



UNIVERSITÉ DE
MONTPELLIER



DEEP BRAIN STIMULATION

Dr POULEN Gaëtan, M.D, PhD

Department of Neurosurgery, Montpellier

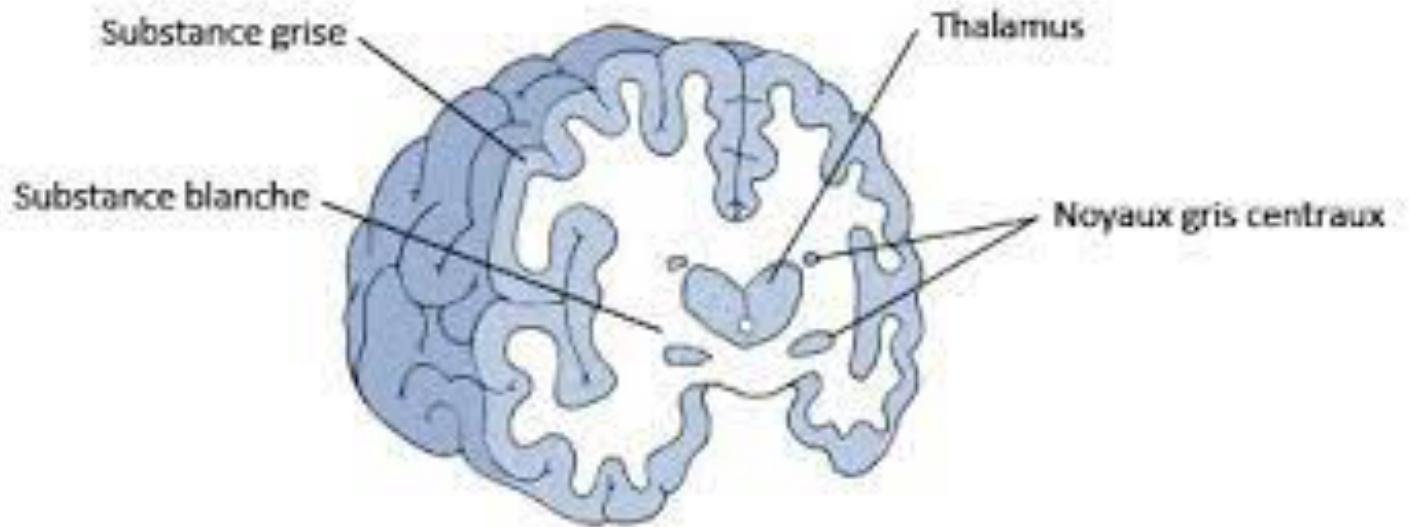
INSERM U1198

What is Deep Brain Stimulation ?

