Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

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Peter Pazmany Catholic University
Faculty of Information Technology

NEURAL INTERFACES AND PROSTHESES

(Neurális interfészek és protézisek)

LECTURE 5

DEEP BRAIN STIMULATION

(Mély agyi ingerlés)

GYÖRGY KARMOS

Investing in your future
New Hungary Development Plan

AIMS:

- In this lecture the students will get acquainted with the techniques used for deep brain stimulation.
- Electrodes implantation technique and electrophysiological methods used for localizing the target area will be discussed .
- Central nervous system disorders will be overviewed in which deep brain stimulation is applied.
- Hypothesized mechanisms responsible for the effect of deep brain stimulation will be discussed.
- Surgical complications and side-effects of deep brain stimulation will be mentioned.

HISTORY OF THE DEEP BRAIN STIMULATION (DBS)

The role of the basal ganglia became generally accepted in movement organization by the 1930s. The early attempt to treat Parkinson's disease by ablating these structures were unsuccessful.

Using the newly developed human stereotactic technique (see Lecture 4) in the fifties stereotactic thalamotomy and pallidotomy were used to correct movement disorders.

By 1970 the Levodopa treatment of the Parkinson's disease became available, overshadowing the neurosurgery. After the side effects of Levodopa were recognized the neurosurgical approach became again important.

At the end of 1980s the team of A. L. Benabid (1987, 1991, 1993) first combined stereotactic lesion and stimulation, then started to use chronic stimulation of the thalamus and finally the subthalamic nucleus.

HISTORY OF THE DEEP BRAIN STIMULATION (DBS)

The first European multicenter DBS clinical study for tremor that included more than 100 patients started in 1992.

In 1995 Medtronic introduced the implantable brain stimulator for Parkinson’s disease and essential tremor first in Europe, Canada and Australia.

The FDA approved the Medtronic Activa Tremor Control Therapy in the United States in 1997.

Since 2002 the DBS became generally accepted as treatment of Parkinson’s disease, dystonia, essential tremor Tourette's syndrome. obsessive–compulsive disorder (OCD) and depression.

Since 1995, more than 80,000 patients worldwide have received deep brain stimulation.

DEFINITIONS

Deep brain stimulation (**DBS**) is a neurosurgical treatment involving the implantation of a medical device called a battery-powered neurostimulator which sends electrical impulses to the target area of the brain.

The **DBS system** consists of three components: the lead, the extension, and the neurostimulator.

The lead (also called an electrode) — a thin, insulated wire — is inserted through a small opening in the skull and implanted in the brain. The tip of the electrode is positioned within the targeted brain area. The extension is an insulated wire that is passed under the skin of the head, neck, and shoulder, connecting the lead to the neurostimulator.

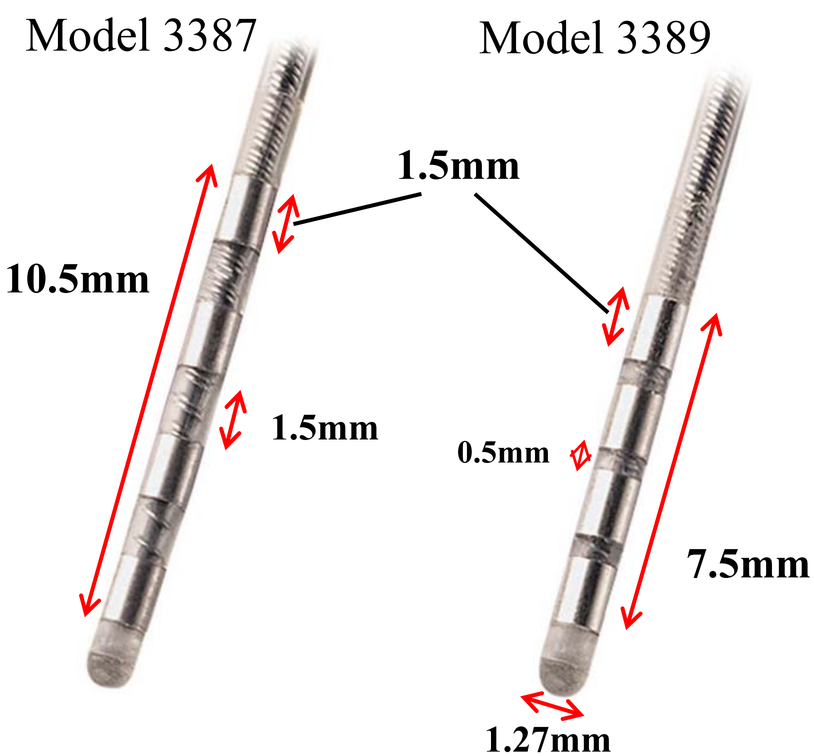
DEFINITIONS

Battery-powered neurostimulator (pacemaker) is encased in a titanium housing. It can be programmed by radiofrequency way. Its electrical pulses interfere with neural activity at the stimulated site. It is usually implanted under the skin of the chest, wires go under the skin to the electrodes implanted to the brain.

DBS lead consists of four wire insulated in polyurethane with four ring shape electrodes at the tip.

DBS LEADS

Medtronic



www.medtronic.com

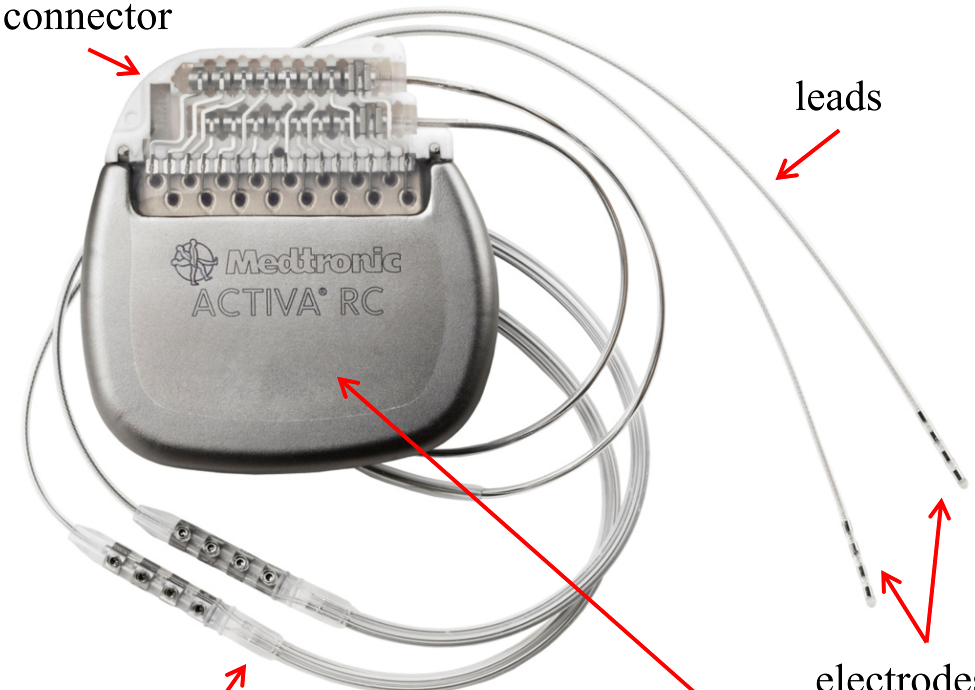
Commercially available DBS leads produced by Medtronic consists of four thin, insulated, coiled wires bundled within polyurethane insulation. Each wire ends in a 1.5 mm electrode, resulting in four electrodes at the tip of the lead. The length of the lead is 40 cm.

The leads have blunt tip to avoid damaging the brain during implantation.

The insulated wires subcutaneously go along the head, neck, and shoulder to connect the lead to the implanted neurostimulator.

Activa RC Deep Brain Neurostimulator

Medtronic **Model 37612**



www.medtronic.com

The neurostimulator is pacemaker-like device that contains a battery and microelectronic circuitry for controlled electrical pulse generation. The neurostimulator is implanted subcutaneously near the clavicle, and generates electrical signals that are delivered by the extension and lead(s) to the targeted structures deep within the brain.

