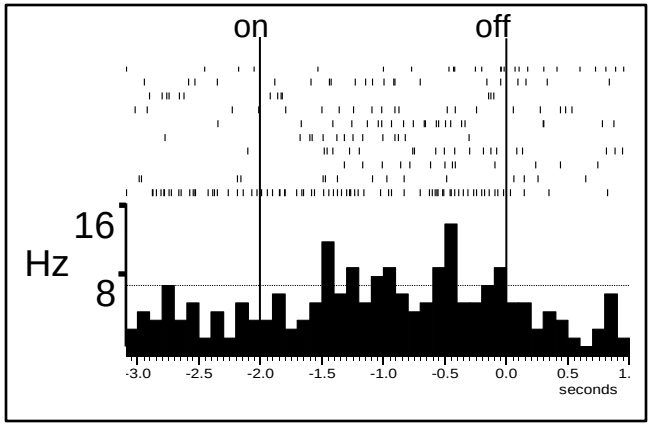
sad

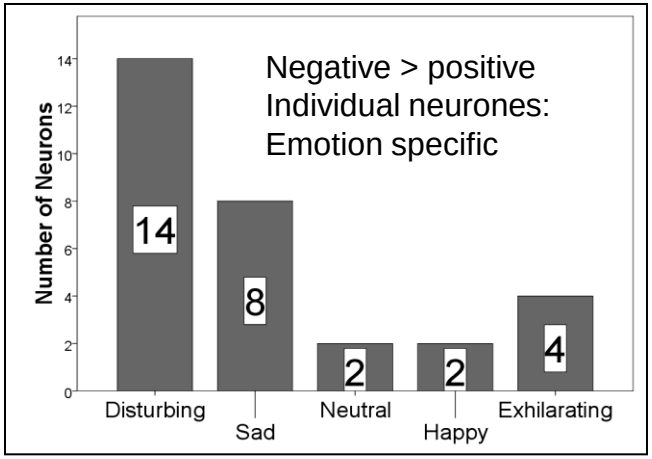
exhilarating

disturbing









Next Steps
How does DBS change this?

Toronto data
Laxton et al.
Biol Psych 2013

Consider Acute Effects of Stimulation

Hypothesis: acute mood change is 1° antidepressant effect

Lighter, less resistance

I feel more engaged

Less tension, I can move

I feel more optimistic

'I have just suddenly shifted from a state of all consuming internal focus to realizing that there are a number of things around to do…'

Blinded Identification of BEST behaviors

I am on rock.
No longer drowning

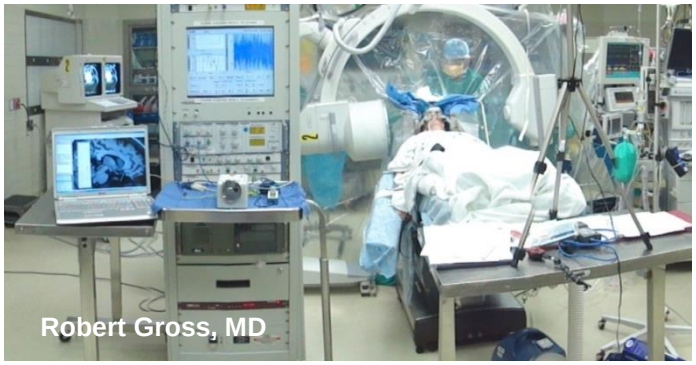
At issue:
Patient Self-reports are idiosyncratic.

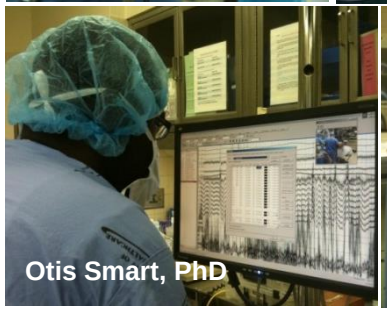
However, are also highly reproducible.

Requires individualized Testing/sensing

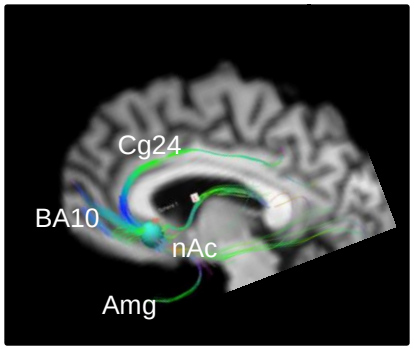
Testing Causal relationships in Real Time

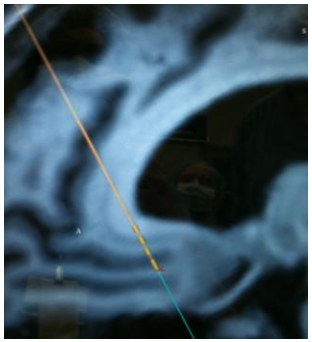
Location specific Behavior and Physiology effects in Surgery





