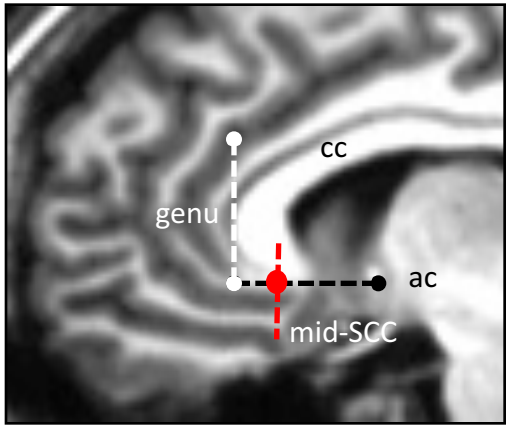
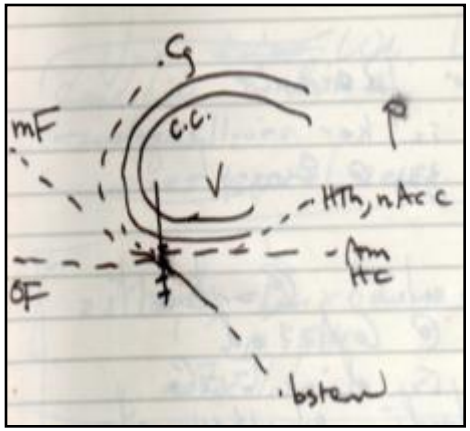
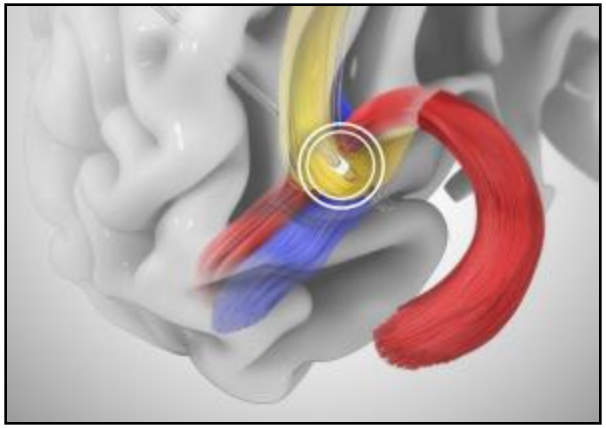
Rethinking Depression and its Treatment: Insights from Studies of Deep Brain Stimulation







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North Carolina Psychiatric Association
September 11, 2016
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Disclosures

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Stanley Medical Research Institute
Hope for Depression Research Foundation
NIMH (C McIntyre) 1R01MH102238, 1R01MH106173

Off-Label Use of Devices: DBS electrodes/pulse generators
1. Medtronic Inc. (UT, Emory)
2. St. Jude Medical, Inc (Emory)

Emory DBS studies: FDA IDE: G060028 (PI: HM), G130107 (PI: HM)
Clinicaltrials.gov ID#: NCT00367003, NCT01984710
research devices donated by SJM and Medtronic and EGI

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

Consultant: St Jude Medical Inc / Neuromodulation Division

Genealogy

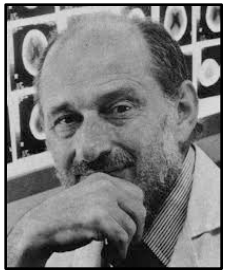
6 degrees of separation

USC

Leslie Weiner

Harvard

Ross Baldessarini



Norm Geschwind

Richard Mayeux

Lewis Rowland

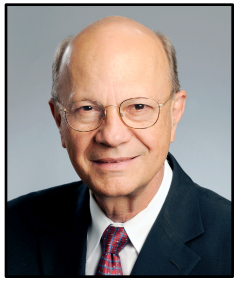
Neurological Institute of NY Columbia

Johns Hopkins

Henry Wagner

Bob Robinson

Sergio Starkstein



Mahlon DeLong

Guy McKahnn

UTHSCSA

Peter Fox

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Mario Liotti

Steve Brannan

U Toronto

Don Stuss

Zindel Segal

Sid Kennedy

Andres Lozano

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Psychotherapy

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C Ramirez

Patient Coordination

S Quinn

L Denison

DBS for Depression: Motivation

> Depression…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 1991

Treatments are available, but not always effective (more Tues)

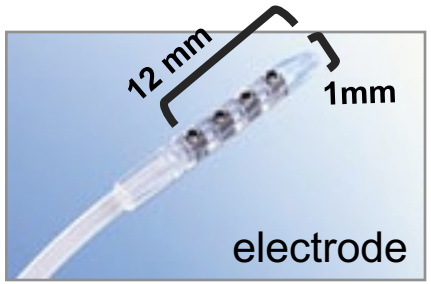
- 10% become treatment resistant over time
- few options if fail ECT

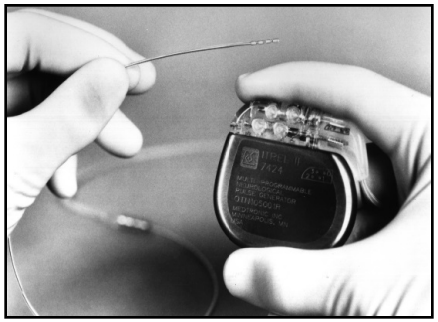
Rationale for Neuromodulation as a Potential Strategy

- advances in functional neurosurgery and imaging
- experience in Parkinson's disease