Specifiations for Activa RC Deep Brain Neurostimulator

Medtronic **Model 37612**

Size: 54 mm x 54 mm x 9 mm

Weight: 40 g

Battery: rechargeabel

Battery life: 9 years

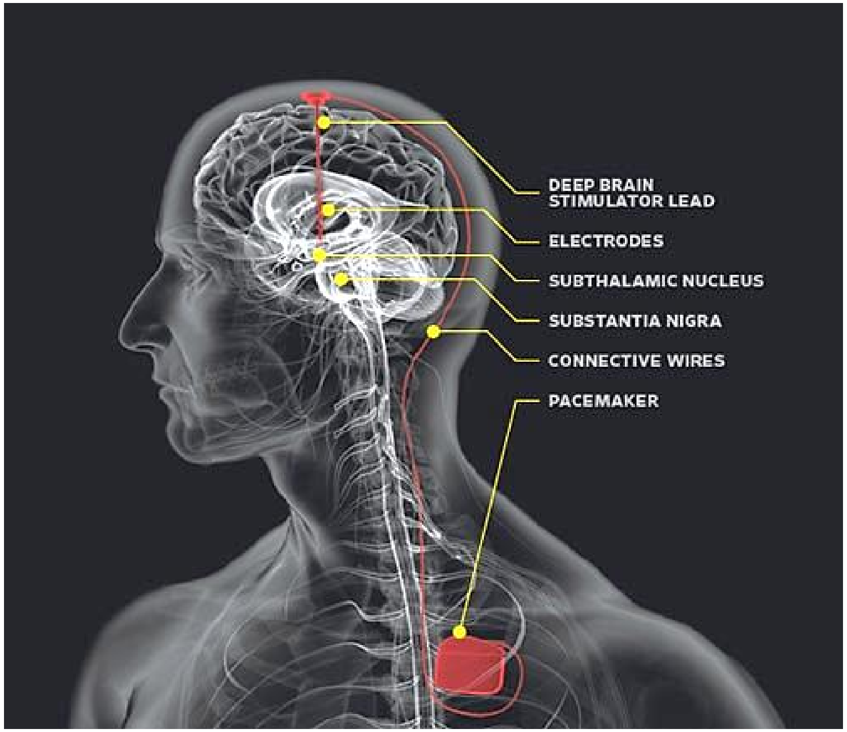
Stimulation parameters:

Pulse rate: 2 - 250 Hz (voltage mode)
30 - 250 Hz (current mode)

Pulse width: 60 to 450 μs

Electrode configuration: Up to 4 electrodes per lead defined as anode, cathode or off

Case: Defined as anode or off



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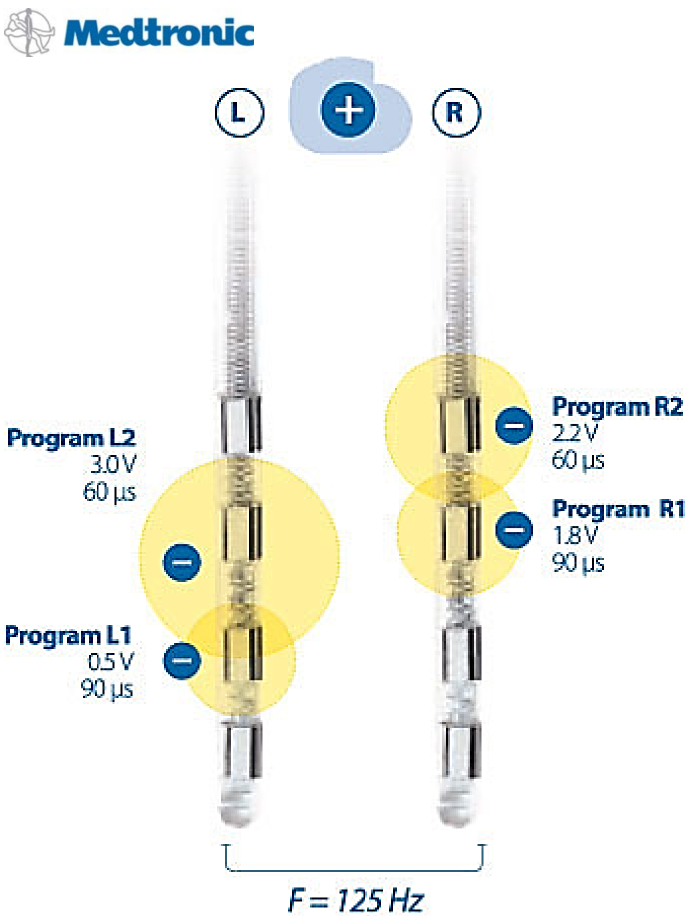
PROGRAMMING OF ACTIVA RC



www.medtronic.com

Two pulses with different combinations of active electrodes, amplitudes and pulse widths can be programmed for each lead. The pulses are delivered in an alternating interleaved fashion, which may allow clinicians to overcome targeting challenges through programming.

An example shown uses two programs on each DBS lead, with all programs in this example in the unipolar mode (bipolar programs or mixtures of unipolar and bipolar programs can be used also). The pulses are delivered: L1, R1, L2, R2.

DBS PATIENT PROGRAMMER 37642

www.medtronic.com

The patient using an Activa RC DBS stimulator can control the stimulator.

The DBS patient programmer has two modes: simple and advanced. The mode and its settings are clinician-determined on an individual patient basis and can be changed at any programming session.

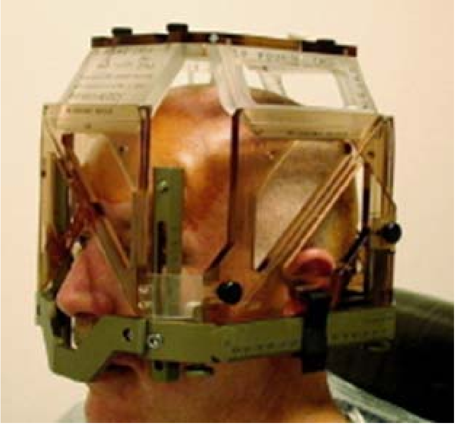
In simple mode the system is working in a preprogrammed way. The patient can check the status of the DBS device without making any therapy changes.

In advanced mode the physician has the ability to set up four therapy groups with different stimulation parameters. The patient can toggle between groups and adjust therapy within physician-defined limits. If permitted to do so, the patient can adjust rate, amplitude, and pulse width.

DBS SURGERY 1

After careful examination of the patient the DBS surgery is carried out in two phases:

- During the first stage, the DBS lead is implanted stereotactically into the target nucleus.
- During the second stage, the DBS lead is connected subcutaneously to an implantable neurostimulator which is inserted into a pocket beneath the skin of the chest wall, like a pacemaker.



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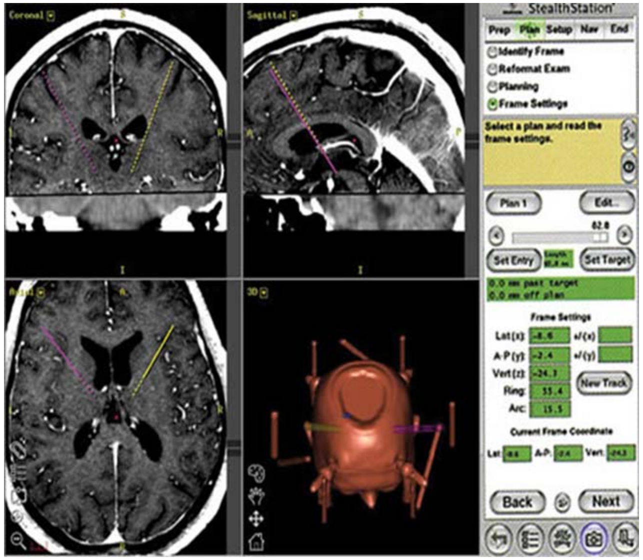
DBS SURGERY 1

At the beginning of the surgery the stereotactic head frame is attached to the patient's skull under local anesthesia to keep the contact with the patient during the electrode implantation.

A targeting MRI is performed and with the planning software (see Lecture 4) the stereotactic coordinates are calculated. The leads are attached to the electrode holder of the stereotactic apparatus.



www.medtronic.com

DBS SURGERY 3

For lead placement, small (~8-15 mm) burr holes are made in the patient's skull.

