FENS Neuroethics Seminar

- The William Safire Seminar on Neuroethics
- FENS 2012 Barcelona
- July 15, 2012
Invading the Brain: What are the Ethical Issues on Invasive Treatments for Brain Disorders?

DBS for Depression

Helen Mayberg, MD
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The William Safire Seminar on Neuroethics
FENS 2012 Barcelona
July 15, 2012
Disclosures

Grant Support: NIMH, CIHR, NARSAD, Dana Foundation, Stanley Medical Research Fund, Woodruff Fund

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

issued March 2008, St. Jude Medical Inc, assignee

Consultant: St Jude Medical Inc / Neuromodulation Division

Emory DBS study: FDA IDE: G060028 (PI: HM)
Clinicaltrials.gov ID#: NCT00367003
research donated by SJM
DBS for Psychiatric Disease: Issue 1

Scientific

- Rationale
- Trial Design
- Patient Selection
- Safety Efficacy

1. What is threshold to proceed to a clinical trial?
2. Is an animal model necessary? (which one for TRD?)
3. Common or different standards for different diseases?
4. Trials: new/different outcome measures, timeline? (not a drug)
5. How to enable/ensure scientific refinement once in trials?
Context: Subcallosal Cingulate DBS for Depression
Rationale and proof of principle testing (first patient May 13, 2003)

Depression Circuit Model

Attention-cognition-Action

Transient Sadness
Activation of SCC25
Depression: Overactive SCC25

CBF PET
FDG PET

Dep Recovery w/ meds
reduced SCC25 activity

DBS Procedure
Adapt Methodology
Used for PD, tremor

Pre-op MRI
Pre-op PET

Electrode Target:
SCC white matter

Post-op MRI
6 mo DBS PET

Confirm electrode placement
Recovery with DBS
SCC25 suppression

Electrode Target:
SCC white matter

Electrode Contacts:
dMF9, vMF10, OF11

SCC, MCC

Depression:
Overactive SCC25

Funding: NARSAD, Toronto Western Hospital, no industry

JNP 1997
Deep Brain Stimulation for Treatment-Resistant Depression

2005 Pilot: 6 cases
6 mo open DBS
4/6 Resp; 3/6 remission

2008 extended cohort to 20 pts
1 mo open DBS
60/55% Resp 6mo/1yr

2011 Spain; Open DBS
8 pts 87% 6m, 62% 1 yr

2011 long term f/u 20 pts
62/46/75% R 1,2,3 yrs
64% at last f/u out to 6 yrs

2010 Industry pilot 21 pts, 3 CA sites
6 mo open DBS: 48% Resp sites

2012 Emory IDE: 17 Patients including 7 BP II
Single Blind, Placebo lead-in
58% Rem 92% Resp at 2 yrs; latest:75%

Basis for BROADEN study

Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression

2005 Pilot: 6 cases
6 mo open DBS
4/6 Resp; 3/6 remission

2008 extended cohort to 20 pts
1 mo open DBS
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Basis for BROADEN study
Studies testing other Brain Targets

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


2009 Industry Pilot 3 US sites
15 pts 6 mo Open label
40% Resp; 53% R last f/u
Basis for RECLAIM STUDY

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

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

2010, 2012 Germany 10 MDD
1 year Open, LTF
5/10 R 1 yr, 5/11 R LTF

Single Cases: Inferior Thalamic Penduncle: Jiminez et al Neurosurgery 2005 (Mexico)
1 year open label, no further studies reported

Lateral Habenula: Satorius et al Letter, Biol Psychiatry 2010 (Germany)
1 year open label, no further studies reported

Update Reclaim: Biol Psych meeting
4 mo Randomized Placebo Controlled
Stopped after 30 pts 3 sites
20% R active; 14%R sham 4 mo
1 year F/U open active 21%
Treating depression
Deep impact
A way of switching depression off
Mar 3rd 2005 | from the print edition

The New York Times Magazine
A Depression Switch?
By DAVID DOBBS
Published: April 2, 2006

DISCOVER
Mind & Brain / Depression & Happiness
Top 100 Stories of 2009 #20: Can a Shock to the Brain Cure Depression?
Deep brain stimulation is looking like a viable treatment for a growing list of brain issues.
By Kathleen McGowan
From the January/February special issue published online January 16, 2010