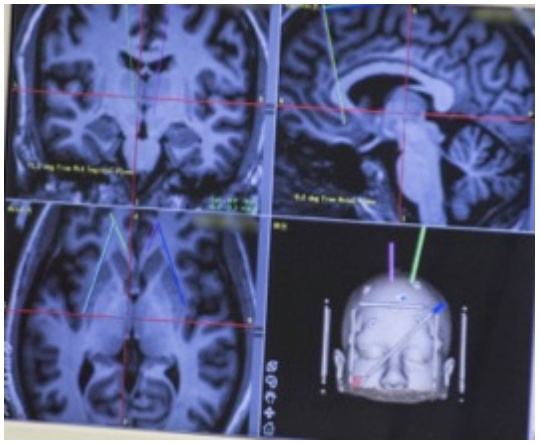
DBS 101: Basic Procedure

Equipment

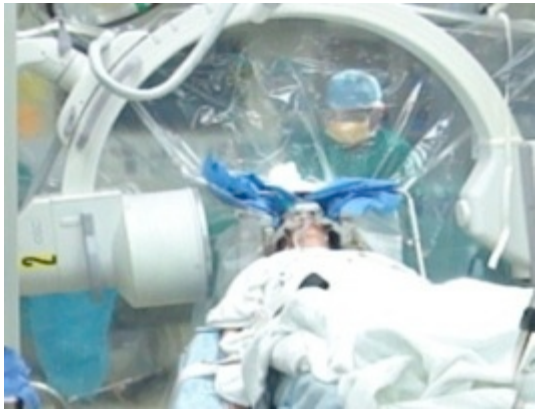




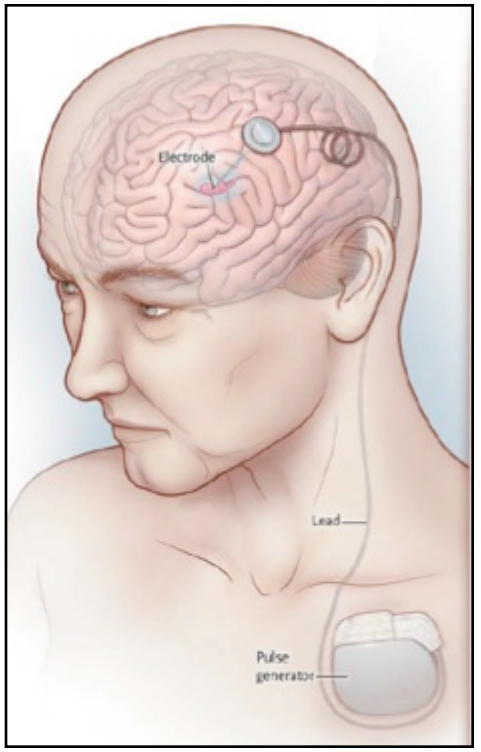
IPG: implantable pulse generator



MRI Guided targeting



Stereotaxic Implantation
+/- awake, recording, testing

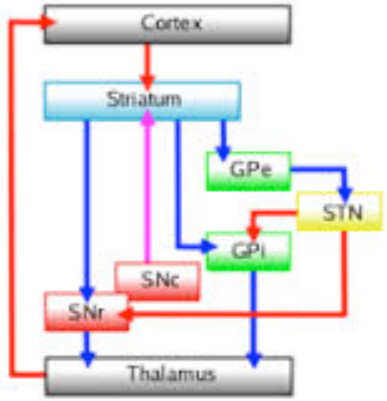


DBS system in situ
disease specified location
130Hz/90us/3-8mA
chronic continuous stim

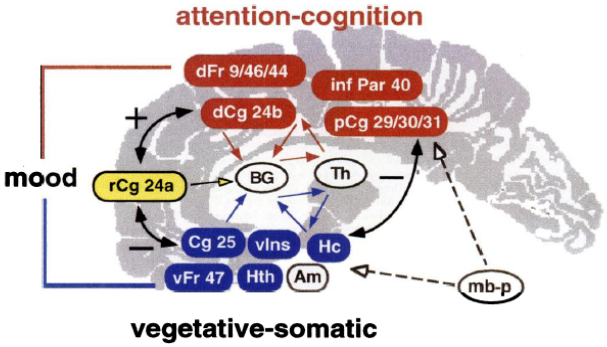
First Step: Define the Circuit

Deconstruct syndrome into component dimensions

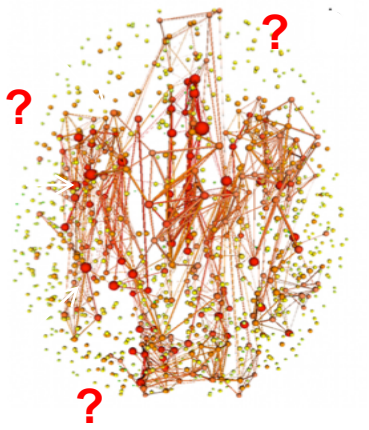
Parkinson's Disease



Depression



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



- WHERE to stimulation (critical node)
- WHAT should happen (endpoint, target engagement)
- WHO to stimulate (patient selection biomarker)

Target core symptom(s)
can this be defined?

"A gnawing agony; a painful self-loathing that consumes all your energy and attention…"

DBS #7 2004

"Can't get away from inside yourself…"

DBS #29 2011

"In depression, faith in deliverance, in ultimate restoration, is absent. The pain is unrelenting, and what makes the condition intolerable is the foreknowledge that no remedy will come—not in a day, an hour, a month, or a minute.

William Styron, 1991

Pain + Avolition

SCC25 DBS for Treatment Resistant Depression

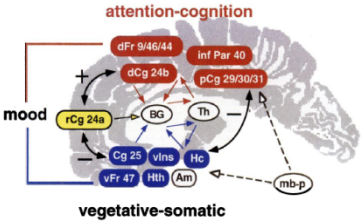
experimental evolution 2005-2016

Neuron, Vol. 45, 1–10, March 3, 2005,

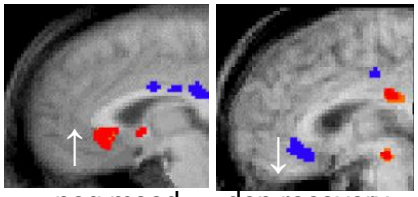
Deep Brain Stimulation for Treatment-Resistant Depression

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]

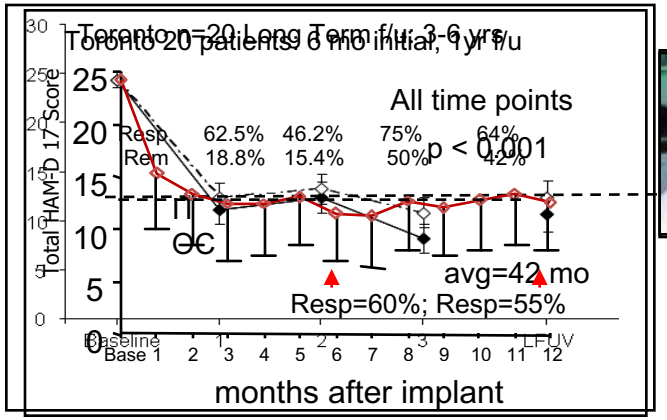
Model



Rationale for Target

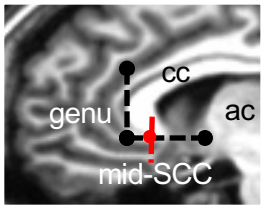


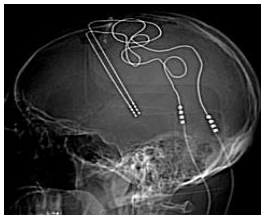
neg mood dep recovery



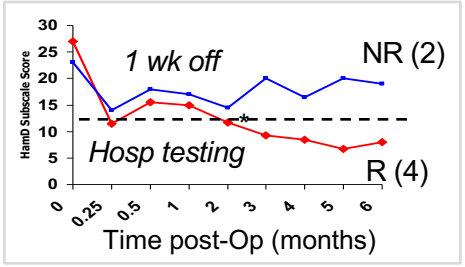
Kennedy Am J Psych 2011
Lozano Biol Psych 2008