A burr-hole ring is affixed to each opening.

A combination of microelectrode recording and stimulation is used to refine the desired target physiologically.

Stereotactic frame guidance and techniques are then used to place the lead to the targeted area.

www.medtronic.com

DBS SURGERY 4

Test stimulation is performed to confirm good therapeutic benefit (for example, reduced rigidity and/or tremor) with minimal or no side effects.

Once lead placement is confirmed, the DBS lead is anchored to the skull with a burr hole cap.

A brain MRI is obtained immediately postoperatively, to confirm proper electrode placement and to make sure that no hemorrhage has occurred.

Mogilner et al., 2001

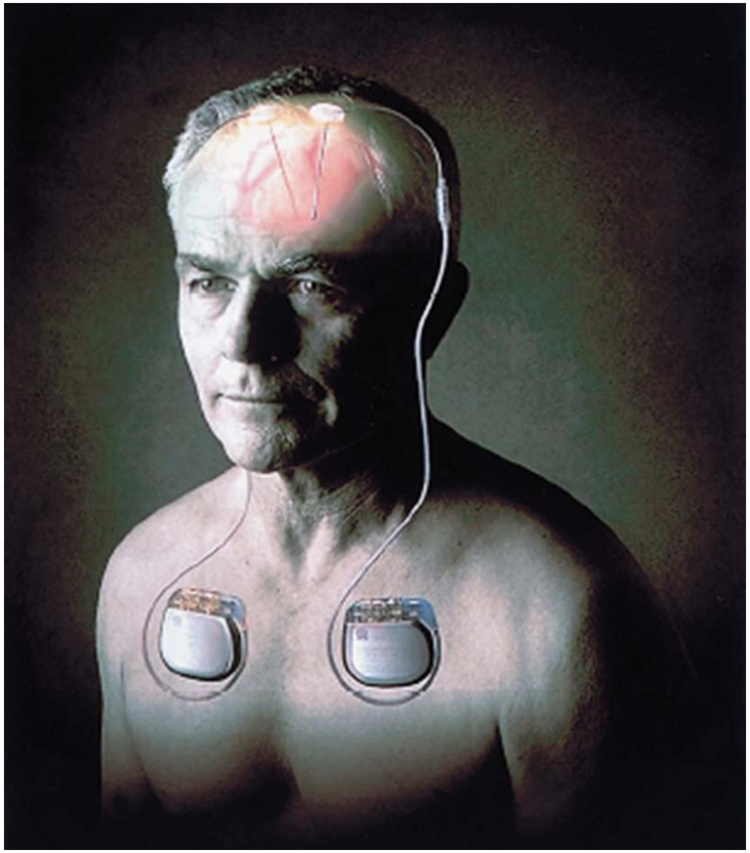
DBS SURGERY 5

The second stage of the surgery is done under general anesthesia.

A small incision is made in the subclavicular area to create a pocket and the neurostimulator is placed in the pocket.

The lead and the neurostimulator are connected by an extension wire that is tunneled under the scalp, the skin of the neck, and down to the pocket.

For bilateral applications, these steps are repeated for the other side.



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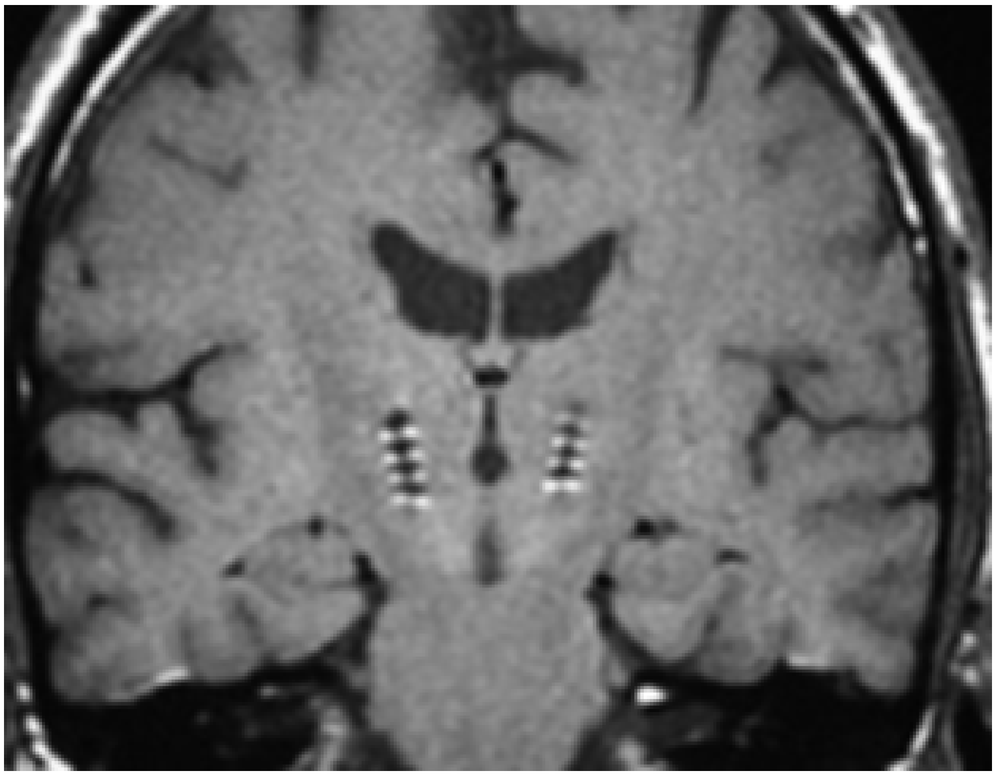
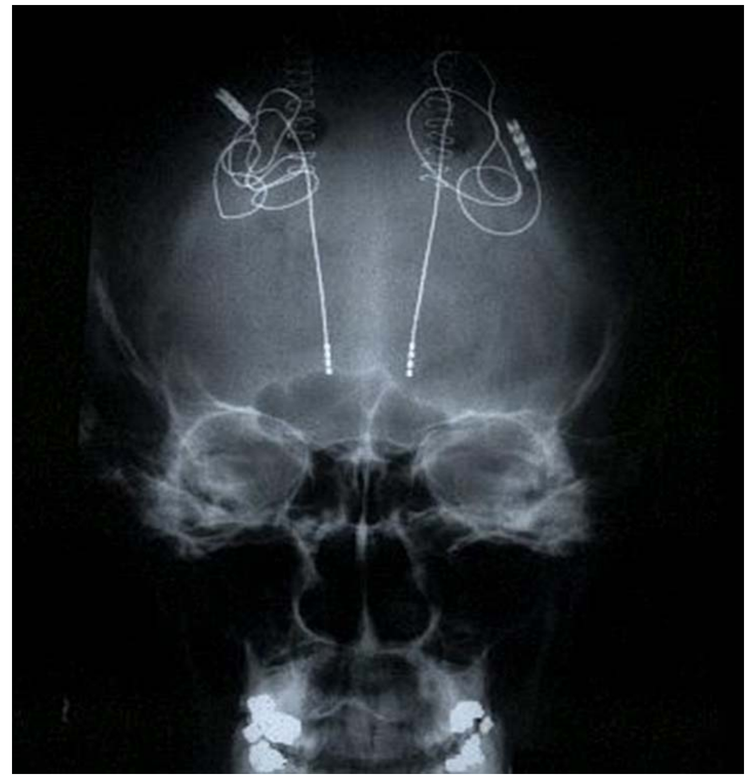
MRI AND X-RAY SHOWING DBS ELECTRODES IN THALAMUS

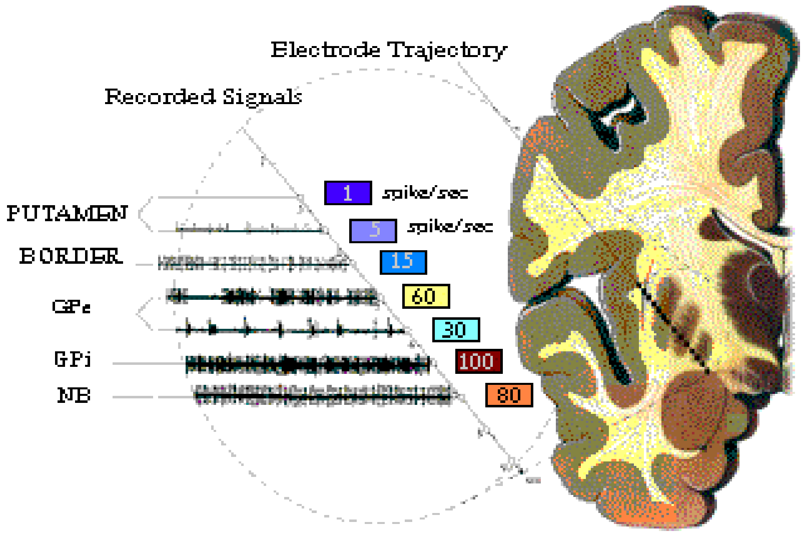




ELECTROPHYSIOLOGICAL GUIDANCE SYSTEM FOR TARGET LOCALIZATION

The electrophysiological pattern of the *STN* nerve cells, is made up of asymmetrical spikes at rather high frequency and exhibiting bursting patterns in PD. They respond to passive contralateral limb movements and proprioceptive inputs, and exhibit tremor synchronous activity.

