Innovation from a Neurosurgeon’s Perspective

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Professor and Vice Chair
UCI Department of Neurosurgery
Innovation from a Neurosurgeon’s Perspective

First in Human Trial
Date with a Scientist
From Innovation to Entrepreneurship
DBS for Obesity: Conducting a First-in-Human Study

A Big Problem
Swinging for a Home Run
How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. Get approval
6. Secure funding
7. Identify patients
8. Conduct the study
9. Publish research
How to Conduct a First-in-Human Study

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42% of the U.S. adult population is obese, including 9.2% with severe obesity.

There is an alarming rise of obesity in children, with 18.5% suffering from obesity.

Medications are largely ineffective, and only result in sustained weight loss in ~10% of patients.
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Surgical Treatment for Obesity

Surgical treatment reserved for morbidly obese
Bypass, banding, intragastric balloon placement.
Morbidity as high as ~30%.
Rife with complications:
micronutrient deficiency, dumping syndrome, ulcers, hernias.

Success after surgery?
Despite “successful” bariatric surgery, many patients regain a significant amount of weight.
Neurosurgery for Obesity

**Ventromedial hypothalamus (VMH, “satiety” center) and lateral hypothalamus (LH, “feeding” center)**

Lesioning studies in animals were first to suggest these functions of the hypothalamus.

Clinical evidence from patients with tumors in these regions also corroborated findings in animal studies.

Experiments have shown selective damage to LH neurons impairs food ingestion w/o affecting motor/swallowing functions.
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Biochemistry and Physiology

Leptin, ghrelin, and insulin
Three chemicals important in energy homeostasis.
Experiments in animals have shown decrease in food intake with administration of exogenous leptin/insulin into the brain.

Leptin resistance
May be associated with obesity; analogous to insulin resistance.
DBS could be used to substitute the action of leptin on its receptors within the hypothalamus.
Hypothalamic Neurocircuits Involved in Glucose Metabolism

Morton GJ 2007
An Energy Balance Problem

Energy in = food intake

Energy out = resting metabolic rate (RMR) + exercise + thermic effect of food

When energy in is greater than energy out, this causes obesity

DBS may be able to influence both sides of the energy equation
Resting Metabolic Rate

The lionshare of “energy out” is resting metabolic rate (RMR)

RMR contributes to obesity by acting as a buffer against weight loss – RMR decreases in response to caloric restriction

Previous efforts to increase RMR (thyroid hormone, amphetamines) for weight loss have had significant side effects
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Deep Brain Stimulation?

Established Treatment
Well-established treatment for movement disorders and recently for psychiatric disease (OCD, Depression, Tourette’s)

Proven Safety
Proven safety profile, both adjustable and reversible with the ability to modify parameters as needed

*Unlike in movement disorders and psychiatric disease, effects on weight may not be readily apparent initially*
Animal Studies of DBS for Obesity

<table>
<thead>
<tr>
<th>Authors</th>
<th>Animal</th>
<th>Substance</th>
<th>Target</th>
<th>Laterality</th>
<th>Acute vs Chronic</th>
<th>Mode</th>
<th>Intensity (μA)</th>
<th>Frequency (Hz)</th>
<th>Pulse Width (μs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anand et al.</td>
<td>Cat</td>
<td>Standard Chow</td>
<td>VMH</td>
<td>Unilateral</td>
<td>Acute</td>
<td>Bipolar</td>
<td>NA*</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>Wyrwicka et al.</td>
<td>Goat</td>
<td>Standard Chow</td>
<td>VMH</td>
<td>Unilateral</td>
<td>Acute</td>
<td>Unipolar</td>
<td>NA*</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td>Morgane</td>
<td>Rat</td>
<td>Standard Chow</td>
<td>VMH</td>
<td>Unilateral</td>
<td>Acute</td>
<td>Bipolar</td>
<td>NA*</td>
<td>60</td>
<td>200</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>Dog</td>
<td>Standard Chow</td>
<td>VMH</td>
<td>Unilateral</td>
<td>Acute</td>
<td>Bipolar</td>
<td>100</td>
<td>50</td>
<td>1,000</td>
</tr>
<tr>
<td>Ruffin et al.</td>
<td>Rat</td>
<td>Standard Chow</td>
<td>VMH</td>
<td>Unilateral</td>
<td>Acute</td>
<td>Bipolar</td>
<td>20 or 25**</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sani et al.</td>
<td>Rat</td>
<td>High-fat Diet</td>
<td>LH</td>
<td>Bilateral</td>
<td>Chronic</td>
<td>Bipolar</td>
<td>NA*</td>
<td>180-200</td>
<td>1,000</td>
</tr>
</tbody>
</table>