Health Wire
Bipolar May Benefit From Deep Brain Stimulation
Wednesday, January 4, 2012 8:28 AM
By Brenda Sokolowski

THE WALL STREET JOURNAL
Wiring the Brain, Literally, to Treat Stubborn Disorders
By MELINDA BECK

THE WALL STREET JOURNAL
Changing Minds: Area 25
February 11, 2009 5:56 PM
By Daniel Schorr

60 MINUTES

Brain Stimulation May Help Mental Illness
Deep Brain Electrical Stimulation Shows Promise
By Andy Segal, CNN
POSTED: 4:42 pm EST January 2, 2012
UPDATED: 1:45 am EST January 3, 2012

nature
International weekly journal of science
Brain electrodes fix depression long term
First placebo-controlled trial of implanted electrodes is positive.
Alison Abbott
03 January 2012

More evidence that deep brain stimulation may help treat mental illness
January 2nd, 2012
04:04 PM ET
Managing Therapeutic Misconception

- All DBS targets are the same
- Equivalent safety and efficacy
- How to choose? (Pt, Dr, PI)
- Trial: Urgent vs Elective pts (S/I)
- Restricted eligibility criteria (BP1)
- If it is safe, why wait for trial results?

1. Should patients have continued access to an experimental Tx that works for them but is found to be unsafe, or not effective overall?
   a. Who should pay? What if company goes bankrupt?
   b. Who should assume responsibility? (PI, surgeon, other Dr?)
   c. Experimental device vs new use of approved device

2. When does an experimental procedure become a treatment?

3. Fast track for intractability/suicidality
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

Patient Perspective: If it is safe, why should I have to wait for the randomized clinical trial results? How good is good enough for me to have access? I have the money and I am willing to take the risk… What do I have to lose?
DBS for Psychiatric Disease: Issue 3

Framing Expectations

- Can DBS do it all?
- What should we expect?
- Shared responsibility, changing roles
- PI, Patients, Families, Dr.

1. PI-Investigator: How to quantify effectiveness?
   - Different standard for an invasive procedure? (lower or higher)
   - Better vs well; temporary vs sustained vs relapse-free; side-effects
   - What is critical biological effect of DBS? (more research)

2. Patient: Burden of Wellness. Passive to active Role in own recovery
   - if intractably ill, expect nothing (stuck, no bandwidth)
   - focus on 1º symptoms when sick (make pain go away)
   - Need Life Style Change (reverse old habits/devt new ones) Therapy/Rehab
   - new priorities (need a job; where to start) Training/opportunity
Ethical Principles & DBS
beneficience
non-maleficence
respect for autonomy
1. DBS: 2 lessons from Parkinson’s disease and Movement Disorders
2. Progress in non-invasive brain stimulation

John Rothwell
UCL Institute of Neurology, London, UK
1. Numbers are important

Deep Brain Stimulation for Parkinson Disease

An Expert Consensus and Review of Key Issues

Jeff M. Bronstein, MD, PhD; Michele Tagliati, MD; Ron L. Alterman, MD; Andres M. Lozano, MD, PhD; Jens Volkmann, MD, PhD; Alessandro Stefani, MD; Fay B. Horak, PhD; Michael S. Okun, MD; Kelly D. Foote, MD; Paul Krack, MD, PhD; Rajesh Pahwa, MD; Jaimie M. Henderson, MD; Marwan I. Hariz, MD, PhD; Roy A. Bakay, MD; Ali Rezai, MD; William J. Marks Jr, MD; Elena Moro, MD, PhD; Jerrold L. Vitek, MD, PhD; Frances M. Weaver, PhD; Robert E. Gross, MD, PhD; Mahlon R. DeLong, MD

Conclusions: (1) Patients with PD without significant active cognitive or psychiatric problems who have medically intractable motor fluctuations, intractable tremor, or intolerance of medication adverse effects are good candidates for DBS.