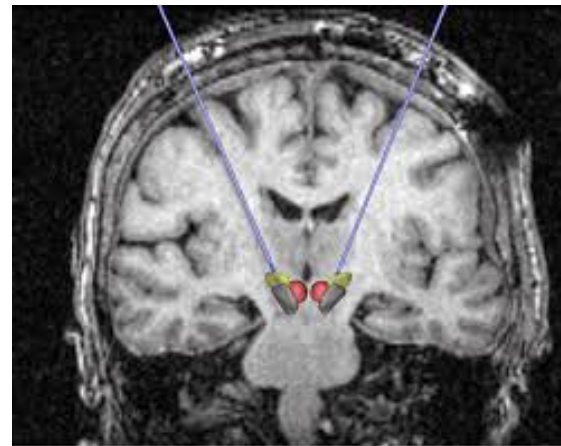
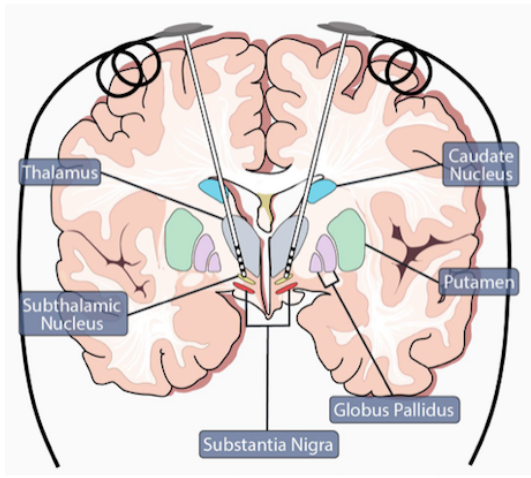
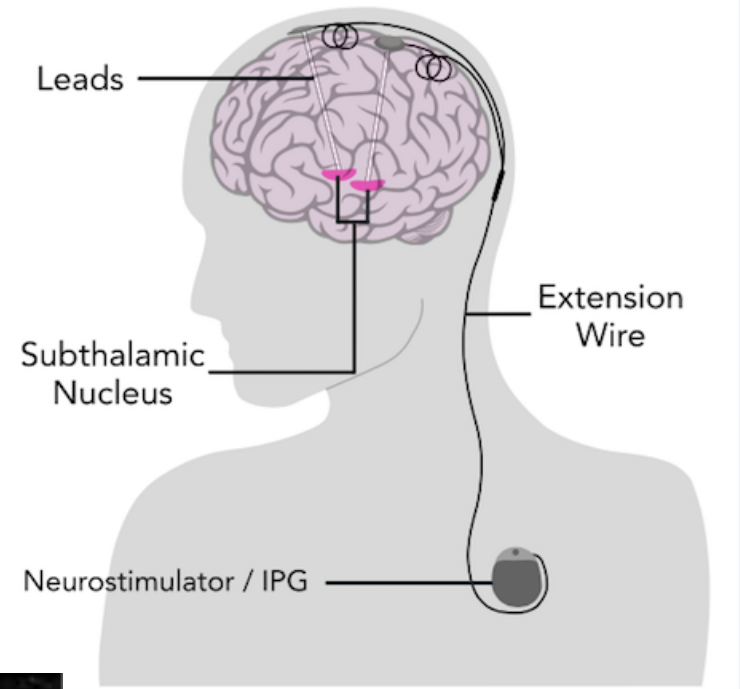
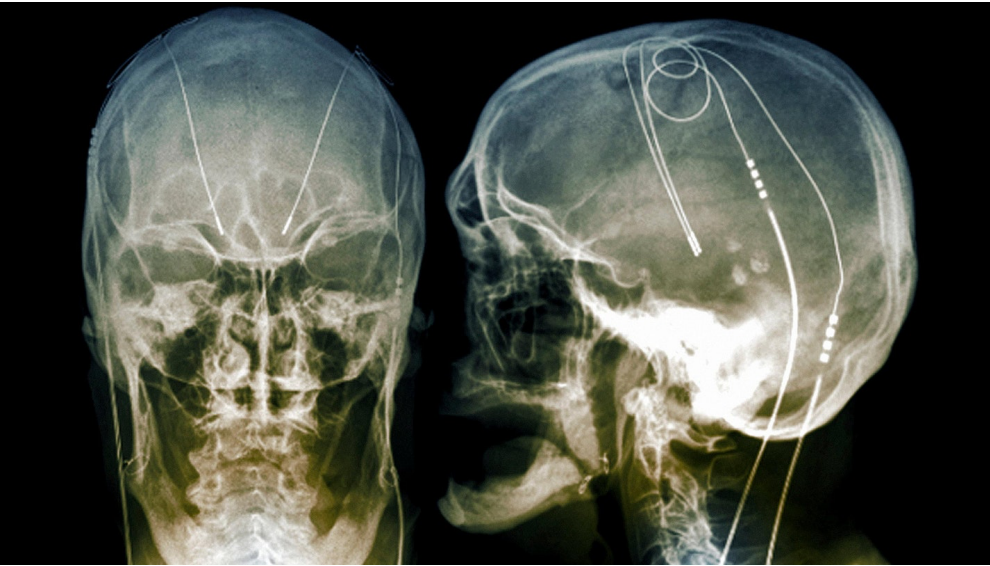


What is Deep Brain Stimulation ?

Neuro-anatomy: some reminders



What is DBS ?



