Deep Brain Stimulation and Depression: A Decade of Progress

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Brain & Behavior Research Foundation Webinar
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Disclosures

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

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

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

issued March 2008, St. Jude Medical Inc, assignee

Consultant:  St Jude Medical Inc / Neuromodulation Division
DBS Team

University of Toronto

A Lozano  S. Kennedy  C. Hamani

R Gross  P Holtzheimer  S Garlow  P Riva Posse  A Crowell

Neurosurgeroy

Psychiatry and Psychophysiology

Imaging: DTI, PET, fMRI, Modeling

Electrophysiology

Animal Models

Affective/Cog NS/Psychology

Psychotherapy

Biostats

Patient Coordination

K Choi  C McGrath  J Rajendra  C McIntyre  O Smart  V Tiruvadi  D Rainnie  T Madsen

S Hamann  C Inman  L Ritschel  C Ramirez  M Kelley  S Quinn  M Woody
Context: Proof-of-Principle Pilot Study 2005
6 month open-label, chronic, continuous DBS in 6 patients

Pre-op MRI
Post-op MRI
Pre-op PET
Δ 6 months DBS

Electrode Targeting
Confirm electrode placement
Pts vs Controls
Responders

Funded by NARSAD, Toronto Western hospital
Status Quo: treatments available; not always effective

< 40% achieve remission with first treatment
no reliable biomarkers to guide treatment selection
relapse, recurrence common

~ 10% become treatment resistant over time
only experimental options if fail ECT (ablation, VNS, ketamine)

Thinking 2001: Neuromodulation as a Potential Strategy

1. Advances in stereotaxic neurosurgery
2. Experience in other neurological disorders
3. Knowledge from structural/functional imaging
Prototype Neurological Disorder
DBS for Parkinson’s Disease

Diagnosis
Syndrome → Pathology

Treatment
Pathology→ Chemistry

Rx
L-dopa 1963

Benabid et al. Appl Neurophysiol 1987
Delong, Alexander, Strick 1986

Hi freq
130Hz
DBS

Circuit Tuning

Circuit Lesions

Define Circuits

STN DBS. Courtesy Andres Lozano U Toronto

FDA approved 1997 ET, PD 2002
>100,000 pts implanted.
No Δ basic technology in 25 yrs
Can we Treat Depression Like PD?

Critical Questions:

• Is there an “illness” circuit
• What changes are necessary/sufficient?
• Where should we stimulate?
• Which patients?
Defining Depression Circuits
Deconstruct syndrome into component dimensions

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

Adapted from Alexander, Delong, Strick 1986
Step 1: Define candidate regions in circuit
Imaging studies of structure and function

Focal Strokes ↓ MRI volume, Glia ↓ MRI volume

Robinson 1983
Drevets 97; Ongur 98
Sheline, 1999

Parkinson’s        Unipolar        Bipolar

Mayberg et al. AJP 1988
Starkstein Brain 1989
Ann Neurol 1990
Neurol 1992
J Nuc Med 1994
NeurReport 1997
J NPCNS 1997
Baxter et al. 1985
Kruger et al. 2003

Variability

Baxter AmJP 1985

Early clues to possible subtypes?
Step 2: What regions change with treatment? treatment specific effects

Emotion Regulation
Self-awareness
Insight

Is one node, compartment, or behavior most critical?

Mayberg J Neuropsych Clin NS 1997
McGrath et al JAMA Psych 2013
Step 3: What are core clinical features are key?

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

“Psychic energy throttled back close to zero. Nearly immobilized, a trance of supreme discomfort.”

