

Targeted Modulation of Macrocircuits

Case Study: DBS in Treatment Resistant Depression

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Consultant	St. Jude Medical Neuromodulation, Inc

This presentation describes an experimental use of a device (FDA IDE G060028/S002)

Deep Brain Stimulation for ANY Indication

What do we need to know?

- the “illness” circuit
- putative response pathway(s)
- behavioral endpoint
- what changes are critical
- brain target to stimulate
- appropriate patients

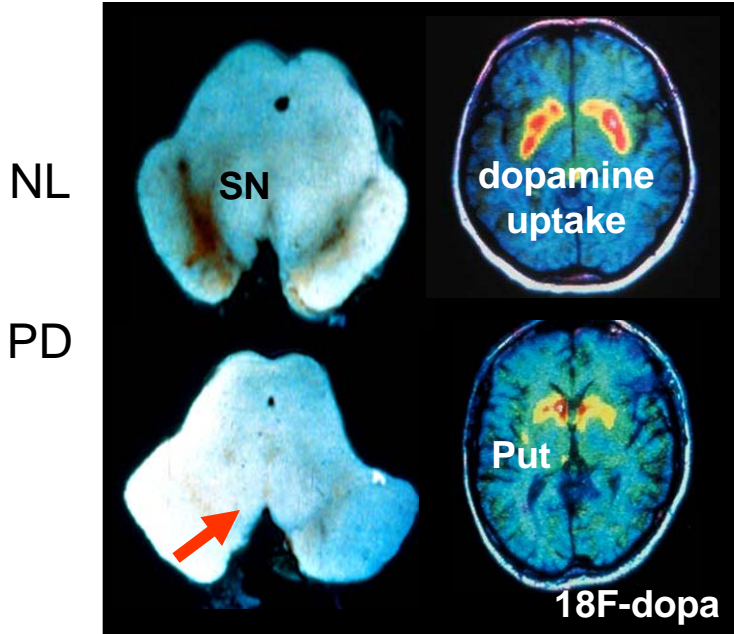
**Scientific
facilitators**



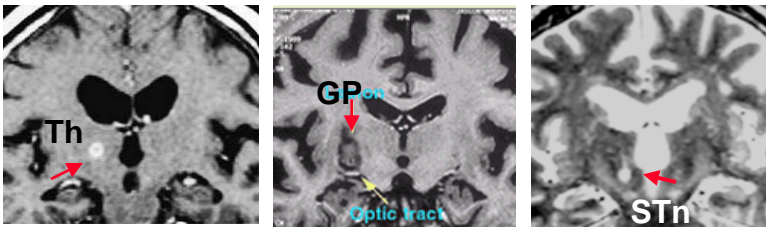
1. availability of structural/functional imaging
2. advances in stereotaxic neurosurgery
3. disease models

Parkinson's Disease as Model System

2 pathology → chemistry
L-dopa 1963

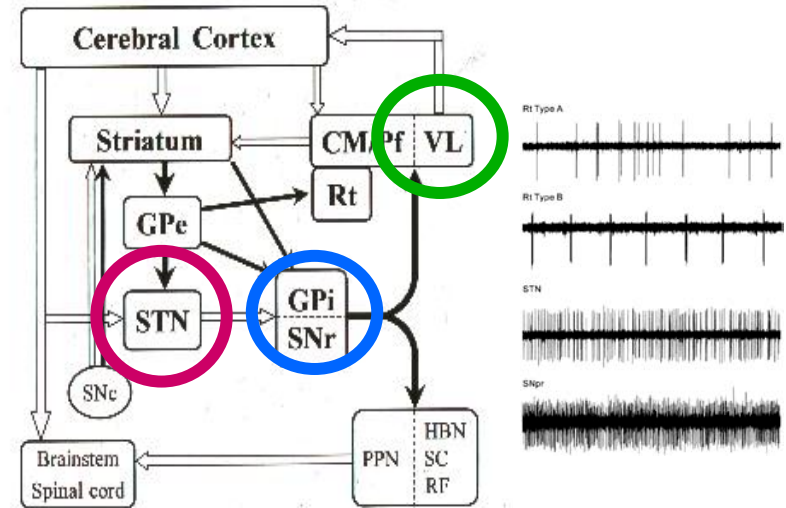


1 Lesions 1940-1967
interrupt putative circuits

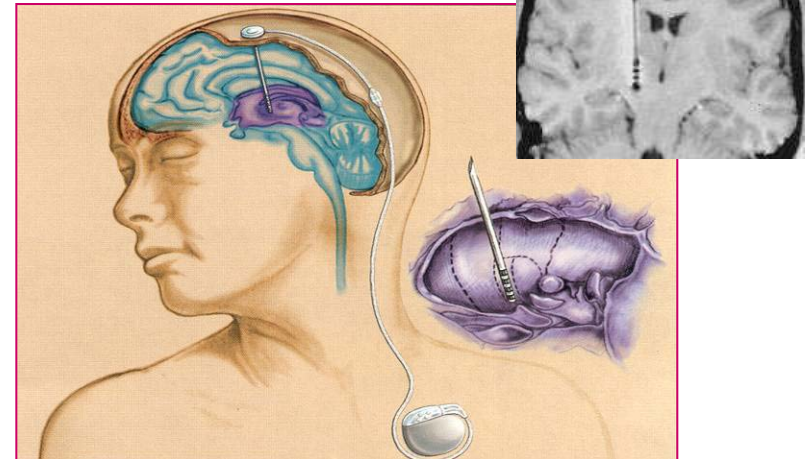


Bergman, Wichmann, DeLong. Science 3 249:1436, 1990

3
Circuits
Chemistry in
Anatomical/
physiological
context



4 Applied Engineering
Neuromodulation

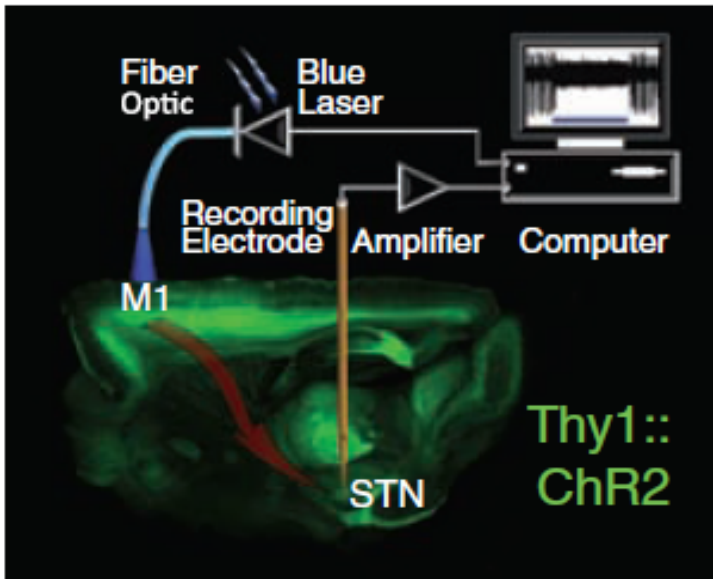


Benabid et al. Appl Neurophysiol. 1987;50(1-6):344-6 VIM.

Parkinson's Disease as Model System

5

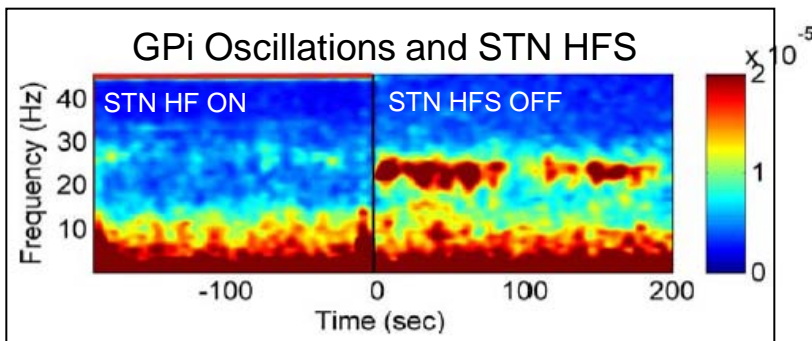
DBS mechanisms using optogenetics



Gradinaru et al Science 2009

4

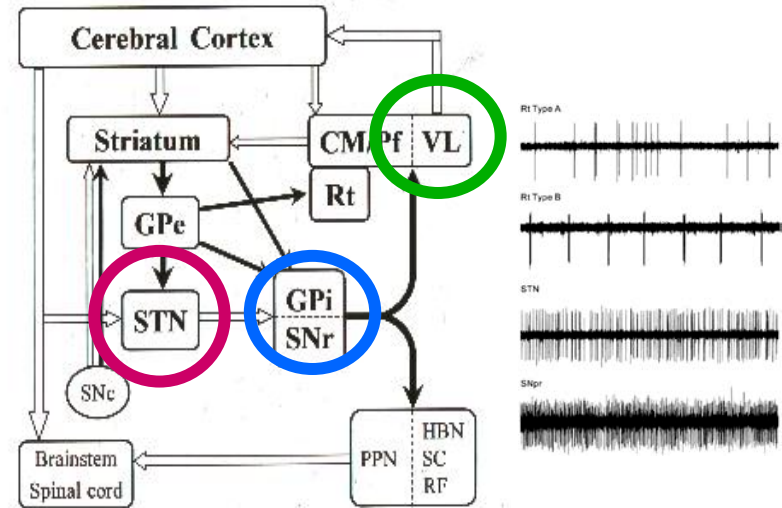
DBS effects on Oscillations



Kuhn et al JNS 2009

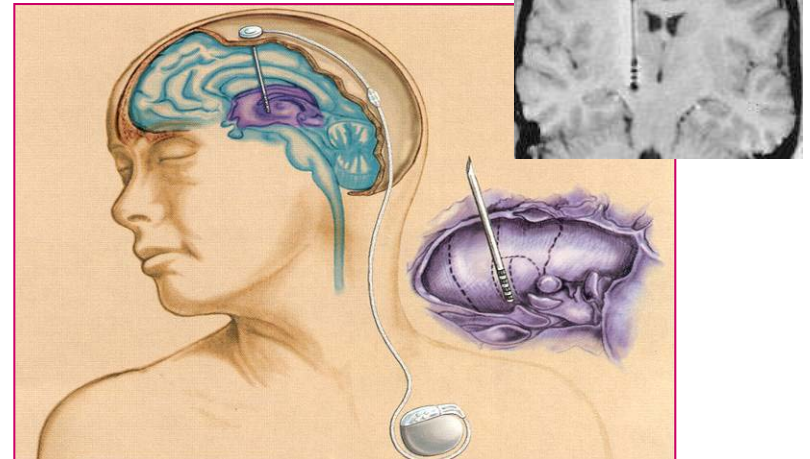
3

Circuitry in anatomical/physiological context



4

Applied Engineering Neuromodulation



Benabid et al. Appl Neurophysiol. 1987;50(1-6):344-6 VIM.

Depression: 1st person perspective

“The madness of depression is the antithesis of violence.
It is a storm indeed, but a storm of murk.
Soon evident are the slowed-down responses, near paralysis,
psychic energy throttled back close to zero.
...nearly immobilized and in a trance of supreme discomfort...
a condition of helpless stupor in which cognition is replaced by
that positive and active anguish.”

William Styron
Darkness Visible, 1991

“It is a positive and active anguish,
a sort of psychical neuralgia
wholly unknown to normal life.”