Microstimulation is performed with the microelectrode used for recording, with current intensities up to 10 milliamps for short periods (10 to 30 seconds).

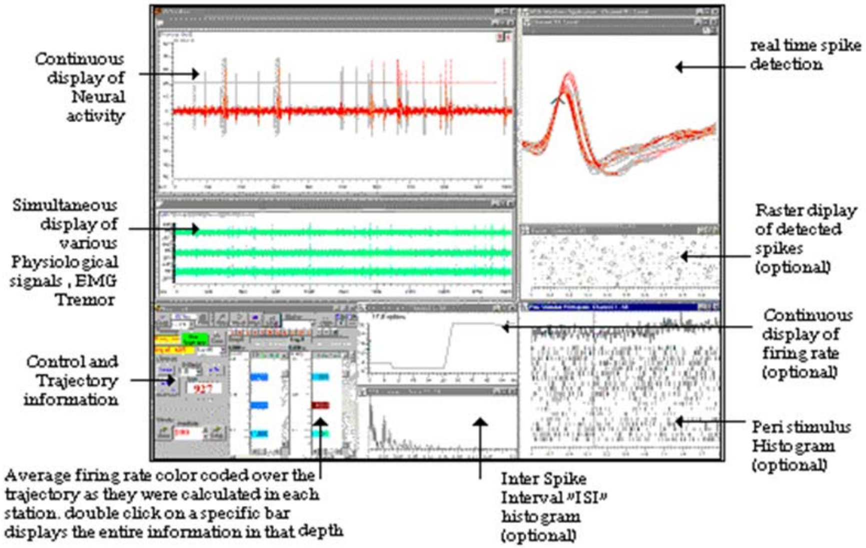


www.alphaomega-eng.com

ELECTROPHYSIOLOGICAL GUIDANCE SYSTEM FOR TARGET LOCALIZATION

This essential step allows the observation of beneficial effects (improvement of PD symptoms) inside the target and of side effects (limiting factors for efficient stimulation) outside of it.

When the best track has been identified, the corresponding microelectrode is removed and replaced by a chronic lead.



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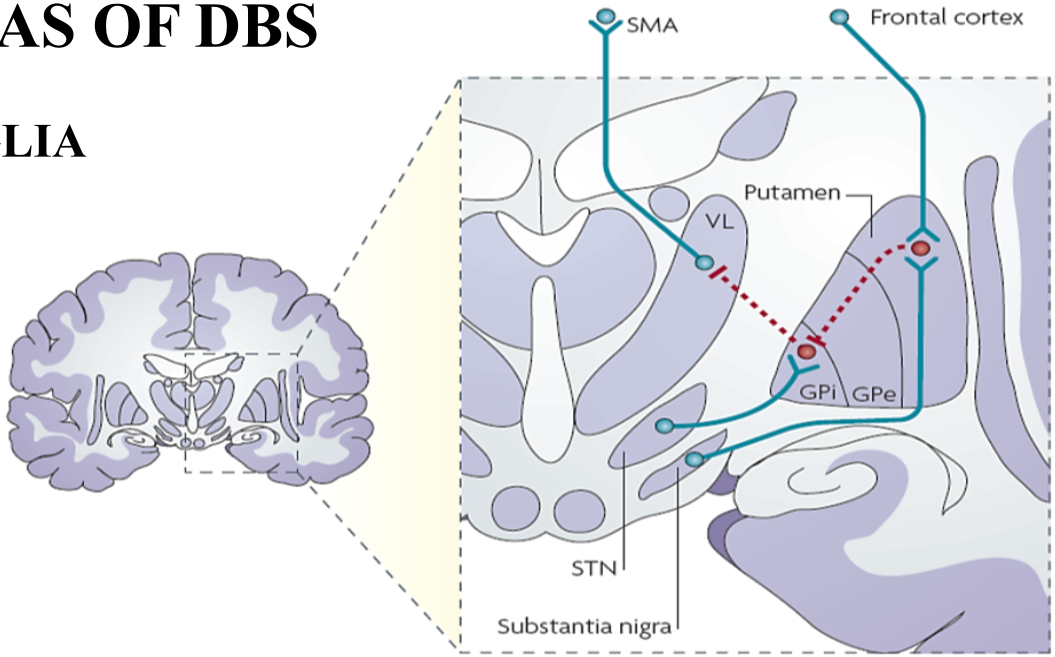
TARGET AREAS OF DBS

BASAL GANGLIA



DBS for the treatment of movement disorders such as Parkinson's disease, dystonia and tremor has mainly targeted structures in the basal ganglia. In the figure, blue lines represent stimulatory connections, red dotted lines represent inhibitory connections. STN, subthalamic nucleus; GPe, external globus pallidus; Gpi, internal globus pallidus; SMA, supplementary motor area; VL, ventrolateral nucleus of the thalamus.

(*Kringelbach et al., Nature Reviews Neuroscience*, 2007, 8:623-635)

TARGET AREAS OF DBS

DBS target for *Parkinson's disease* tremor is the **subthalamic nucleus (STN)**. The long-term effects of using high-frequency (130–185 Hz, pulse width 60-150 µs, 1-2.5 V,) DBS for Parkinson's disease are well documented. DBS trials for Parkinson's disease have shown substantial improvements in symptoms, as measured by motor and daily living scores, as well as reductions in the patients' medication.

The preferred target for *dystonia* and *spasmodic torticollis* is the **internal globus pallidus (GPi)**. The most commonly used DBS parameters for dystonia differ from those for Parkinson's disease, with a broader pulse width (200–400 µs) and higher voltage (typically between 2.2 and 7 V), leading to rapid battery consumption.

Essential tremor is usually treated with DBS in the **ventral intermediate nucleus of the thalamus (Vim)**. Long-term effects of DBS in Vim have produced an average tremor reduction of over 80% in most patients.

(*Kringelbach et al., Nature Reviews Neuroscience*, 2007, 8:623-635)

PARKINSON'S DISEASE (PD)

The disease is named after the English doctor J. Parkinson, who first described its symptoms in 1817. These are mainly movement related, including tremor at rest, rigidity, bradikinesia (slowing of movement) and difficulty with walking and gait. In late stage cognitive and behavioral problems arise, with dementia. Other symptoms may include sensory, sleep and emotional problems. PD can significantly impair quality of life.

PD is a progressive degenerative brain disease, it results from the death of dopamine containing cells in the substantia nigra projecting to the basal ganglia. The cause of cell-death is still unknown.

The first symptoms usually appear at middle age the incidence of PD rises with aging. There are forms of PD with young onset.

TREATMENT OF THE PD

Currently there is no known cure for PD.

The aim of the pharmacological treatment is to increase the levels of dopamine in the brain. The main drug families are Levodopa, dopamine agonists and MAO-B inhibitors. At early stage the therapy solves the motor problems.

However, with disease progression, drug dosages are increased and drug-induced side effects and motor fluctuations occur more frequently. These motor fluctuations are usually characterized by end-of-dose wearing off and dyskinesias. End-of-dose wearing off is the decline in mobility that occurs a few hours after a dose of an antiparkinson medication. With disease progression, the duration of benefit from each dose becomes shorter and the wearing off phenomenon occurs earlier after each dose. Dyskinesia is the abnormal involuntary movement caused by medications in PD.