* Only voltage was reported in these studies: Morgane, 1.0-3.0 V; Anand et al., 2.0 V; Wyrwicka et al., 0.5-1.0 V; Sani et al., 2.0 V

** Constant current administered

LH lateral hypothalamus, VMH ventromedial hypothalamus, NA not available
Stimulation Targets for DBS in Obesity

Lateral Hypothalamus (LH)

- Projects to: cortex, basal ganglia, hypothalamic regions, PAG, reticular formation, and ventral horn of the spinal cord
- Receives input from: nucleus accumbens, amygdala, hippocampus, and nucleus of the solitary tract, and arcuate nucleus
  - Arcuate nucleus is outside BBB and hence could serve as a mediator of circulating hormones
  - It could influence the LH through direct projections
- Weight loss following LH stimulation is not related to decreased food intake or increased activity
  - Hypothesized to be due to increased metabolism (Sani et al. 2007)
**Stimulation Targets for DBS in Obesity**

**Ventromedial Hypothalamus (VMH)**
- High frequency stimulation leads to increased food intake
- Low frequency stimulation leads to decreased feeding

**Nucleus Accumbens**
- Obesity may result from a patient’s desire for food that overrides normal satiety mechanisms
- Neuromodulation of the reward system may allow normal satiety mechanisms to achieve homeostasis

**Leptin, Ghrelin, Neuropeptide Y, and GLP-1**
- Shown to modulate reward system in addition to effects on energy and metabolism
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Go to Canada! But Protect Your IP


Approvals

IRB Approval
- Safety and Stature
- Join the Committee

FDA Approval
- Early Feasibility Study
- First in Human Study
- Traditional Feasibility Study
- Pivotal Study

Right of Reference Letter
- Ask and You Shall Receive (as long as you are a high volume clinician)

Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 1, 2013

The draft of this document was issued on November 10, 2011.

For questions regarding this document, contact CDRH’s Andrew Farb, 301-796-6343, Andrew.Farb@fda.hhs.gov or Dorothy Abel, 301-796-6366, Dorothy.Abel@fda.hhs.gov, or CBER’s Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.
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Secure Funding

• Intramural
  • Department
  • Medical School
  • University
  • Philanthropy

• Extramural
  • State
  • Societies
  • Foundations
  • NIH
  • $250,000-$500,000

• Industry
How to Conduct a First-in-Human Study

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Inclusion Criteria

1. Male and female patients age ≥ 18 years.
2. BMI ≥ 40 kg/m² or ≥ 35 kg/m² with a comorbid condition.
3. Failure of bariatric surgery (gastric banding or bypass).
4. Chronic obesity diagnosed by an eating disorder specialist with expertise in the treatment of obesity.
5. Stable at present body weight for a 6-month period.
## Patient Demographics and Treatment History

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Pre-DBS Body Weight (lbs)</th>
<th>Pre-DBS Body Weight (BMI)</th>
<th>Prior Surgical Weight Loss Treatment</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>F</td>
<td>278.7</td>
<td>49.4</td>
<td>Gastric Bypass 2001</td>
<td>HTN</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>F</td>
<td>326</td>
<td>48.1</td>
<td>Gastric Bypass 2001</td>
<td>Sleep Apnea, DM2, HTN, Migraine</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>314</td>
<td>45.0</td>
<td>Gastric Bypass 2003</td>
<td>Lower Extremity Edema</td>
</tr>
</tbody>
</table>

HTN Hypertension, DM2 Type 2 Diabetes Mellitus
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LH Targeting

- CRW frame
- Indirect targeting *(6.5mm lateral to AC-PC line, 4.5mm post to AC, 3mm below AC-PC line)*
- CT / MRI fusion
- MER, microstimulation, macrostimulation
- Postoperative MRI
Microstimulation
Evoked Responses