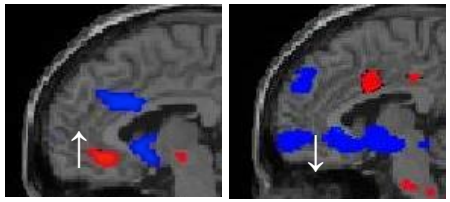
anatomic targeting



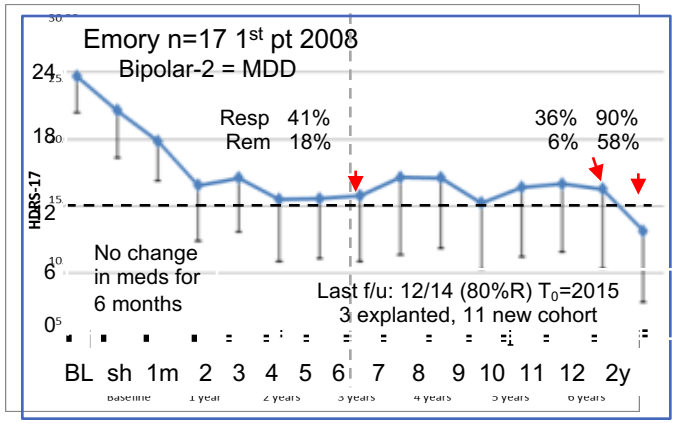


Bilateral DBS
130Hz 90us 4V





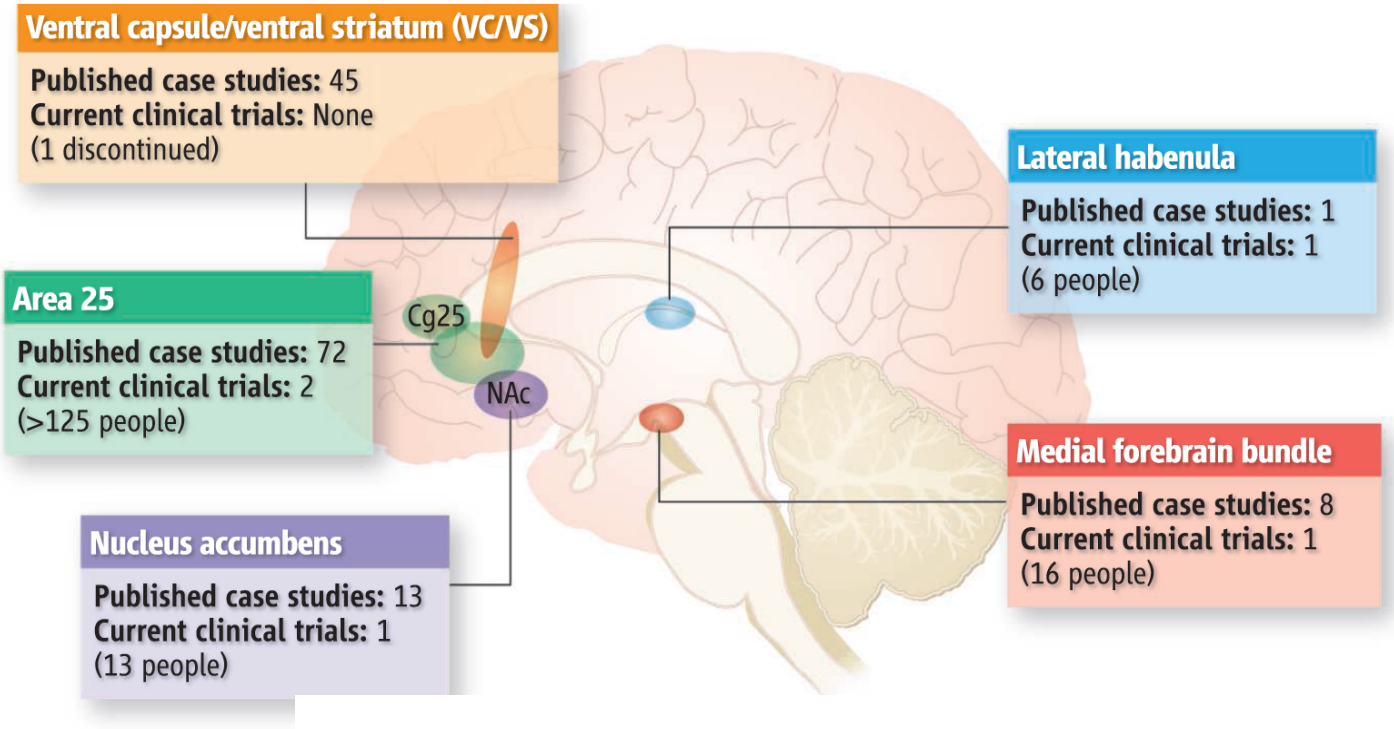
pre-op 6mo DBS



last count: 3 explanted
21/25 (84%) responders

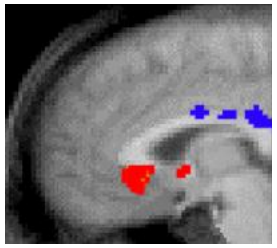
Mayberg Neuron 2005; Lozano Biol Psych 2008; Kennedy Am J Psych 2011

Other Centers, Other Targets, Different Logic



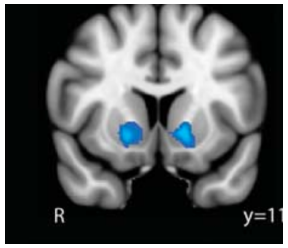
Science Focus News 2013

↑SCC25
↓PM/MCC



Hi NA + hi Psychomotor

Same circuit, different node?
Different patients, Different dominant symptoms? Different targets?
issues with RCT.



↓vSt

Low PA + Low energy

Lessons Learned, Next Steps

details matter

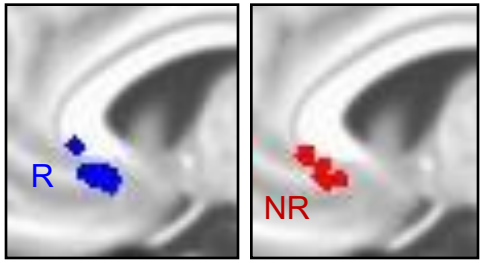
1. WHERE (target location, contact selection)
2. WHO (patient selection, TRD subtypes)
3. WHAT (acute/chronic target engagement biomarkers)
4. REFINE (closed loop; relapse anticipation/prevention)

device trials ≠ drug trials.
reduce sources of variance
before attempting further RCTs