What is DBS ?



- Rechargeable Generator
- Several times a week
- Transcutaneous
- Life time of rechargeable generators : around 15-20 years



Animal models

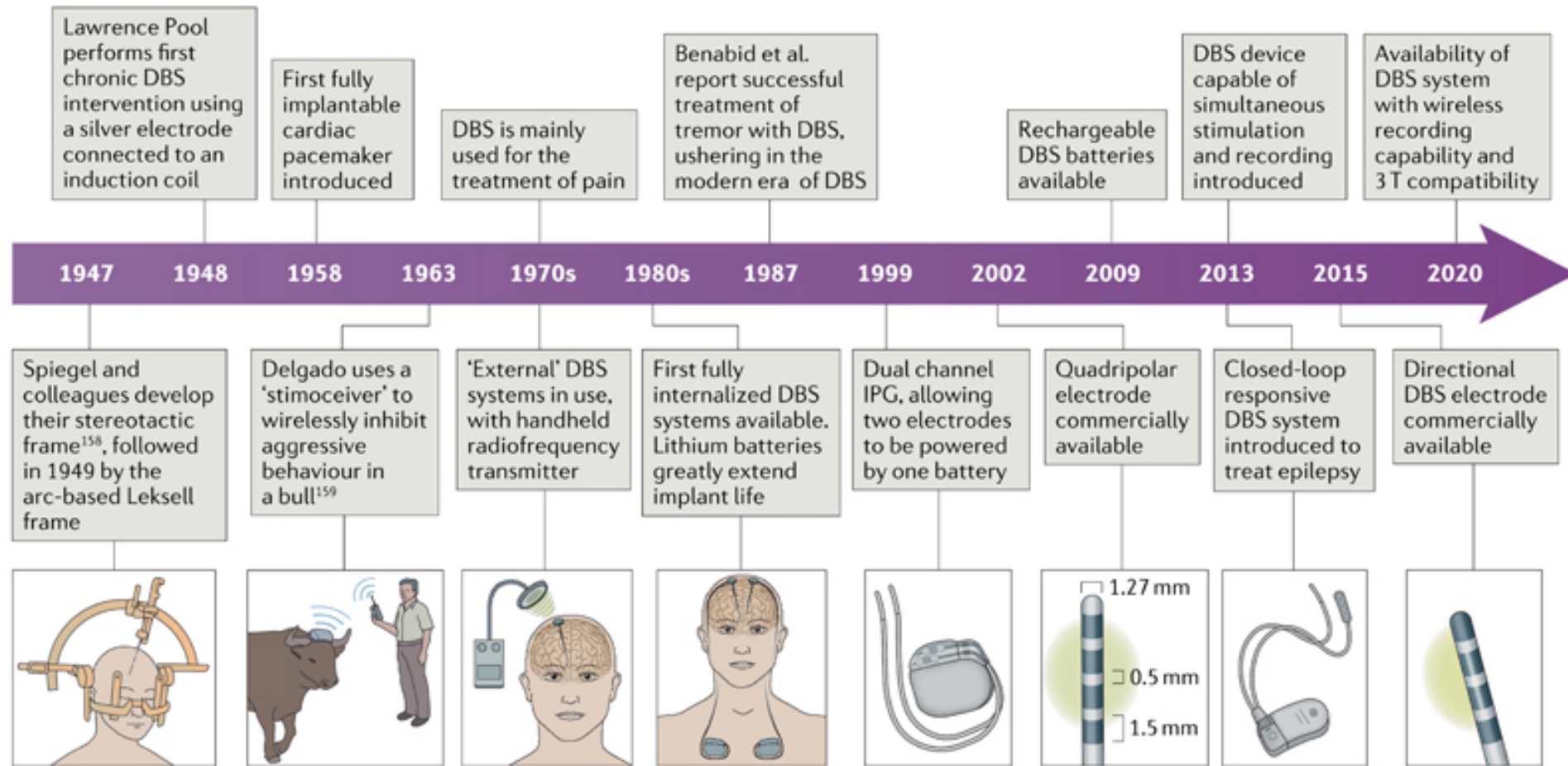
use of animal models to understand brain circuits

