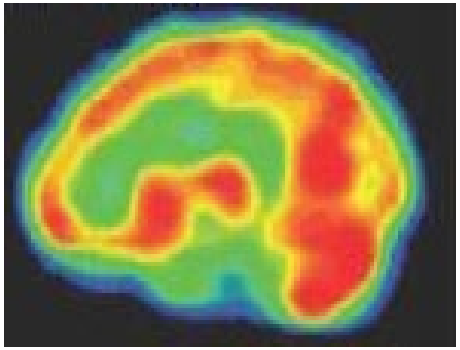
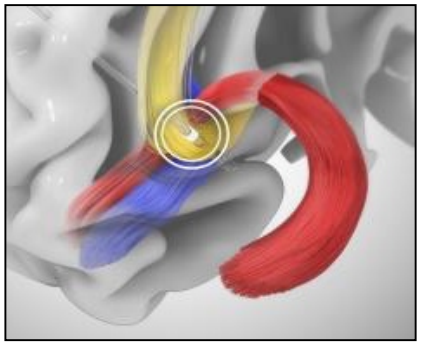
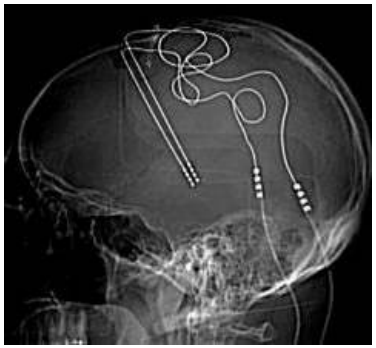
DBS for Treatment-Resistant Depression: a (5 year) Progress Report

Helen Mayberg MD

Center for Advanced Circuit Therapeutics
Icahn School of Medicine at Mount Sinai
New York

October 15, 2019

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants

Disclosures

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

1. Medtronic Inc. (Toronto, Emory, MSSM)
2. Abbott Labs/St. Jude Medical, Inc (Emory)

Patent: US2005/0033379A1 (Andres Lozano, co-inventor)
issued March 2008, Abbott Labs, assignee

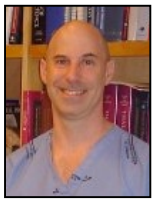
Consultant: Abbott Labs

NARSAD Distinguished Investigator Award 2002
BBRF Webinar 2014
Today: 5 year update

Emory Depression DBS Team

Clinical Implant Programming

Neurosurgery



R Gross

P Holtzheimer

Psychiatry

S Garlow

P Riva-Posse

A Crowell

Psychotherapy

R Hershenberg

Patient Coordination

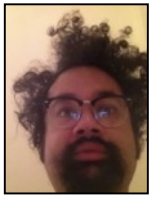
S Quinn

L Denison

DBS Biometrics and Mechanisms

Imaging

K Choi



J Rajendra

Electrophysiology

A Waters

O Smart

V Tiruvadi

A Veerakumar

M Sendi

S Alagapan

Modeling, Behavioral Biometrics

C McIntyre
Case Western
modeling

B Howell
ENTICe
modeling

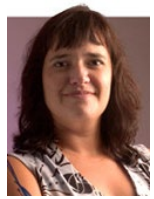
D Obatusin
Comp Sci

T Denison
Oxford
Engineering

S Nemati
BMI ML/AI

S Hamati
Computer Sci

C Inman.
Cog NS



M Kelley
Biostatistics

NIMH 1R01MH102238, 1R01MH106173, BRAIN UH3NS103550
FDA IDE: G060028, G130107 (PI: HM)
Clinicaltrials.gov ID#: NCT00367003, NCT01984710

THE DANA FOUNDATION

HOPE FOR DEPRESSION RESEARCH FOUNDATION

NIH National Institute of Mental Health

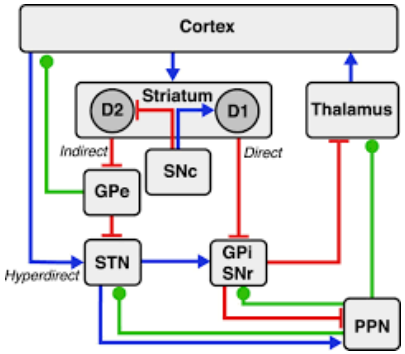
BRAIN INITIATIVE

Axiom 2019

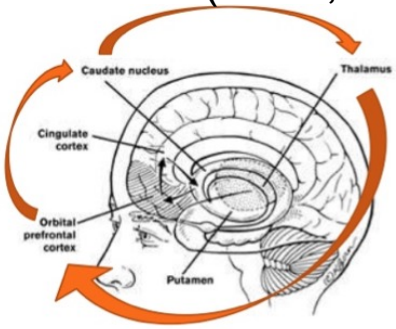
neuropsychiatric disorders are circuitopathies

Movement Disorders

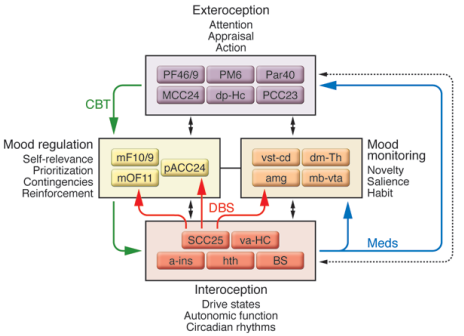
PD
ET
Dystonia
(TS)
(Paralysis)



Obsessive-Compulsive Disorders (OCD, TS)

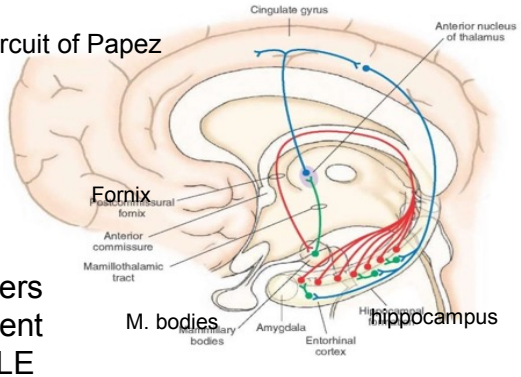


Mood Disorders (MDD, PTSD, anxiety)



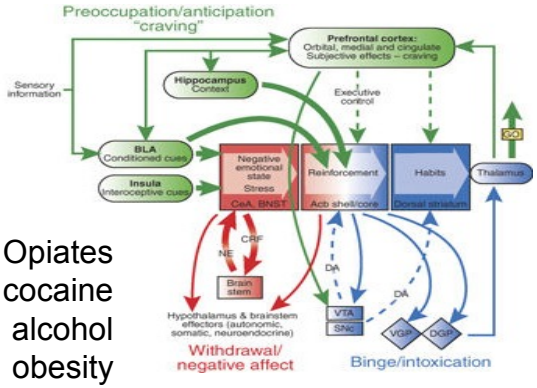
Seizures, Memory

Circuit of Papez



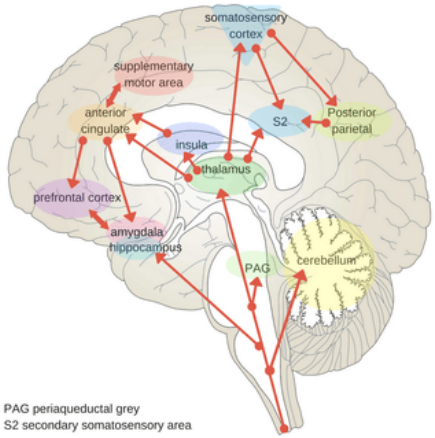
Alzheimers
Enhancement
TLE

Addictive Disorders



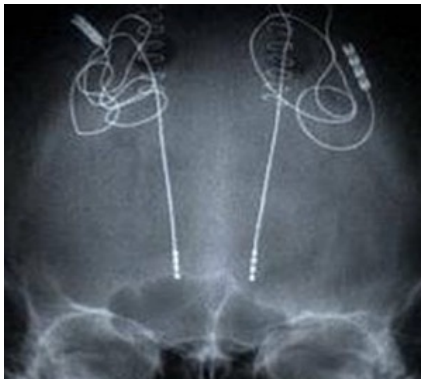
Opiates
cocaine
alcohol
obesity

Chronic Pain



Focal Modulation of Disease Circuits

general approach (invasive/non-invasive)



- WHY? (define need)
- WHERE to stimulate (critical node)
- WHAT should happen (target engagement, endpoint)
- WHO to stimulate (patient selection biomarker)
- HOW to stimulate (intermittent, continuous, closed loop)

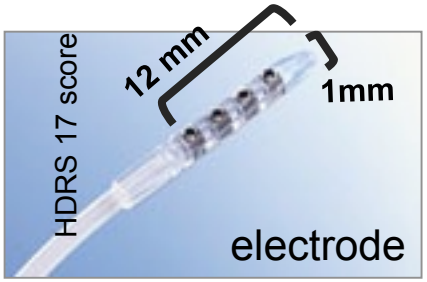
Goal - Match Target to disease, symptom, patient

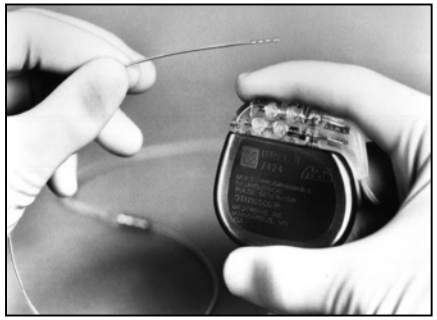
- Devise personalize algorithm to optimize response

DBS 101: Basic Procedure

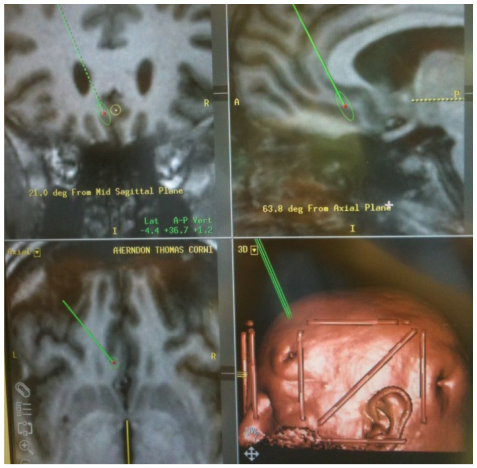
Target and modulate a neural circuit

Equipment

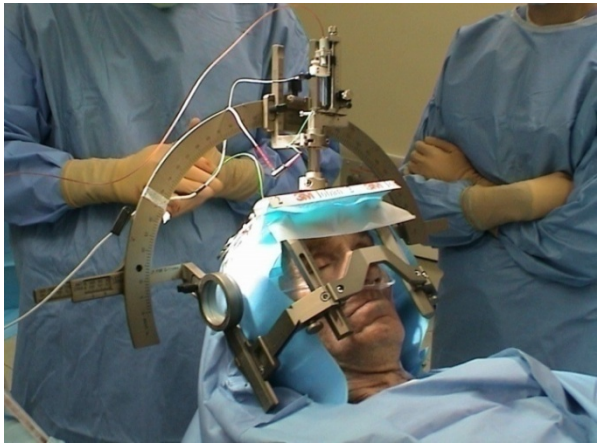




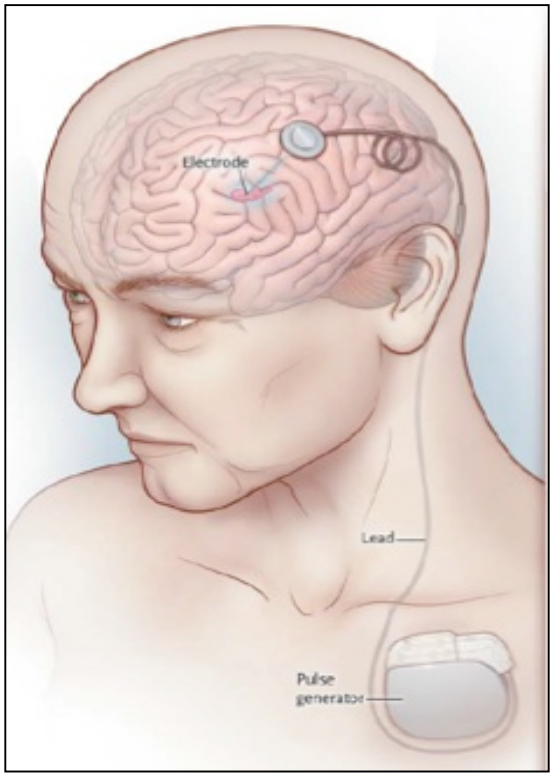
IPG: implantable pulse generator



MRI/CT Guided targeting



Stereotaxic Implantation
+/- awake, recording, testing



DBS system in situ
disease specified location
chronic continuous stim

DBS for Depression: Motivation 2001

Why?