William James 1902
The Variety of Religious Experience

Major Depressive Episode: DSM-IV Criteria

≥ 5 symptoms including
depressed mood and/or decreased interest (anhedonia)

- Sleep disturbance
 - Significant weight change
 - Psychomotor agitation/retardation
 - Pervasive loss of energy/fatigue
 - Difficulty concentrating
 - Feelings of worthlessness/excessive or inappropriate guilt
 - Recurrent thoughts of death/suicide
- ✓ Symptoms persist most of the day every day for ≥ 2 weeks

Chronicity remains critical to definition

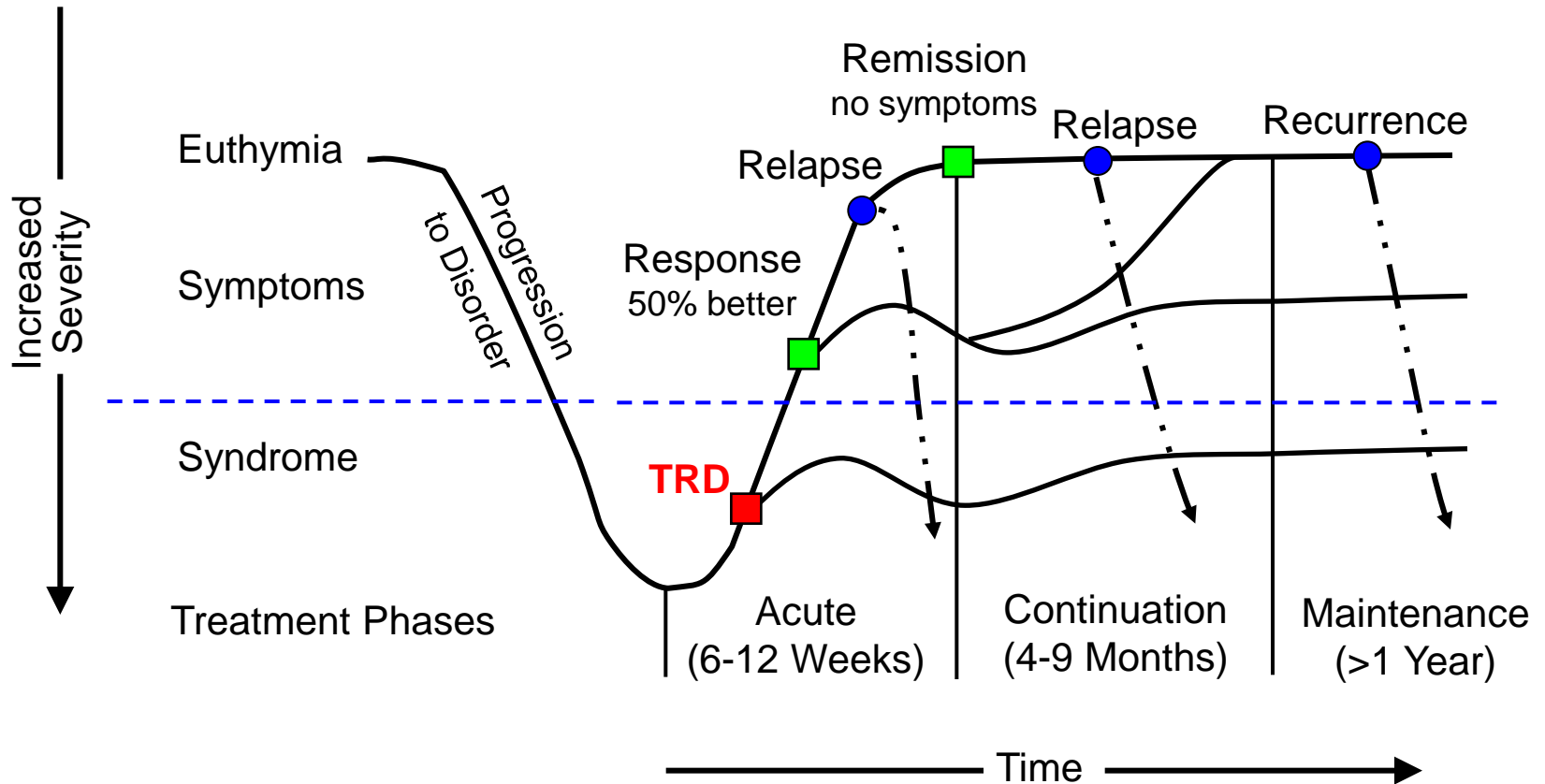
Emotion still 1^o, but more ambiguous (↑neg vs ↓pos)

Many secondary symptoms (require chronic mood Δ?)

How different (or not) is this from sustained chronic stress?

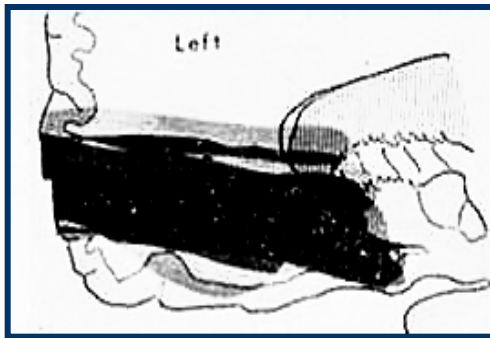
Course of Depressive Episode/Disorder

dev't of new modulation strategies in this context

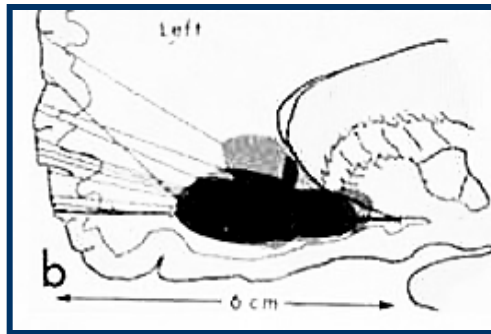


GOAL: Get out of episode; Keep people from relapsing

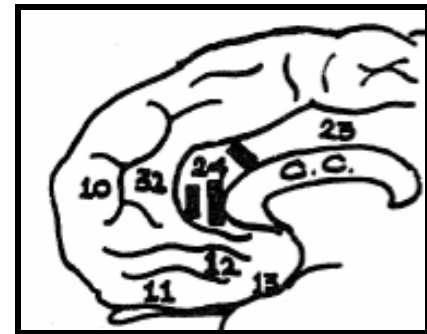
Historic Perspective: surgery for intractable melancholia



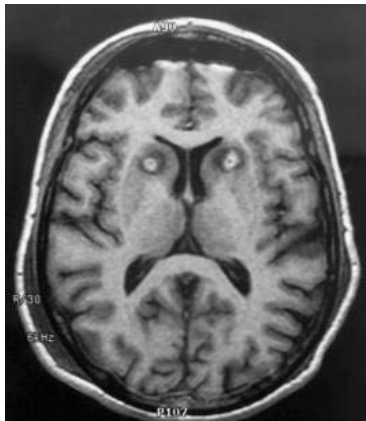
Orbital undercutting
1937-1948



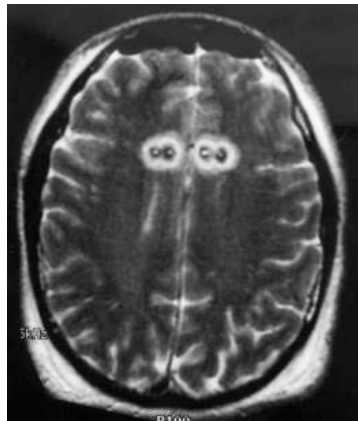
Yttrium Subcaudate
tractotomy 1964



Cingulo-tractotomy
1965-1972



Anterior
Capsulotomy



Dorsal
Cingulotomy



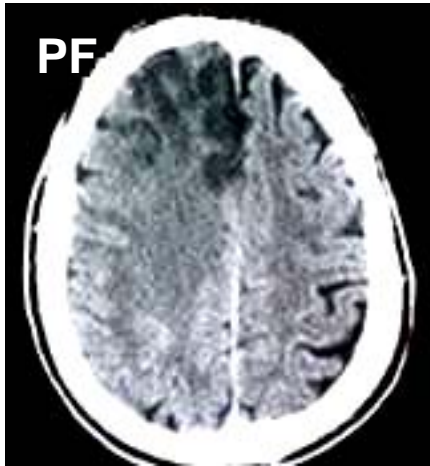
Subcaudate
tractotomy

1. Resp Rate: 30/30/30 rule
2. SAEs: seizures, Fr cog deficits, personality Δ
3. Crude structure-function correlations.
4. Critical white matter disconnection unknown.

Defining Depression Circuits 1

Structural studies: Lesion-deficit correlations

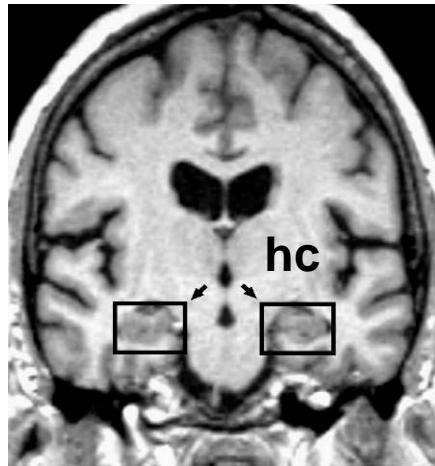
Post Stroke



Robinson 1983

frontal pole

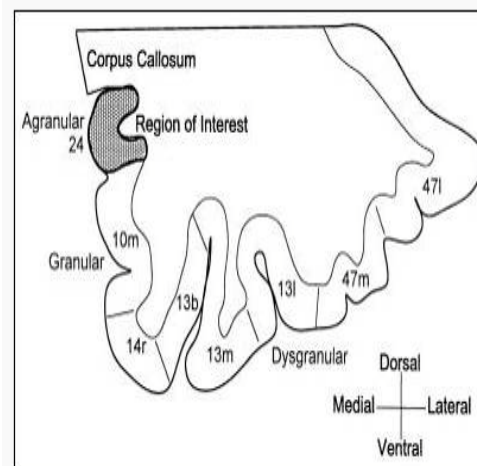
↓ MRI volume



Sheline, 1999

hippocampus

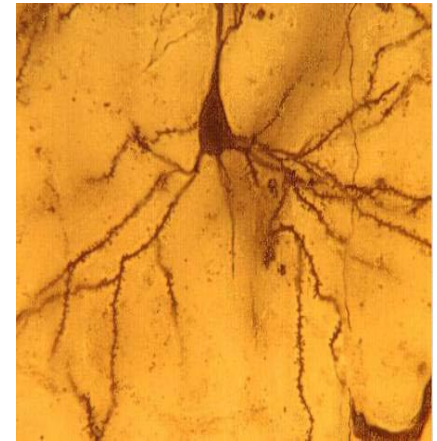
↓ MRI vol, Glia



Drevets 97; Ongur 98

VM-Frontal/Cingulate

Δ Spines/Dendrites



McEwen, Chattarji, Radley

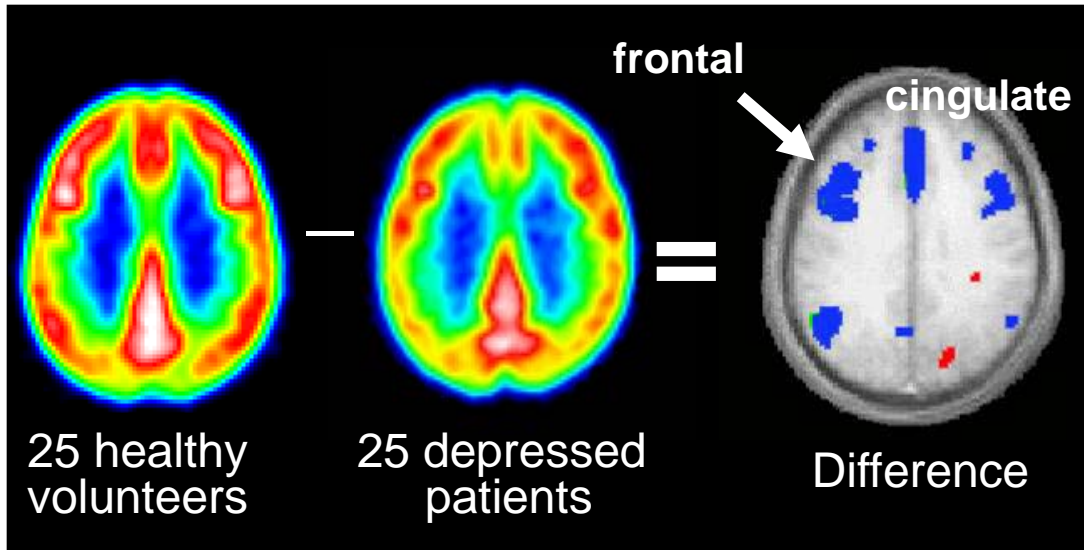
↓hc ↓IL/PL ↑amg

Some structural changes may be reversible
Impact on functionality?