(6) Subthalamic nuclei DBS may be complicated by increased depression, apathy, impulsivity, worsened verbal fluency, and executive dysfunction in a subset of patients. (7) Both globus pallidus pars interna and sub-
PARKINSON DISEASE

Deep brain stimulation in Parkinson disease—what went wrong?

Paul Krack and Marwan I. Hariz

Deep brain stimulation of the subthalamic nucleus or the internal pallidum can be an effective treatment for the disabling motor complications arising from dopaminergic treatment for Parkinson disease. The subthalamic nucleus has emerged as the preferred target for such treatment; however, no data exist to guide the choice between these two sites.
2. DBS may not always be reversible

Sustained Relief of Dystonia Following Cessation of Deep Brain Stimulation

Matthew O. Hebb, MD, PhD, Paula Chiasson, MSc (OT), Anthony E. Lang, MD, Robert M. Brownstone, MD, PhD, and Ivar Mendez, MD, PhD

Division of Neurosurgery, Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada; Movement Disorders Centre, Toronto Western Hospital, Toronto, Ontario, Canada; Department of Anatomy and Neurobiology, Dalhousie University, Halifax, Nova Scotia, Canada

Abstract: We describe the unusual clinical course of a patient with cranial dystonia (i.e., Meige syndrome) and additional upper limb involvement, who developed sustained relief of motor symptoms following cessation of a prolonged course of bilateral pallidal deep brain stimulation (DBS). Early response to therapy proved titratable and reversible; however, the patient gained independence from DBS in the fifth postoperative year and has since been more than a year without treatment or exacerbation of motor symptoms. Among the potential explanations for these neurological benefits lies the intriguing possibility that DBS therapy may have the capacity to induce plastic change that lessens or obviates the need for further treatment in susceptible patients. © 2007 Movement Disorder Society
Shaping reversibility? Long-term deep brain stimulation in dystonia: the relationship between effects on electrophysiology and clinical symptoms

Diane Ruge, Laura Clif, Patricia Limousin, Victoria Gonzalez, Xavier Vasques, Marwan I. Hariz, Philippe Coubes and John C. Rothwell

John Rothwell IoN
Transcranial magnetic stimulation (TMS)

Transcranial direct current stimulation (TDCS)
TMS is used to treat depression

O’Reardon et al (2007). 301 patients major depression with no benefit of prior treatment

Multicentre randomised. 10 Hz, 3000 pulses, 120% RMT, left DLPFC.

Treatment lasted 4-6 weeks

FDA approval granted after this study

John Rothwell IoN
2 weeks of daily TDCS in subacute stroke patients improves outcome (Kheder et al, in press)
SAVANT-LIKE SKILLS EXPOSED IN NORMAL PEOPLE BY SUPPRESSING THE LEFT FRONTO-TEMPORAL LOBE

ALLAN W. SNYDER\textsuperscript{1,2}, ELAINE MULCAHY\textsuperscript{1,2}, JANET L. TAYLOR\textsuperscript{3}, D. JOHN MITCHELL\textsuperscript{1}, PERMINDEE SACHDEV\textsuperscript{3}, AND SIMON C. GANDEVIA\textsuperscript{3}

\textsuperscript{1}Centre for the Mind, The University of Sydney, NSW 2006 and The Australian National University, ACT 0200, Australia
allan@centreforthemind.com

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Transcranial Direct Current Stimulation during Sleep Improves Declarative Memory

Lisa Marshall, Matthias Mölle, Manfred Hallschmid, and Jan Born
Institute of Neuroendocrinology 123a, University of Lübeck, 23538 Lübeck, Germany

TDCS during sleep increases number of words recalled from a word list learned prior to sleep
Conclusion

• Non-invasive brain stimulation has potential for therapeutic effects

• BUT the ease of application means it is not possible to control its range of application

• At the moment the effects are relatively small
Gene and cell therapy: How far are we from a clinical treatment?

Roger Barker
Cambridge Centre for Brain Repair and Department of Neurology
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PARKINSON’S DISEASE- STRATEGIES FOR REPAIR

- It is common.
- It causes major disability;
- It is incurable;
- It has a well defined dopaminergic cell loss

GROWTH FACTORS
either as gene therapy or direct infusions

CELL TRANSPLANTS

WHY?