Evoked responses more useful than MER for guiding electrode placement

Within LH: nausea and thermal sensations

Lateral to LH: paresthesias

Ventromedial to LH: anxiety
### Intra-Operative Macrostimulation

<table>
<thead>
<tr>
<th>Voltage (V)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5V</td>
<td>no change</td>
</tr>
<tr>
<td>5V</td>
<td>little indigestion</td>
</tr>
<tr>
<td>5V</td>
<td>little nausea</td>
</tr>
<tr>
<td>3V</td>
<td>burp</td>
</tr>
<tr>
<td>5V</td>
<td>nausea, inc BP</td>
</tr>
<tr>
<td>4V</td>
<td>nausea</td>
</tr>
<tr>
<td>5V</td>
<td>nausea</td>
</tr>
<tr>
<td>5V</td>
<td>slight nausea - little cold</td>
</tr>
<tr>
<td>6V cold, 7V hot</td>
<td>nausea</td>
</tr>
<tr>
<td>8V</td>
<td>no nausea, head hot</td>
</tr>
<tr>
<td>5V</td>
<td>no nausea, head hot</td>
</tr>
<tr>
<td>5V nausea, real hot</td>
<td></td>
</tr>
<tr>
<td>5V nausea</td>
<td></td>
</tr>
<tr>
<td>4V nausea</td>
<td></td>
</tr>
<tr>
<td>3V nausea</td>
<td></td>
</tr>
<tr>
<td>2V nausea</td>
<td></td>
</tr>
<tr>
<td>4V nausea</td>
<td></td>
</tr>
<tr>
<td>5V nausea</td>
<td></td>
</tr>
<tr>
<td>6V nausea</td>
<td></td>
</tr>
<tr>
<td>5V nausea, little cold</td>
<td></td>
</tr>
<tr>
<td>5V nausea</td>
<td></td>
</tr>
<tr>
<td>6V nausea</td>
<td></td>
</tr>
<tr>
<td>5V nausea, getting warm</td>
<td></td>
</tr>
<tr>
<td>5V nausea, warm</td>
<td></td>
</tr>
<tr>
<td>5V nausea, warmer</td>
<td></td>
</tr>
<tr>
<td>5V nausea, warm</td>
<td></td>
</tr>
</tbody>
</table>
Metabolic Chamber

- Airtight room
- Records oxygen consumption and carbon dioxide production minute-to-minute
- Records spontaneous physical activity by a microwave detector

Once a month, the accuracy and precision of the chamber is assessed by propane combustion tests

Calculates resting metabolic rate (RMR) in kcal/min
Metabolic Chamber

Louisiana State University
Pennington Biomedical Research Center
Baton Rouge, LA
RMR Calculated Over Periods with Minimal Spontaneous Activity
Psychological Metrics

**Gormally Binge Scale**
Patient #1 had improved such that her Binge Scale score was within the normal range while the other 2 participants continued to score in the moderate binge eating range.

**Cognitive Restraint Subscale**
Patient #1 improved into the high range while the other 2 patients remained in the low range.

**Hunger Subscale**
Patient #1 had a Hunger score of 0 at post-operative follow-up and commented that “this was the first time in her life that she didn’t have to fight constant hunger.”

**Body Shape Questionnaire**
Patient #2 and #3 had increase to normal.

**Impact of Weight on QOL**
Pre- and post-op testing revealed that DBS did not worsen a participants QOL.
Biochemical Analysis

• Serial blood testing of the following nutritional studies, pituitary hormones, and neuroendocrine/neuropeptide studies did not reveal significant changes with LH DBS stimulation:

• fasting glucose, hemoglobin A1C, serum calcium, serum magnesium, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, serum iron, TSH, free T4, total T4, T3, FSH, LH, serum cortisol, folate, vitamin B12, ACTH, fasting insulin, insulin-like growth factor, growth hormone, leptin, ghrelin, AGRP, NPY, PYY, and adiponectin.
Summary of average resting metabolic rate (RMR) changes with bilateral monopolar stimulation of individual DBS contacts during metabolic chamber experiments in three patients undergoing LH DBS

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Contact 0</th>
<th>Contact 1</th>
<th>Contact 2</th>
<th>Contact 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Change</td>
<td>28% increase at 5.5 volts</td>
<td>Indeterminate</td>
<td>No change at 0-5 volts; Indeterminate at &gt;5 volts</td>
</tr>
<tr>
<td>2</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
<td>Indeterminate</td>
<td>15% increase at &gt;5 volts</td>
</tr>
<tr>
<td>3</td>
<td>Indeterminate</td>
<td>9% increase at &gt;4 volts</td>
<td>Indeterminate</td>
<td>21% increase at &gt;4 volts</td>
</tr>
</tbody>
</table>