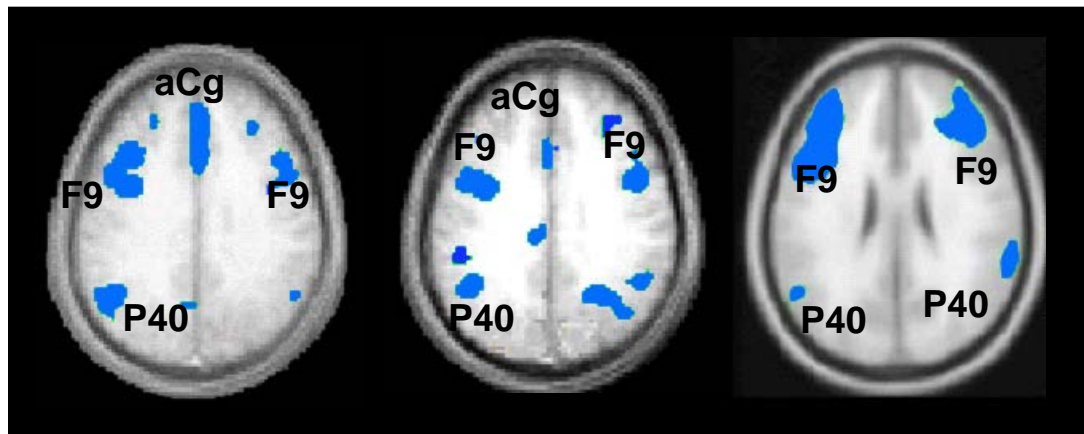
Defining Depression Circuits 2

functional lesion-deficit correlation studies

Glucose
Metabolism
FDG PET



↓Frontal
most common.
also Cingulate,
Amygdala, and
others.



Ann Neurol 1990
Neurology 1992
J NeuroPsych 1994
J Nuc Med 1994
NeuroReport 1997
Biol Psych 2003

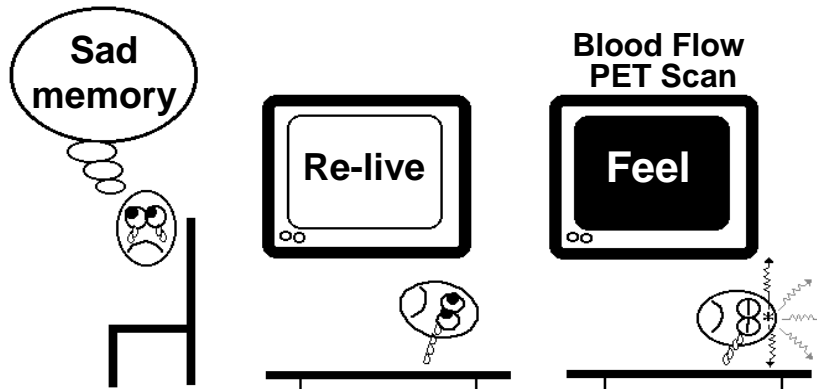
Unipolar

Parkinson's

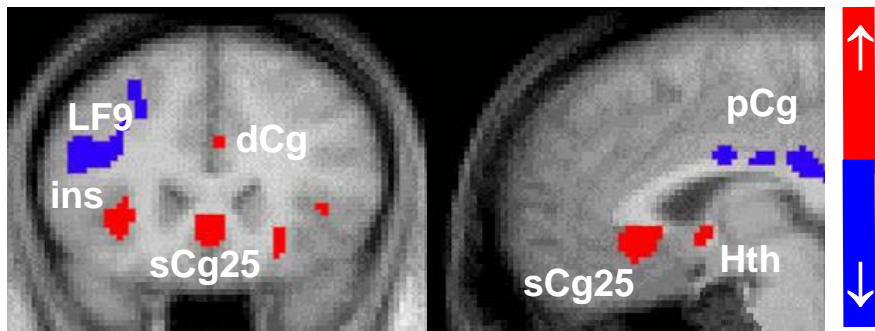
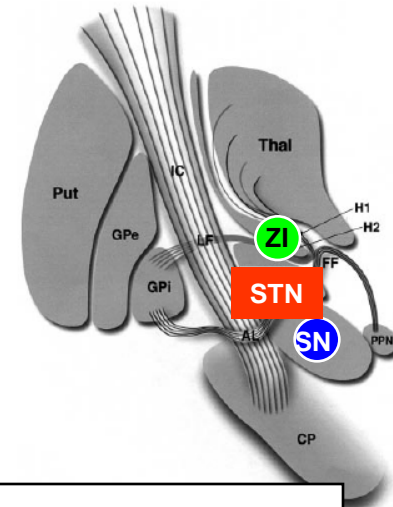
Bipolar

Defining Depression Circuits 3

focus on mood explicitly



STN DBS Target



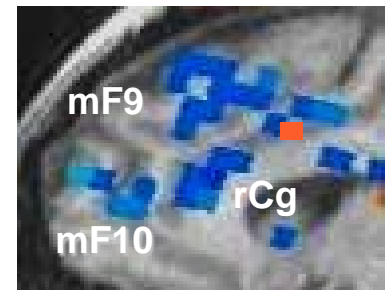
Healthy women, no history of depression

↑ Limbic ↓ Cortex

“I wanted to cry, but couldn’t–
It was such a deep down hurt.”

“Similar in ways to being depressed,
but a hundred times worse”

Subcortical
stim →
remote
Frontal ↓



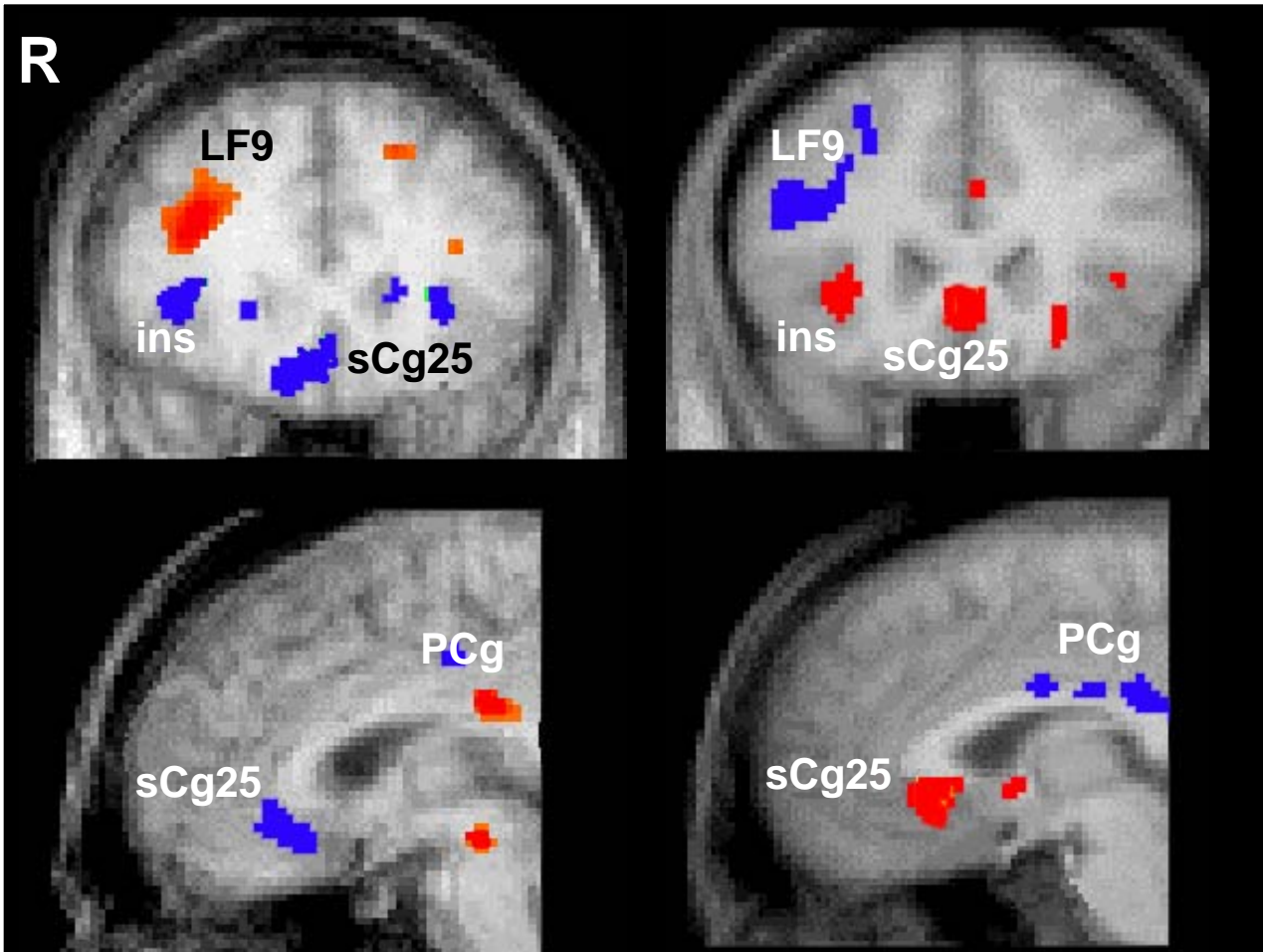
Stefurak et al. Mov Dis 2003

Defining Depression Circuits 4

Treatment studies

6 wk Recovery w/SSRI
FDG PET

Transient Sadness
CBF PET



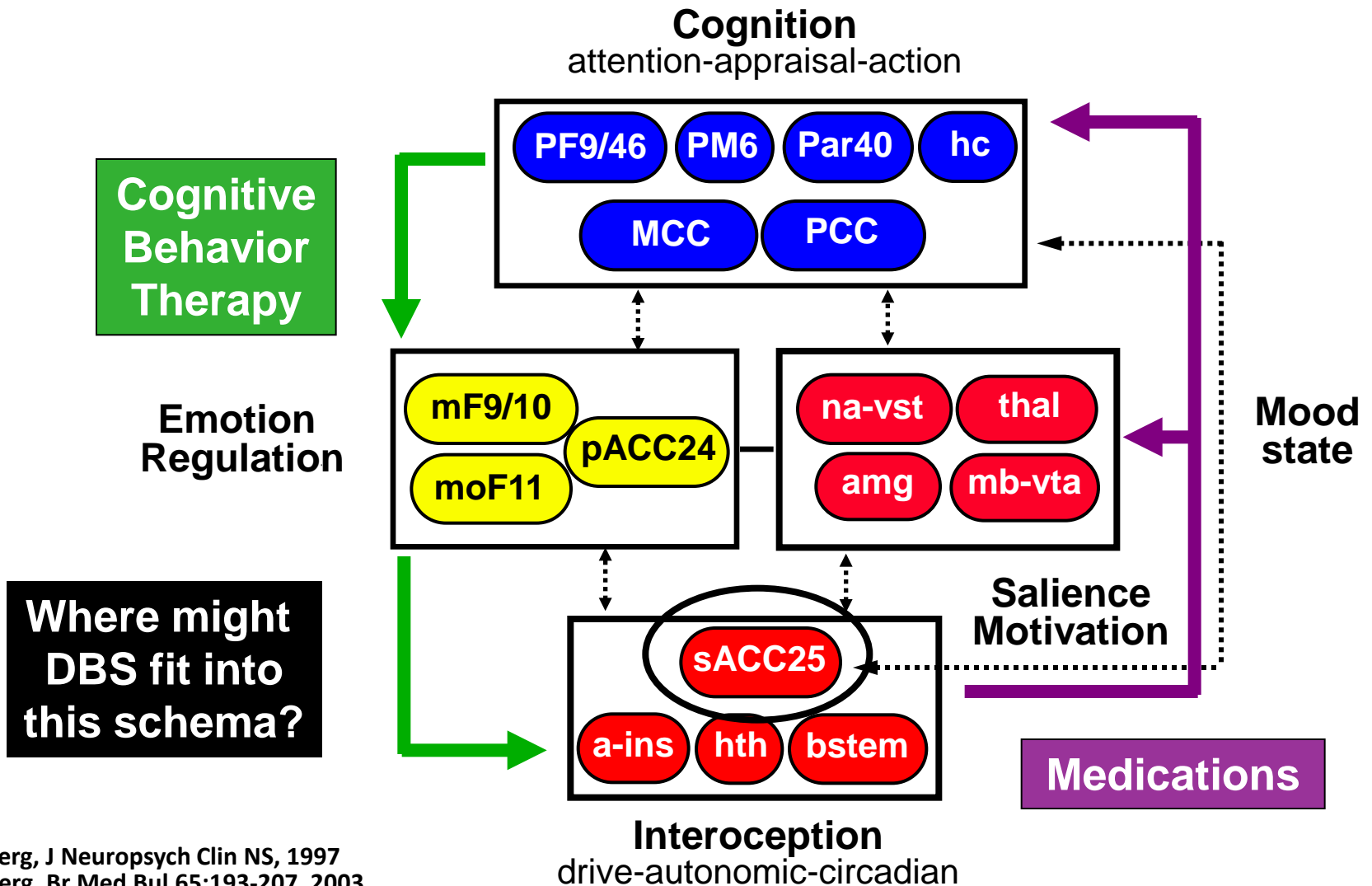
Limbic + Cortex
 Reciprocal
 sCg25-Fr
 Interactions