Indication	Animal model	Main contribution
Parkinson disease	MPTP in non-human primate	<ul style="list-style-type: none">Abnormal activity detected in the STN¹³⁸STN lesion improves motor dysfunction^{36,37}STN high-frequency stimulation improves motor dysfunction³⁹
Epilepsy	Pentylenetetrazol in guinea pigs and rats	<ul style="list-style-type: none">Lesioning of the MMT ameliorates epilepsy⁴⁰Electrical stimulation of the ANT ameliorates epilepsy⁴²
Huntington disease	Transgenic rat model	<ul style="list-style-type: none">Electrical stimulation of the GPe improves choreiform movements¹³⁹
Compulsivity-related behaviour	Polydipsia rat model	<ul style="list-style-type: none">Electrical stimulation of the BNST effectively reduces compulsive-like behaviour¹⁴⁰
Depression-like behaviour	CMS rat model	<ul style="list-style-type: none">Serotonin and BDNF are involved in the mood-related effects of electrical stimulation of VMPFC¹⁴¹Electrical stimulation of different brain areas has differential influences on mood-related effects⁴⁷

ANT, anterior nucleus of the thalamus; BDNF, brain-derived neurotrophic factor; BNST, bed nucleus of stria terminalis; CMS, chronic mild stress; GPe, globus pallidus externus; MMT, mammillothalamic tract; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; STN, subthalamic nucleus; VMPFC, ventromedial prefrontal cortex.

Lozano AM et al.
2019

Is it new ?



Lozano AM et al. 2021

Indications

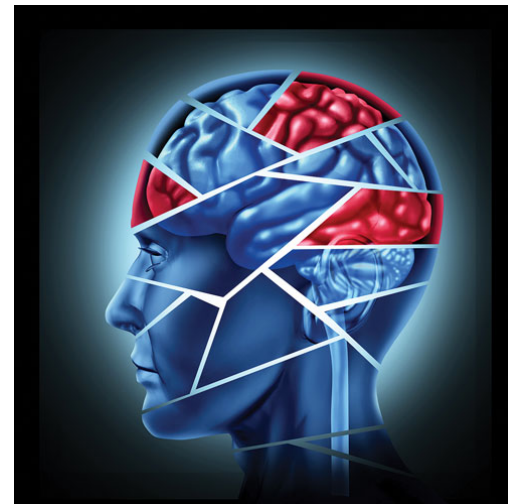
Movement disorders:

- Parkinson
- Dystonia
- Huntington
- Essential Tremor

Psychiatric disorders:

- OCD
- Severe Depression
- Addiction (cocain, ...)
- Tourette Syndrom

Epilepsia

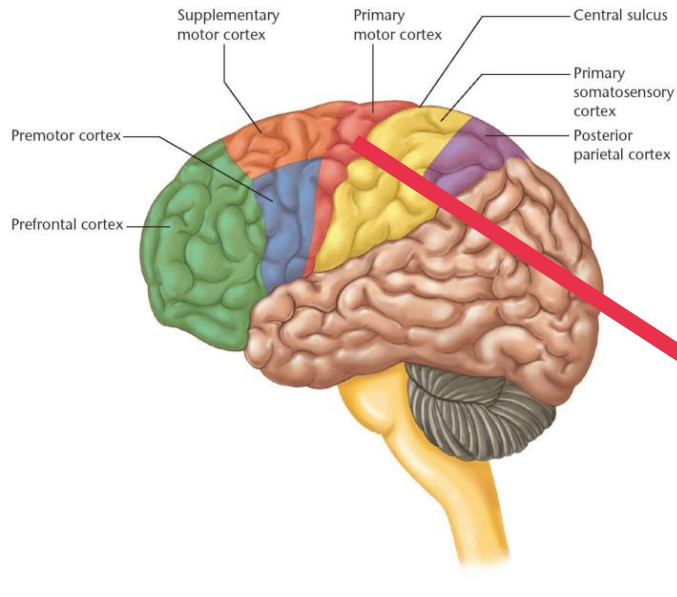


When ?

