Neuromodulation for central pain

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Disclosures

• IntElect Medical
• Monteris
• Boston Scientific
• NIH study section

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Neurosurgical Neuromodulatory Alternatives for Post-Stroke Pain

• OFF label

• “Last resort” neuromodulatory options

• Offered to selected patients

Central Pain

Melzac and Wall 1965
Central Pain

- **Neuromatrix**

[Diagram showing neural connections]

Melzac 1999

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Central Pain

- **Thalamocortical rhythms**

  Massive connections
  Thalamus → Cortex
  Cortex → Thalamus

  Lesions affect normal connectivity
  Abnormal rhythms have been linked with chronic pain
  - Thalamic recordings
  - Magnetoencephalography

Melzac 1999
The model's global thalamocortical geometry and white matter anatomy was obtained by means of diffusion tensor imaging (DTI) of a normal human brain.


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Neurosurgical Neuromodulatory Options

- DBS
- Motor Cortex Stimulation
  - Spinal cord stimulation?
  - Peripheral nerve stimulation?
DBS

Common targets

• Vc Sensory Thalamus (VPM / VPL)
  • Paresthesia producing

• PVG
  • Endorphin release
  • Pain pathway modulation
Vc (VPL/VPM)

- Classically targeted for Neuropathic pain
- Paresthesia producing
- Stimulation perception similar to SCS

Thalamus axial cut

DBS technique
DBS for pain

Outcomes

Deep Brain Stimulation

- Levy 1987: 141 patients average F-U 80 mo.
  - 84 with deafferentation and 57 with nociceptive
  - Deafferentation pain treated predominantly with VPM/VPL stimulation and nociceptive pain with PVG stimulation
  - 83 (59%) implants following the trial
  - At 80 mo, 31% maintained significant pain relief

- Worse results in anesthesia dolorosa and paraplegia
**DBS: Vc / PVG**

- **Kumar 1997**: 68 patients, average F/U 78 mo
  - 43 pts with FBSS, 6 with peripheral neuropathy
  - 53 (77%) internalizations after the trial period
  - 42 (62% of the initial patients) maintain adequate pain relief

- Best results
  - FBSS, peripheral / trigeminal neuropathy

- **Worse Results**:
  - Thalamic pain, spinal cord injury

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**Deep Brain Stimulation**

- **Coffey 2001**: Multi-center trial of DBS with 2 phases, the second using the 3387 model.
  - 15 diagnosis: Thalamic (11) accident (9) and post laminectomy (8)
  - 50 implants / 37 internalizations

- 22% of internalized with >50% at 3 mo and 14% at 24 mo
DBS: Vc / PVG

- Coffey 2001:

  … No correlation between efficacy and electrode location

  Sponsor did not pursue DBS FDA labeling for chronic pain

Motor Cortex Stimulation
MCS: Motivation

• New technique based on new electrophysiological findings in animal models

• Major frustration with DBS outcomes

MCS: Rationale


Can cortical stimulation modulate abnormal thalamic activity associated with chronic neuropathic pain?
MCS: Rationale
Post tractotomy thalamic activity

26 (± 9.7) spikes/s
Interspike interval = 39.3 (± 12.5) ms/s

42 (± 7.9) spikes/s
Interspike interval = 21.7 (± 5.9) ms/s

Cortical Stimulation effectively increased interspike intervals in lesioned animals but not in normal animals.

MCS: Rationale

Cortical stimulation can reduce thalamic hyperactivity associated with a central lesion…

… in the spinal cord.

In this model, there is anatomical preservation of the thalamocortical connectivity.
MCS: Rationale

Human trial developed after testing the effects of MCS in the feline spinal cord tractotomy model.

- Peripheral injury
- Central lesions (stroke)

Results
Motor Cortex Stimulation

• Tsubokawa 1991
  – Limitations in DBS for pain outcomes
  – MCS an alternative to treat central pain and peripheral neuropathic pain
  – 5 of 12 patients w/ complete resolution of the pain at 1 year f/u
  – 3 patients w/ partial pain alleviation

• Meyerson 1993
  – 10 patients → 6 facial pain, 4 post-stroke. 4-28 mo F-U
    → > 50% relief in 6 patients
    → No improvement among stroke patients

Motor Cortex Stimulation

• Nguyen 1997:
  – 20 patients with average 25 mo follow-up
  – 75% of patients achieved satisfactory improvement (>40% pain relief)
  – 50% had good or excellent improvement (>60% pain relief)
    – Facial pain did better than stroke pain