Depressed Patients

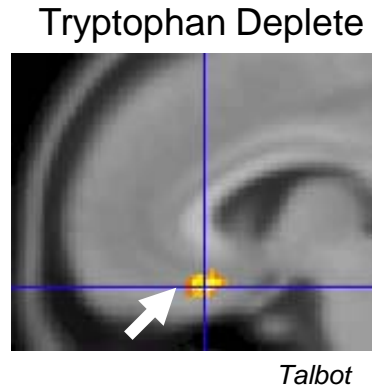
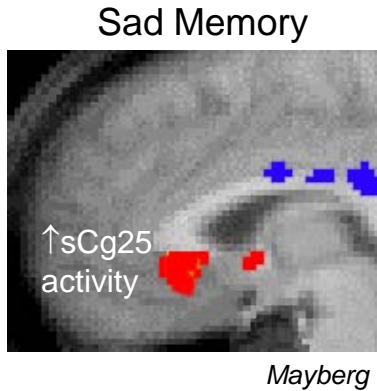
Healthy Volunteers

Putative “Depression” Network ~ 2001

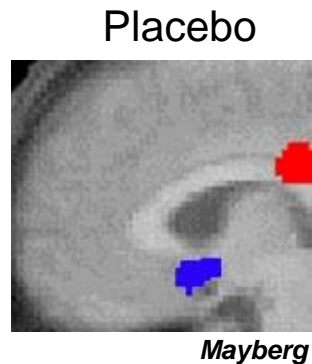
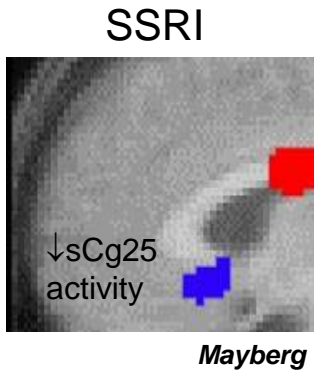
defined using functional imaging



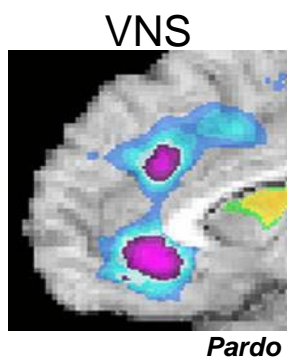
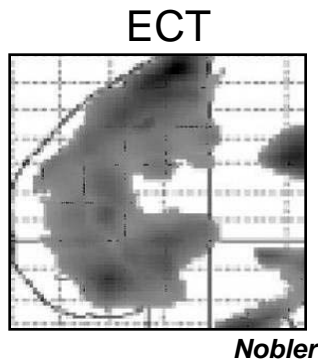
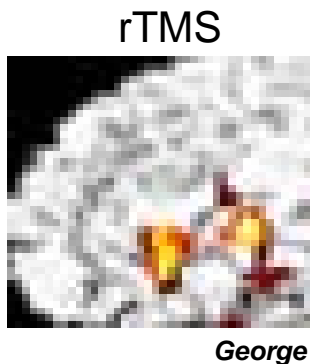
Critical Role of Subcallosal Cingulate (sCg25) converging evidence



Increased sCg25
with induced
depressed mood



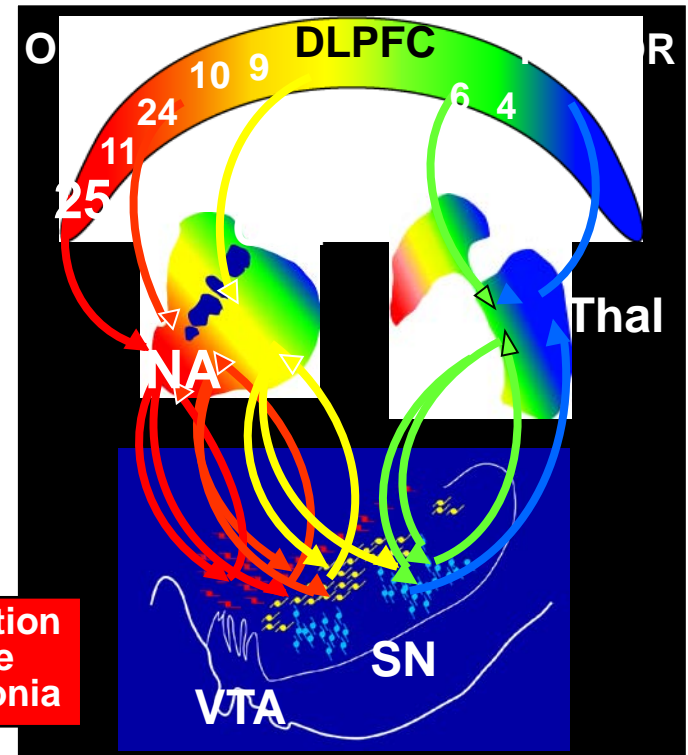
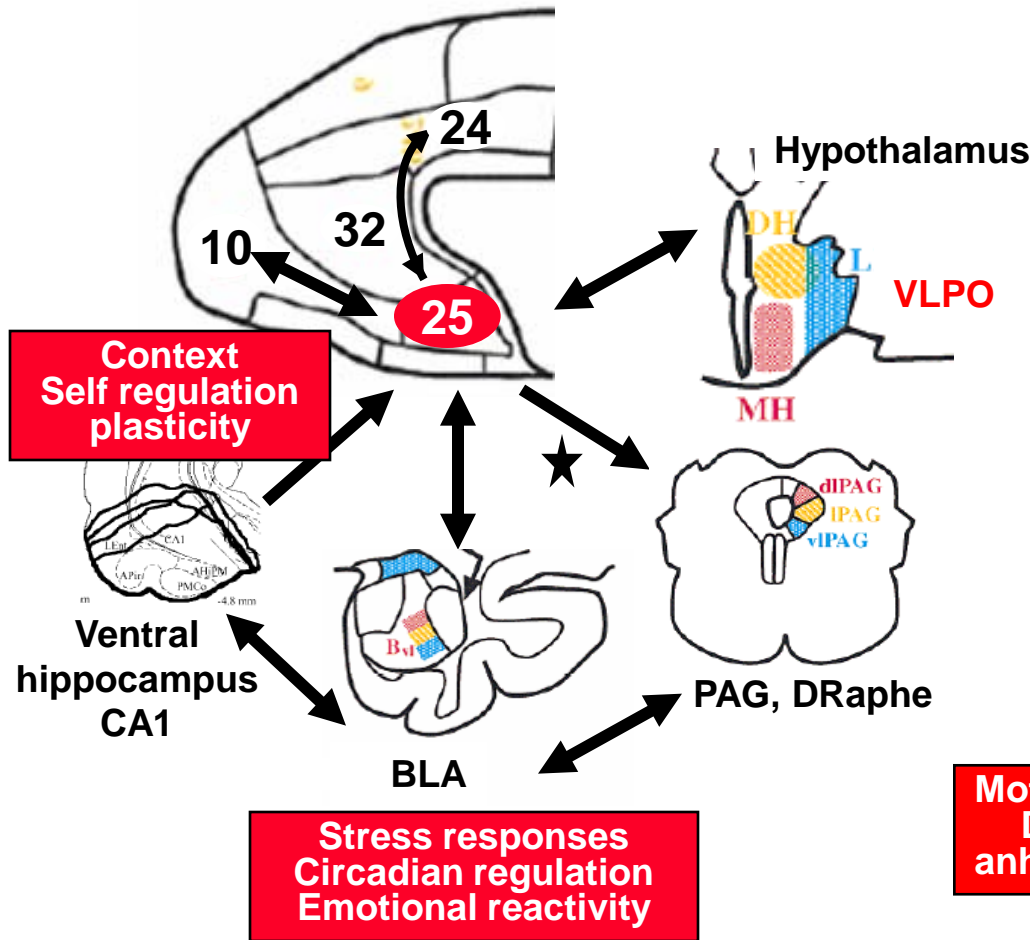
Decreased sCg25
with diverse successful
treatments



Hypothesis:
TRD=dysregulated sCg25
Target the problem at its origin
Impacting it and its connections

Likely Impact of sCg25 Modulation

based on known structural connections

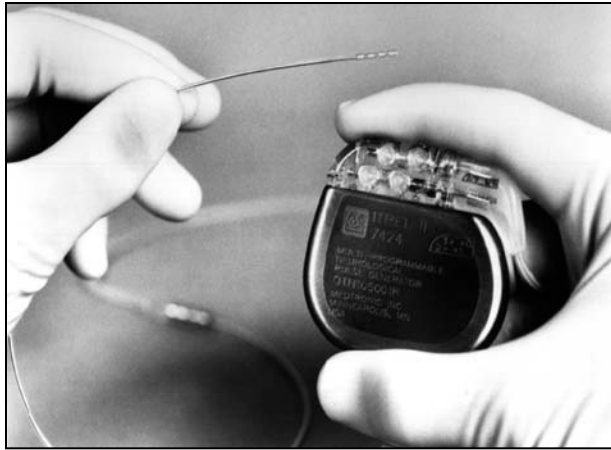


Ongur and Price JCN 1998
 Ishikawa & Nakamura JNS 2003
 Saper, Scammell, Lu Nature 2005
 Pezawas, et al. Nat Neuroscience 2005

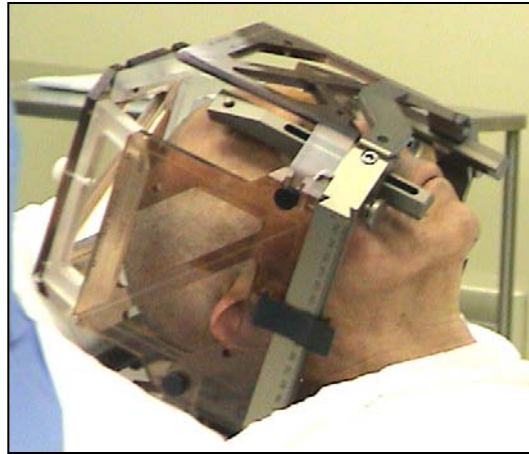
Haber, J. Neuroscience 2000

Deep Brain Stimulation (DBS)

