Deep Brain Stimulation
INTRODUCTION
What is Deep Brain Stimulation?

- Deep brain stimulation (DBS) is surgical treatment involving the implantation of a medical device called “brain pacemaker”, which sends electrical impulses to specific parts of the brain.
History of Deep Brain Stimulation

- A.D. 46 - Ancient medicine: Scribonius Largus suggested applying the live ray to the head of a patient suffering from a headache. This remedy was later used for hemorrhoids, gout, depression, and epilepsy.

- 1786 – Luigi Galvani discovered that nerves and muscles are excited by electricity.

- 1809 – Luigi Rolando showed that brain is electrically excitable.

- 1870 - G. Fritsch and E. Hitzig verified body movements by electrical currents on cerebral tissue (motor cortex) → possibility that neurological disorders affecting volitional movement could be treated with electrical stimulation.
History of Deep Brain Stimulation

- 1875 – David Ferrier produced an analogous map of functional localization of human brain by transposition of monkey brain map with lesion and stimulation technique.

- 1960s – Cardiac pacemaker was introduced. Technological advances made possible the implantation of a comparable device for the focal stimulation of brain.

- 1960 – Hassler et al., stimulation of the ventrolateral thalamus for tremor

- 1973 – Hosobuuchi et al., for pain
History of Deep Brain Stimulation

• 1983~1990 – Recordings in the basal ganglia of both normal and MPTP-treated monkeys helped to define the operational principles of basal ganglia-thalamocortical loops, and showed for the first time pronounced over-activity in a part of the basal ganglia called the subthalamic nucleus (STN)

• 1990 – Lesions of STN in monkeys were shown to completely and permanently reverse the effects of MPTP

• 1993 – The first report from Benabid’s clinic of the use of DBS in the STN to treat Parkinson’s Disease. Benabid’s group had first used DBS in the thalamus as early as sides of the brain, which is now the standard approach in PD patients

• 1997 - FDA approved DBS of the thalamus for PD and essential tremor

• 2002 – FDA approved DBS STN and GPi for symptoms of PD
Before DBS was developed, the main surgical treatment for Parkinson’s disease was lesioning.

While the lesioning surgery, the spot was ensured by observing response of patient when electric stimulation with 20-50 Hz frequency was applied. E.g.) posterior – sense of tingling, lateral – contraction of hand or face

In 1987, a French neurosurgeon, Benabid experimented the effect of pulses with from 1 to 100 Hz, and found that tremor was suppressed at 100 Hz.

Initial target was the thalamus, and later studies on animal have found the subthalamic nucleus is more effective target.
**Timeline**

- **1786**: Luigi Galvani’s experiment of nerve and muscle excitation by electricity
- **1870**: Fritsch and Hitzig verified movement induced by cortical stimulation
- **1875**: The first analogous map of functional localization of human brain by David Ferrier
- **1876**: Lesioning on the thalamus was introduced as treatment for Parkinson’s disease
- **1897**: L-Dopa therapy for Parkinson’s disease is introduced
- **1950’s**: DBS on thalamus for tremor was suggested by A.-L. Benabid and P. Pollak
- **1950’s**: Lesioning on the thalamus was introduced as treatment for Parkinson’s disease
- **1960’s**: DBS on thalamus for tremor
- **1987**: DBS on thalamus for tremor was suggested by A.-L. Benabid and P. Pollak
- **1992**: DBS on GPi for Dyskinesia is suggested
- **1993**: DBS on STN for Parkinson’s disease is suggested
- **1997**: FDA approved DBS on thalamus for tremor
- **2000**: DBS on PPN for falls and freezing of gait
- **2005**: DBS on PPN for falls and freezing of gait

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**Neural Prosthetic Engineering**

http://www.medtronicdiabetes.com/
Target Applications

• Validated for movement disorders
  – Parkinson’s disease, essential tremor, dystonia...

• Under validation for affective disorders
  – Obsessive-compulsive disorder, depression, Tourette’s syndrome...

• Other various disorders
  – Chronic pain, anorexia, dementia...
Parkinson’s Disease

- Parkinson’s Disease (PD) is a neurodegenerative disorder of unknown cause which belongs to a group of conditions called motor-system disorders.

- PD and its related disorders occur when certain neuron become impaired. These are the result of the loss of dopaminergic neurons.

- Loss of dopamine causes the nerve cells to fire out of control, leaving patients unable to direct or control their movement normally.
Parkinson’s Disease

- Forward bent posture
- Staring gaze
- Rigidity
- Tremor
- Flexed elbows and wrists
- Short shuffling steps

Parkinson’s Disease

Edited from video of youtube video - https://www.youtube.com/watch?v=47anvWA3an4
Dystonia

- Dystonia is a neurological movement disorder in which sustained muscles contractions causes twisting and repetitive movements or abnormal postures.

- It is often initiated or worsened by voluntary movements, and symptoms may overflow into adjacent muscles.

- Dystonia does not have a specific cause. It seems to be related to a problem in the basal ganglia.
Dystonia

Chronic Pain

• Chronic pain is literally, pain that lasts a long time. It is often defined as any pain lasting more than 12 weeks.

• It is not clear what is exact cause of chronic pain. It may arise from an initial injury such as a back sprain, or there may be an ongoing cause such as illness.