- It is common.
- It causes major disability;
- It is incurable;
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PARKINSON’S DISEASE - STRATEGIES FOR REPAIR

GROWTH FACTORS
either as gene therapy or
direct infusions

CELL TRANSPLANTS
GDNF for PARKINSON’S DISEASE

Direct brain infusion of glial cell line–derived neurotrophic factor in Parkinson disease

- Patients clinically better
- Patients imaging better
- A single patient at post mortem had dopaminergic sprouting around site of GDNF delivery
- BUT a double blind placebo controlled trial found no benefits for GDNF...
- AND more recently...
A GDNF like gene therapy for Parkinson’s disease..

Gene delivery of AAV2-neurturin for Parkinson’s disease: a double-blind, randomised, controlled trial


√ SIGNIFICANT IMPROVEMENTS IN SOME MEASURES BUT ONLY AT 18 MONTHS AND NOT WITH F-DOPA PET

REMEMBER:
Negative trial findings do not imply a failure of therapy but a sub-optimal delivery of that agent..e.g. issues of PATIENT SELECTION; DRUG DELIVERY; TRIAL DESIGN..
PARKINSON’S DISEASE - STRATEGIES FOR REPAIR

GROWTH FACTORS either as gene therapy or direct infusions

CELL TRANSPLANTS
The development of fetal VM cell therapies for PD


1st patients with advanced PD treated with fetal VM grafts

Development of fetal VM transplants in animal models experimentally

~50 patients grafted with VM tissue using an open label approach

INITIAL TRIAL SHOWED A MAIN CLINICAL EFFECT BUT NOT IN ALL CASES...

[Graphs showing time spent in "off" state for patients 3 and 4, before and after transplantation, with medications such as Selegiline 10 mg and L-dopa used.]
The development of fetal VM cell therapies for PD

Double blind placebo control trials with N=40 and 34

NEW “BIG” TRIAL SHOWED NO SIGNIFICANT MAIN CLINICAL EFFECT ...... WITH PROBLEMS OF GIDS

SO WHAT DO WE DO?

YET STILL FROM OLD STUDIES BEST OUTCOME SHOWS
TRANSEURO

**Patient Selection:**
- Younger;
- <10 years duration;
- Minimal LIDs;

**Future (ES/iPS) stem cell based studies**

**Template for future novel therapies in PD**

**EXPERIMENTAL WORK**

- Optimise the dissection and storage of tissue

**CLINICAL TRIALS**
- Open label study
  - N=20
  - 3 years with safety end-point

**2010**

**2012**

**2014**

**LETTER**

Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson’s disease

- Suojie Ke et al.
- Joo-Won Moon et al.
- Seng Huat Ong et al.
- Viet M. Giai et al.
- Enrico Broccoli et al.
- Zhiqian Ye
- Luis Carrella

Gao and Aminian

- Chris Aimone
- Amanda Bach
- Li Chuan Yang
- M. Glenn Boeuf
- D. James Farmer
- Jeffrey H. Kordower
- Viviana Silvia Steiner

Nature 6th Nov 2011
Gene and cell therapy: How far are we from a clinical treatment?

We are there but the results are very variable - WHY?

1. THERE ARE NO GOOD ANIMAL MODELS OF PD TO TEST NEW AGENTS

2. PARKINSON’S DISEASE IS HETEROGENEOUS AND CHANGES WITH DISEASE PROGRESSION - SO WHEN SHOULD ONE TREAT AND IN WHICH PATIENT TYPE? [And this is limited by CAPACITY TO CONSENT as well]

3. THE OPTIMAL WAY TO DELIVER THAT AGENT IS A GUESS - SO NEED TO OPTIMISE WHEN IN THE DISEASE COURSE TO TREAT; AT WHAT DOSE; WHERE AND HOW?

4. HOW WE MEASURE EFFICACY IS NOT CLEAR nor IS THE NEED TO HAVE A SHAM ARM?

SO WE SHOULD VIEW EXPERIMENTAL THERAPEUTICS AS AN ITERATIVE PROCESS RATHER A HOSTAGE TO A SINGLE PREMATURE DOUBLE BLIND PLACEBO CONTROLLED TRIAL