Mood
Interest
Activities
Weight
Sleep
Activity
Energy
Concentration
Guilt
Suicide

Treatments are available, but not always effective

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

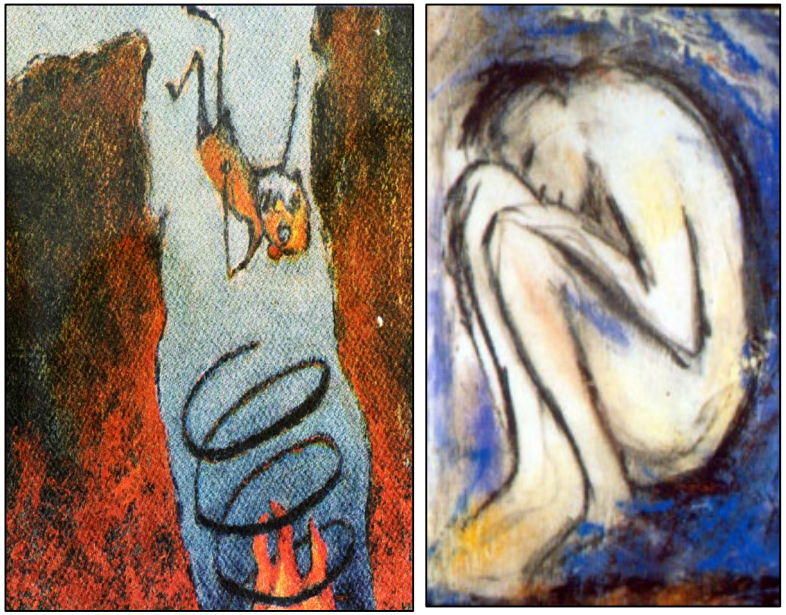
Rationale for Neuromodulation as a Potential Strategy

- advances in functional neurosurgery and imaging (essential)
- experience in Parkinson's disease (naïve but a start)

DBS for TRD

What are we trying to treat?

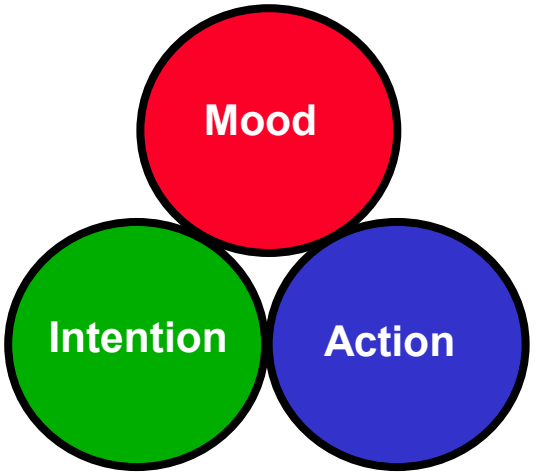
"A gnawing agony; a painful self-loathing that consumes all your energy and attention…"



nearly immobilized and in a trance of supreme discomfort…

William Styron.
Darkness Visible 1991 (2004)

"Can't get away from inside yourself…"



What might recovery look like?
can move; be without pain?
Return of agency?

Proof-of-Principle Pilot Study: 6 TRD patients

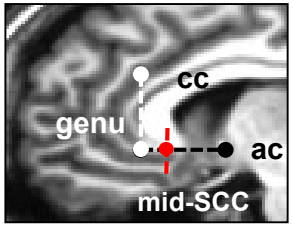
6-month open-label DBS, 1st pt 2003, published 2005

Neuron, Vol. 45, 1–10, March 3, 2005,

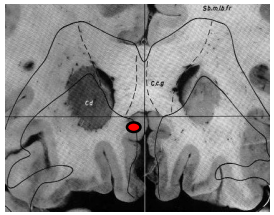
Deep Brain Stimulation for Treatment-Resistant Depression

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]

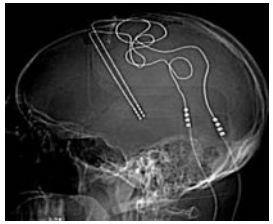
Method



Target

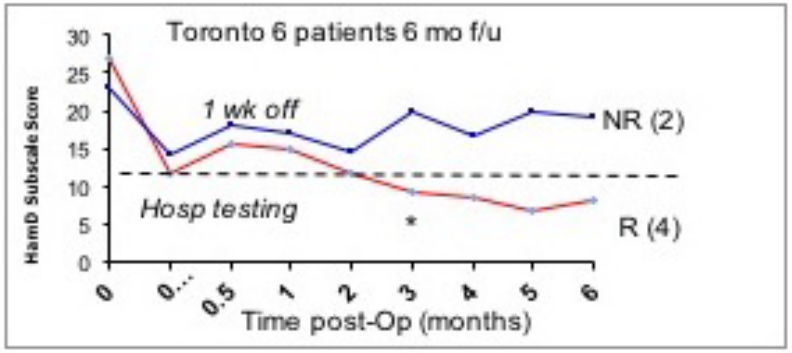


SCC WM

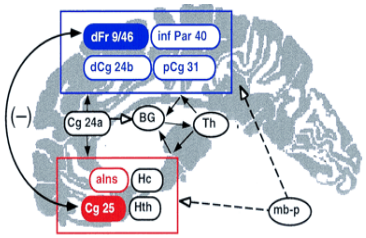


130Hz 90us 4V

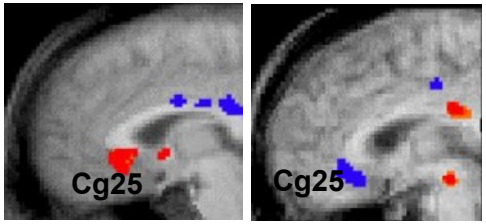
Outcome HAM-17 (Classic Dep Rating Scale)



Rationale



Goal



psychic pain
neg mood

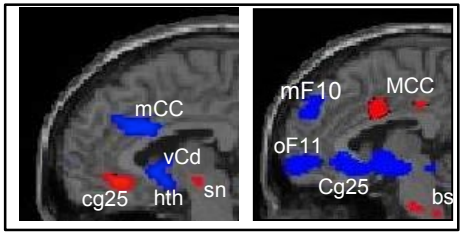
depression
recovery

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

Hypothesis: blocking BA25 will also change regions connected to it

Simple Minded Approach
unambiguous, go-no-go outcomes
TRD pts >4yr CE, >4 Rx, fail ECT, Ham>20

mechanism
CBF PET



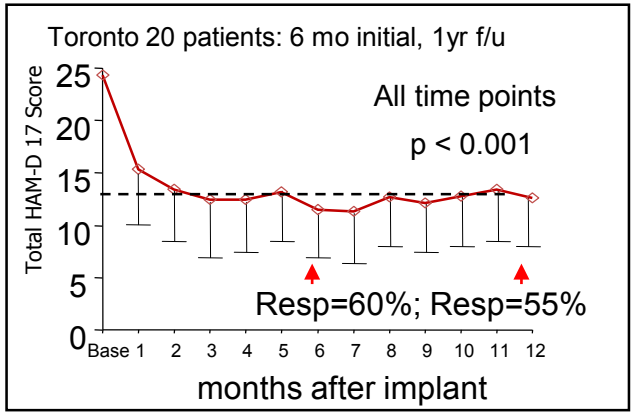
Baseline
Ham17=27±2

6m Change
Ham17=7.8±3

Phase 2: Extension, Replication, Maintenance

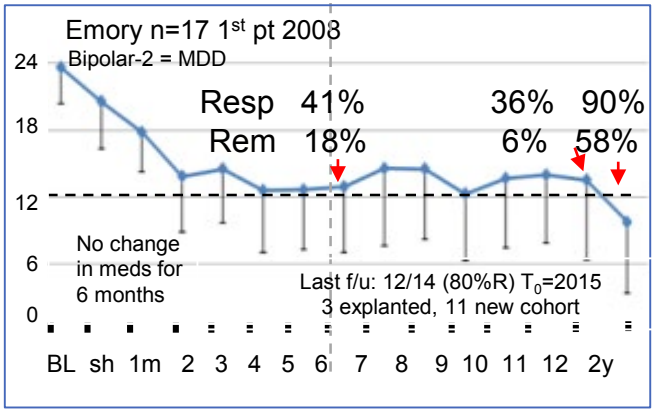
Expansion to other sites 2008-2012

6m open label, 6m continuation



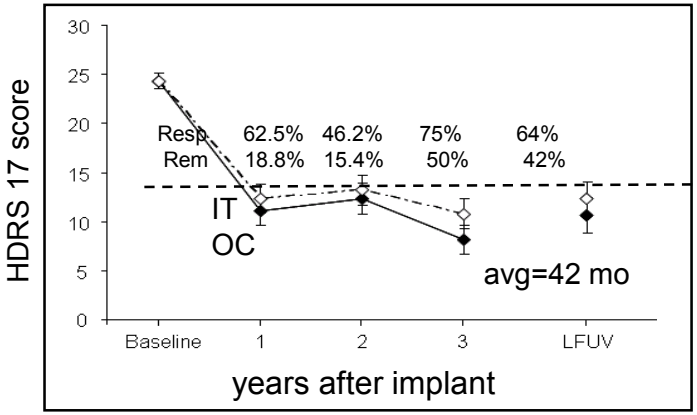
Lozano Biol Psych 2008

1 mo placebo single blind, 18m open



Holtzheimer et al. Arch Gen Psych 2012

Toronto n=20 Long Term f/u: 3-6 yrs



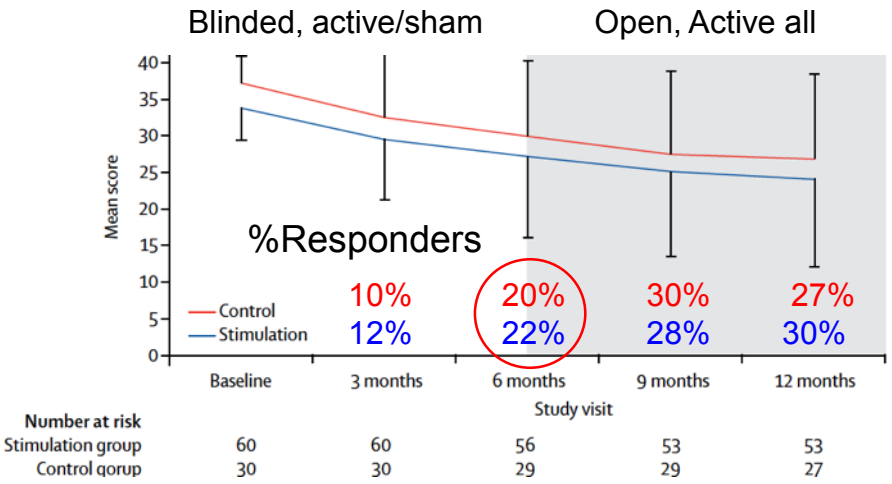
Kennedy Am J Psych 2011

Data presented
Jan 2014 BBRF
Webinar
(very optimistic)
New science underway

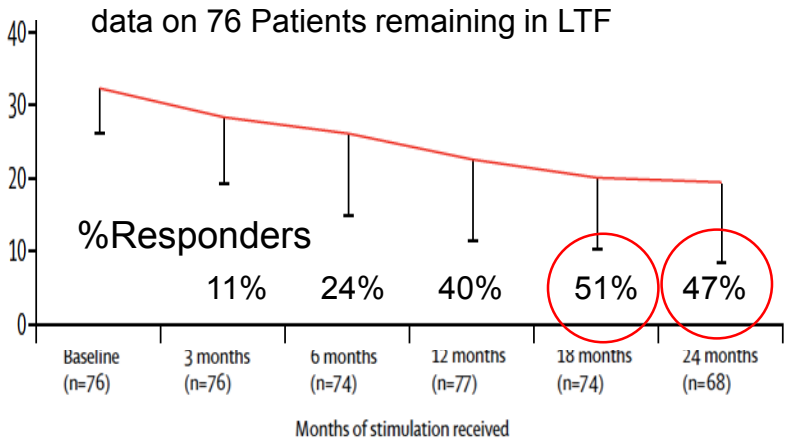
In Parallel: BROADEN Multi-center RCT

SCC DBS for TRD 2008-2014, published 2017

Part 1: Randomized blinded 6m; open 6m



Part 2: Long Term Follow-up, 2y active DBS



15 Centers: 200 planned/90 implanted/4 NR expl<6m
Study halted 2014; data on half of intended sample
Age ≈ 50 (47/90 female)
MDD (5 episodes lifetime)
Current episode duration ≈ *9-11 years*
Past treatments: *20 lifetime; 8 adequate Tx*
previous *ECT=80%, hosp=80%*