These side effects of the used drugs resulted in the renaissance of the neurosurgical treatment of PD.

ESSENTIAL TREMOR

Essential tremor is a progressive movement disorder whose most characteristic feature is a rhythmic tremor (4–12 Hz) of the arms, head and chin that is apparent during voluntary movements such as eating and writing. Any sort of physical or mental stress will tend to make the tremor worse. Head tremor may be more frequent in women while postural hand tremor may be more severe in men.

The pathophysiology of essential tremor is not known The cerebellar-brainstem-thalamic-cortical circuits probably are involved. Essential tremor is familial in at least 50-70% of cases.

No specific cure is known. Drug treatment may include beta blockers and antiepileptic drugs.

The prevalence of essential tremor is estimated at 0.3-5.6% of the general population. It is increasing with age.

DYSTONIA

Dystonia is the term to describe a movement disorder in which sustained muscle contractions cause twisting and repetitive movements. The movements, which are involuntary and sometimes painful, may affect a single muscle; a group of muscles such as those in the arms, legs, or neck; or the entire body. Dystonia may lead to abnormal posturing, particularly on movement. It can be focal, segmental or generalized.

Direct symptoms may be accompanied by secondary effects of the continuous muscle and brain activity, including disturbed sleep patterns, exhaustion, mood swings, mental stress, difficulty concentrating,

Cause of Dystonia is not known. There are hereditary forms, secondary Dystonia can be caused by different forms of trauma.

No specific treatment is known. Drug therapy involves antiparkinson drugs and muscle relaxants.

TOURETTE SYNDROME

Tourette syndrome is a neurological disorder with a strong genetic component and onset in childhood. It is characterized by multiple motor and phonic tics. Tics are repetitive stereotyped motor movements or vocalizations involving discrete muscle groups.

The syndrome was named after Georges Gilles de la Tourette (1859–1904), a French neurologist who first described the symptoms.

Both genetic and environmental factors can be cause of the Tourette disorder.

No specific cure is known. The treatment of Tourette's focuses on identifying and helping the individual manage the most troubling or impairing symptoms (behavioral and psychological therapies).

Medications available to help symptoms (neuroleptics, antidepressants) have adverse side effects.

SUGGESTED VIDEO CLIPS TO DEMONSTRATE MOVEMENT DISORDERS AND THE EFFECT OF DBS

Short video clips can be downloaded from the homepage of the Medtronic Inc. demonstrating the movement disorders and the effects of DBS. http://professional.medtronic.com/therapies/deep-brain-stimulation/presentations-and-downloads/index.htm#tab1

Parkinson's Disease: DBS Activated and Deactivated

This split-screen video shows a female patient as she attempts to perform a few simple actions, such as extending her hand, touching her forefingers together, and walking down a hall. The left screen shows her actions without deep brain stimulation. The right screen shows her actions with DBS. No sound.

http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@sa/@br/@corp/documents/interactivemedia/dbs-slide-21-zip.zip

Essential Tremor Pre-Op

In this video, a voice-over narrator discusses the progression of essential tremor throughout the course of the disease. Meanwhile, an essential tremor patient demonstrates difficulty with several different tasks requiring dexterity.

http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@sa/@br/@corp/documents/interactivemedia/dbs-slide20-26-zip.zip

Essential Tremor: Lynn with Keys

This split-screen video shows a female patient as she attempts to unlock and open a door. The left screen shows her actions without deep brain stimulation. The right screen shows her actions with DBS. No sound.

http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@sa/@br/@corp/documents/interactivemedia/dbs-et-lynn-zip.zip

Dystonia Pre-Implant

In this video, a voice-over narrator describes some of the primary symptoms of dystonia, and indicates that there are a variety of types of dystonia. Meanwhile, a patient illustrates the sustained twisting and repetitive movements and abnormal postures typical of dystonia.

http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@sa/@br/@corp/documents/interactivemedia/dbs-slide-20-33-zip.zip

PHYSIOLOGICAL MECHANISM OF THE DBS

Our knowledge on the mechanisms of action of DBS are still limited. The clinical applications of DBS preceded the scientific understanding of its mechanisms of action.

In the recent years intensive research was carried out to reveal the physiological mechanisms of the DBS.

One of the difficulty of this area is that because of ethical reason and the invasive nature of the DBS no experiments can be performed in the patients. The results of the animal experiments can be translated only in a limited way.

The present knowledge on the physiological mechanisms of the DBS is mainly relying on modeling studies.

THE PARADOX OF THE DBS

The paradox of DBS: ***how can stimulation result in similar therapeutic outcomes as lesioning of the target structure?***

Four general hypotheses:

1. DBS generates such a strong depolarization in the target area neurons that no repolarization is possible
   → ***depolarization blockade***
2. DBS stimulates only inhibitory fibers incomming to the target area
   → ***inhibition of the target area neurons***
3. DBS stimulation results in transmission failure of the efferent output of stimulated neurons as a result of depletion of transmitter vesicles
   → ***synaptic depression***
4. The high frequency DBS suppresses the pathological rhythm of the target area neuronal networks
   → ***modulation of pathologic network activity***

PHYSIOLOGICAL BASIS OF THE DBS

Electrical stimulator can produce constant voltage or constant current.

The current generated by constant voltage stimulator depends on the impedance of the tissue while at constant current stimulator it is independent until a certain level.

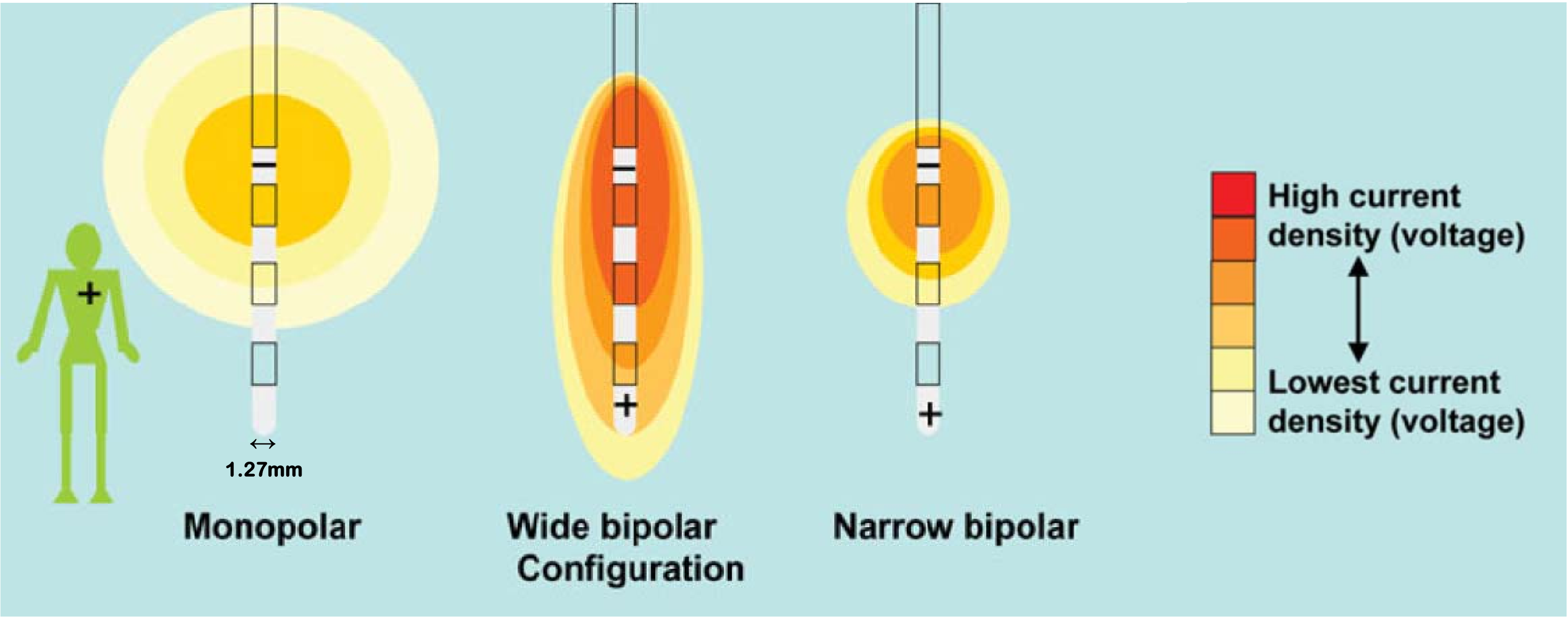
Animal experiments proved that after an electrode is implanted into the brain, there is a foreign-body reaction that results in the attachment of proteins and cells directly to the electrode contact and accumulation of glia surrounding the device. These result an increase of electrode impedance. High frequency stimulation reverses some of these impedance changes. The impedance changes may directly affect the voltage distributions generated in the brain.