- Stimulation was performed in monopolar mode with the case or pulse generator always acting as the anode (positive contact)
- Pulse width (90 microseconds) and frequency (185 Hz) were kept constant during all stimulation settings
- Calculations were deemed indeterminate when patient motion made it difficult to ascertain whether RMR changes were due to stimulation or motion
3D LH stereotactic anatomy

LH reconstructed from Mai stereotactic atlas with superimposed electrode contact locations from all 3 patients

Patient 1 (red)
Patient 2 (green)
Patient 3 (blue)

Images courtesy of Kirk W. Finnis Phd, Medtronic Neuromodulation
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Body Weight (lbs) Prior to Optimized Settings</th>
<th>Body Weight (lbs) at Last Follow-up</th>
<th>Months at Optimized Settings</th>
<th>Percentage Change in Body Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>305</td>
<td>302</td>
<td>16</td>
<td>0.9% Decrease</td>
</tr>
<tr>
<td>2</td>
<td>325</td>
<td>285</td>
<td>11</td>
<td>12.3% Decrease</td>
</tr>
<tr>
<td>3</td>
<td>359</td>
<td>300</td>
<td>9</td>
<td>16.4% Decrease</td>
</tr>
</tbody>
</table>
Promising Results
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A Multidisciplinary Endeavor

Title
Lateral hypothalamic area deep brain stimulation for refractory obesity: A pilot study with preliminary data on safety, body weight, and energy metabolism

Authors

Published
Journal of Neurosurgery: April 5, 2013
Date Night with a Scientist

- **Advanced Agent - Robotics Technology Lab**
- **Air Lab**: The AIR lab develops and tests perception and planning algorithms for unmanned air vehicles.
- **Argo AI Center for Autonomous Vehicle Research**
- **Auton Lab**
- **Biomedical Image Guidance**
- **Biorobotics Lab**
Smith and Nephew Buys BBT

Navio™

The Navio surgical system is smaller, smart instrumentation that offers surgeons and patients a big advantage in precision bone cutting.

**Navio™**

- **Smart instrumentation**: Intelligence that you can hold in your hand. Navio smart instrumentation combines intraoperative navigation, powerful CT-free implant planning features and instrumentation that helps reproduce accurate results time and time again.

- **Robotic-assisted precision**: Precision instrumentation that doesn’t push back, handheld tools provide ease of access to the incision site and take advantage of the surgeon’s skilled hands.

- **Smaller footprint**: Operating Room space is at a premium and the small footprint of the Navio system allows for easy integration into existing OR workflows. By staying small and nimble, Navio provides flexibility to the nursing staff and leverages minimal setup and maintenance.

- **Patient-specific, CT-free procedure**: A CT-free approach does not require pre-operative imaging beyond normal x-ray film. Based on a patient-reconstructed kinematic reference frame and acquired key anatomic landmark points and surface maps, Navio provides the opportunity to plan the placement of the implant and balance of the joint to each patient’s specific needs.

**Navio delivers the precision of robotics in a handheld, smart instrument. Precision Freehand Sculpting, the core technology, allows the system to deliver accurate and reproducible results in an efficient and ergonomic package that avoids the traditional pitfalls of large industrial-style robotic equipment.**

With minimal soft-tissue impact, Navio enabled procedures are becoming very attractive to potential patients suffering on the sidelines with knee pain. Surgeons can approach their partial knee replacements with the confidence that robotics-assisted surgical systems provide a consistent platform to optimally orient an
External Ventricular Drainage

inTRAvent Medical Partners’ Bedside Neuro-Navigation Device Obtains FDA 510(k) Clearance
SOLOPASS® is designed to provide imaging and guidance to improve the placement of external ventricular drains, one of the most common procedures in neurointensive care.

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Steelers Fan

Introducing the new 2nd Skull® Pro Band
An officially licensed product of the Royal Spanish Soccer Federation
I-Corps and Dural Repair

UCI Beall
Applied Innovation

CORPS
NSF Innovation Corps

Discover your product’s place in the market through an immersive learning process for campus innovators.
Patch (10)/dura/clips (50) covered in sealant

FIG. 6E
Innovation from a Neurosurgeon’s Perspective

First in Human Trial

Date with a Scientist

From Innovation to Entrepreneurship
You can’t do this alone
Build your team

Be patient!
This is a long process

Plan for disappointment
Home runs are only in baseball