Progressive change over time
Contact changes ∝ improvement
No DTI to verify details
role of psychotherapy after 1 year?
Study end: min 2y; range 2-6y, battery Q2y
At study end: Explant or RC offered
Brio #44; Explant #37; Deaths #4; other #5

Holtzheimer et al. Lancet Psychiatry Oct 2017

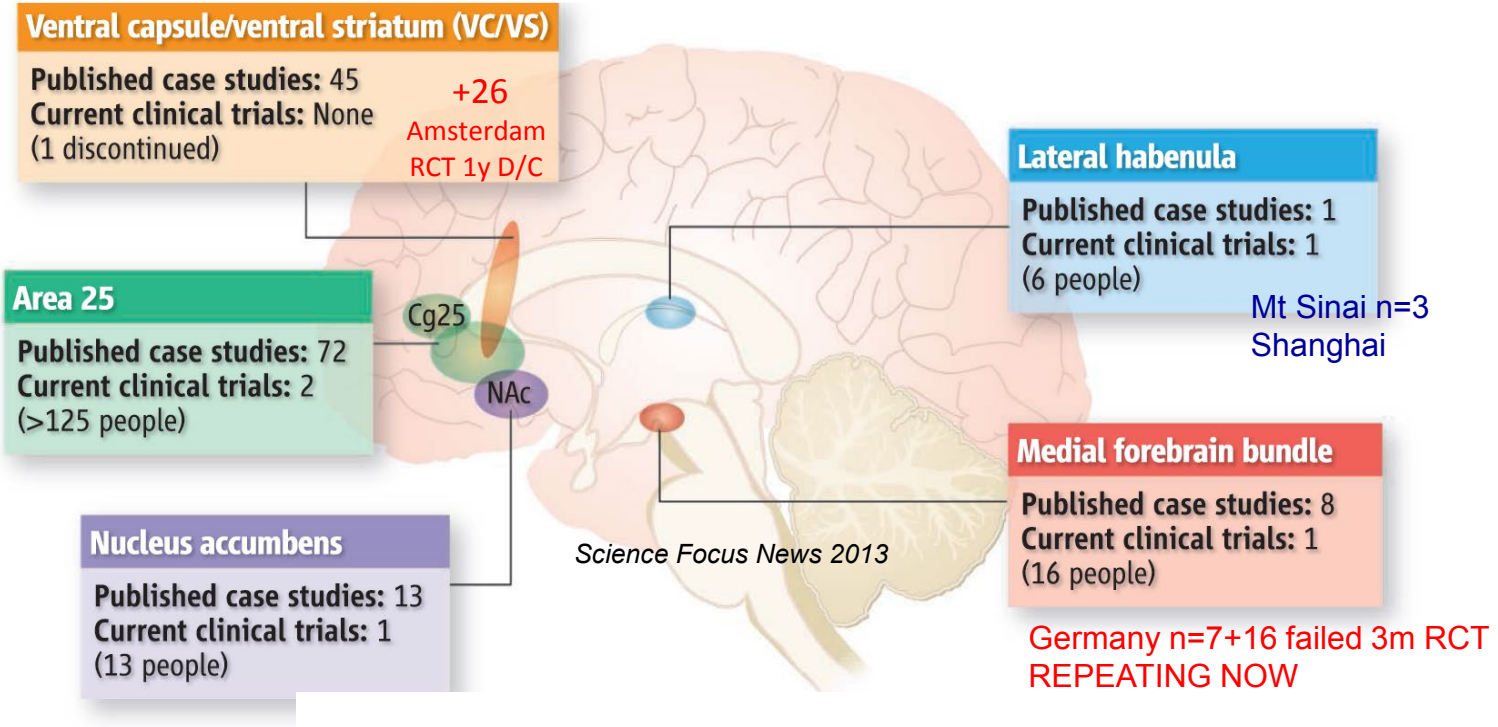
Sponsor: St Jude Medical

Other Centers, Other Targets, Other Logic

Open label ≠ RCT

MDT
RECLAIM
n=30
HALTED

SJM
BROADEN
n=90
HALTED



All Targets: ≈ 320 total pts implanted
SCC: 162 pts (+ >50 unpublished)
VC/VS: 71 pts
MFB: > 33 pts (ongoing RCT)

What are we missing?

Binary Public Response to 'Failed' RCTs

impact on patients and scientists

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Much-touted Deep-Brain-Stimulation Treatment for Depression Fails Another Trial

The much-touted deep-brain-stimulation treatment for depression has failed a second major trial.

By John Horgan on July 9, 2015 3

July 2015

New Scientist

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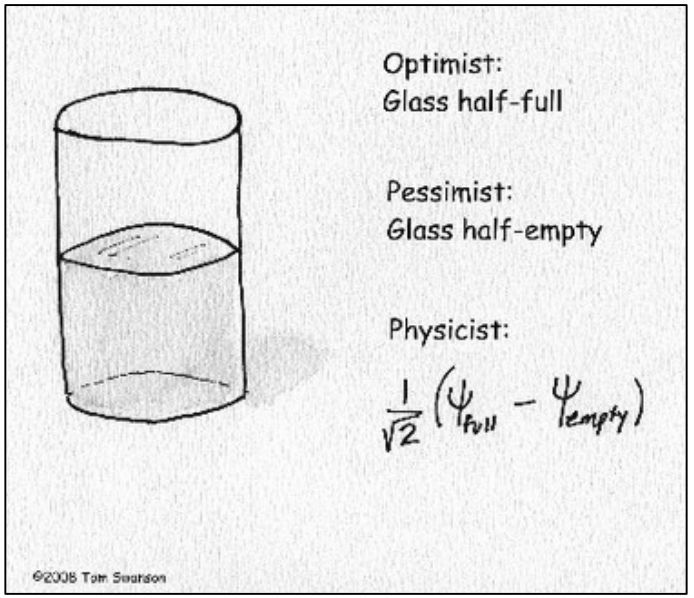
LEADER 21 October 2015

Lifting the gloom over depression and deep brain stimulation

The failure of two big clinical trials should be seen as a setback, not a terminal blow



First Question: Is it worth pursuing?

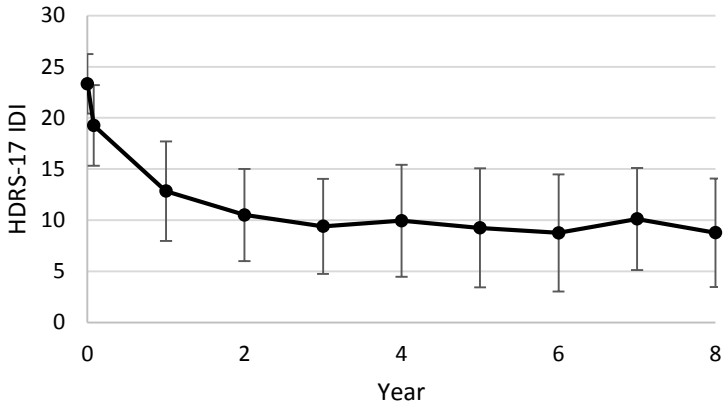
A Crowell

Emory Strategy: Follow the Data

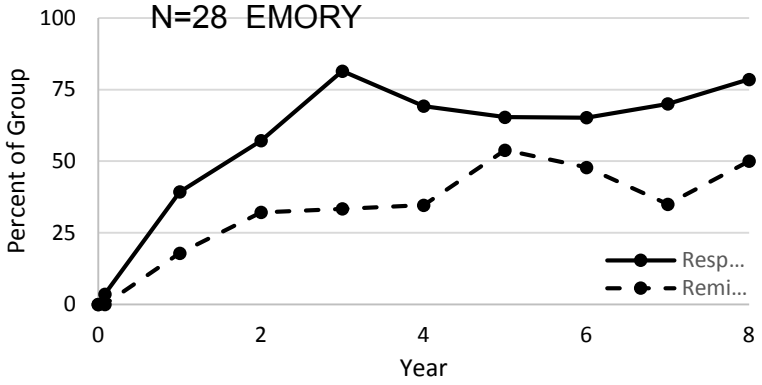
sustainability; discontinuation, relapse/recapture

P Riva-Posse

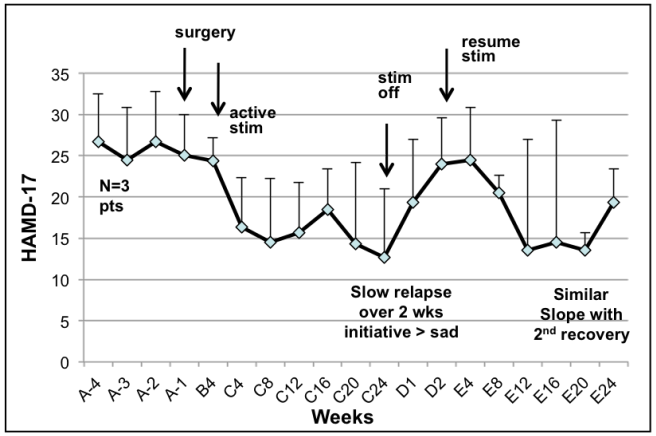
HDRS scores over 8 years



Response and Remission Rates

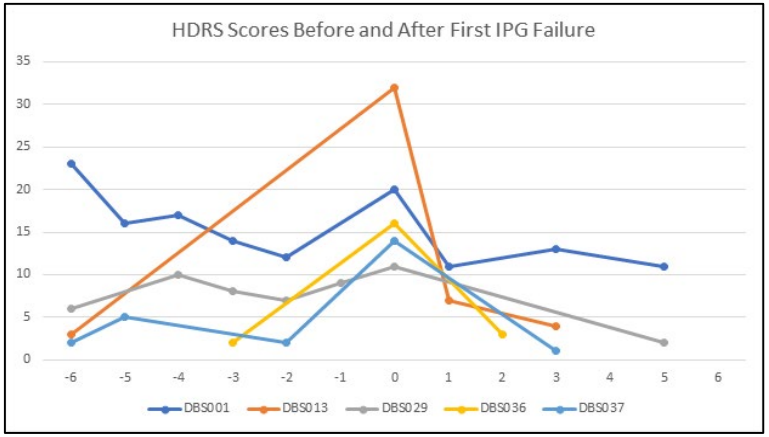


Blinded Discontinuation



Holtzheimer et al Arch Gen Psych 2012

Naturalistic discontinuation (battery failure)



A Crowell et al. Am J Psychiatry online Oct 4

How to Reconcile?

focus on responder / non-responder differences

1. WHO: patient selection, TRD subtyping.
2. WHERE: target selection, precision targeting
3. WHAT: Readouts of recovery, timecourse
4. HOW: parameter adjustments what/when to maintain
   Closed loop, on-demand, set-and-forget or fine-tune