THE EFFECTS OF DBS DEPENDS ON SEVERAL FACTORS:

1 . geometric configuration of the stimulating electrode contacts

2. electrical properties of the brain tissue

1 . GEOMETRIC CONFIGURATION OF THE STIMULATING ELECTRODE



Electric field induced by different types of stimulation. At monopolar stimulation reference electrode is the house of the neurostimulator. Monopolar, wide and narrow bipolar configuration induce different fields.

Montgomery, E.B.Jr.: Deep Brain Stimulation Programming, Principles and Practice. Oxford Univ. Press. 2010

1 . GEOMETRIC CONFIGURATION OF THE STIMULATING ELECTRODE

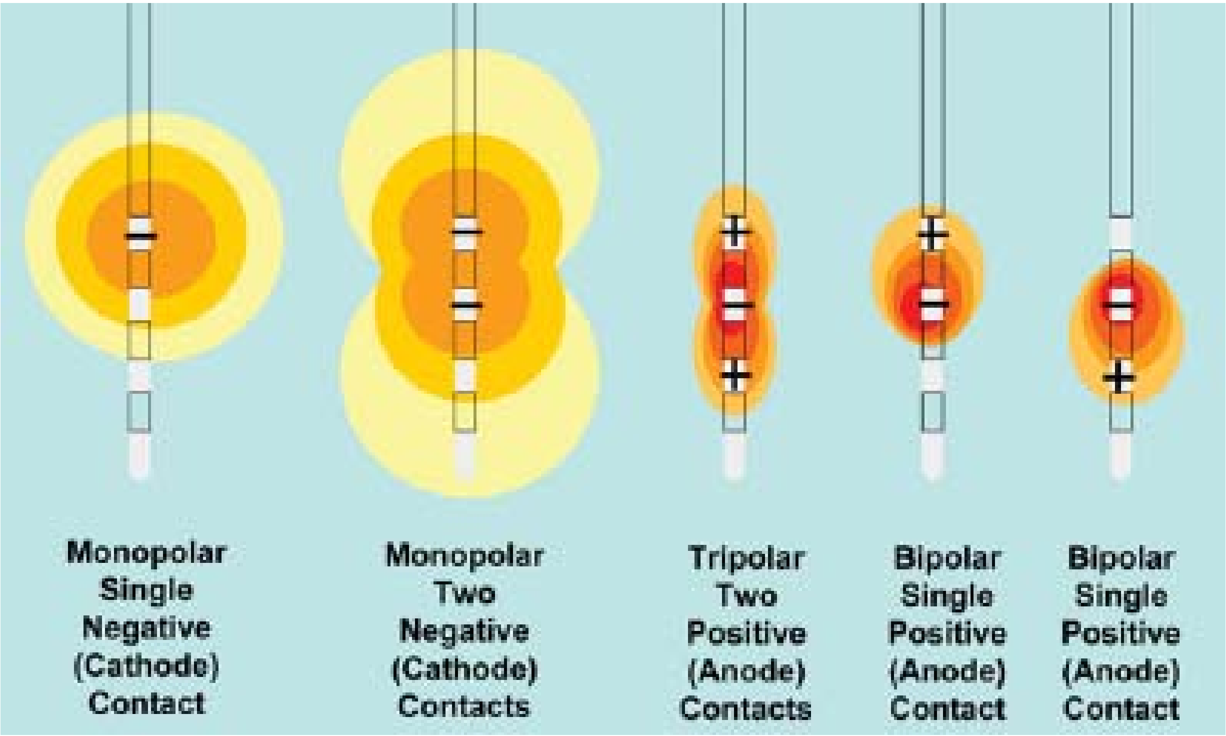
The volume of activated tissue depends on the type of stimulation.

At monopolar stimulation, the electrical current is widely distributed, the current density (measured in microcoulombs per surface area of the electrical contact during each phase of the DBS pulse) is not great.

At bipolar configuration, the electrical current is less widely distributed, the electrical current density is concentrated and consequently greater.

The size of the contacts and the intercontact distance (see slide 8) is relatively large compared to the target area (e.g. STN). By different combination of polarity of the electrode contacts the area of stimulated tissue can be modified (see next slide).

MODIFICATION OF THE STIMULATED AREA (cont.)



By different combination of polarity of the electrode contacts the area of stimulated tissue can be modified.

Montgomery, E.B.Jr.: Deep Brain Stimulation Programming, Principles and Practice. Oxford Univ. Press. 2010

2. ELECTRICAL PROPERTIES OF THE BRAIN TISSUE

Threshold parameters of the neural elements can be characterized by the chronaxie. Myelinated axons have the lowest chronaxie (30-200 us) while the threshold of the cell bodies and dendrites is much higher (chronaxie: 1-10 ms). → electrical stimulation at threshold intensity activates the efferent axon rather than the cell body. (See Lecture 2.)

From electrical point of view target structures of DBS in the brain are nonhomogeneous (dependent on location) volume conductors. The white matter is electrically anisotropic (dependent on direction). Electrical stimulation induces a complex three dimensional extracellular electrical field. This field depends on the type of stimulation (monopolar, bipolar), the distance of the contact, etc. Orientation of the cell body and the in relation to current flow is an important determinant.

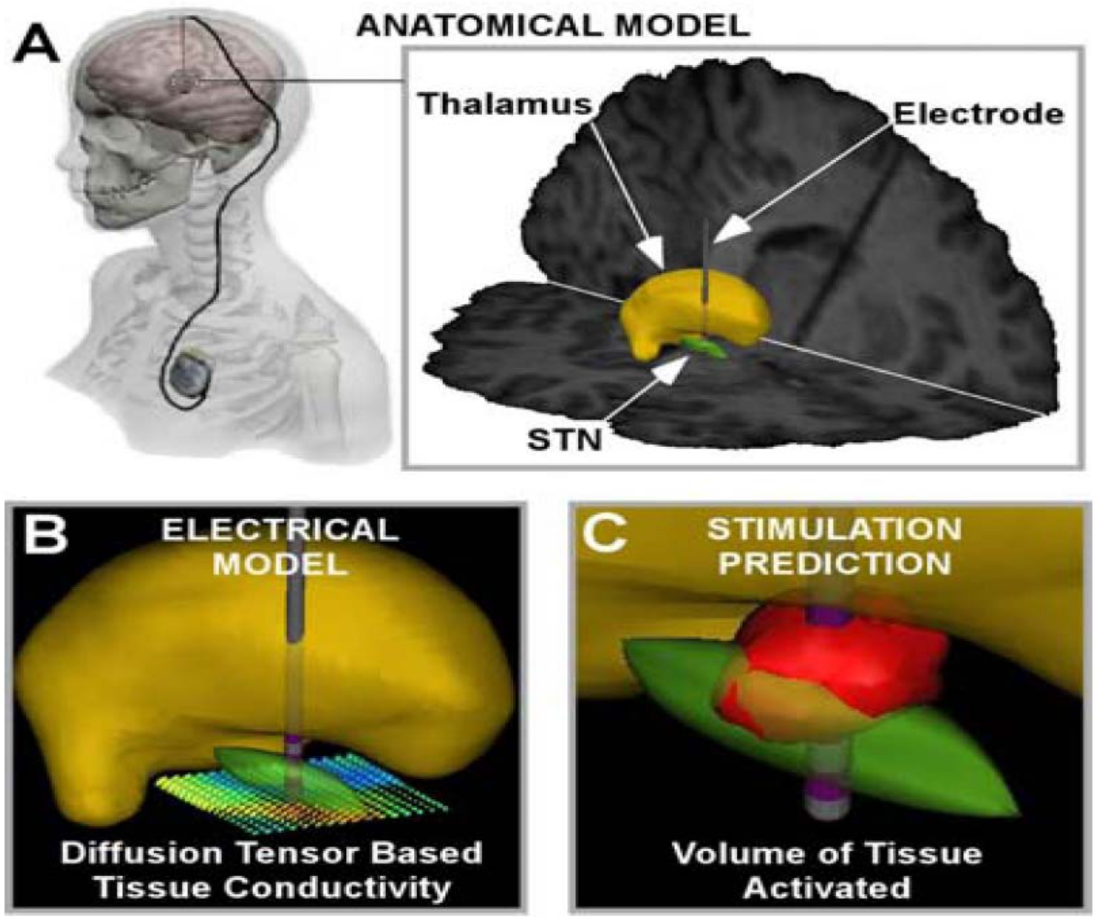
The effect of this field on the neural elements is related to the second spatial derivative of the extracellular potential distribution.