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

Hypothesis

Map Negative Mood Directly

Personal sad memory CBF PET

William James 1902

William Styron 1991

Toronto DBS #7
Step 4: Isolate necessary and sufficient regions
Converging findings in the subcallosal cingulate SCC25

Sad Memory

Increased sCg25 with induced depressed mood

Tryptophan Deplete

Mayberg

Talbot

↓volume; ↓glia

Hypothesis:

TRD = dysregulated SCC25.
Target this critical hub

SSRI

SNRI

Placebo

Decreased SCC25 with diverse successful treatments

SSRI

SNRI

Placebo

↓SCC25 activity

Mayberg

Kennedy

Mayberg

rTMS

ECT

VNS

George

Nobler

Pardo
Back to the Beginning: Area 25 DBS for TRD
Pt #1 May 13, 2003 Toronto

Depression Circuit Model
- Attention-cognition-Action
- Cg 25
- Cg 24a
- pm F6
- dFr 9/46/10
- inf Par 40
- dCg 24b
- pCg 23/31
- Vegetative-circadian
- Pons

CBF PET
- Transient Sadness
- Activation of SCC25

FDG PET
- Dep Recovery w/ meds
- reduced SCC25 activity

Path Connections
- Impacted fibers based
- On tract tracing studies

Anatomical Target
- Stereotactic MRI
- Surgical Implantation
- While Awake

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

Eligible Patients
- MDD only GAF<50
- Episode >1 yr, Ham17>20
- Failed 4 meds, ECT, PsyTx
- No medical/psych comorbidity
Toronto: Continued Proof-of-Principle Testing
Unblinded, safety and efficacy testing of chronic stimulation

**PRIORITY COMMUNICATION**

Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression
Andres M. Lozano, Helen S. Mayberg, Peter Giacobbe, Clement Hamani, R. Cameron Craddock, and Sydney H. Kennedy

2008

**PRIORITY COMMUNICATION**

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

2011

20 patients: 1 Year Follow-up

All time points
p < 0.001

Resp=60%; Resp=55%

Long Term f/u: 3-6 yrs, n=14

Resp
Rem
IT
OC

avg=42 mo
Emerging Questions

- Predictors
  - Who are the right Patients?
  - Can surgery, parameters be further optimized?

- What does DBS do?
  - ↓negative mood or ↑positive mood?
  - Mood PLUS motivation, vegetative features, cognition?
  - Do different brain target differentially affect different symptoms?
  - Can rehabilitation enhance DBS effects; facilitate plasticity?

- Basic Mechanisms
  - What regions/pathways/cell types are most critical
  - reverse-engineering to animal models
  - Real-time readouts (brain radio, actigraphy)
  - platform for non-invasive alternatives?
Other Brain Targets Under Study

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

Biological Psychiatry Feb 2009

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


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

Biological Psychiatry (2010) epub Dec 2009

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

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

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

Biological Psychiatry (2013) epub Apr 2013

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

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

7 MDD, 12 wk-33 wks open; 6/7 Responders at 12 wks MADRAS=14.6; 4 of 6 in remission
**Emory Studies: Replication, Extension**

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

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

- **Devices donated by St. Jude Medical, IDE: G060028/S002**
- **Funding:** Dana, Stanley, Woodruff Found’n, Emory Hosp
- **10UP/7BP2; 10W/7M; age 42±9, MDE 5.3+4y**
  - Meds stable, 1 mo placebo, 6 mo open DBS
  - First patient Jan 12, 2007

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

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

**Funding:** Dana, Stanley, Woodruff Found’n, Emory Hosp
**Devices donated by St. Jude Medical, IDE: G060028/S002**
**No change in meds for 6 months**

- **Last f/u: 12/14 (80%R) T₀=Jan07**
  - 3 explanted, 11 new cohort

**Subgroups**

- **BP=MDD at all time point**
- **No induced mania/hypomania**

**Response & Remission**

- **6 mo**
  - Response 42%
  - Remission 18%
- **1 yr**
  - Response 36%
  - Remission 36%
- **2 yr**
  - Response 65%
  - Remission 58%

**HDRS Baseline**

- **No change in meds for 6 months**
Is Recovery Stable Without Continued DBS?

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

Holtzheimer et al. Arch Gen Psych 2012
Potential Sources of Response Variability
Patient selection, surgical precision

Evaluation of electrode placement

Toronto

initial target

active contacts

Emory

Resp

Non-R

Standardized to AC-PC mean MNI space

Standardized to Mean %genu-AC

Simple localization uninformative. What are we missing?