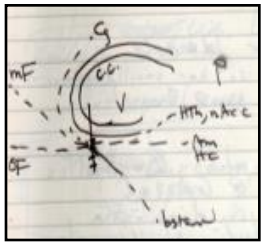
Step 1: Where

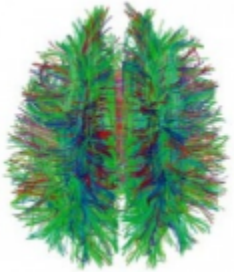
Refine methods for Precision Network Targeting

target not a coordinate



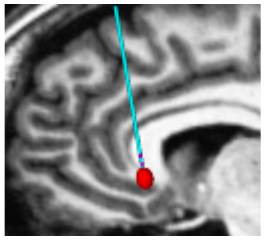
need network

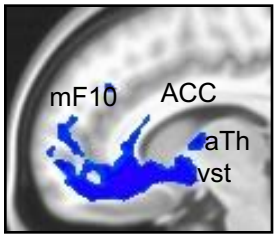


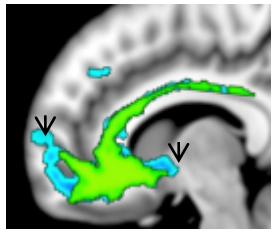


VTA model | Common map | convert NR-R

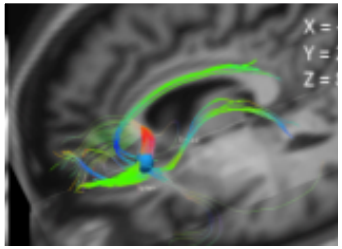
Cohort 1
6m R=41%
n=7/17



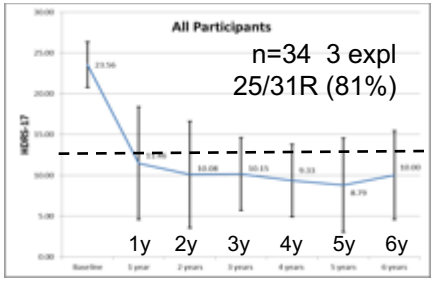




Cohort 2
DTI planning
6m R=73%
n=8/11



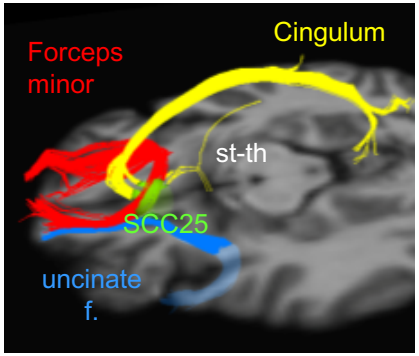
d-DTI in single Ss



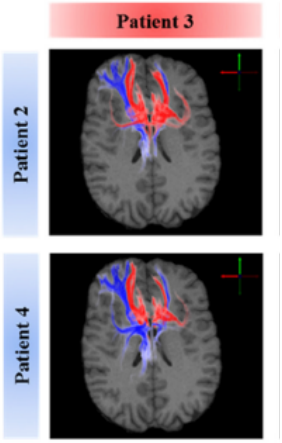
n=28 28 28 26 6 14 10

Test method on data from other DBS targets

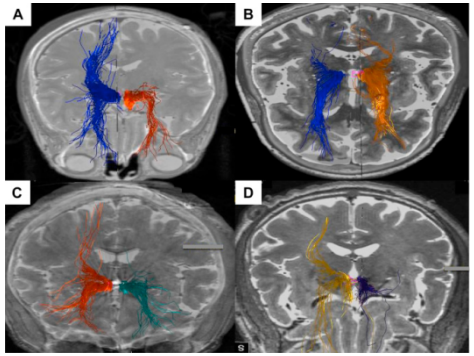
SCC Target



vC-vSt target



MFB target

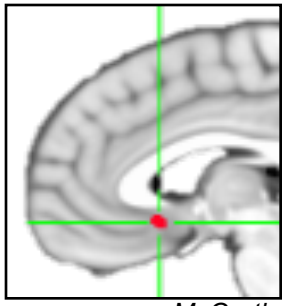


Step 2: Who

Patient Selection Biomarkers

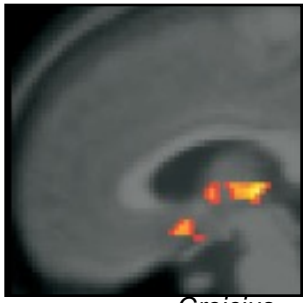
PET, rs-fMRI
↑ SCC25
in TRD

CBT+SSRI



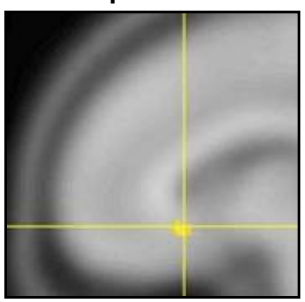
McGrath

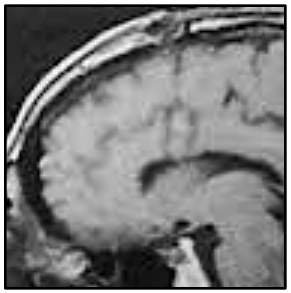
multi-drug



Greicius

TRD pre ablation



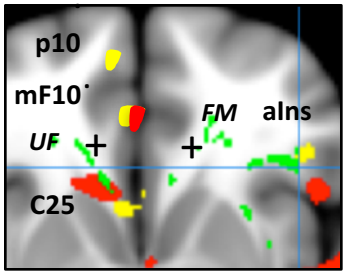


Doughterty

d-MRI PET fMRI

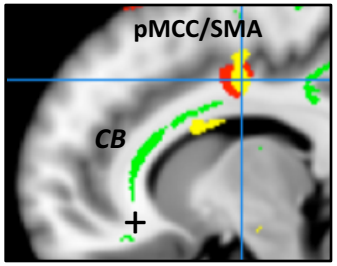
K Choi C McGrath J Rajendra

Beyond
↑ SCC25
think
connectivity

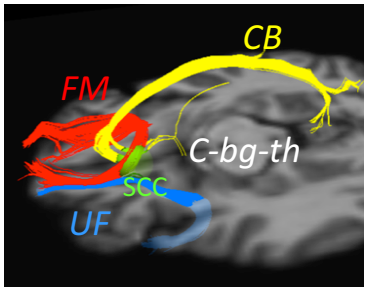


vmF10-p10
uF/Fm

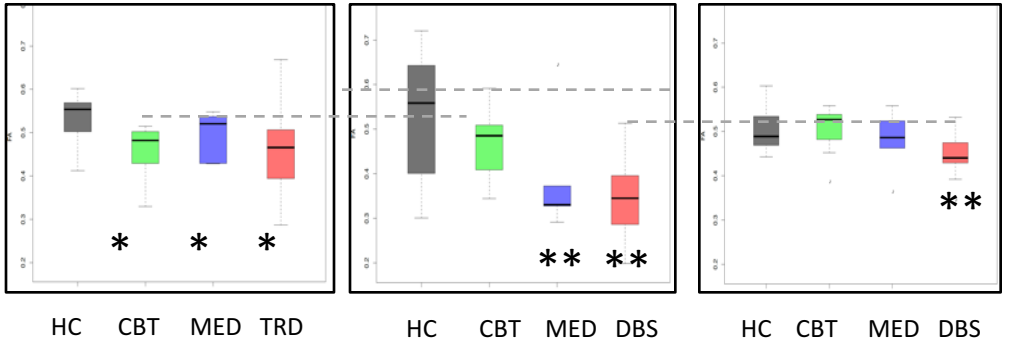
ant Thal
Ctx-thalamic fs.



pMCC/SMA
Cingulum b.