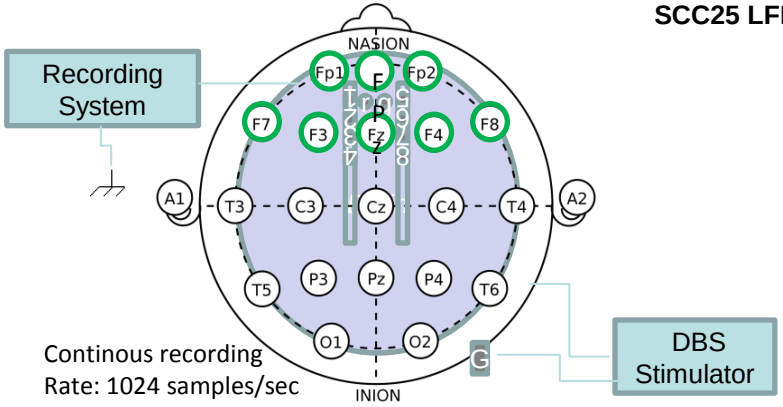
New cohort: n=10; randomized, blinded
8 active, 4 sham, repeat best, fixed setting
Spont self report, video
SCC LFP/Fr EEG, SCR, HRV, facial EMG





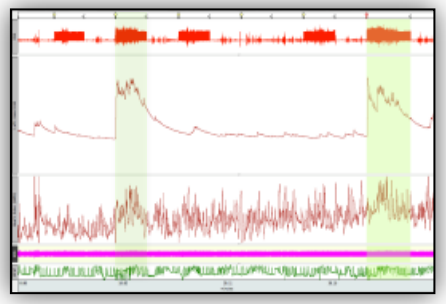
Contact in DTI-defined 'target' Δ

SCC25 LFP

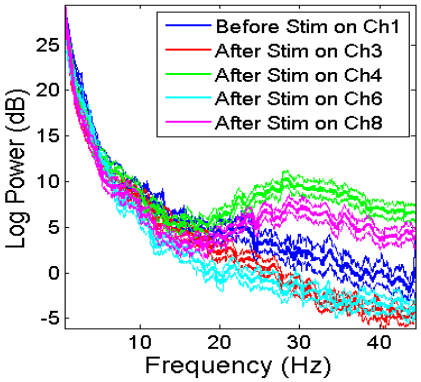


LFP
EEG
eCOG

Continous recording
Rate: 1024 samples/sec
Concurrent video



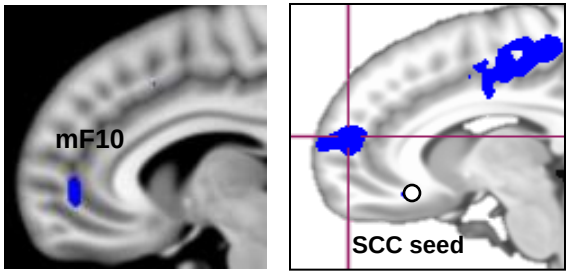
GSR, HR



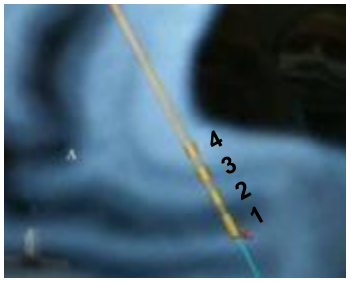
Goal: Multi-Modal Biometrics

Guide DBS patient selection and parameter optimization

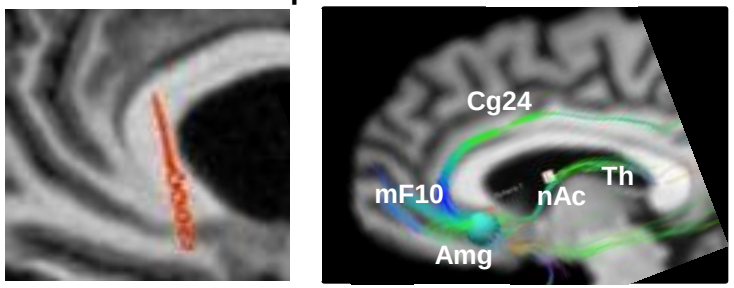
Confirm TRD Subtype
CBF PET resting fMRI