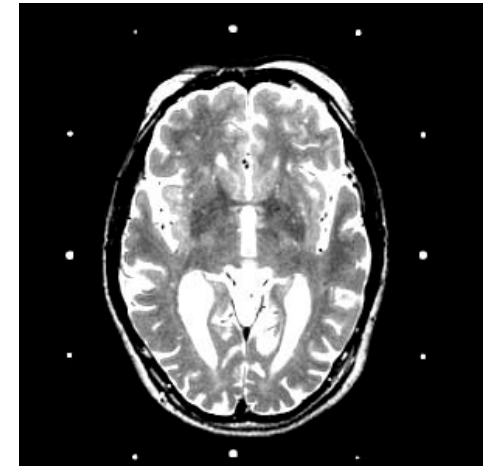
general procedure



Hardware: electrode + IPG

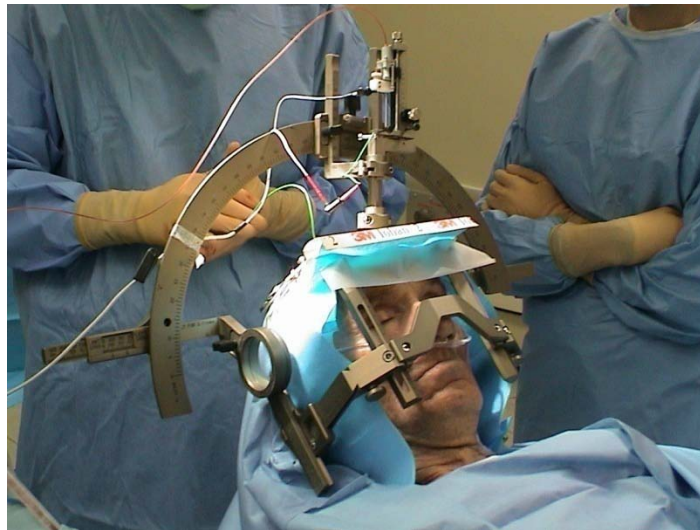


Stereotaxic Frame



MRI: target localization

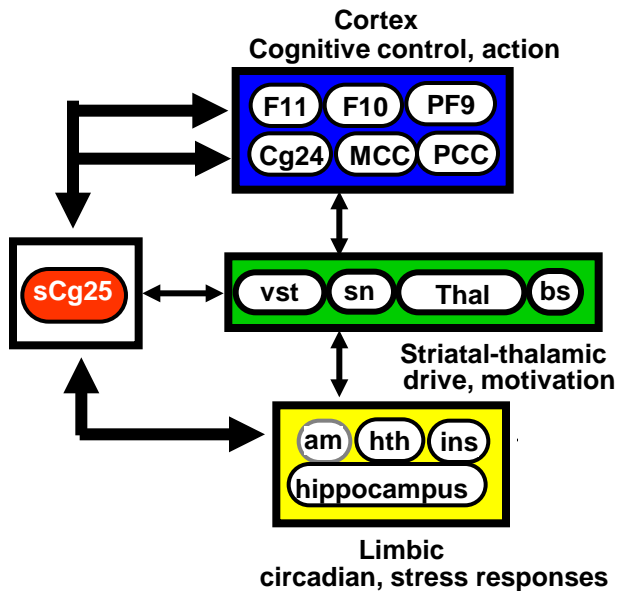
Implantation



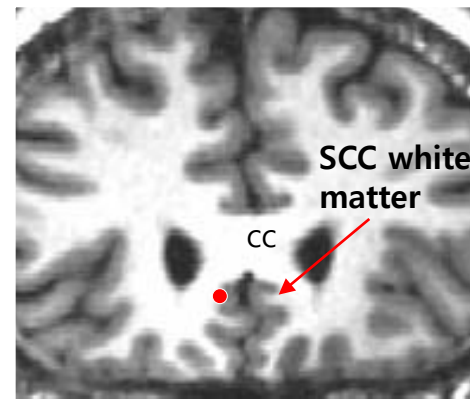
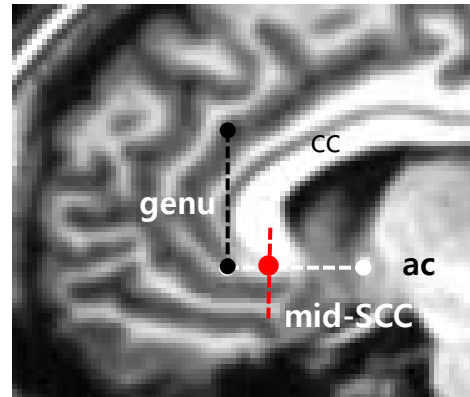
Patient Awake
MRI based target coordinates
Microelectrode verification
Behavioral testing (units, LFP)
Macrostim (side effects, LFP)

Direct 'Circuit' Modulation using DBS

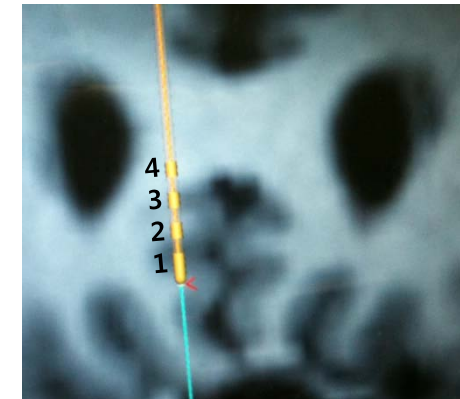
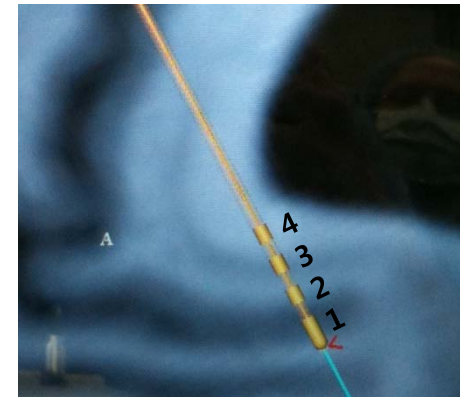
block aberrant sCg25 activity with 2° effect on connections



Anatomical Targeting Plan



Micro-electrode localization



Focus: Treatment Resistant Depression
Failed response to available therapies including ECT

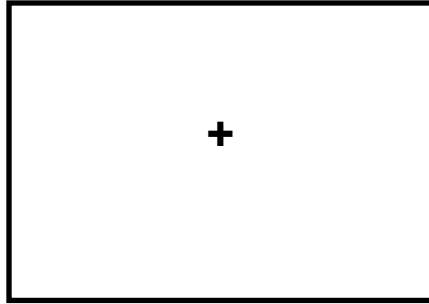
Interrogating SCC Neurons

emotional scenes

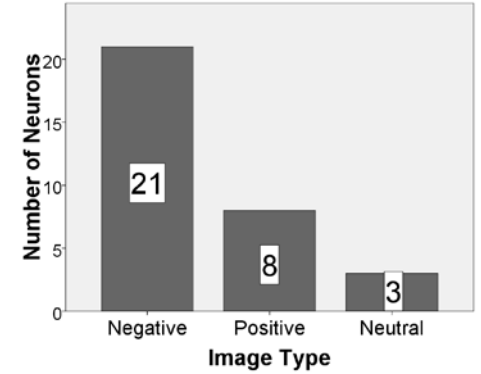
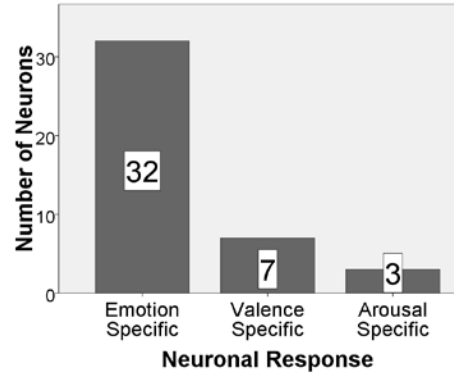
Passive viewing



Neutral 2 seconds



3-5 seconds



arousal



happy



sad



exhilarating



disturbing



valence

16
Hz
8



A single neuron specifically responsive to image type 1 (disturbing) with corresponding raster plot and peri-stimulus histogram.

Intra-operative acute stimulation effects

Spontaneous Self-Reports

Sense of intense calm, quiet, relief

Dissipation of visceral symptoms

resolution of the 'pain,' dread, void, mental heaviness

Interoceptive Release
(↓ distress)

Followed by

↑ interest, energy, awareness

↑ attention, motor speed, spont speech

Δ visual perception; colors, clarity, brightness, details

Δ PANAS: ↓ negative, ↑ positive scores

Exteroceptive awareness
(↑ engagement)

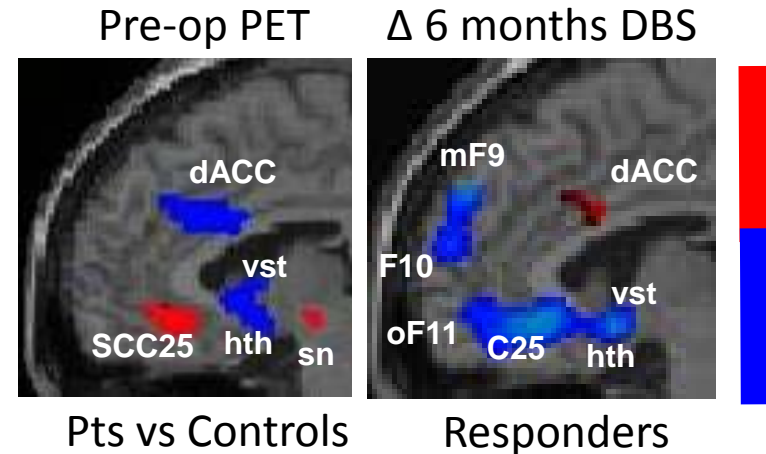
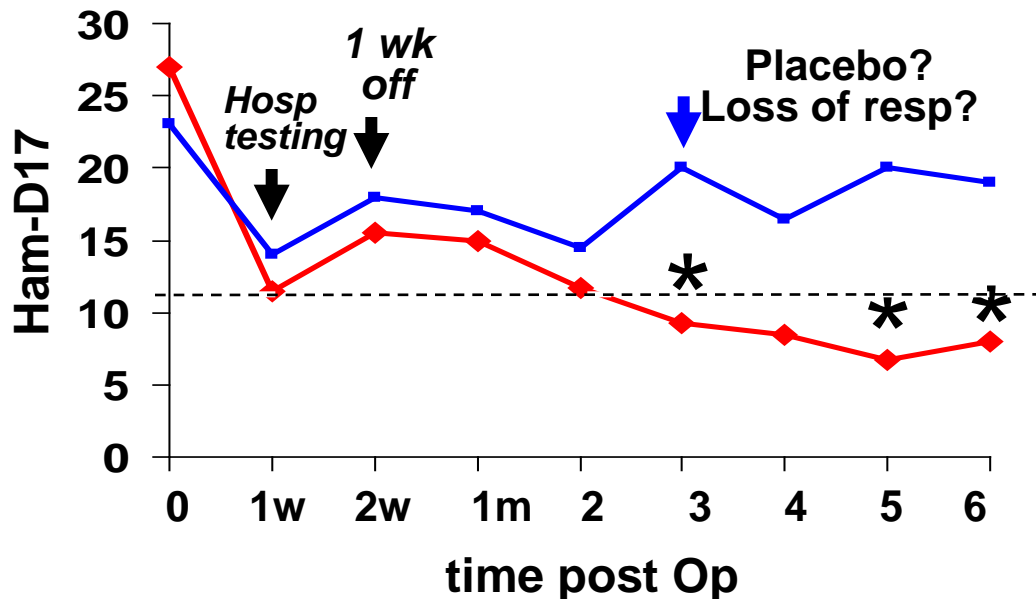
No Acute Adverse Effects (i.e., mania, anxiety, autonomic changes)

1. Acute behavioral effects: contact and voltage specific.
2. When present, used to chose contact for chronic stimulation.
3. Opportunity: window to core symptoms, DBS mechanisms?