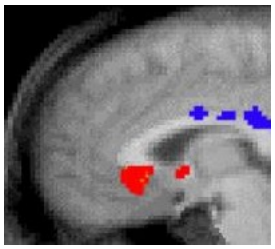
Needed at level of individual patients

Start where you can test a null hypothesis

Who: TRD Subtyping

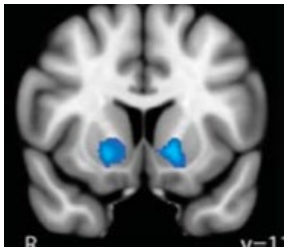
TRD patients are NOT homogeneous

Hi negative mood
psychomotor slow

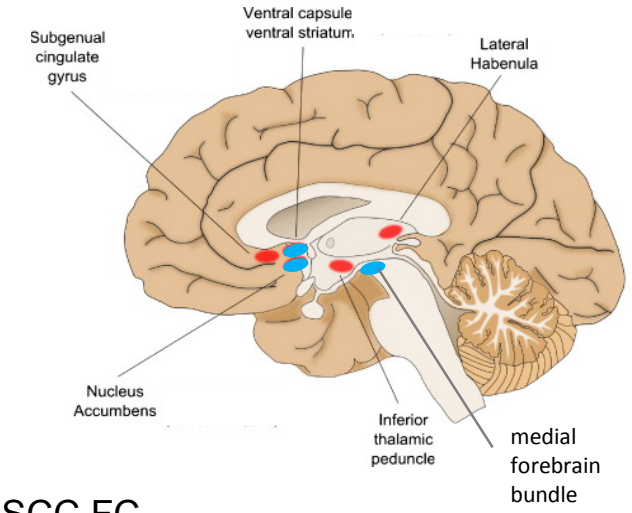


↑SCC25; ↓PM/MCC

Low positive mood
low motivation



↓ventral striatum



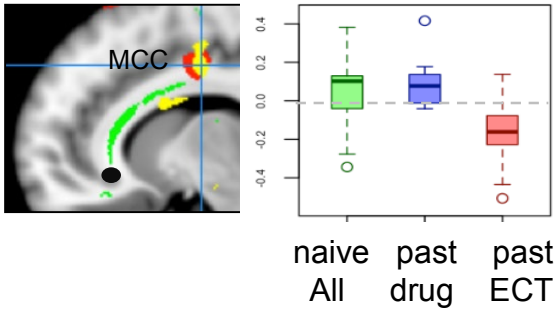
SCC FC

YIA: K Choi

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

Brain biomarker of eligibility?
regional abnormalities differ by
Type/number Past Tx failures

SCC FC fMRI
WM FA dMRI
CBF PET

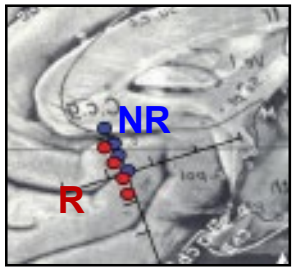


Where: Are we in the right place?

surgical targeting, contact selection, connections

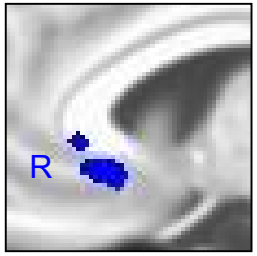
Location of Active Contact R vs NR

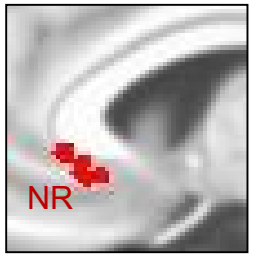
Toronto



Hamani JNS 2008

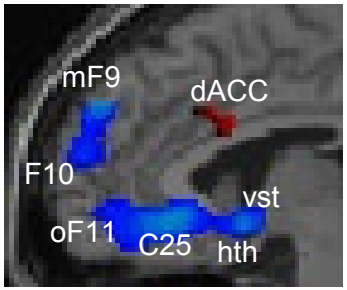
Atlanta



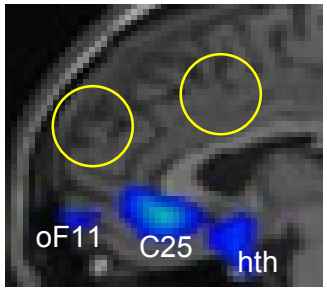


Riva Posse and Choi Biol Psych 2015

First Clue: Local and Remote CBF PET changes 2005

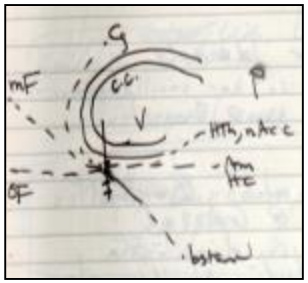


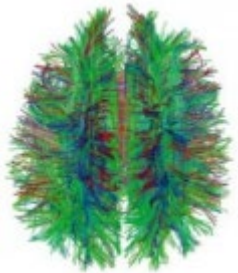
Responders



Non-Responders

Consider full network not just the target

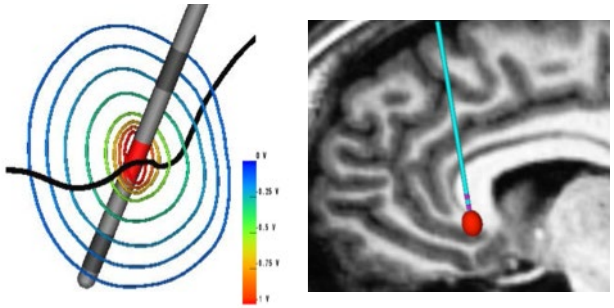




diffusion MRI

Characterize Common Response 'Circuit'
necessary and sufficient network not a single region

Voltage Field Model
Volume of Tissue Activated



Butson & McIntyre Brain Stim 2008

TAM as seed for DTI
Using specific DBS lead,
WM tracts/location
Indiv stim parameters

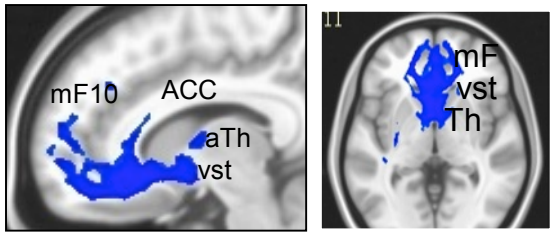
C McIntyre
(Case)

K Choi

P Riva-Posse

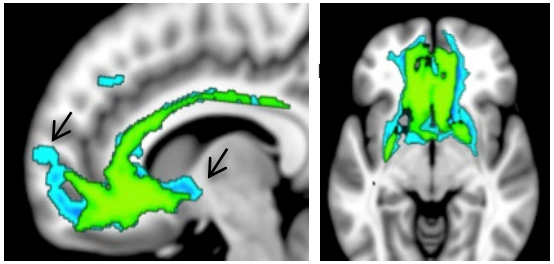
Probablistic Tractography

6 mo
Resp
N=6



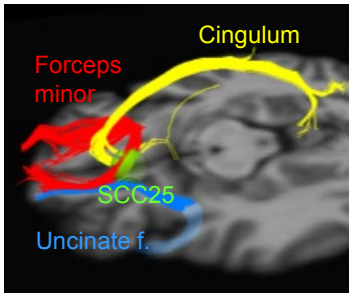
Modeled Voxels
common to all 6m R
same map in all 2y R

NR to R
w/ contact
change
n=5



impact missing
mF and thalamus

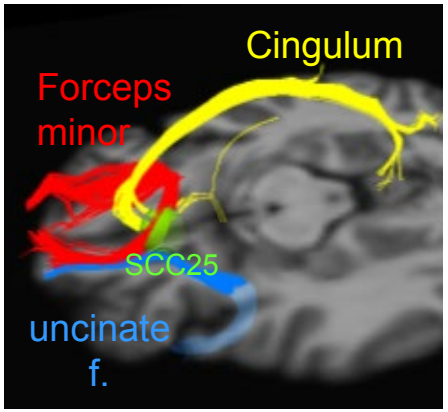
Riva Posse and Choi et al Biol Psych 2015