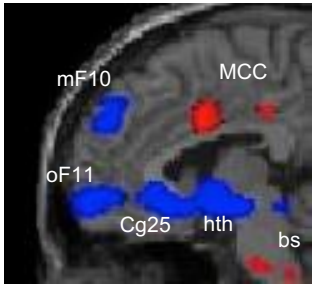


FA-DTI



link to genes?

Step 3: What
recovery with DBS is not linear



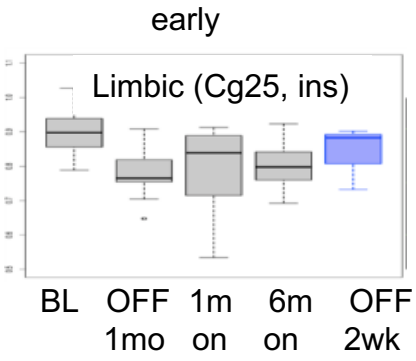
1 2
Network Reset/Switch
acute, rapid

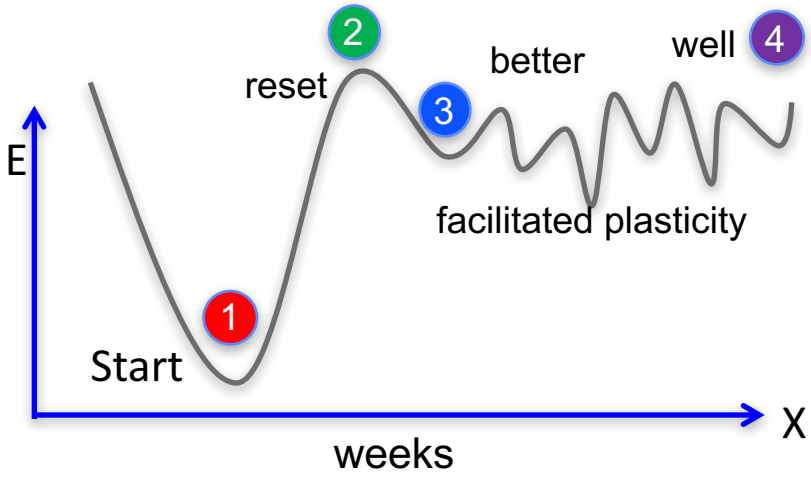
3 4
Network Plasticity
delayed, progressive

What ever you just did,
It is as though I suddenly shifted
from a state of all consuming internal
focus to realizing that there are a
number of things around to do…

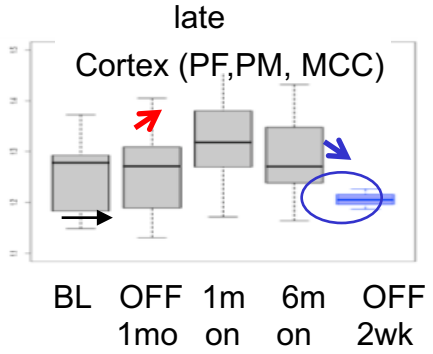
I know I still have a
long way to go,
but I am no longer in the hole.
Now it comes down to me…

Instead of being
in a deep canyon,
I am up on on a ledge.



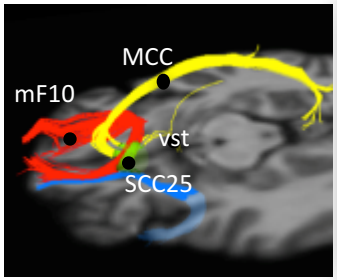


DBS doesn't make it easy—
Just makes it possible.
Now my efforts have impact.

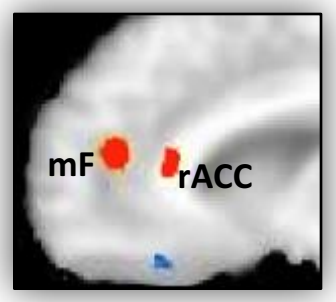


Step 4: What Would be Useful?

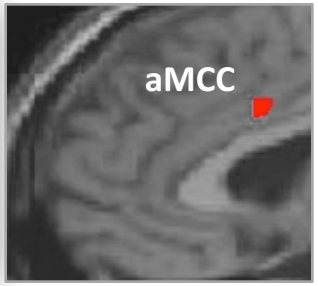
readout of acute and chronic network effects



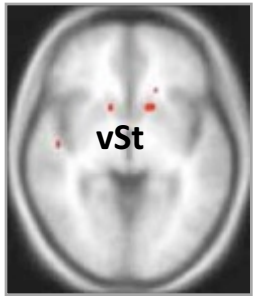
'network'



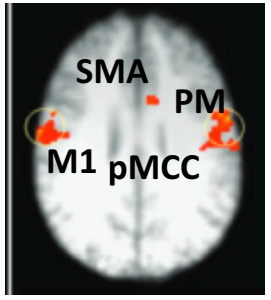
Emotional
Self-relevance
(insight, bias)



Body awareness
HR, BP, GSR
(interoception)



Positive affect
anhedonia
(Salience)



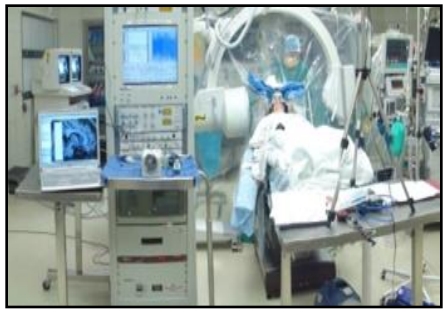
Willed action'
facial expression

Strategy: reverse engineer observations from conventional DBS

- define target engagement (beyond anatomy)
- where to measure: local or remote or both
- parameter tuning/optimization (once engaged)
- maintenance (adjustment for plasticity/adaptation)
- response metric (eliminate clinical ratings)
- relapse detection and prevention (recurrence from life stress; discontinuation)

Behavioral Confirmation of DTI Targeting

patient self report linked to impacted tracts



DTI targeting
randomized stim
130Hz 90us 6mA
9 patient: R/L leads
8 contacts; 108 trials

Type 1
interoceptive change

- I feel lighter
- I feel less heavy
- I can breathe
- the tension is gone
- the pain is gone