• Consisting of pain may induce sleep disturbance, decrease appetite, and mood change. These difficulties make hard to carry out daily activities.
Chronic Pain

THEORETICAL BACKGROUND
Then, how does DBS work?

- DBS is suggested as alternative to ablating target structures in the thalamus or basal ganglia, and shows similar therapeutic outcomes with it.

- But the mechanisms of the therapeutic action of DBS remains still uncertain, even though it works.

- DBS works by inhibiting or activating target neurons in thalamus and in basal ganglia.
Most main target structures of DBS for treatment of movement disorders are in the basal ganglia. But it varies in specific location as target application.

- For PD, globus pallidus interna (GPI) and subthalamic nucleus (STN) have been found as safe and efficacious targets, and recent study has identified the pedunculopontine nucleus (PPN) as potential target for PD.

- For dystonia, GPI is preferred. And commonly used parameter is differ from those of PD with a broader pulse width (200-400 μs) and higher voltage (2.2-7 V).
Neural Network Involving Motor Circuits

When the decision of movement is made, the information from the frontal cortex passes through the complex loop of basal ganglia, then returns to the supplementary motor area via the thalamus.

Also, GPi and STN are found out as safe and efficacious targets of DBS for Parkinson’s disease from animal model.

• The motor symptoms of Parkinson’s disease is caused by cell death of dopaminergic neurons of the SNc.
• Fundamental of DBS is applying stimulation to a node in the pathway to suppress its activity. Usually, its STN.
Stimulation Parameters

• The general therapeutic stimulation parameters are roughly ranged in
  – Monopolar cathodic pulses with 1-5 V amplitude (A), 60-200 μs pulse duration (DR), 120-180 Hz frequency (f)

• But these parameters have been derived primarily by trial and error. And also, it varies as target application or target cell changes.

PRACTICAL DEVICES
• Founded in 1949 at Minneapolis, Minnesota.

• Developed implantable battery-powered cardiac pacemaker in 1960s.

• The system of DBS is based on the cardiac pacemaker. → Therefore, package located at chest and long leads are needed for connect to brain.
Cardiac Pacemaker

• The first field of Medtronic was battery operated cardiac pacemaker. It regulates the rhythm of heartbeat.

• Cardiac pacemakers before Medtronic had to be plugged into a wall outlet to operate. It was very dangerous while situations like power outage.

• Now, cardiac rhythm disease management division brings about $ 5 billion revenue to Medtronic.
Cardiac Pacemaker vs. Deep Brain Stimulator

- Fundamental system of cardiac pacemaker and DBS are almost the same.
- Also, location of surgery for stimulation package is the same, too.
Products

• Areas
  – Implantable Cardiac Pacemakers
  – Deep Brain Stimulator for Dystonia, Essential Tremor, Parkinson’s Disease
  – Implantable Cardioverter Defibrillator
  – Low-Pressure Pulse Generator for Meniere's Disease Management
  – Implantable Neurostimulator for Chronic Pain/Neuropathy
  – Other Surgery Related Products

http://www.medtronic.com/
# DBS Products

## Table of Specifications

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<tr>
<th>Power Supply</th>
<th>Primary Cell</th>
<th>Rechargeable Battery (9 years)</th>
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Deep Brain Stimulation

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Spinal Cord Stimulation

- Spinal cord stimulation (SCS) is literally, a medical treatment which applies electrical stimulation to spinal cord directly for some neurological diseases. Especially, it is frequently used for patients with chronic pain.

- The beginning of applying electric stimulations to pain was introduced via “gate control theory” by Melzack and Wall[7] in 1965. The dorsal horn of spinal cord was indicated as the gate of pain signal from peripheral nerve to brain. In 1971, efficacy of electric stimulation on epidural spinal cord was reported.
Spinal Cord Stimulation

• As in other neuromodulation therapies, exact mechanisms of spinal cord stimulation is uncertain. But some experimental reports show the local neurochemical alteration in dorsal horn with SCS, and it may results in suppression of neuron hyper-excitability.

• SCS device is usually implanted in the lower abdominal area or gluteal region since it is used for chronic pain of low back or pelvic limb.
Spinal Cord Stimulation

![Spinal Cord Stimulation Diagram]
Medtronic in 2015

• Business Scale
  – Market cap: about $100 billion.
  – Total Revenue: $17.005 Billion
  – Medtronic operates in more than 140 countries, employs over 85,000 people and has more than 53,000 patents.
Boston Scientific

- Started with steerable catheter in 1979.
- Total sales in 2014: $7.38 billion
  - Cardiac Rhythm management: $2.139 billion (~29%)
  - Neuromodulation: $472 million (~6.4%)
St. Jude Medical Inc.

- Total sales in 2014: $5.62 billion
  - Cardiac Rhythm management (50%)
  - Neuromodulation (mostly SCS, 8%)
M.i.Tech Corp. NMD System

- Prototype Developed within SNU-YUH team work
- Head-mountable DBS
- Rechargeable DBS
- Optimal-sized, reliable Electrode
- User friendly Controller

Industrial technology development program (10031270) of the Ministry of Knowledge Economy (MKE) of Korea
M.i.Tech Corp. NMD Prototype II

Neural stimulator

Hermetic feedthroughs
(under $5.0 \times 10^{-9}$ sccs @He gas)

Hermetic seal test
Neuropace Inc.

- Founded in 2014, Mountain View, CA.
- Head-mountable neurostimulator for epilepsy