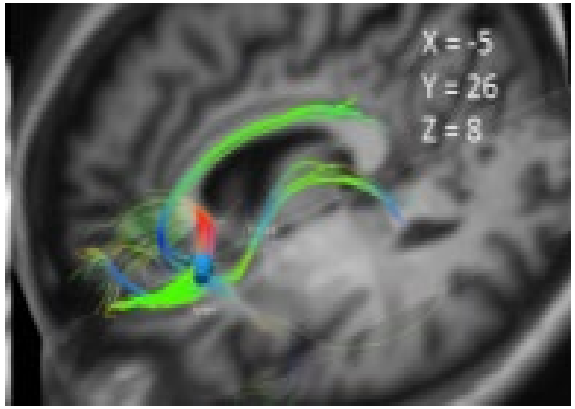
PutativeTemplate
For targeting

Test Benefit of Multipath Targeting Method

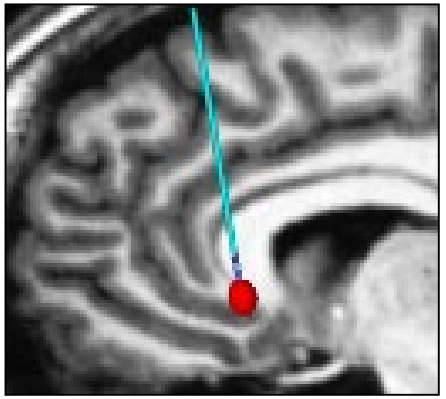
‘Connectomics’ surgery as concept



Target Blue-Print

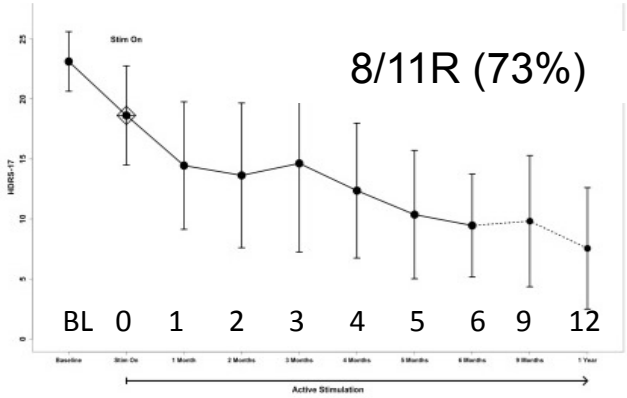


d-DTI in single Ss



Model of Planned VTA
Stim at predefined location

1. Awake testing in OR
2. Chronic DBS at DTI target w/o contact change over 6m
3. single current increase

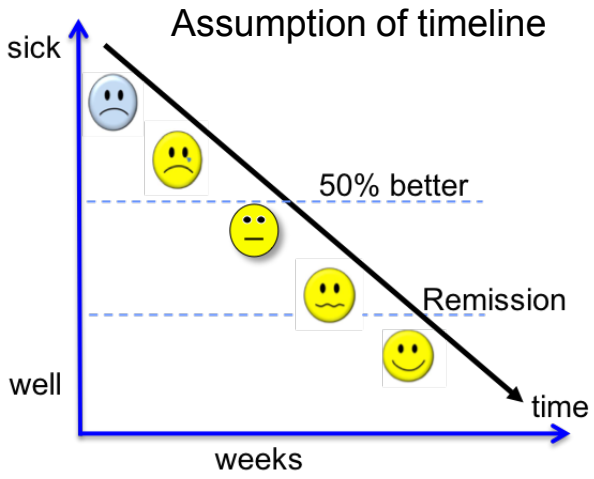


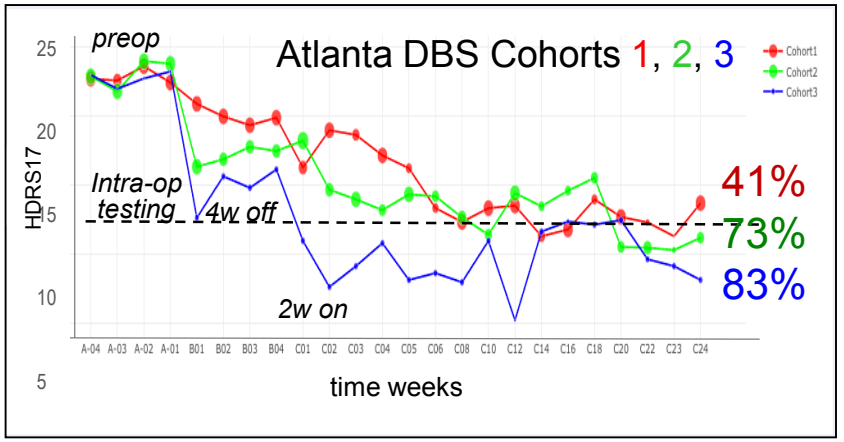
response trajectory

Riva-Posse and Choi et al
Molecular Psychiatry 2017

Further Impact of Target Optimization

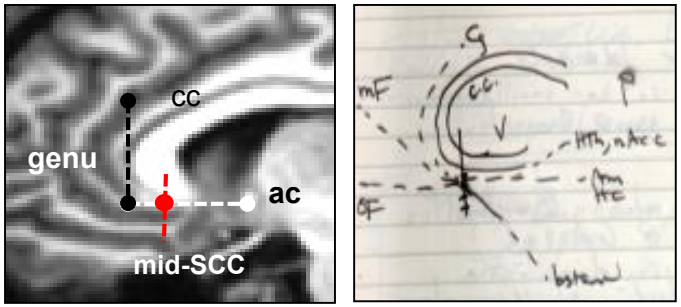
discovery that recovery is not linear





Rate is higher; AND timing is different

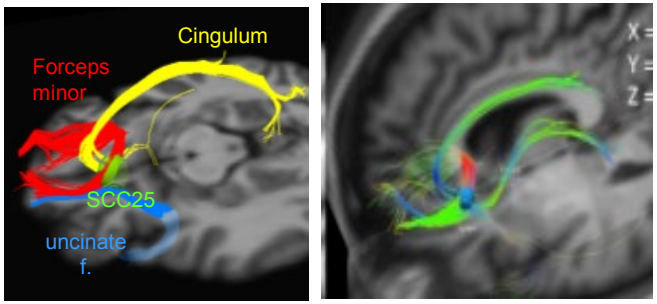
Cohort 1



Anatomical target; derived DTI template

Arch Gen Psych 2012

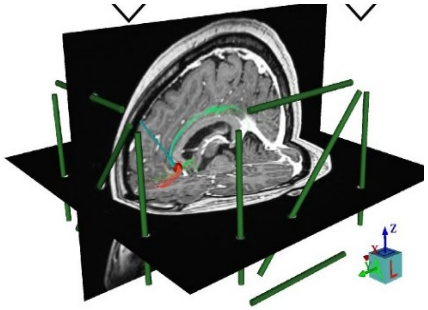
Cohort 2



prospective testing DTI Template

Molecular Psych 2017

Cohort 3

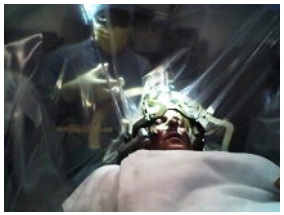


Real time DTI

UH3 in progress 2018

Models to Account for Observed Trajectory

clues to mechanisms; critical for revised study design



First DBS

1

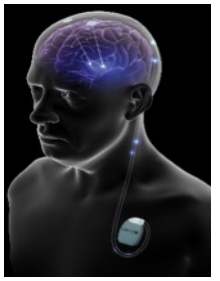
Network Reset/Switch
acute, rapid

What ever you just did, I just suddenly shifted …

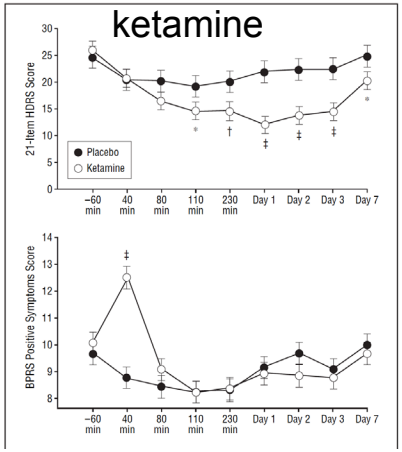
2 3

Network Plasticity
delayed, progressive

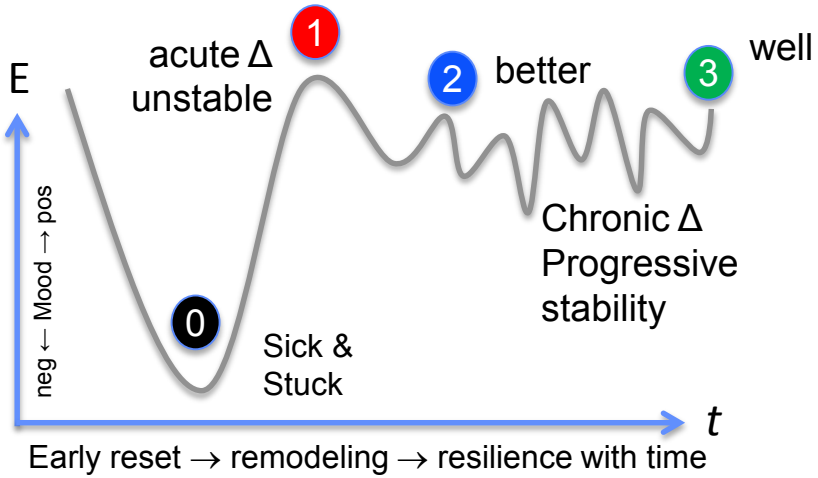
…I didn't realize how much work I would need to do myself..

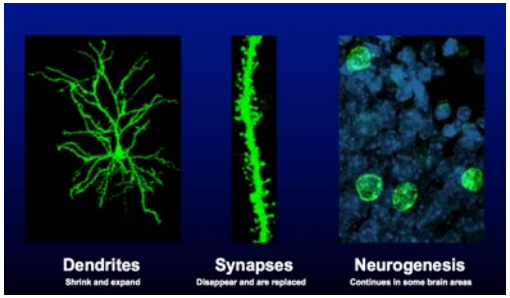


Chronic DBS



Zarate 2006



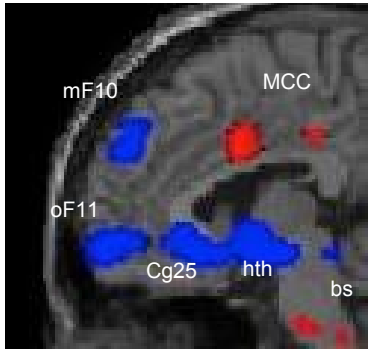


Need differential metrics/temporal sampling for different stages?

Evidence of Differential early/late effects

PET CBF changes

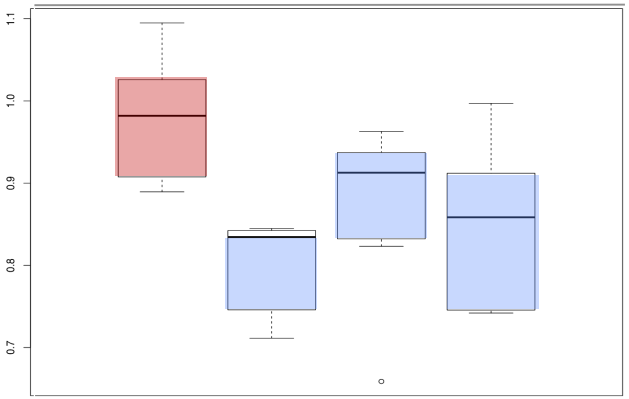
Jungho Cha



First Toronto Findings:
same change pattern
3 and 6 months
of chronic DBS

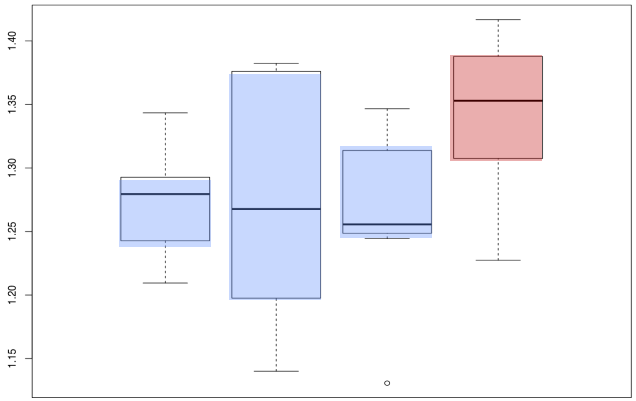
PET Δ Early

Network (Cg25, mF, Ins)
Carryover from stim in OR?



PET Δ Late

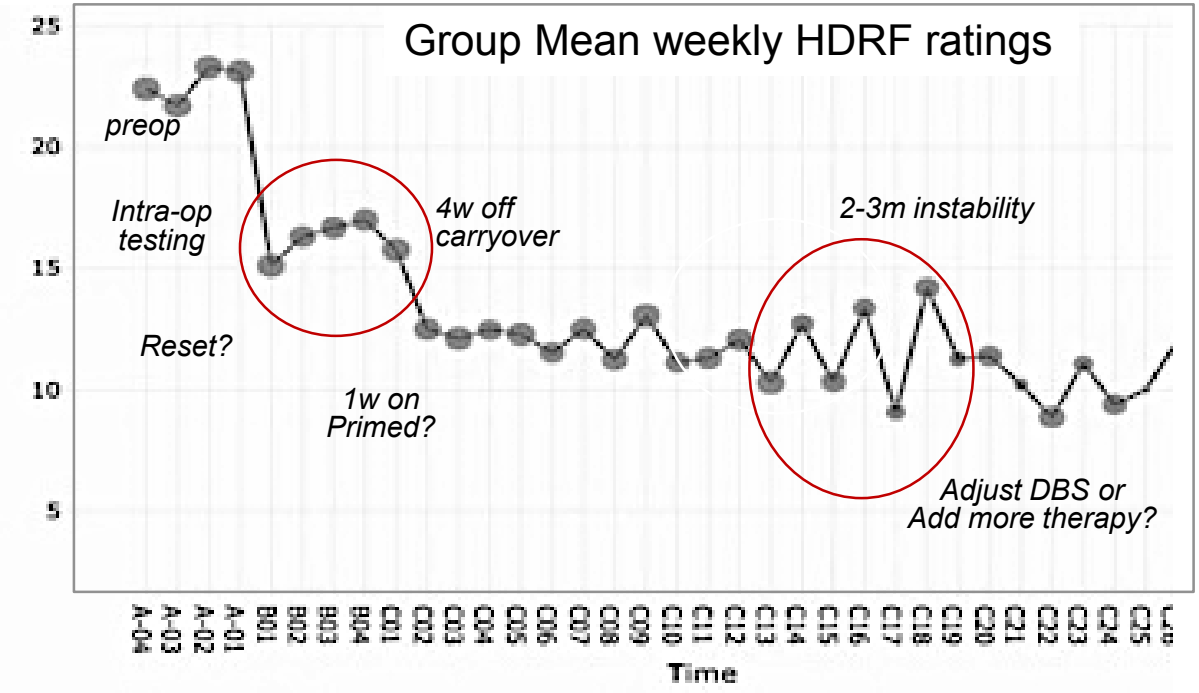
Non-network (Lat PF, PCC + pIns)
Change only with active DBS



Need strategy that captures acute changes
and progression over time with higher temporal resolution

Why does this matter?

(Trial endpoints, treatment adjustments)



NOW: Use the Same DBS settings for all Phases

BUT: Variable response rate in individuals

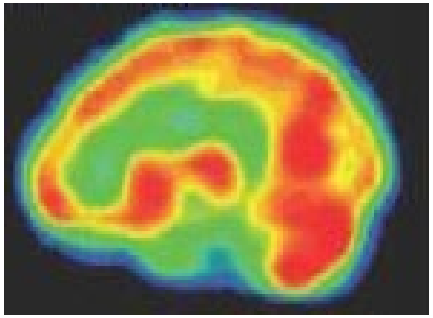
NEED: longitudinal readouts of brain + behavior— relapse vs life stress

HYPOTHESIS: different phases show different effects.

individualize to optimize treatment delivery.