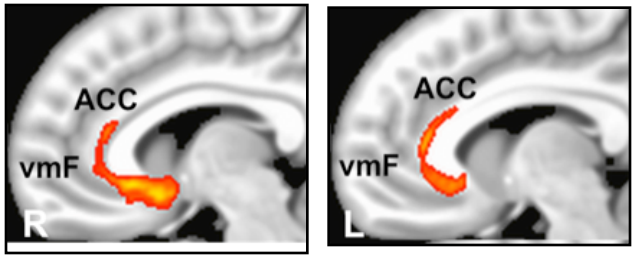
Type 2
exteroceptive change

- I feel more connected
- I feel more optimistic
- I could walk my dog
- I could wash my hair
- can imagine seeing friends

K Choi

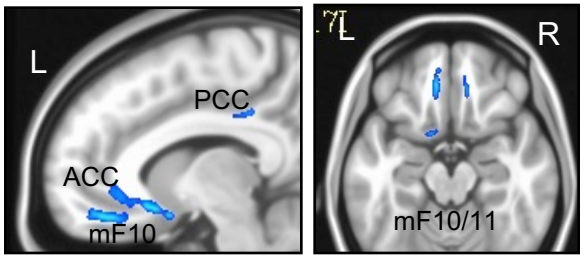
P Riva-Posse

30/72 active; 4/36 sham; 17L, 3R



Type1: CB alone--Left or right
(also tracts with change HR, SCR)

9/72 active (all L); 0 sham



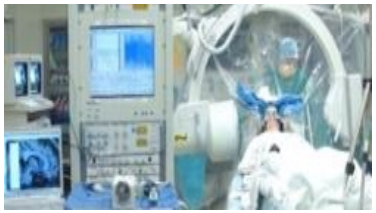
Type 2: always w/ Type 1--bil MF, L-UF, L-CB
L side alone adequate, if hit FM?

Choi and Riva Posse et al
JAMA Neurol Sept 26, 2015

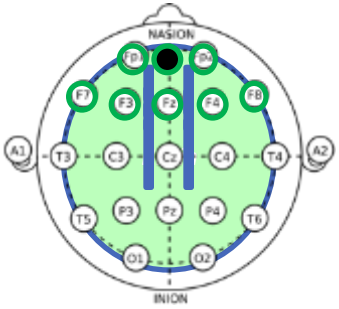
In Search of Depression Control Signals

Current Studies

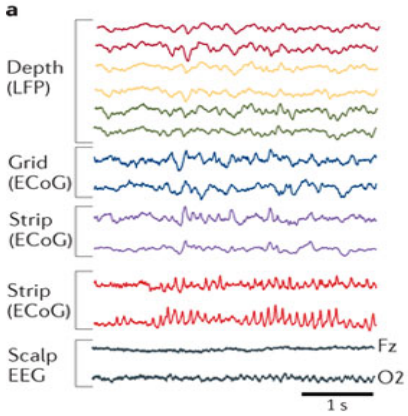
First Effects OR

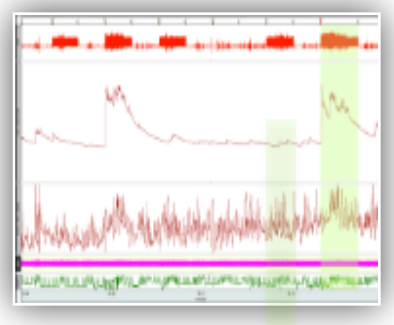


Implantation surgery



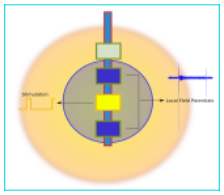
LFP, EEG





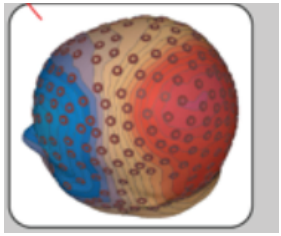
HR, SCR, EMG

Longitudinal continuous recordings



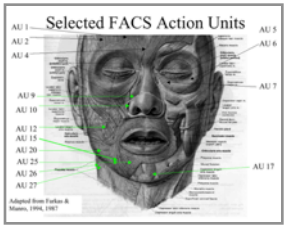
recording DBS lead

Activa PC+S SCC LFP

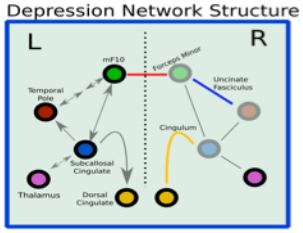


EGI-hdEEG rest/task

actigraphy, GPS, HRV



emotion-motor facial exp

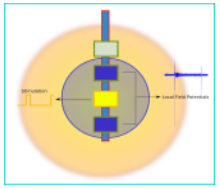


multimodal models

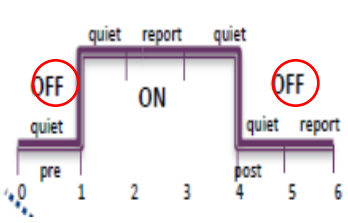
E-physiology of Initial 'Target Engagement'

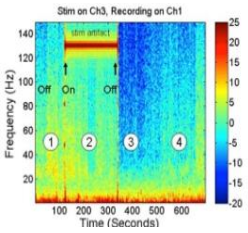
Local SCC LFP changes w/stim at best contacts

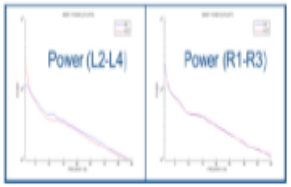
Otis Smart



SCC LFP





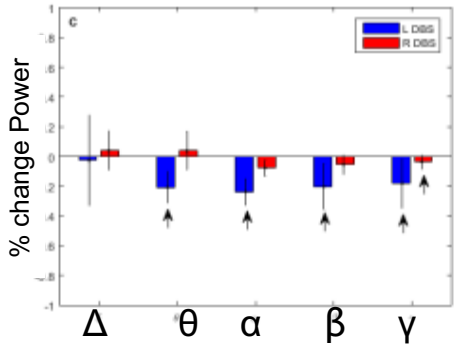


Compute PSD Change

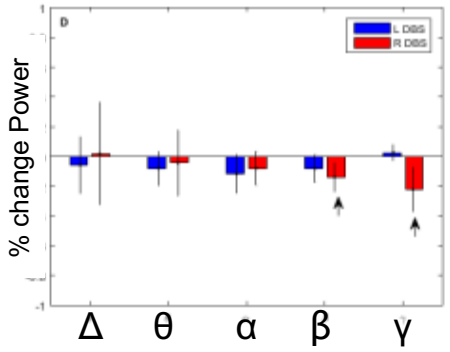
$(PSD_{POST}-POST_{PRE})/PSD_{PRE}$

First stim effects at optimal contact used at 6 mo)
average n=10 Responders

Left Recording

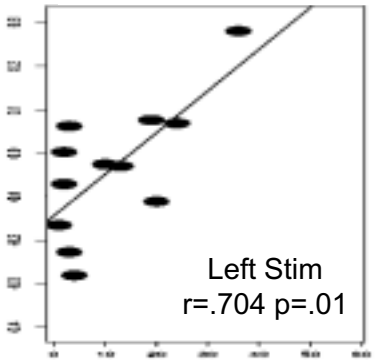


Right Recording



% change theta power post-pre Left DBS n=12

Left SCC Theta

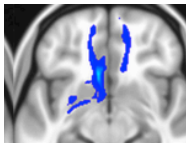


wks to 2w response

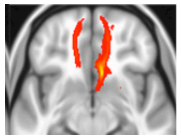
L≠R ipsi resp w/ equivalent impact on GM