• Nuti 2005:
  – 31 patients with average 4 year F-U
  – 50% with pain relief > 40%
    – Early response predicted outcome
Motor Cortex Stimulation

Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response

YOSHI KATAYAMA, M.D., PH.D., CHIKASHI FUKAYA, M.D., AND TAKAMITSU YAMAMOTO, M.D., PH.D.
Department of Neurological Surgery, Nihon University School of Medicine, Tokyo, Japan

Conclusions. These findings suggest that the pain control afforded by MC stimulation requires neuronal circuits that are maintained by the presence of intact corticospinal tract neurons originating from the MC. Preoperative evaluation of motor weakness of the painful area appears to be useful for predicting a favorable response to MC stimulation in the control of poststroke pain.

Modulation of thalamocortical pathways

- Greater efficacy in patients with peripheral neuropathy

Preservation of thalamocortical anatomy

- Reduced efficacy in stroke patients compatible with the rationale and pre-clinical studies
- Stroke patients with hemiplegia less likely to respond

Likely severe damage to thalamocortical connections
DBS of the ventral internal capsule and ventral striatum

The Cleveland Clinic Study

DBS of the VC/VS

**Rationale based on:**

- Our experience with DBS for Depression
- The neuromatrix theory
- Known association between depression and chronic pain
Depression and Pain

If the neuromatrix is composed of somatosensory, behavior and cognitive components and DBS can modulate the neural networks related to mood and depression.

Melzac 1999

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


Background: We investigated the use of deep brain stimulation (DBS) of the ventral capsula/ventral striatum (VC/VS) for treating refractory depression.

Methods: Fifteen patients with chronic, severe, treatment-refractory depression who were treated with DBS at three collaborating clinical sites. All patients received continuous stimulation and were followed for a minimum of 6 months to a maximum of 4 years. Outcome measures included the Hamilton Depression Rating Scale—24 item (HDRS), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Global Assessment of Function Scale (GAF).

Results: Significant improvements in depressive symptoms were observed during DBS treatment. Mean HDRS scores declined from 33.1 at baseline to 11.1 at 6 months and 14.3 at last follow-up. Similar improvements were seen with the MADRS (34.5, 17.3, and 15.2, respectively) and the GAF (43.1, 55.5, and 67.8, respectively). Remission rates were 48% at 6 months and 53% at last follow-up (MADRS: 46.7% and 53.3%, respectively). Remission rates were 20% at 6 months and 49% at last follow-up with the HDRS (MADRS: 36.4% and 33.3%, respectively). The DBS was well-tolerated in this group.

Conclusions: Deep brain stimulation of the VC/VS offers promise for the treatment of refractory major depression.
... Can DBS of the ventral striatum / ventral capsular area modulate the affective sphere of pain?

- Prospective, double blinded, randomized trial
- NIH funded / CMS reimbursed
- FDA approved IDE

Malone et al, 2009
Pain anticipation and disability

- Chronic unrelenting pain leads to disability
- Disability is mediated not only by current pain but also the anticipation of next pain
- Upper extremity disability mediated by allodynia and fear of limb usage
- Resolution of pain anticipation will alleviate disability

Magnetoencephalography as a tool to measure pain anticipation in patients with thalamic pain syndrome
Magnetoencephalography as a tool to measure pain anticipation in patients with thalamic pain syndrome

Dorsolateral prefrontal cortex
Post central gyrus (M1): ipsilesional

Intraoperative Stimulation:
Similar to depression, at lower voltages
Functional topography of the ventral striatum and anterior limb of the internal capsule determined by electrical stimulation of awake patients

Andre Machado, Suzanne Haber, Nathaniel Sears, Benjamin Greenberg, Donald Malone, Ali Rezaie

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<td>1 patient</td>
<td>Up mood, manic</td>
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Summary of Inclusion / exclusion criteria (n=10 implants)

• Severe hemibody pain for > 6 months
• Lesion in the thalamic region (or immediately ventral or dorsal to the thalamus)
• Failed at least
  • one antidepressant
  • one antiseizure medication
  • one narcotic

Summary

• Deep brain stimulation and motor cortex stimulation are more effective for peripheral neuropathic pain than for central pain
• Deep brain stimulation of the behavioral and mood pathways is a viable option to manage the affective component of neuropathic pain
• Acute stimulation modulates mood and affect in thalamic pain syndrome patients
• Chronic stimulation expected to down-modulate pain anticipation and pain related disability
Clinical Trial Access Information

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