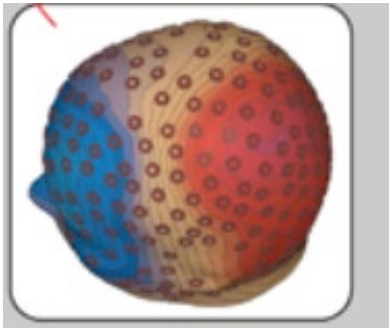
Tracking Chronology of Stimulation Effects

Gen-2 devices: causal models, candidate control signals

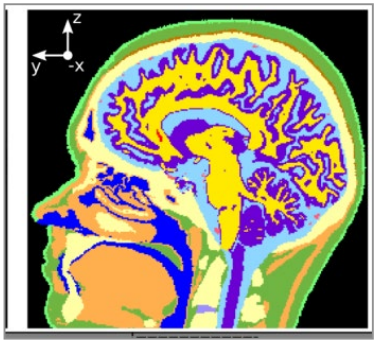


CBF PET
fixed time points

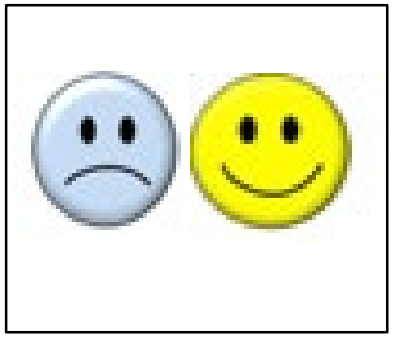
Activa PC+S
ongoing SCC LFP



EGI-hdEEG
intermittent cortical

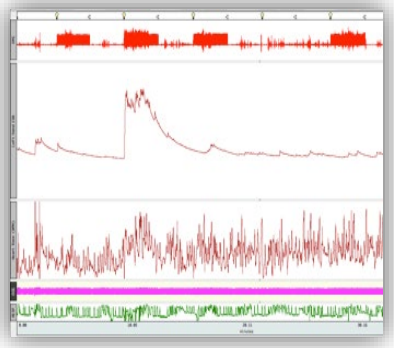


Pt specific
biophysical Models

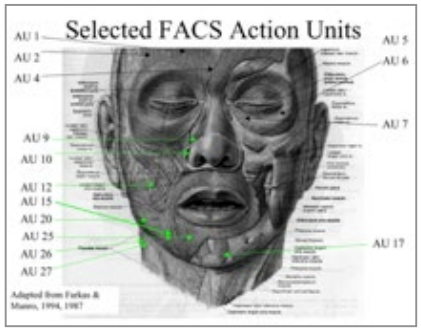


self-reported
mood, ratings

movement
actigraphy, GPS



autonomic
SCR, Heart Rate



emotion expression
video, face mm, voice, words

Revisit first exposure to DBS in the OR

Monitor patient's worst symptoms

pain *paralyzed*

gnawing *vortex*

disconnected *sticky* *buried*

dead *void* *quicksand*

unrelenting

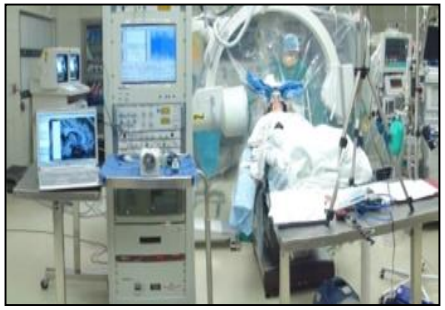
what, when, where change happens?
Don't want to miss potential reset.

K Choi

Characterizing the ‘Depression Switch’

pt self report: first evidence of target engagement?

P Riva-Posse



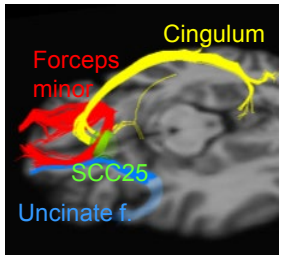
DTI, randomized stim
130Hz 90us 6mA
9 patient: R/L leads
8 contacts, 108 trials

Type 1
interoceptive change

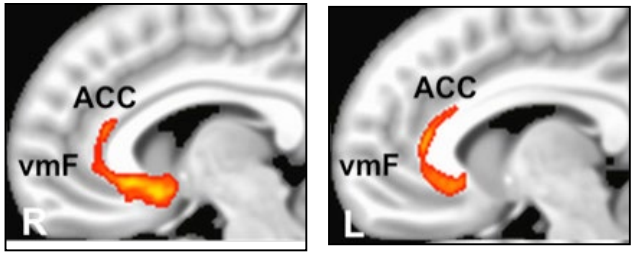
- I feel lighter
- I feel less heavy
- I can breathe
- the tension is gone
- the pain is gone

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

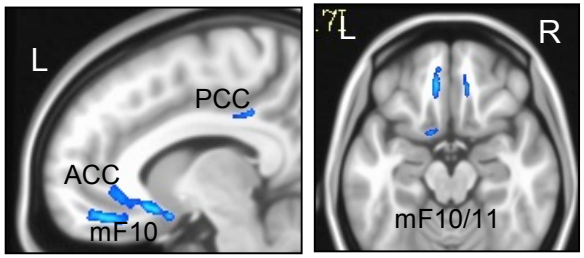


30/72 active; 4/36 sham; 17L, 3R



Type 1: Cingulum Bundle

9/72 active (all L); 0 sham



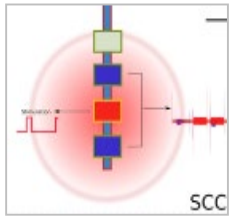
Type 2: CB + Forceps Minor

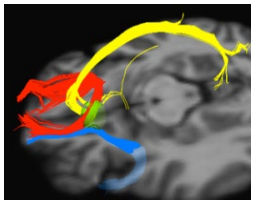
Choi and Riva Posse et al
JAMA Neurol Sept 26, 2015

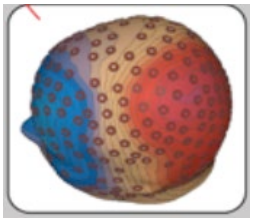
A Waters

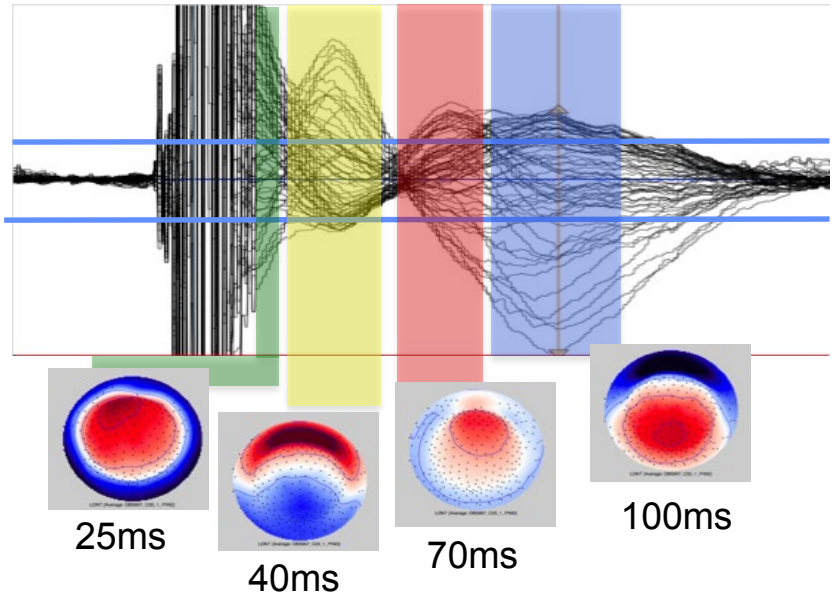
Cortical Readout of Optimal Target

Confirmation in lab prior to starting DBS



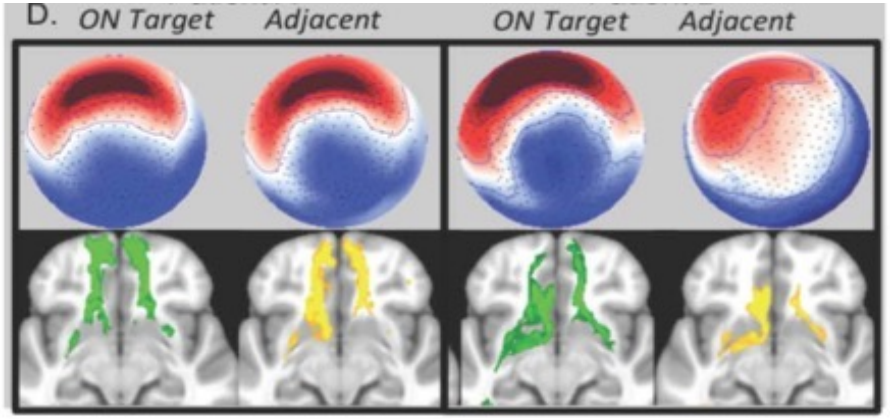






2Hz ERP **ON** Target
based on DTI
Grand Average; n=4, 15 sessions

Patient A Patient B



"ON TARGET" CONTACT	ADJACENT CONTACT	"ON TARGET" CONTACT	ADJACENT CONTACT

Single Subject
ON vs OFF Target
Anatomical specificity

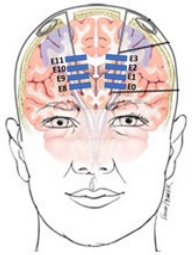
Next step: OR verification

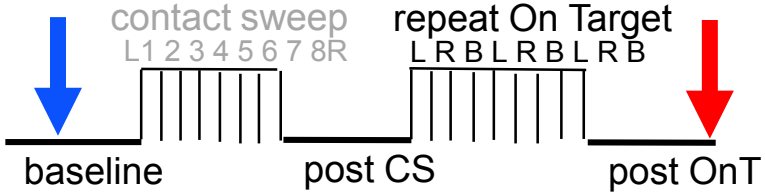
Waters et al. Human Br Map 2018

Mo SE-Sendi

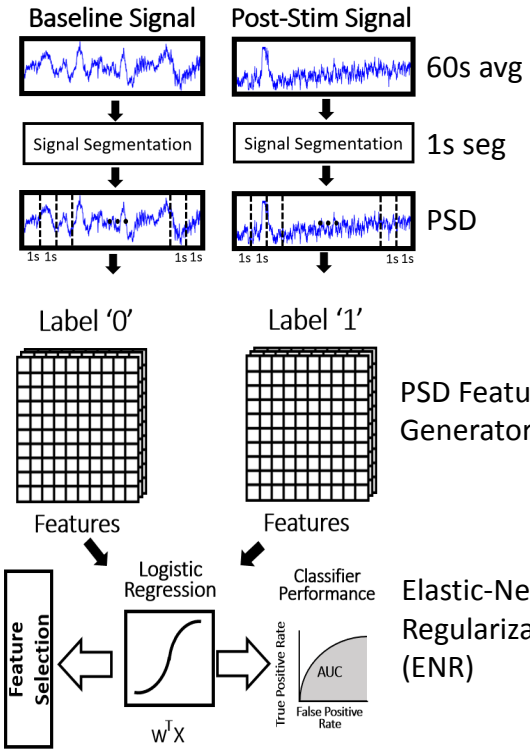
LFP Readout of Depression Switch

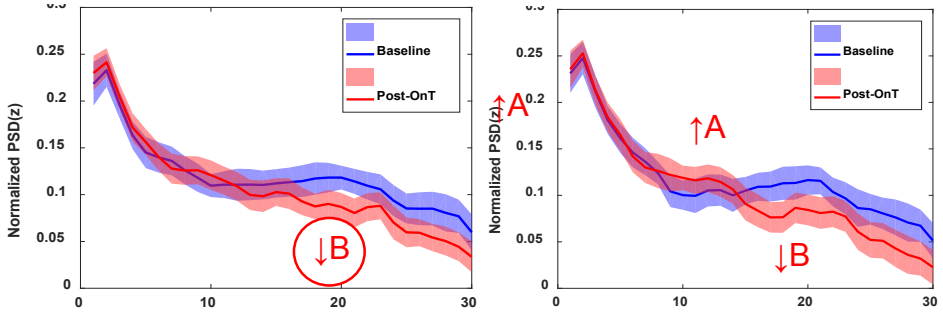
repeated bilat DBS at target in OR

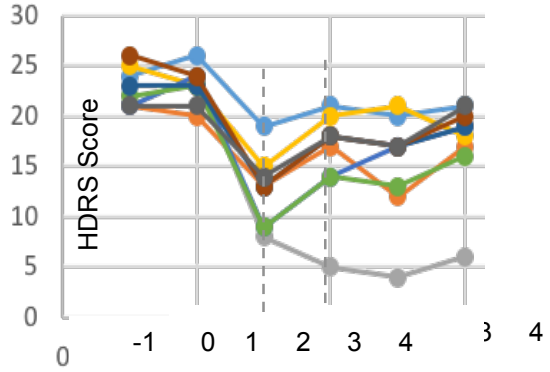




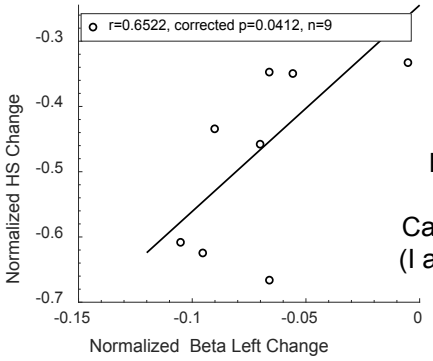
Tension is gone,
I can move







Evidence of carryover. 1-2 weeks



Beta change
Tracks with
Carryover effects
(I am doing more)