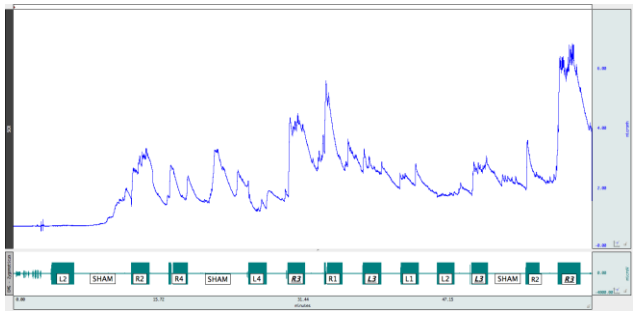
Micro-electrode
Lead localization



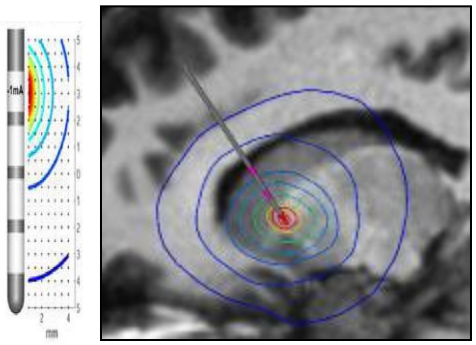
DTI tractography
Define optimal contact



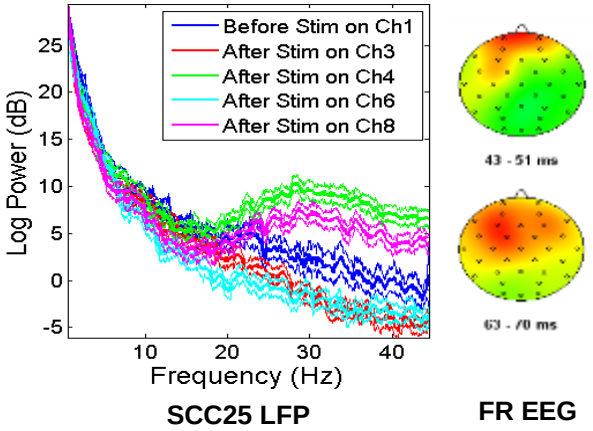
Psychophysics Measures
GSR, HRV, EMG
Target verification



Imaging/Physiology Based
Tissue Activated Models



Real-Time Readouts
Tune critical Δ
closed loop adjustments



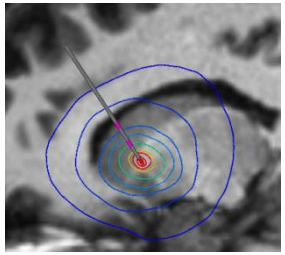
SCC25 LFP

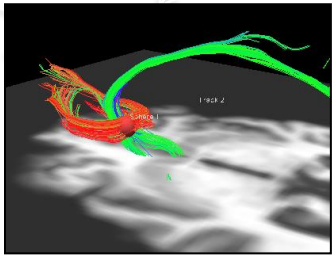
FR EEG

Towards Smarter Stimulation Systems

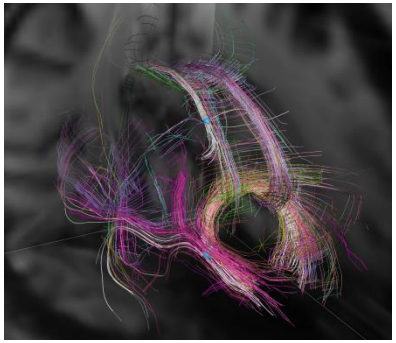
Next generation treatments, next generation neuroscience

Now Preop DTI mapping
Voltage Field Modeling, Preop Planning

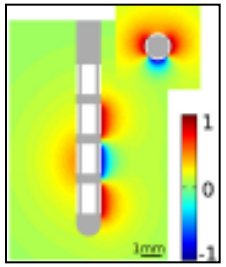




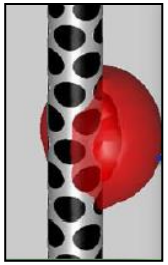
Next Generation
High Resolution
Tract tracing
in vivo
Connectome
Project



Future:
DBS Steering?

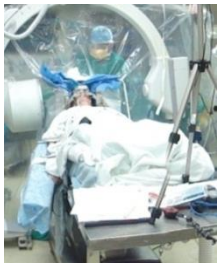


Medtronic



Sapien

Now: Intra-OP
LFP, EEG, eCOG
GSR, HRV, EMG



Next Generation
Real Time Readouts
Off Electrode

Basis for
closed-loop feedback
systems

Evolving Thoughts on Successful Recovery

Time course of effects: relatively stereotypic, with exceptions

- initial switch → Slower relearning/plasticity/new habits
- rapid (<1 mo), slow (>1.5 yrs) seen (likely due to targeting)
- no obvious clinical predictors

Burden of Wellness. Passive to active role in own recovery

- if intractably ill, expect nothing (stuck, no bandwidth)
- focus on 1º symptoms when sick (make pain go away)
- Then, need life-style change (reverse old habits/develop new ones)
- Therapy/Rehab (what type, when?)
- new priorities (need a job; where to start) Training/opportunity

Recovery Takes More Than a Stimulator

Early reset → plasticity + learning over time

That heavy sinking feelings was always there, and now it is gone.
Now, instead of being in a very deep canyon, I am up on a ledge.
I know I still have a long way to go, but I am no longer in the hole.
Now it comes down to me… Toronto #5 (6 mo)

DBS doesn't push positive, It enables positive

I didn't realize how much work I would need to do myself
Emory #29 (1 year)

DBS #29 Atlanta
6 mo post op

DBS #18 Toronto
2 years post op

Goal: Optimize surgery, Parameters and Rehabilitation strategies that consider this changing biology