2. ELECTRICAL PROPERTIES OF THE BRAIN TISSUE

Around the electrode there are *local cells* and their axons that are going to other structures. There are *afferent input fibers* that form synapses to local cells. There are also *fibers of passage* that come from distant structures and innervating other structures. This means that stimulation may have indirect effects through stimulation the input fibers causing synaptic activation or inhibition in the target structure. Activating fibers of passage may have effects on distant structures. Depending on the direction of the fiber tracts their threshold can be different (anisotropy).

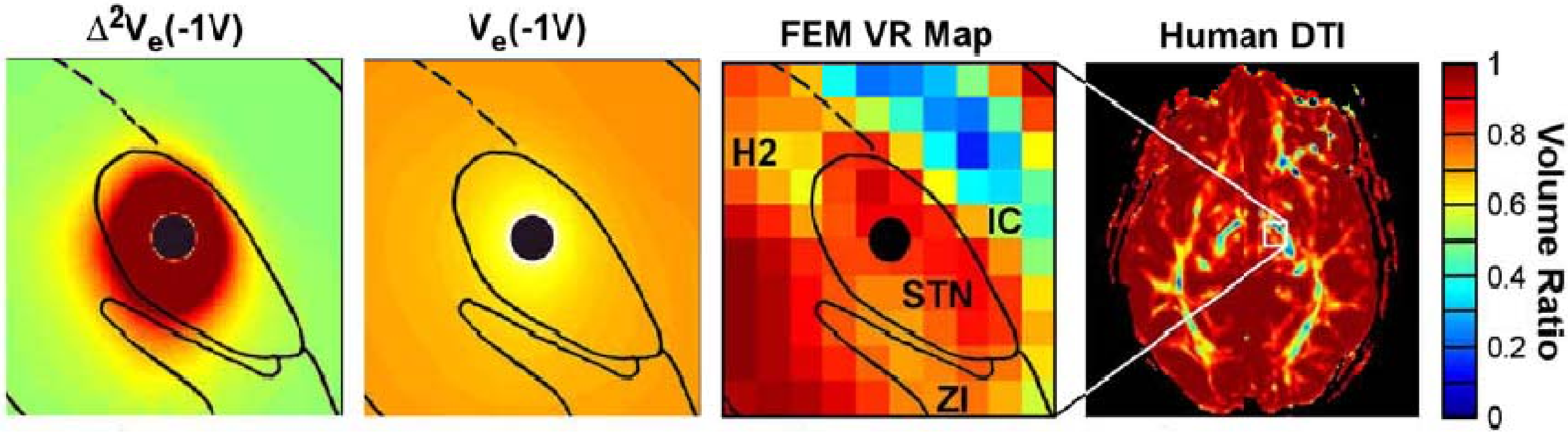
Finite element models (FEMs) were used to describe the electrical fields around the DBS electrodes and predict the volume of the activated tissue.

PRINCIPLE OF MODELING OF DBS



Butson et al., 2005

FINITE ELEMENT MODEL OF THE DBS IN THE STN



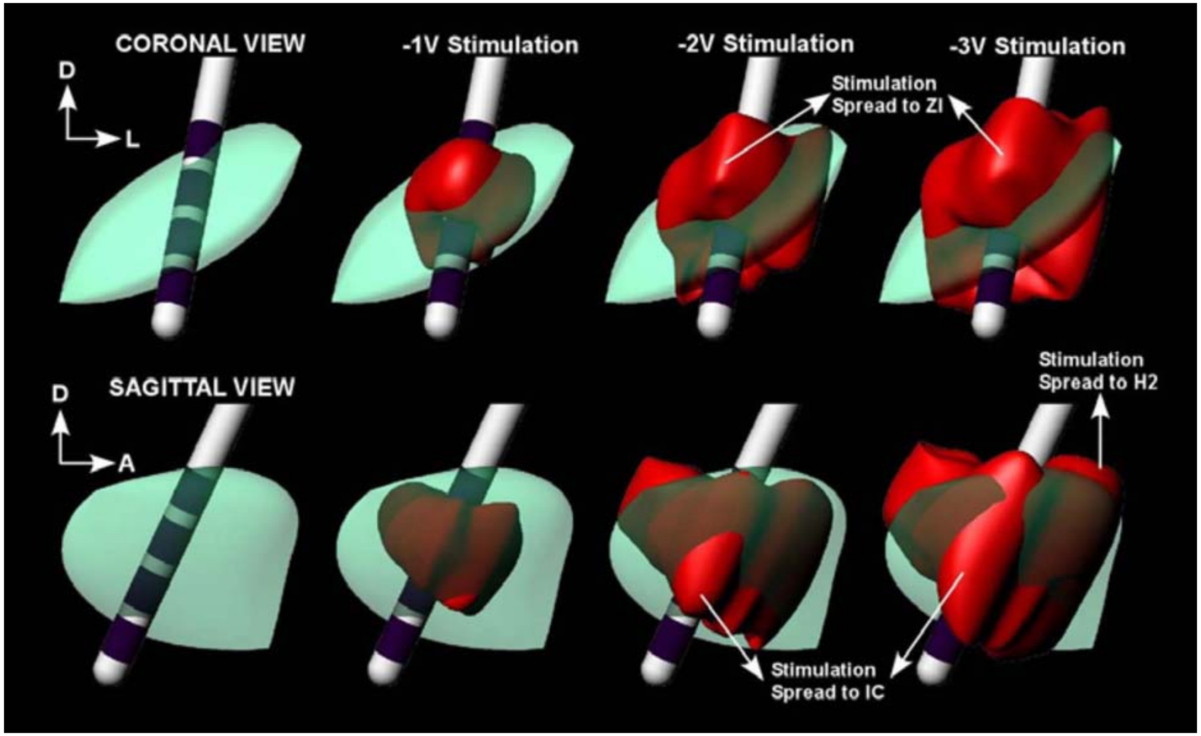
From right to left:

- Anisotropy derived from diffusion tensor MRI of the brain slice
- 10x10 voxels representing the target area with superimposed atlas data
- potential field generated by -1V stimulation
- second spatial difference of the potential field

STN: subthalamic nucleus, IC: internal capsule, ZI: zona incerta, H2: Fields of Forel