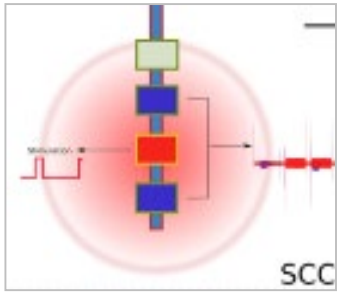
A Veerakumar

SCC Weekly Readout

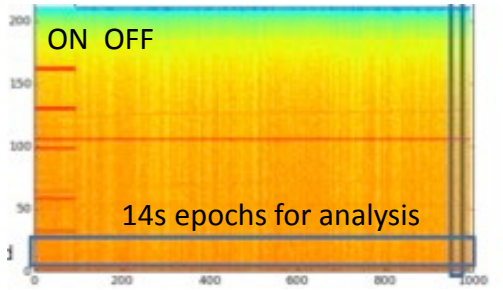
first step towards closed loop DBS delivery

B Voytek

SCC recording montage

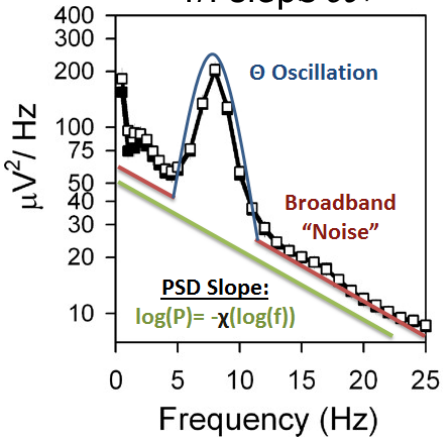


PC+S Chronic recording

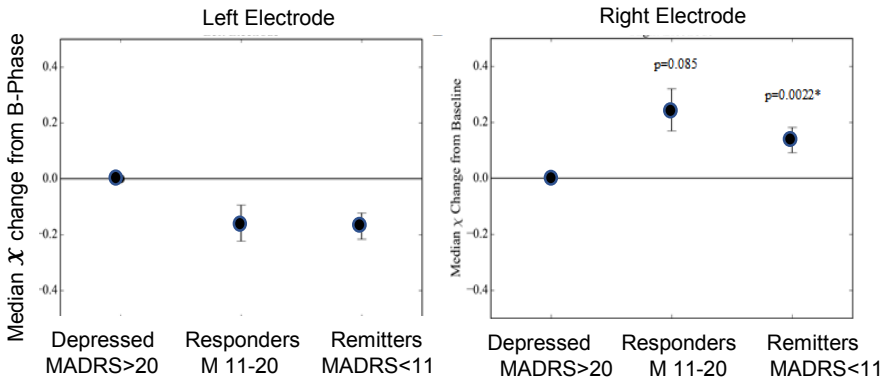


DBS off, weekly lab assessment

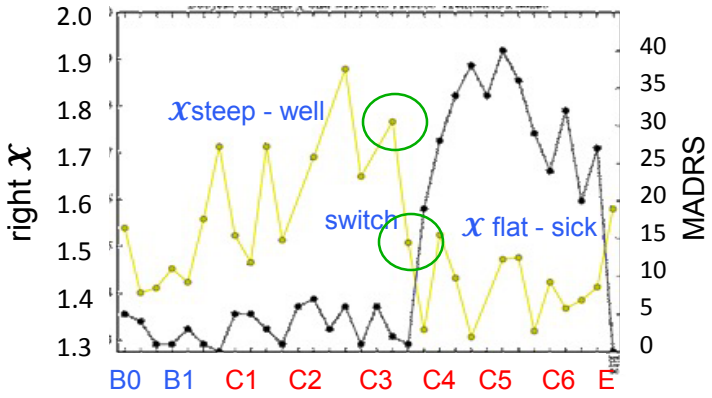
1/f slope $\mathcal{X}$



Slope and Depression Severity regardless of TIme



Single Subject Weekly Slope vs Dep Score



Slope changed 1 week before Clinical Relapse
Putative predictive signal to trigger adjustment

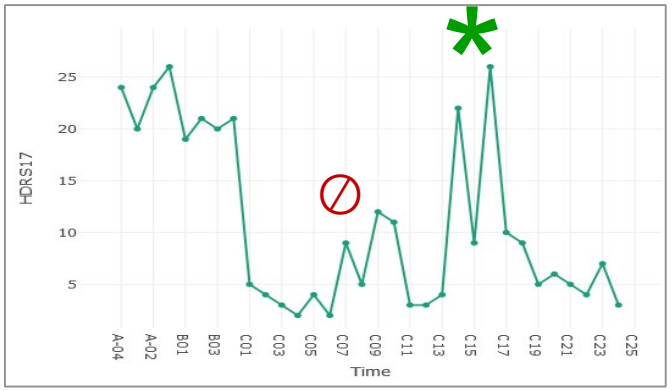
Veerakumar et al J Neurophysiology 2019

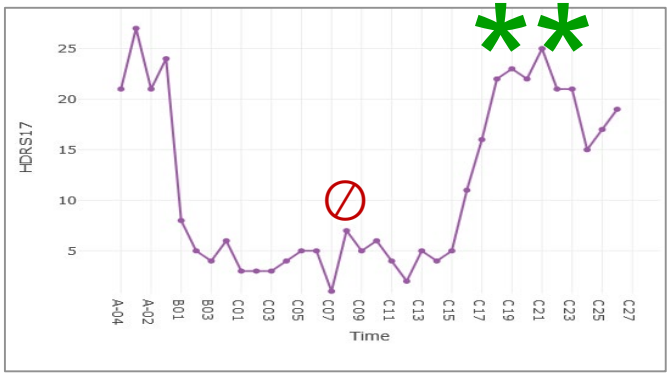
Readouts without Brain or Self-Report?
quantify what seems obvious

DBS 35 preop 1 year of DBS

They look different*
They move more
They do things
They feel better

Distinguish stalled response, impending relapse, transient life stressor





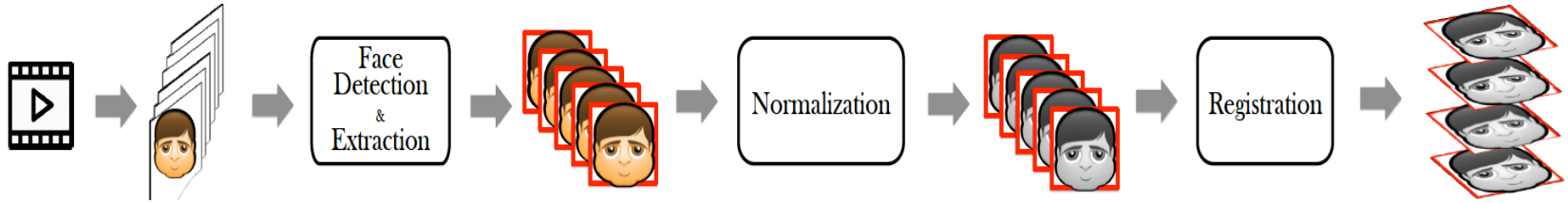
Rating Scales intuitively less reliable with time

S Harati

Tuning DBS based on Facial Expression

Distinguish depressed vs stressed vs well

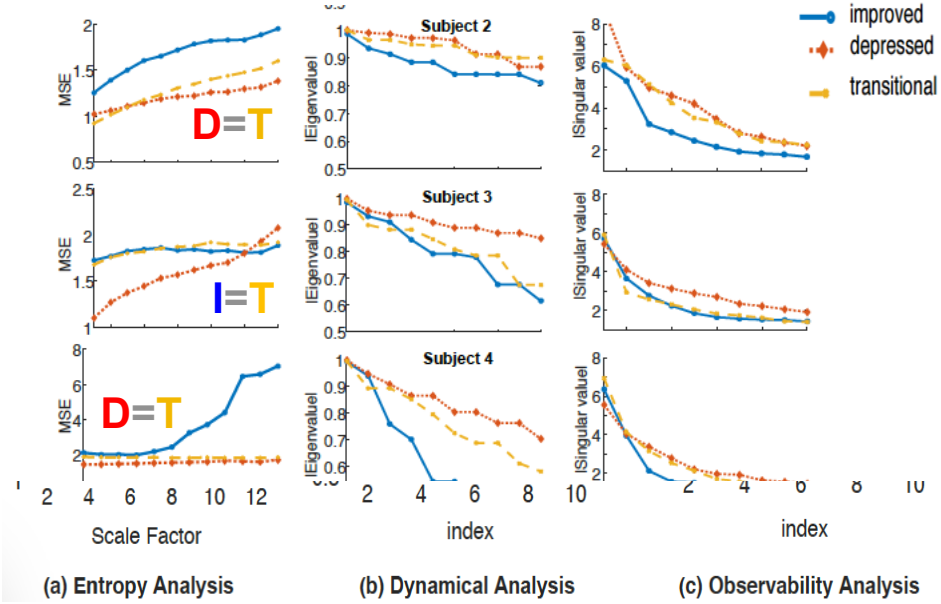
A Crowell



video interview n=9; weekly x 6m
2min clip, spontaneous speech

3 Videos @ patient
Psychiatrist selected
Sick
Well
Rough

What does the face say?



Use to guide dose adjustments

Sahar Harati, Andrea Crowell, HM, Shamim Nemati; IEEE Engineering in Medicine and Biology Society 2016

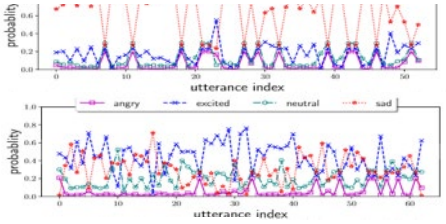
S Harati

Behavioral Tracking
6 mo Outcome Predictions

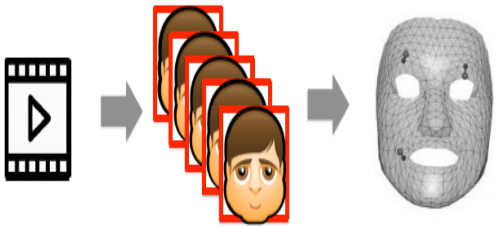
A Crowell

What biomarker best tracks response?

Voice print

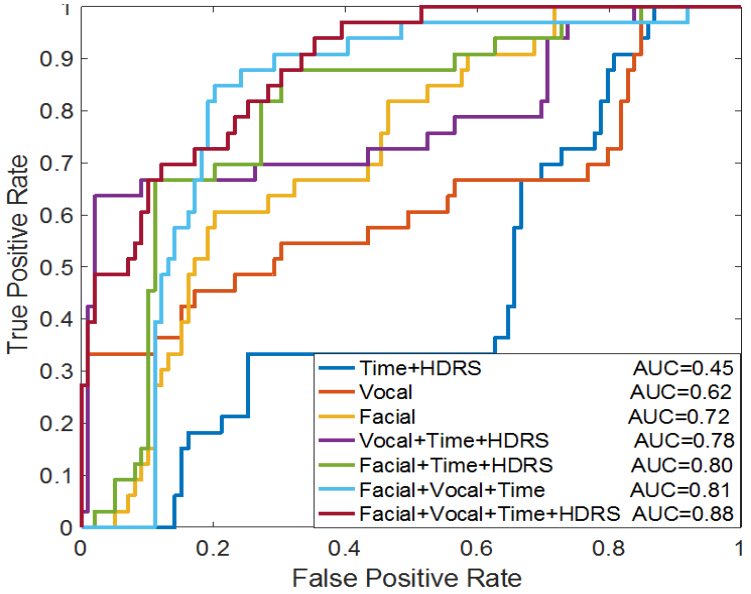


Face print



self-report Rating scales

Can you predict <u>when</u> a Patient will Recover?