VTA DTI
WM, GM
CSF

Left DTI



Right DTI



L≠R independent of impact tracts

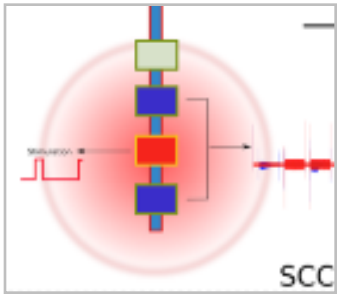
weeks to sustained 2w response

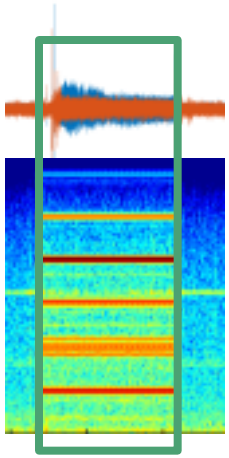
LFP changes with 6 mo Chronic DBS

recordings DBS off

V Tiruvadi

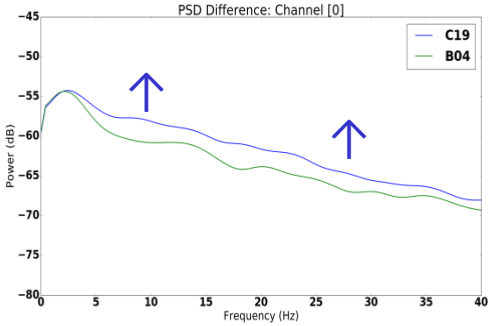
recording montage

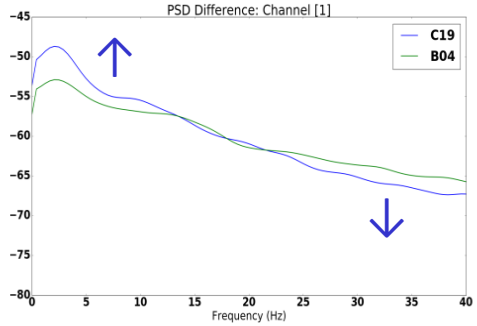


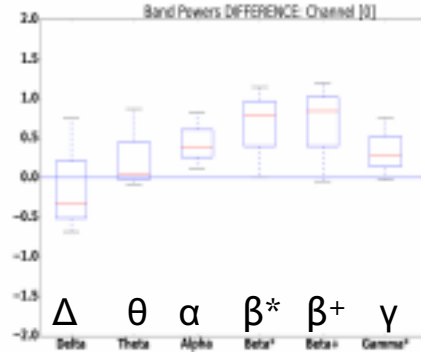


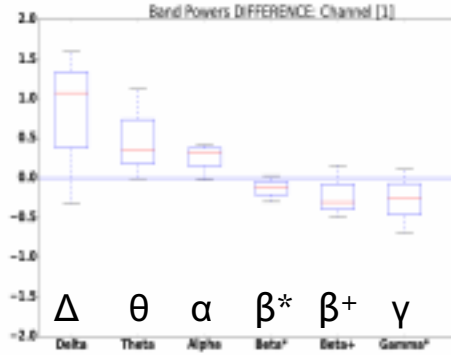
2 min sampling
130Hz 60ms 4V
stim off

Chronic Bilateral DBS 6m vs Baseline





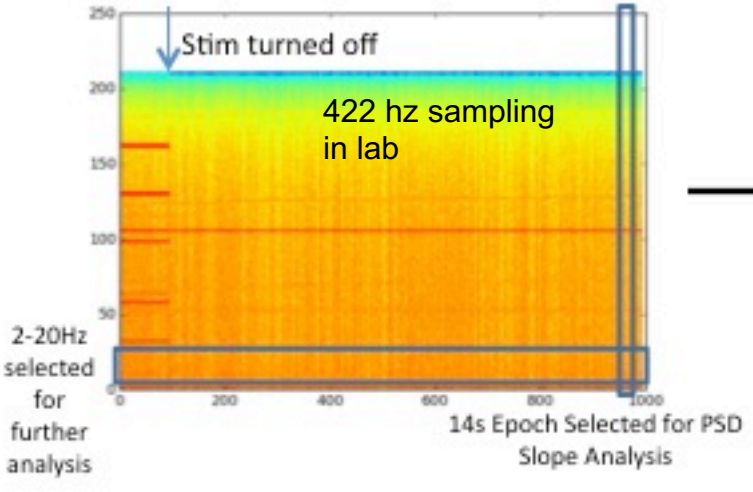


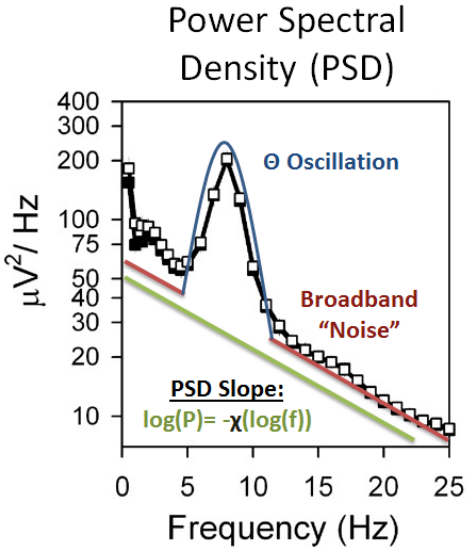


SCC LFP Changes with Chronic DBS

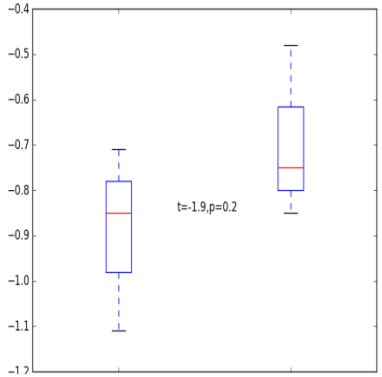
strategy to define response signal in single subjects