McIntyre et al. Clin. Neurophysiol., 2004

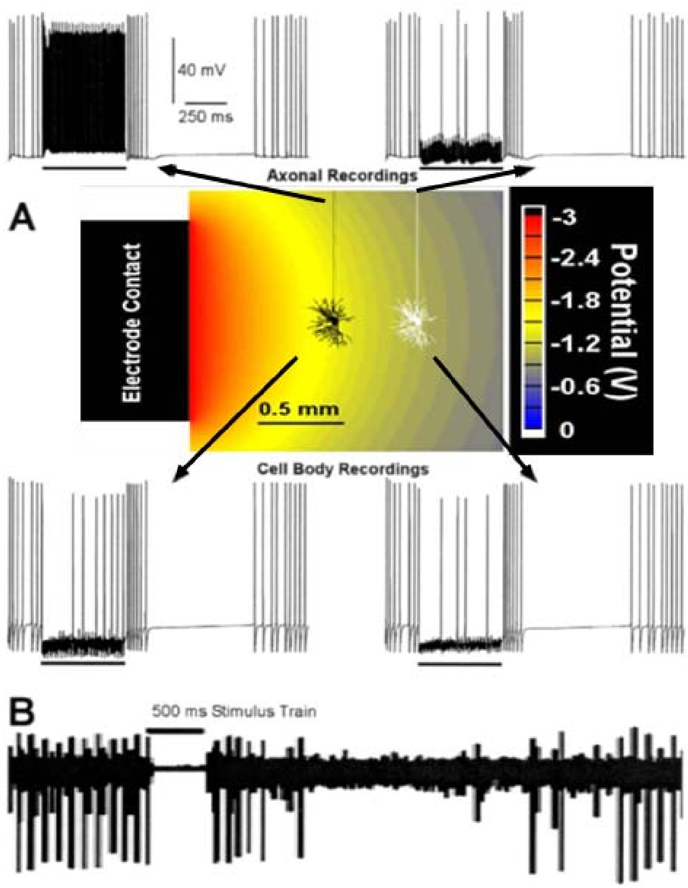
MODELING THE VOLUME OF ACTIVATION DURING STN DBS

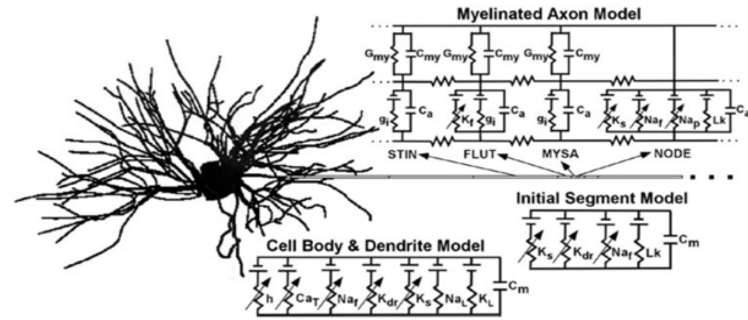


McIntyre, 2005

The STN marked as green, the volume of the activated tissue is marked by red. At higher voltage the activation spread to the surrounding structures.

MODELING OF DBS IN NEURONAL LEVEL





Effect of DBS on model thalamocortical (TC) relay neurons (see above)

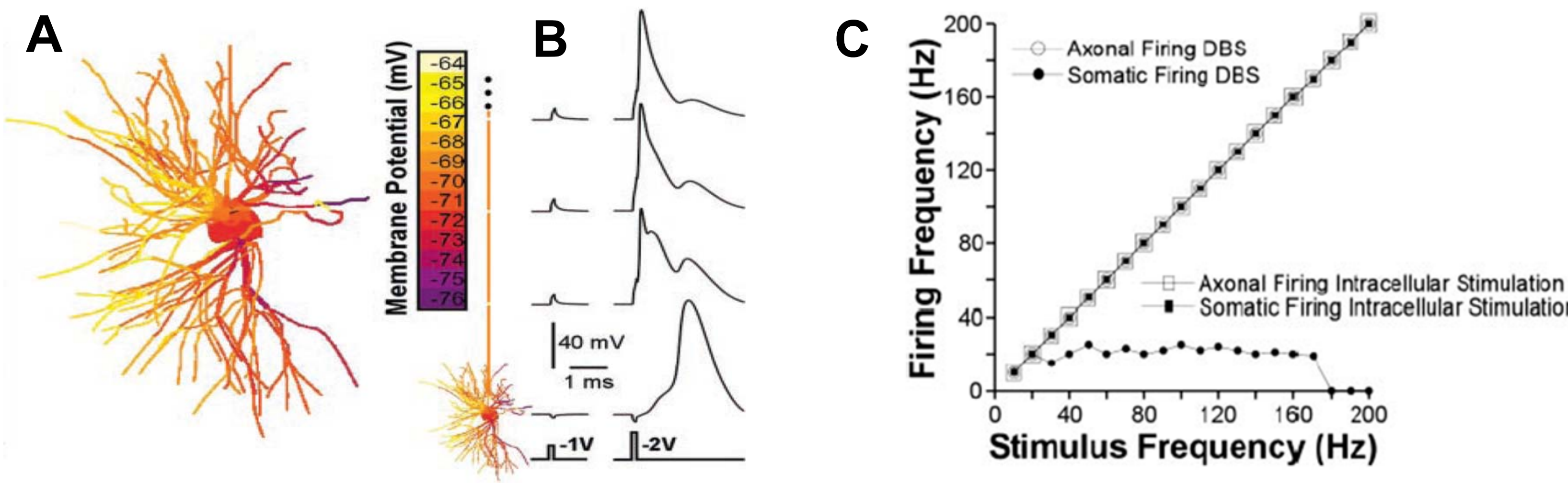
A Stimulation: 150 Hz, 0.1 ms, -3 V, 500 ms train with Medtronic 3375 DBS electrode.
Suprathreshold activation of black neuron (1.5 mm from electrode), subthreshold activation of white neuron (2 mm from electrode).

At black neuron suppressed firing in the cell body, axonal output in one-to one ratio with the stimulation frequency.

B Human intraoperative record of similar stimulation.

McIntyre, 2004

MODELING OF DBS IN NEURONAL LEVEL



A Axonal action potential initiation in model TC relay neuron to extracellular stimulation. Colors indicate the depolarization of the model neuron compartments.

B Recordings from the soma and nodes of Ranvier at subthreshold (-1 V) and suprathreshold (-2 V) 0.1 ms stimulation. The action potential starts earliest at the first node.

C Intra- and extracellular high frequency stimulation generated different firing pattern in the model TC relay neuron. The cell body is unable to follow the stimulus rate at extracellular (DBS) stimulation.

McIntyre at al., 2004

APPLICATION OF DBS IN OTHER DISORDERS

The DBS is now regarded as an efficient therapeutic option for movement disorders. The reversible nature of stimulation is an attractive feature. Currently a series of other disorders are under investigation as candidates for DBS. Here only a list of these are given:

Chronic pain: Thalamus ventr. caudalis, periacqueductal/ periventricular gray, subthreshold stimulation of the motor cortex

Intractable epilepsy: anterior and centromedian thalamus, STN

Major depression: subcallosal cingulate gyrus, Br. area 25

Obsessive-compulsive disorder (OCD): nucl. accumbens, ant. int. capsule

Attempts were made to use DBS in long term coma and minimal conscious state patients. The results are moderate but promising.

SURGICAL COMPLICATIONS AND SIDE EFFECTS OF DBS

In average about 70 percent of the DBS treatments are successful. The improvement of tremor and rigidity is the best, dystonia is less affected, dementia and cognitive deficits are not improved by STN stimulation.

DBS is an invasive therapy. Neurosurgical implantation of electrodes is not entirely risk-free. There is approximately a two to three percent chance of brain haemorrhage or infection during surgery.

Complications related to the implant, such as skin erosions, lead breakage, extension wire failure, or malfunction of the neurostimulator may appear.

Adverse effects of DBS can occur if the electrode placement is suboptimum, it may include dysarthria or hypophonia. Other side-effects of stimulation can be dysphagia, paraesthesias, eyelid opening apraxia.

The most frequently observed long-term neuropsychological side-effect is a decline in word fluency.

LINKS:

Videos show effects of DBS: http://www.kringelbach.dk/nrn/

(*Nature Reviews Neuroscience* 2007, **8**, 623-635.)

www.medtronic.com

www.alphaomega-eng.com

http://emedicine.medscape.com/article/1153743-overview#aw2aab6b3

http://www.parkinsonsappeal.com/dbs/whatisdeepbrainstimulation.html

http://www.mayoclinic.org/deep-brain-stimulation/

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REVIEW QUESTIONS:

- What is deep brain stimulation?
- What are the parameters of the DBS leads?
- What are the characteristics of the neurostimulator?
- What are the steps of the DBS surgery?
- Which are the target areas of DBS?
- What are the main symptoms of the Parkinson’s disease?
- Which movement disorders are treated by DBS?
- What are the hypotheses on the mechanism of action of DBS?
- What are the results of modeling studies on DBS?
- What are the surgical complications and side-effects of DBS?