Hamani et al. J Neurosurg 2009

K Choi et al. unpublished
Deconstruct the DBS Target ‘Circuit’
 mapping white matter tracts to identify critical SCC connections

Approach:
Single Subject Contact Tract Maps

Clues from initial PET:
local + remote Changes
Neuron 2005

Known Fiber tracts
Nonhuman Primate studies
Lehman et al JNS 2012

targeting optimal pathways relevant to placement and programming
Test of Concept
Surgical revision in a 6 month non-responder

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

What was changed?

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

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

TAM method: Lujan et al. Brain Stimulation 2013

Initial 6 mo. slow, unsustained response
6 mo. post 2nd surgery: remission, 8 mo 1st job
Defining the Optimal Response ‘Pathways’
tractography maps common to all 6 month responders

Voltage Field Modeling (TAM)

TAM-seed Probabilistic Tractography

NOW: Prospective Pre-surgical Planning of Optimal Contact

Unpublished
Riva Posse and Choi et al
Biol Psych in review
Behaviors Impacted by Network Dysfunction
Potential biomarkers of DBS effects over time?

Negative Feelings
Tearful, sadness (emotion)

Vulnerability
Rem MDD w/ emotional Stress

Emotional
Self-relevance (insight, bias)

body awareness
HR, BP, GSR (interoception)

Amphetamine
Induced euphoria (reward)

Goals
1. ID biomarkers of 1° pathways
2. Develop/Monitor real-time Δ w/DBS
3. Target for time course mech’n studies
Example: What is Basal State of SCC neurons?

microelectrode unit recording during implantation

Passive viewing scenes

2 seconds

happy
sad
exhilarating
disturbing

Left vs Right

Negative > positive

Individual neurones: Emotion specific

Next Steps
How does DBS change this?

Toronto data
Laxton et al.
Biol Psych 2013
Consider Acute Effects of Stimulation
Hypothesis: acute mood change is 1° antidepressant effect

- Lighter, less resistance
- I feel more engaged
- Less tension, I can move
- I feel more optimistic

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

Blinded Identification of BEST behaviors

I am on rock. No longer drowning

At issue:
Patient Self-reports are idiosyncratic.
However, are also highly reproducible.
Requires individualized Testing/sensing
Testing Causal relationships in Real Time
Location specific Behavior and Physiology effects in Surgery

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

Contact in DTI-defined ‘target’ ∆

Dana Foundation, HDRF
Goal: Multi-Modal Biometrics
Guide DBS patient selection and parameter optimization

Confirm TRD Subtype
CBF PET resting fMRI

Micro-electrode
Lead localization

DTI tractography
Define optimal contact

Psychophysics Measures
GSR, HRV, EMG
Target verification

Imaging/Physiology Based
Tissue Activated Models

Real-Time Readouts
Tune critical $\Delta$
closed loop adjustments

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GSR, HRV, EMG
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Real-Time Readouts
Tune critical $\Delta$
closed loop adjustments
Towards Smarter Stimulation Systems
Next generation treatments, next generation neuroscience

Now Preop DTI mapping
Voltage Field Modeling, Preop Planning

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

Next Generation
High Resolution
Tract tracing
in vivo
Connectome Project

Next Generation
Real Time Readouts
Off Electrode

Future:
DBS Steering?

Medtronic
Sapien

Basis for
closed-loop feedback systems
Evolving Thoughts on Successful Recovery

Time course of effects: relatively stereotypic, with exceptions

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

Burden of Wellness. Passive to active role in own recovery

- if intractably ill, expect nothing (stuck, no bandwidth)
- focus on 1\textsuperscript{o} symptoms when sick (make pain go away)
- Then, need life-style change (reverse old habits/develop new ones)
- Therapy/Rehab (what type, when?)
- new priorities (need a job; where to start) Training/opportunity
Recovery Takes More Than a Stimulator
Early reset $\rightarrow$ plasticity + learning over time

<table>
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<tr>
<th>DBS doesn’t push positive, It enables positive</th>
<th>I didn’t realize how much work I would need to do myself</th>
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<tbody>
<tr>
<td>Emory #29 (1 year)</td>
<td>Emory #29 (1 year)</td>
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| DBS #18 Toronto 2 years post op | DBS #29 Atlanta 6 mo post op |

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