Face-Voice 8-11 wks Predicts 6m Outcome
Min added value of Rating Scale

Hypothesis:
SCC LFP might better track such behavioral readouts than severity scores


K Choi


A Waters


D Obatusin

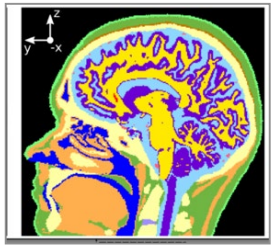
Q-Lab at C-ACT
quantitative biometrics


S Scherrer

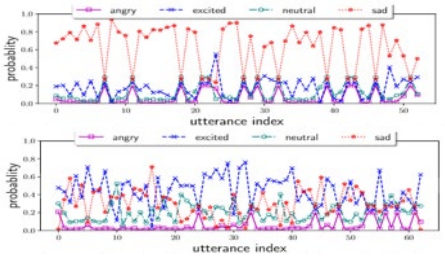

D putrino
Rehab


M Phillips
Designer

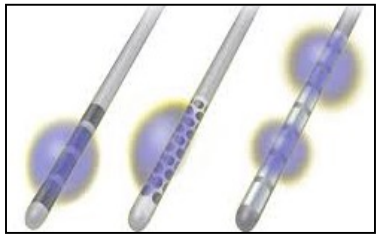
Hi
Imaging
Biophysical
models



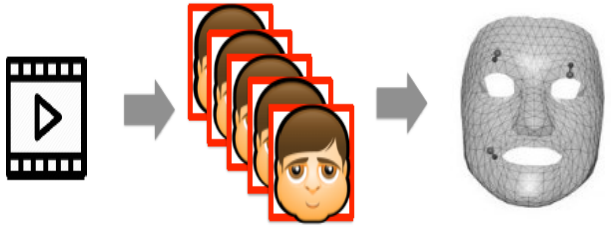
Voice print



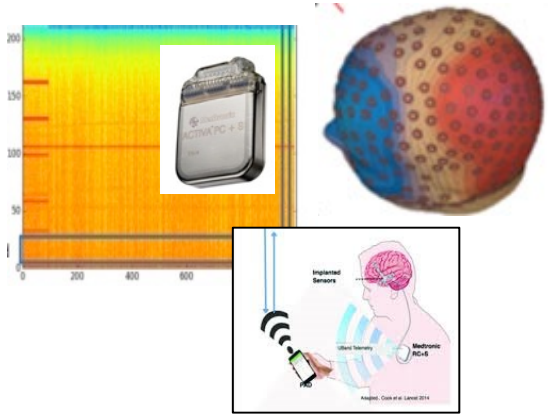
Steerable
Network
Control



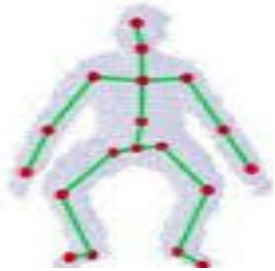
Facial
Expression



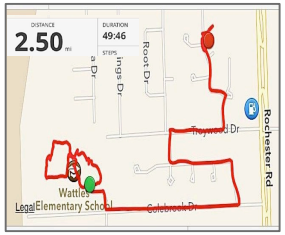
brain
readouts



Activity



movement
dynamics



contour maps

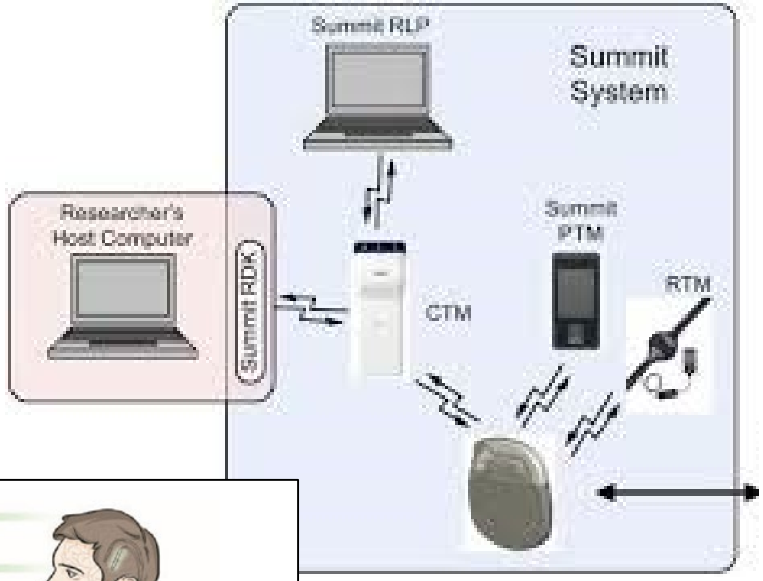
MSSM Experiments
Winter 2019 start

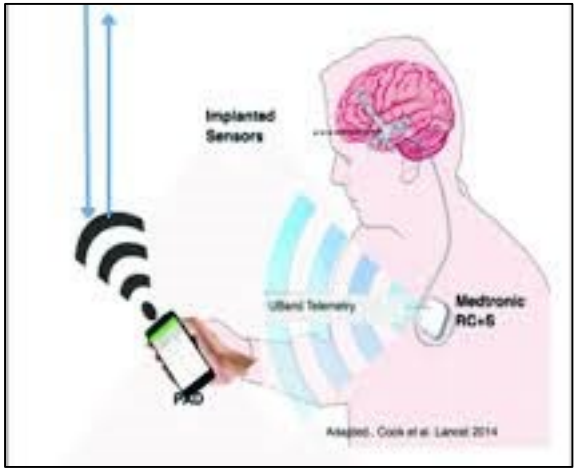
D Obatusin
Mt Sinai

F Afzal

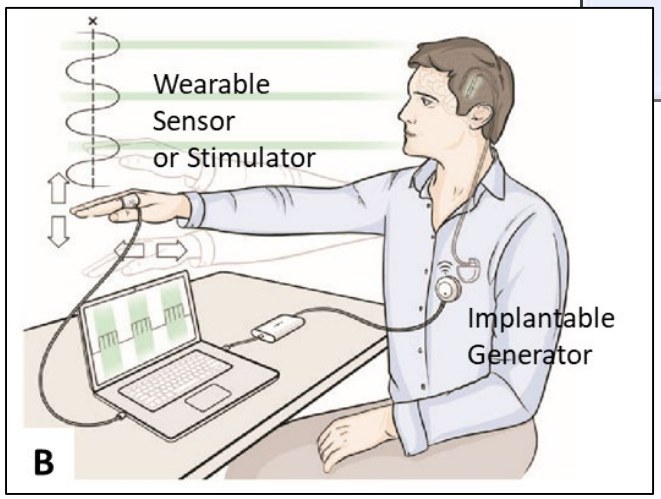
T Denison
Oxford
OpenMind

F Jamshed
Oxford

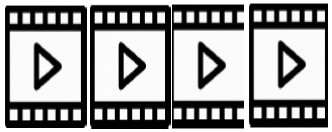




Worrell IEEE J Transl Eng Health Med. 2018



Toth and…Denison Oxford 2019

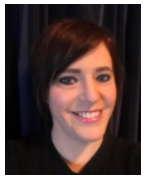


Face + Voice +
Time + ratings
Inputs to model

B Kopell.

M Figee.

S Oneill

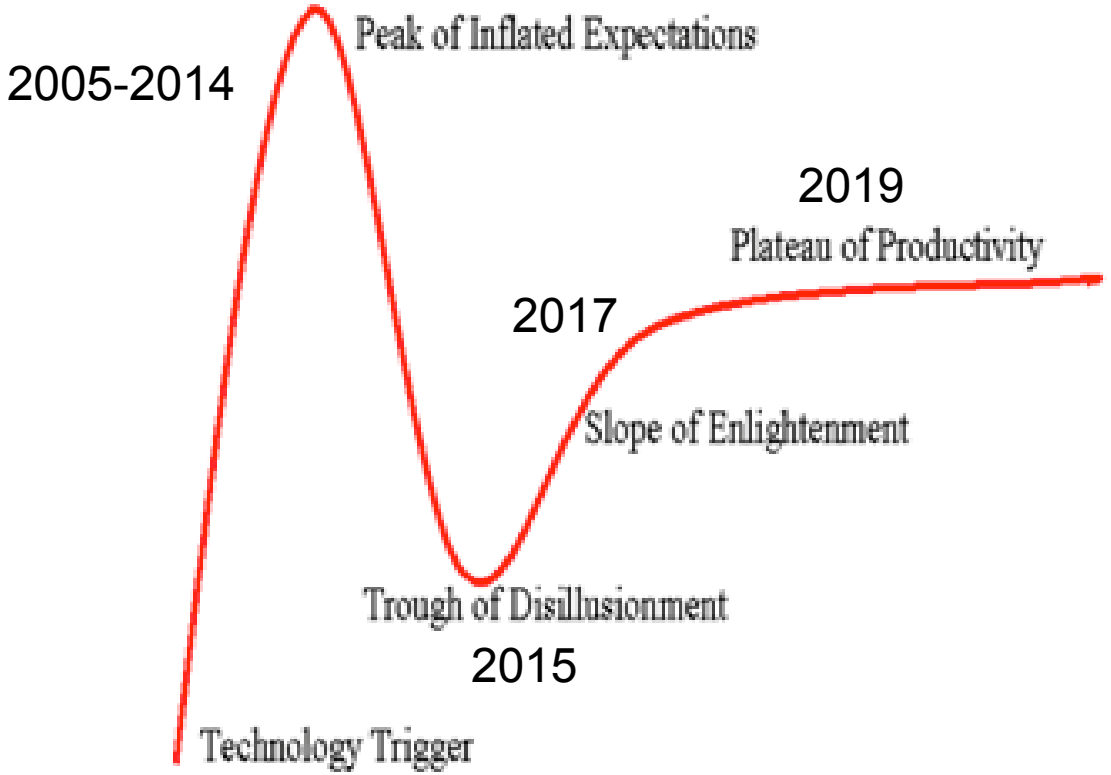


J Gowatsky

L Pagan

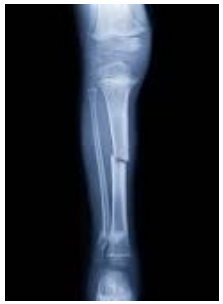
Neurotechnology and Treatment

Evolution not Revolution

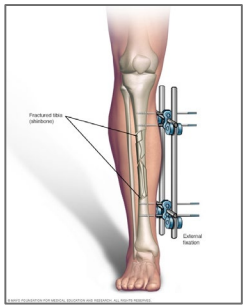


Recovery takes more than a Stimulator

necessary but not sufficient

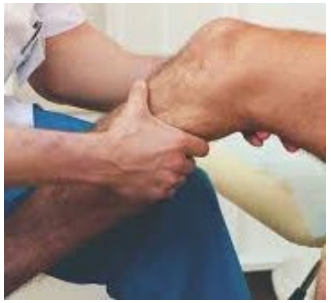


Broken



Reset

Remodel



Rehab/Retrain

Relearn

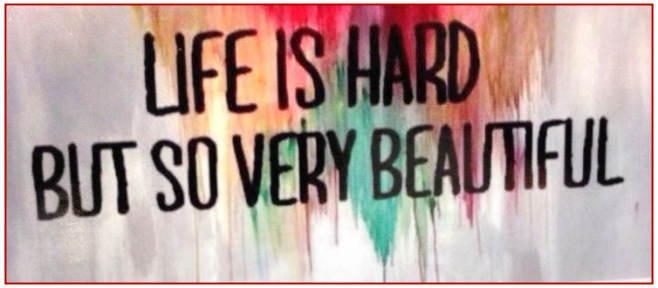
Plasticity

- WANT: meaningful symptom relief, sustained, durable (relapse prevention)
- NEED: Rehabilitation strategies that maximize recovery (resilience)
- LEARN: distress ≠ depressed. (Define readouts that can tell the difference)

Bottom Line: How would you live your life
if relapse was the exception and not the rule?

What do Patients Think?

they get it, but it takes time



I have a lot of learning to do.
I sometimes feel quite lost.
But it is nothing like before.
I'm just trying to figure out who I am
and where I'm headed.
I'm somewhat unhappy,
and I'm definitely overwhelmed,
but I'm not sick.

Emory #17 (3/10/12)

For More Information

Nash Family Center for Advanced Circuit Therapeutics
https://icahn.mssm.edu/research/advanced-circuit-therapeutics

Helen.mayberg@mssm.edu