Deep Brain Stimulation for Treatment-Resistant Depression

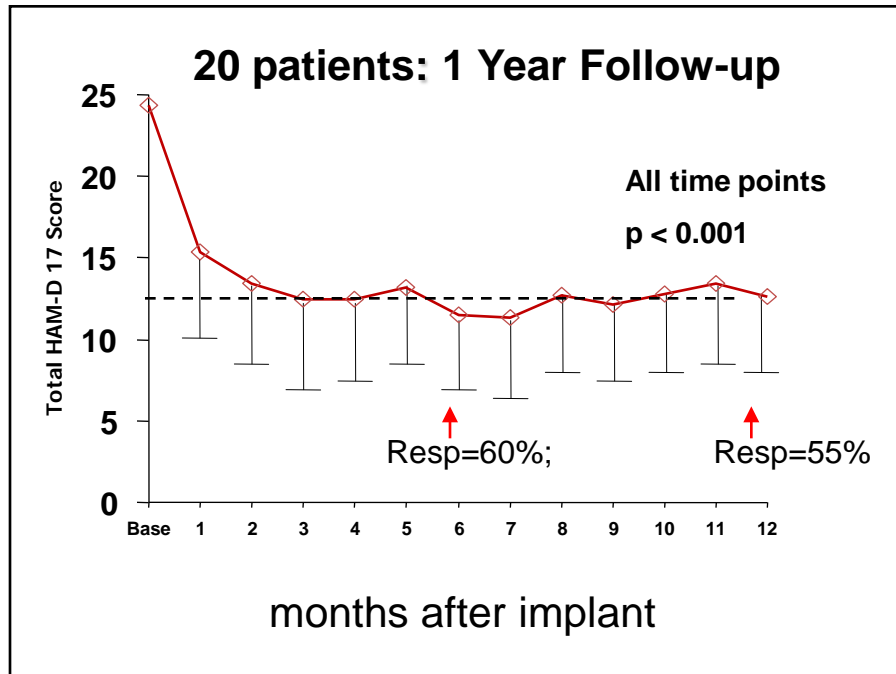
Helen S. Mayberg,^{1,2,*} Andres M. Lozano,^{3,*}
Valerie Voon,⁴ Heather E. McNeely,⁵
David Seminowicz,⁶ Clement Hamant,³
Jason M. Schwab,³ and Sidney H. Kennedy⁴

Pilot: 6 severe TRD, GAF<50
Illness duration avg 5.6 yrs
Failed mult meds, CBT, ECT
6 mo open DBS
4/6 Resp; 3/6 remission

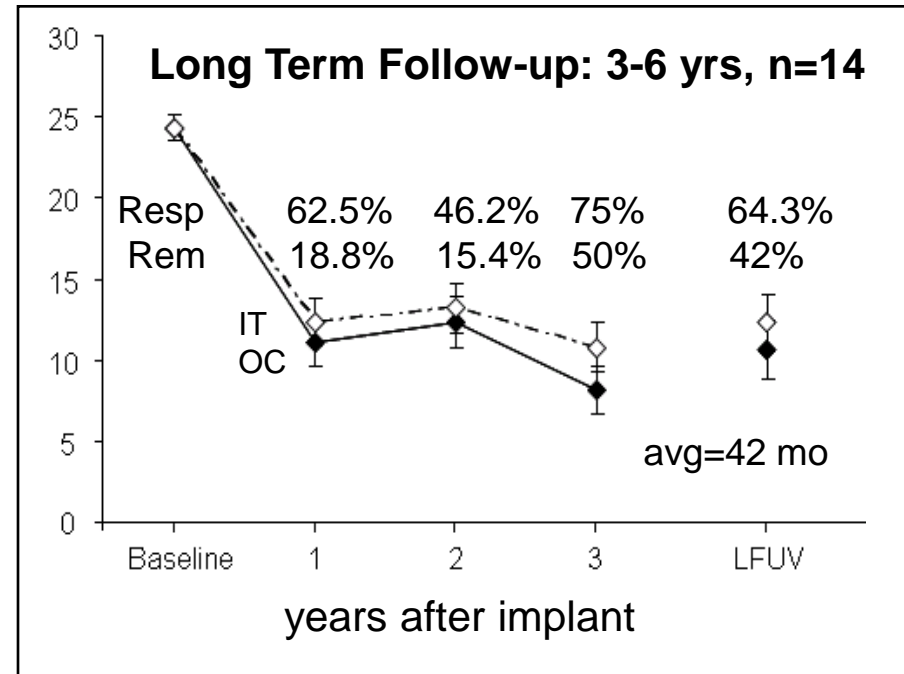


Expansion, Long-term Follow up

Continuous Cg25 DBS, open label Trial n=20



Lozano A, et al. Biol Psych 64:461-67, 2008



Kennedy S, et al. Am J Psych in Adv Feb 1, 2011

Continuous stimulation required to maintain effect.
 Loss of effect over ~2 weeks if turned off, battery drained.
 No acute or late developing side effects; no dose changes over time
 Job, meaningful activities: 10% baseline, 65% 1yr, 90% of responders

Other DBS Targets for depression

Rationale

Target

Published Findings

Ventral Capsule/ Ventral striatum

Malone et al.
Biol Psych 2009



Capsulotomy



gamma knife

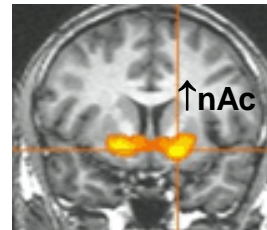


goal: DBS=lesion

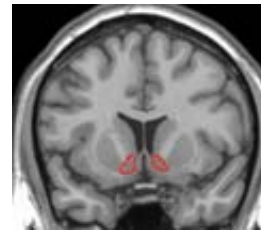
15 MDD
3 sites; 6 mo open
40% Resp, sustained
Transient fear/panic,
nausea/sweat, hypomania

Nucleus Accumbens

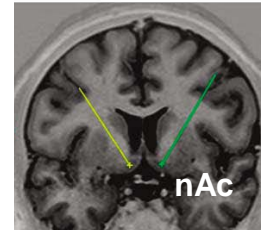
Bewernick et al.
Biol Psych 2010



Pos mood + motivation



goal: local excitation



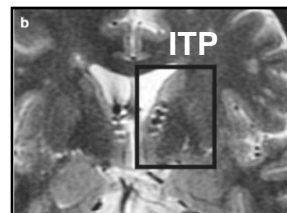
10 MDD
1 site; 1 year open stim
50% Responders
Transient sweating
anxiety/tension, 2S/A

Inf Thal peduncle

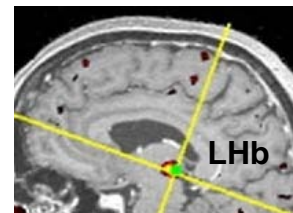
Jiminez et al NSurg 2005

Lateral Habenula

Satorius et al Biol Psych 2010



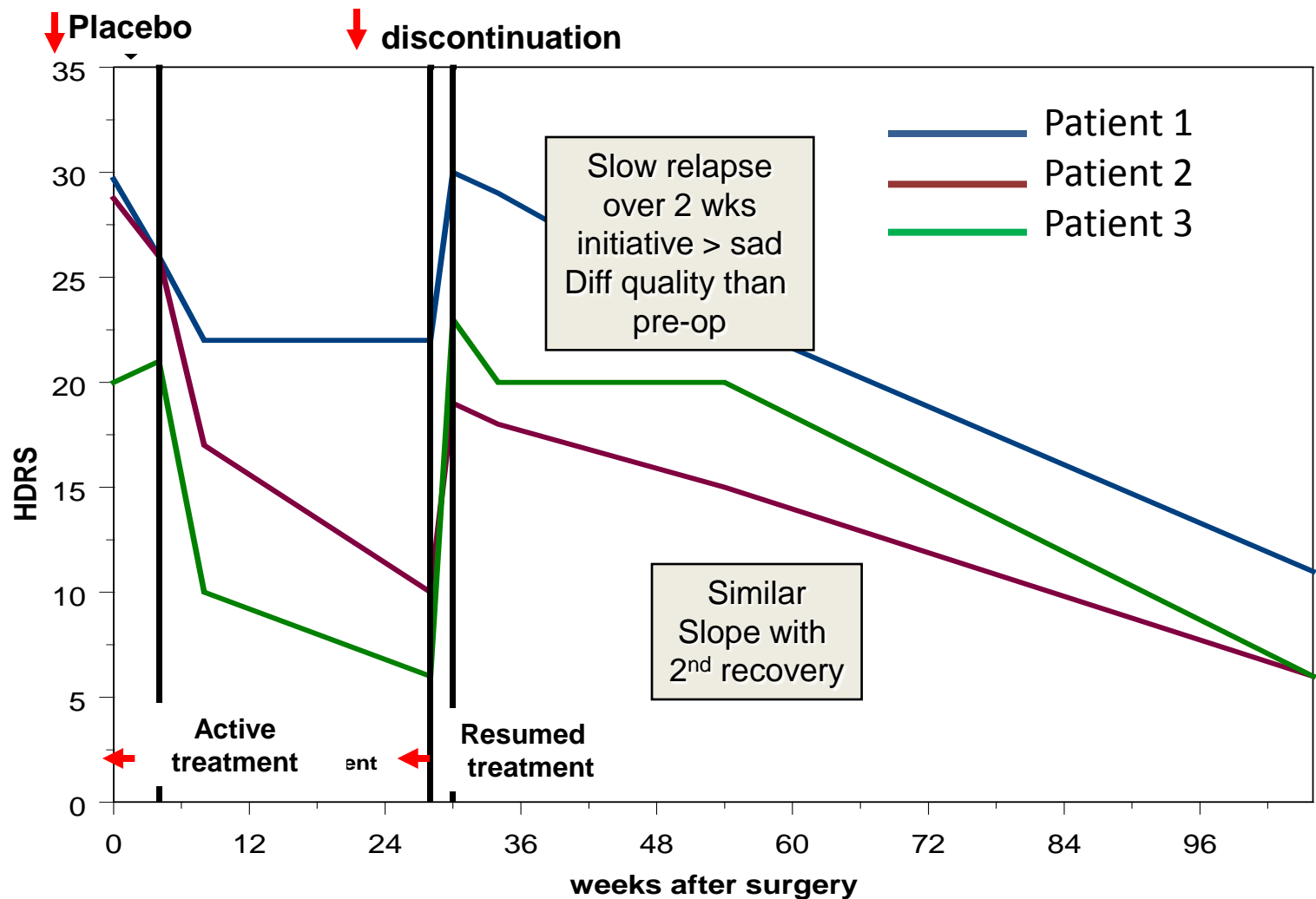
Target Thal-orbFr



Neg reward signal

Single case reports
Fluctuating course,
Both achieved resp

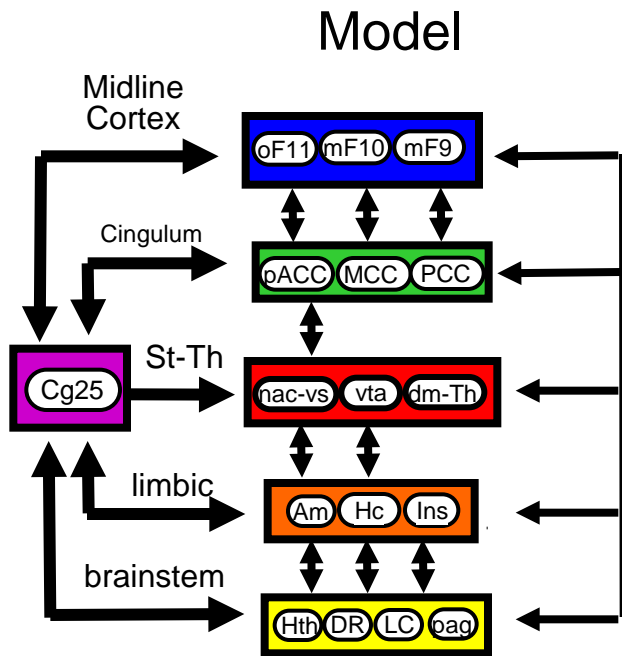
Is Recovery Stable Without Continued DBS?