A Veerakumar





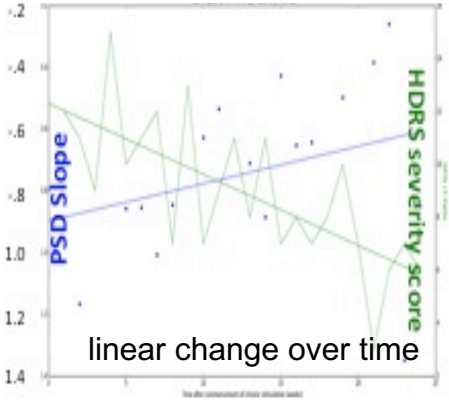
Slope: Baseline vs 6 months



Pre DBS dep

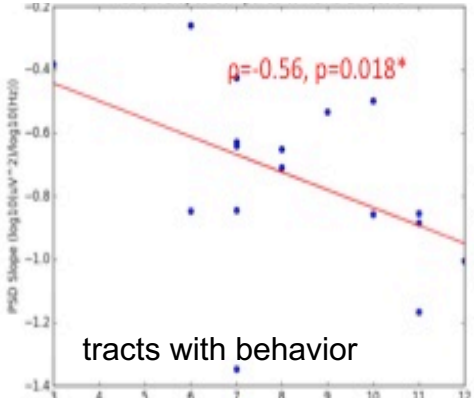
6 mo DBS recovered

DBS 906 slope over time



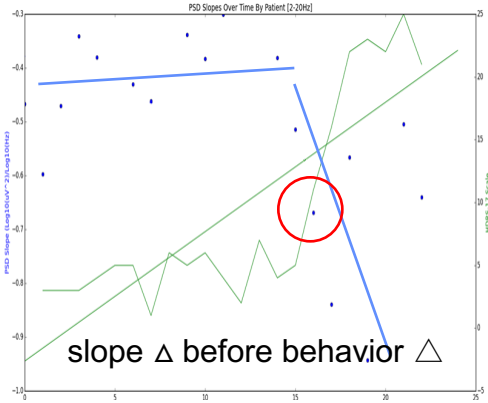
Weeks of active DBS

906 Severity vs Slope



HDRS-17 score

905 slope over time



weeks of active DBS

Is Biomarker at SCC Adequate?

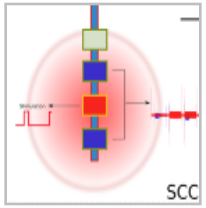
network readout using high density EEG

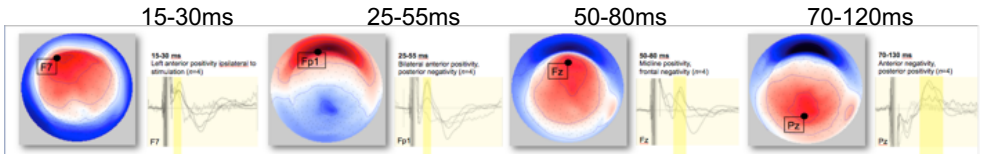
A Waters

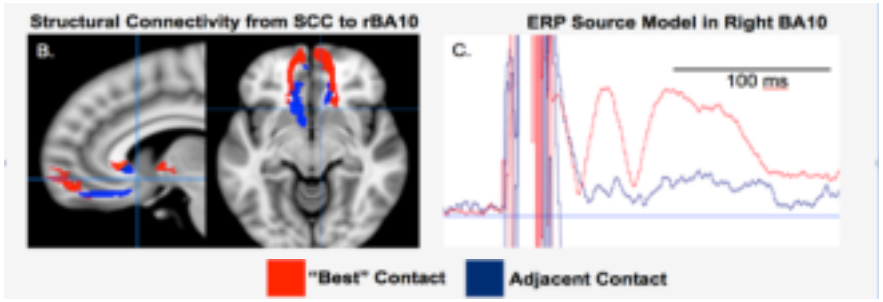
ON vs OFF
target network
differences

1

Acute ERP response
1mo post-op n=4
2 min unilat stim
2-Hz 6mA 60ms



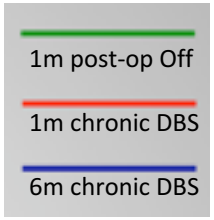


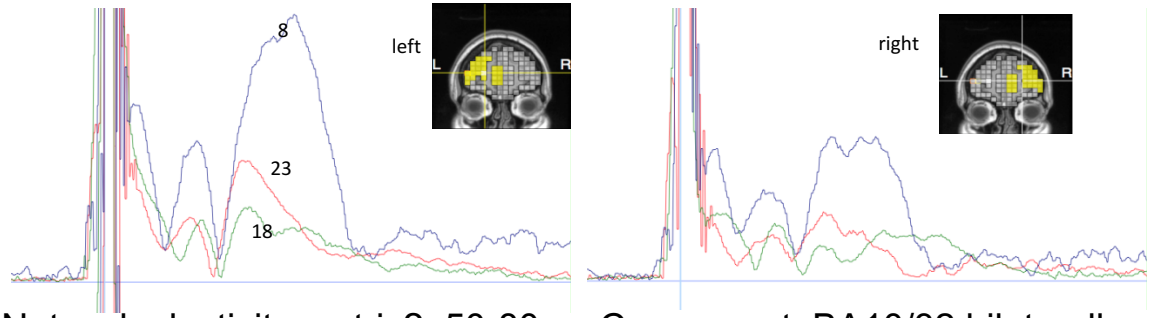


Target Engagement: 50-80ms Component: BA10 bilaterally
R differentiate best/not

2

Chronic ERP response
6m bilateral DBS
Repeat 2m unil stim
2-Hz 6mA 60ms





Network plasticity metric? 50-80ms Component: BA10/32 bilaterally
changes with depression severity score change

Lessons Learned

bi-directional translation

1. Timeline is critical. Acute and Chronic Experiments are both needed
   a. What is target signal: acute (reset); chronic (well)
   b. what is normalization; what is adaptation (good, bad)
   c. effects of discontinuation

2. Use multiple behavioral models
   a. all symptoms may not change with stim at a given target
   b. different symptoms may change at different rates
   c. network may adapt differently to stim at different locations

3. Know the human data and its nuances
   a. need models of treatment resistant
   b. best translational experiments will need to have clinical relevance

Recovery Takes more than a Stimulator

evolving thoughts on successful recovery

I didn't realize how much work
I would need to do myself.

Burden of Wellness. Passive to active role in own recovery

- when intractably ill, expect nothing (stuck, hopeless)
- singular goal: make pain go away
- once pain is gone; can't remember it
- renewed awareness of other problems, priorities
- rehabilitation/plasticity (reverse old habits/develop new ones)

Psychotherapy may be critical
to achieve clinically meaningful effects