- Refractory to other medications
- Severe symptoms
- Disability
- Decrease of quality of life

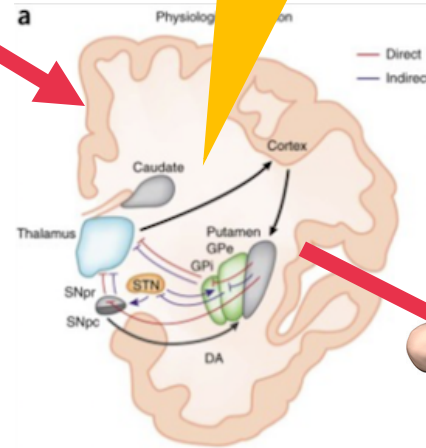
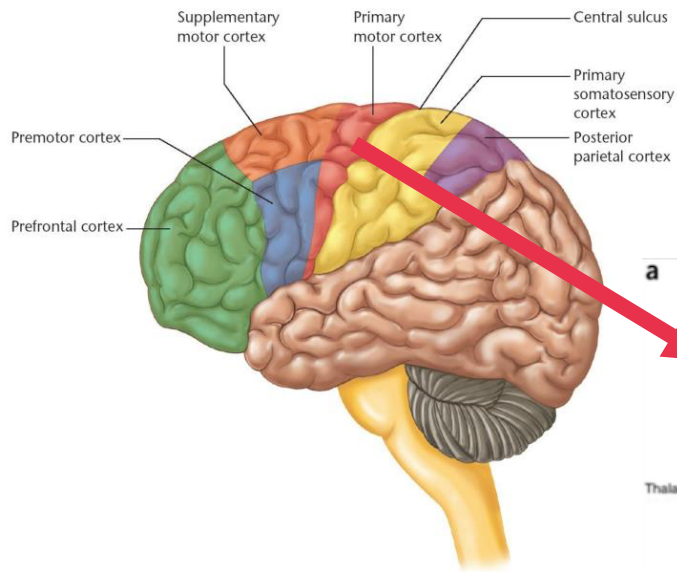