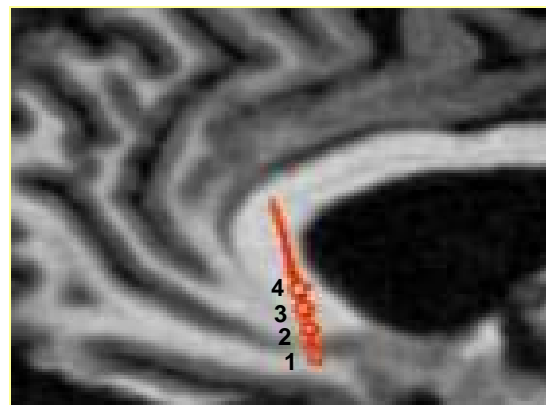
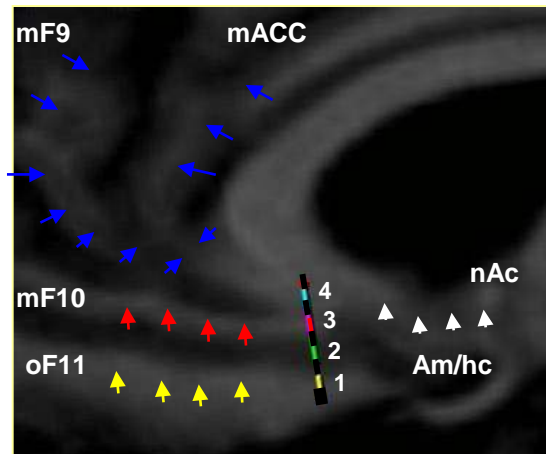
Opportunity: time course of relapse suggests cycling of stimulation possible.
Concern: time course of 2nd recovery not immediate. Mechanisms unclear.
Very different time course of relapse with vC/vSt or Habenula DBS—dopamine?

Rethinking Critical Pathways

Mapping Fibers of Passage thru SCC25

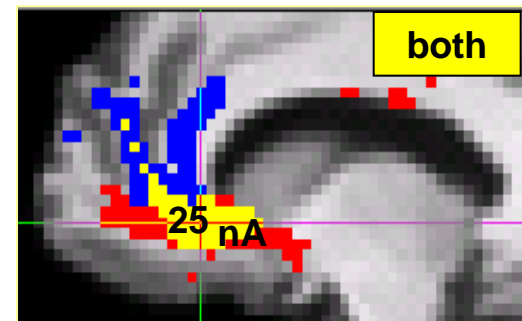
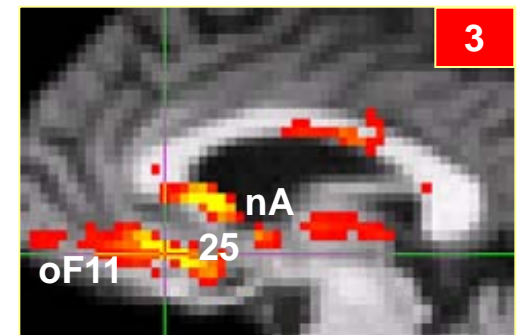
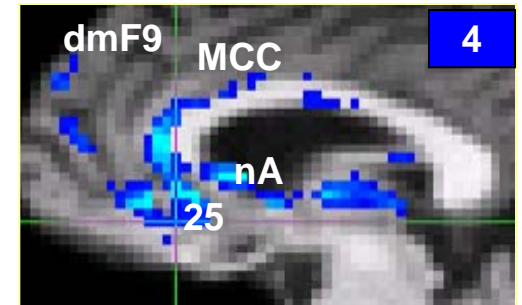


Define tracts affected by stimulation



Post-op CT/MRI merge

Differences between Adjacent contacts

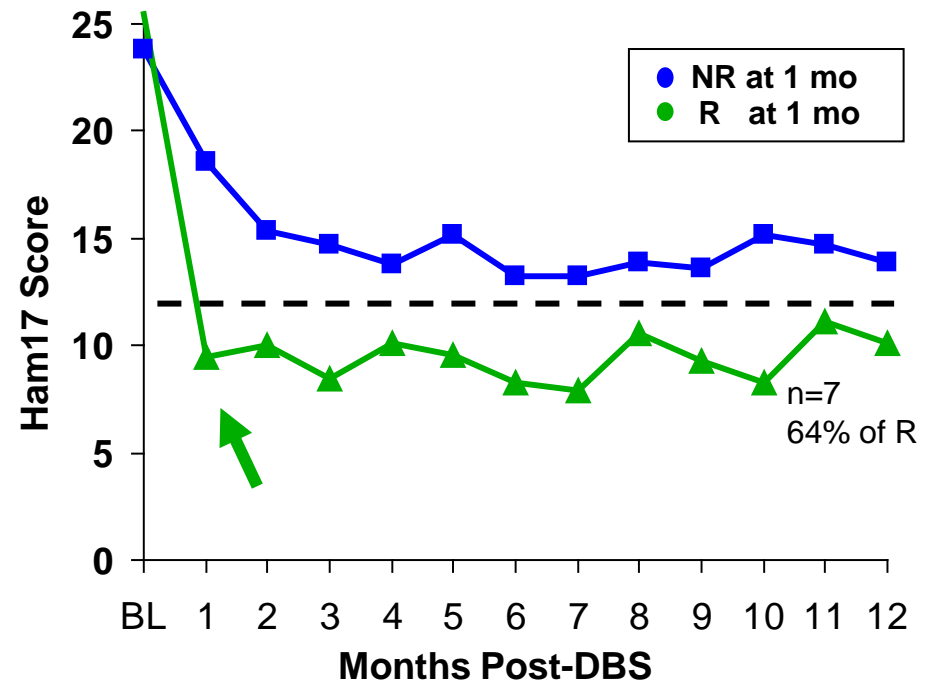


Intra-Operative Behavioral Effects, revisited

Clue to optimal contact and eventual outcome

‘ When you’re depressed, the focus is inward. Whatever you just did, I don’t feel that inward feeling; it has lifted so I am not so focused on myself...’ S13

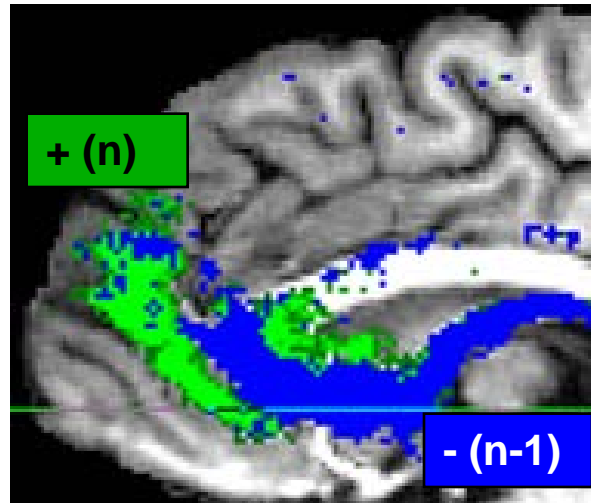
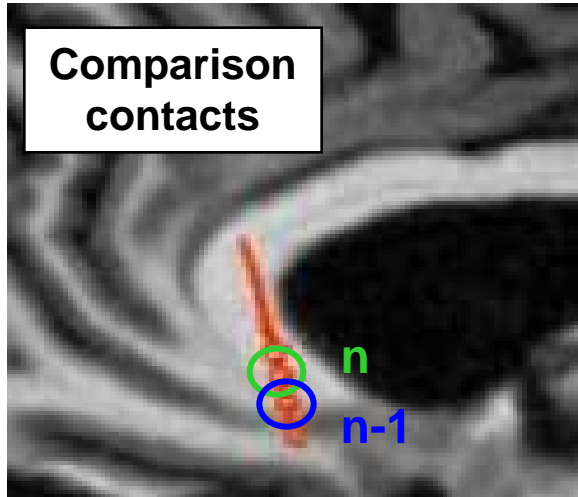
“It is as though I have been locked in a room with 10 screaming children. Constant noise; no rest; no escape. Whatever just happened, the children have just left the building.”



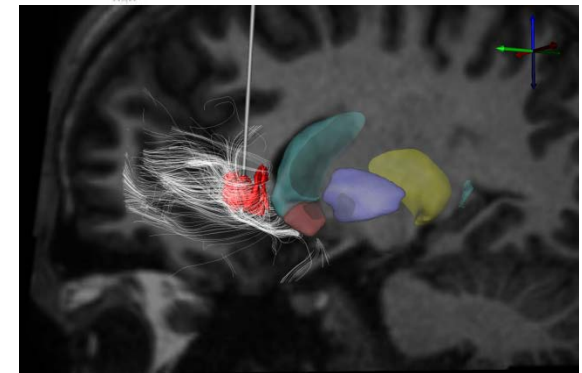
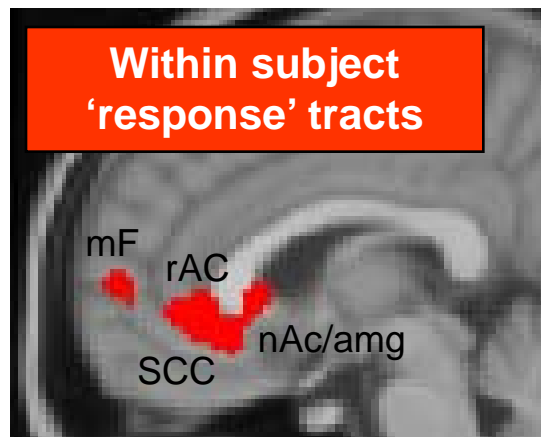
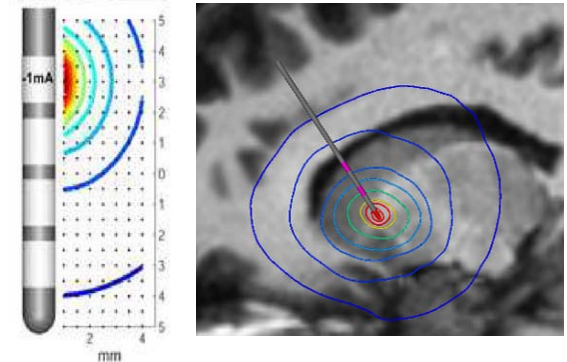
1. Intra-op/early change predictive of long-term outcome
2. Biomarker needed to identify critical pathways
3. Clue to DBS mechanism of action?

What tracts mediate acute effects?

response contact vs non-response contact



Future: Voltage Steering to precise target?



Finite element model & voltage field

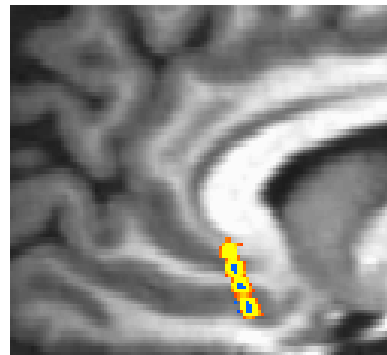
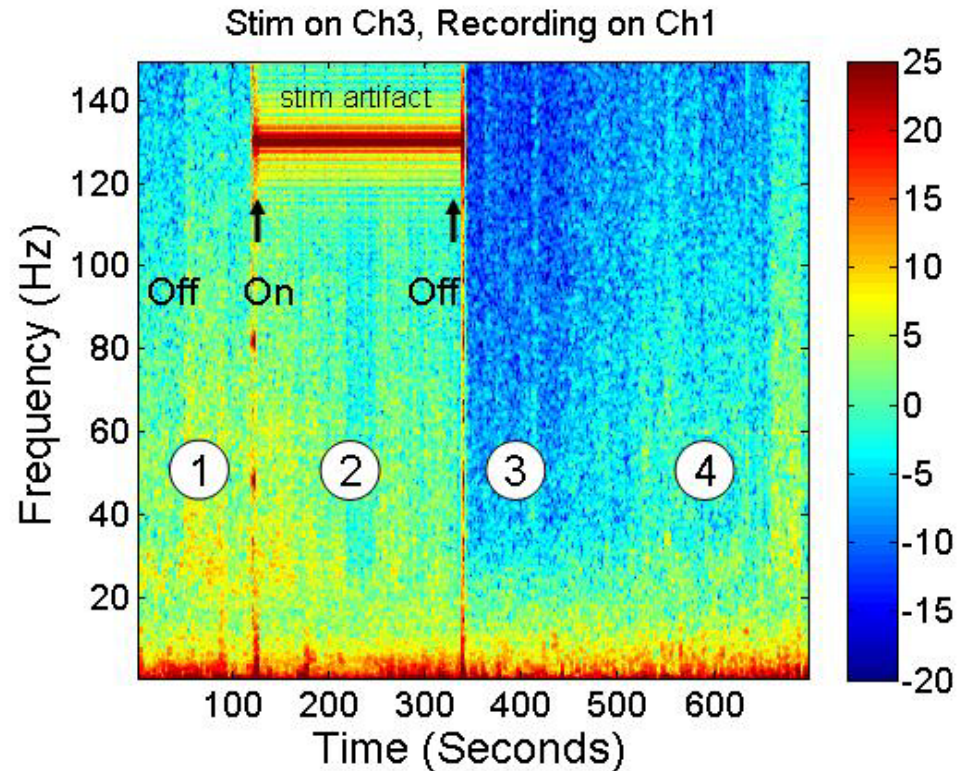
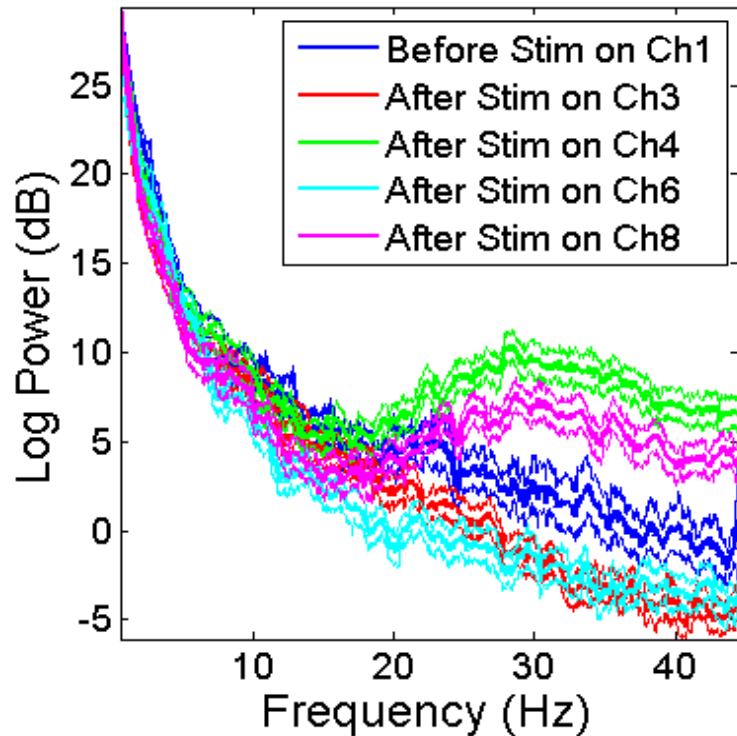
Illustrative Case Report

- 33 year old woman, single depressive episode (x12 years), multiple med failures, failed ECT/psychotherapy
- No behavioral response to acute stimulation at any contact
- Modest improvement from 24 weeks of active SCC DBS (HDRS: 26 → 16, ↓38%)
- HDRS increased to 23 after 12 add'l weeks
 - “I was trying to be hopeful”

Decision: surgical revision, move electrodes to a more optimal location

Real Time Monitoring of acute behavioral effects

Cg25 LFP, Frontal EEG



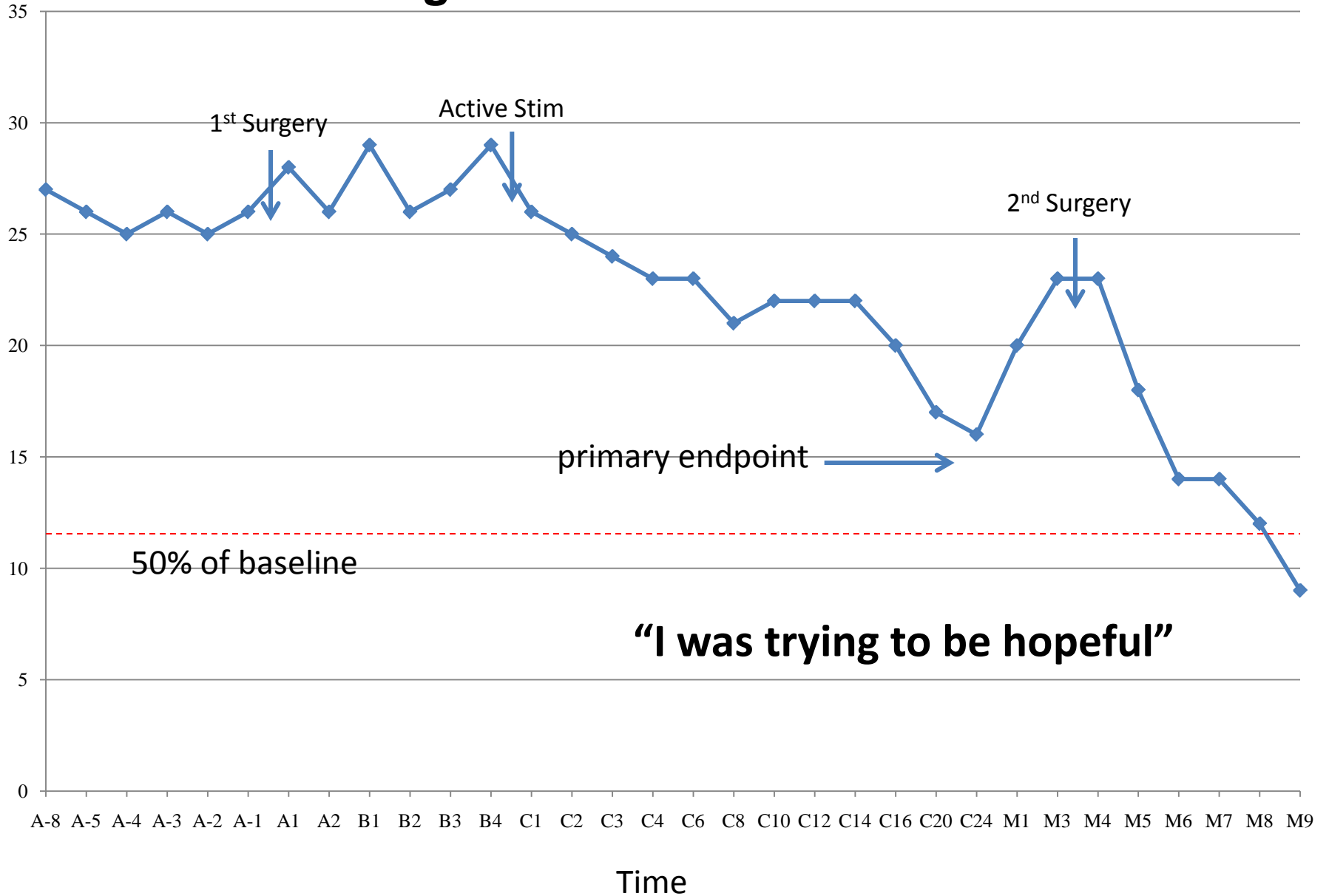
8 LFP, 8 frontal EEG
 5 min awake baseline
 2 min acute DBS; 5 min off
 Consecutive contacts 1-8
 L:1-4 R:5-8

A painful
 constant
 noise.
 so distracting,
 you can't
 feel sad

Contacts 3, 6 only

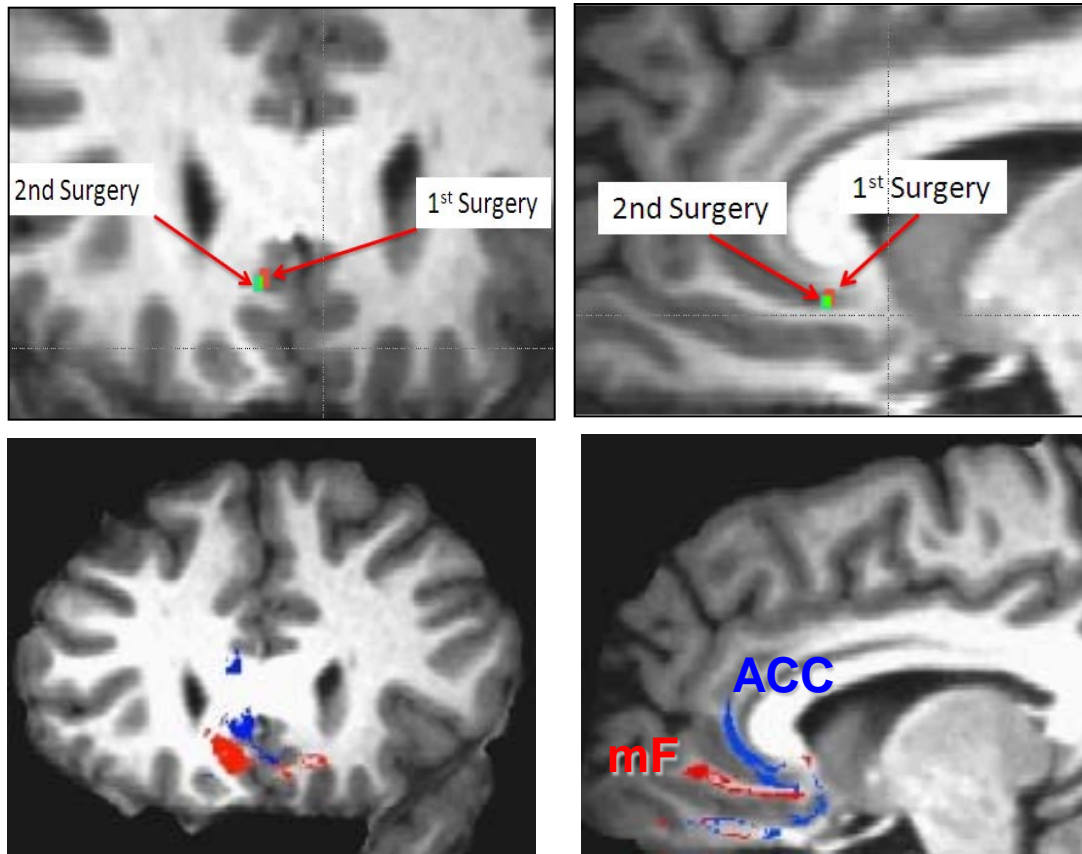
2. Decreased dread, noise
 "feel lighter" more "connected"
3. Room, people more in focus
 Faster speech, more fluent
4. Room turning back inward

Change in Hamilton over Time



Proof of Principle

Change in placement of electrodes made a difference



Chronic Stim Contacts 3/6
Based on OR response

7 months post-2nd surgery:
Clinical remission
8 months, first job in 14 years.

Tracts to medial frontal Not Cingulum
seem to be critical

Reverse Translation: DBS Mechanisms

- Which region/pathway/cell type is most critical
- Local/remote chemistry (microdialysis, PET)
- Electrophysiology (oscillations LFP, combined EEG)
- Habituation, plasticity (LTP/LTD, neurogenesis)
- Cell-specific modulation; optogenetics
- What are the most appropriate animal models?