Cortical areas involved in motor control

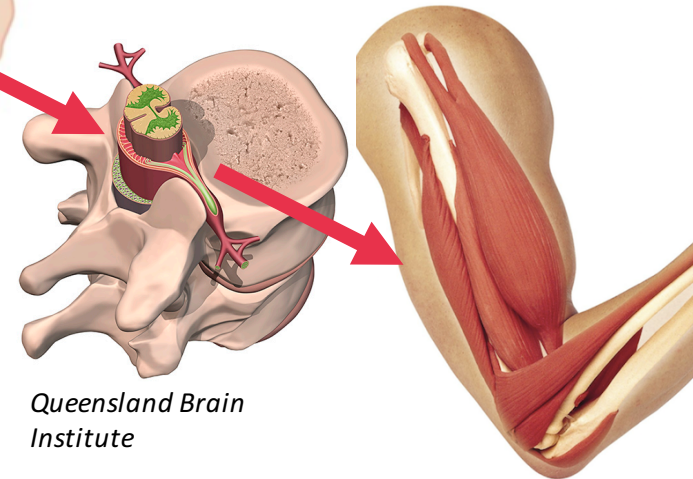


Pathophysiology

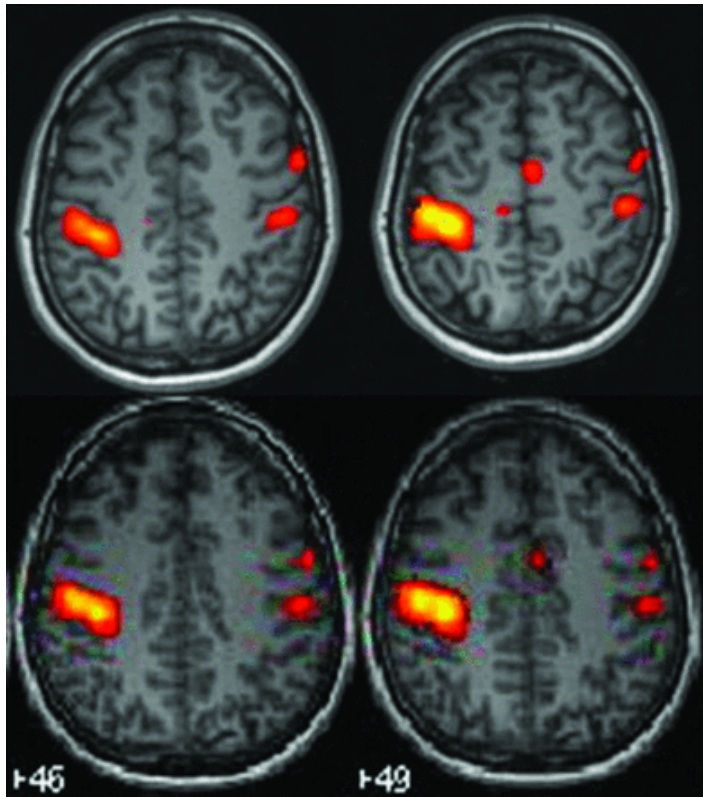
Cortical areas involved in motor control



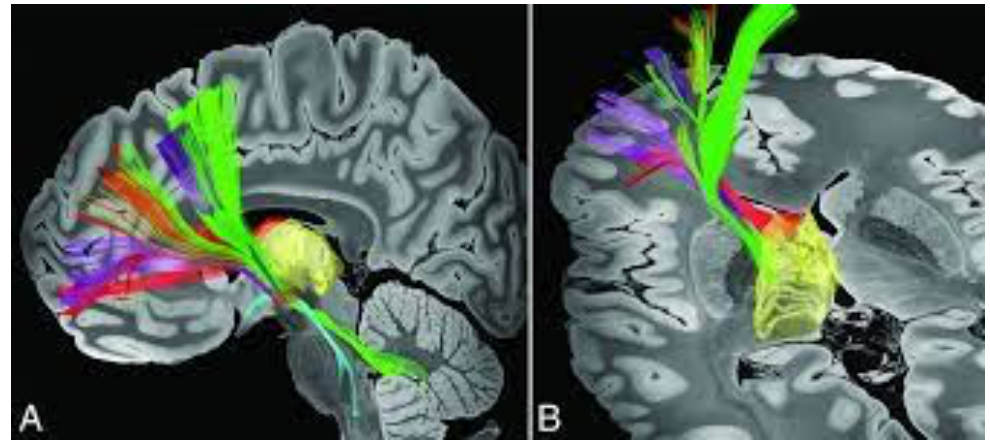
*Calabresi P et al. 2014
Nature Neuroscience*



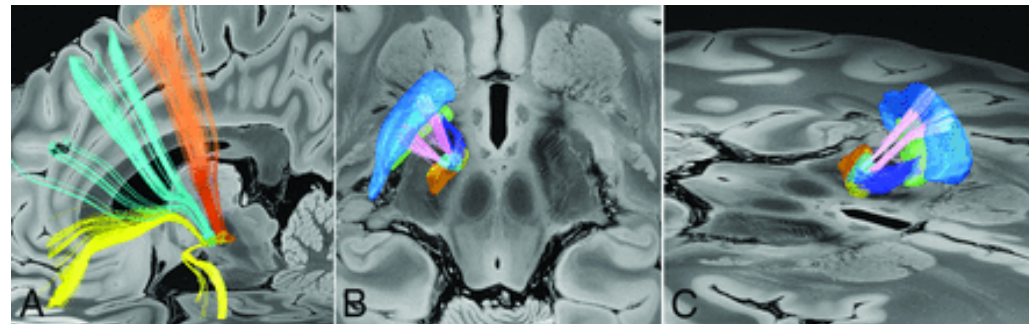
Pathophysiology



**Functional MRI : Left
finger tapping**
Gonzalez-Ortiz S et al. J of
Neuroradiology 2013



Middlebrooks EH et al. 2020
American Journal of Neuroradiology



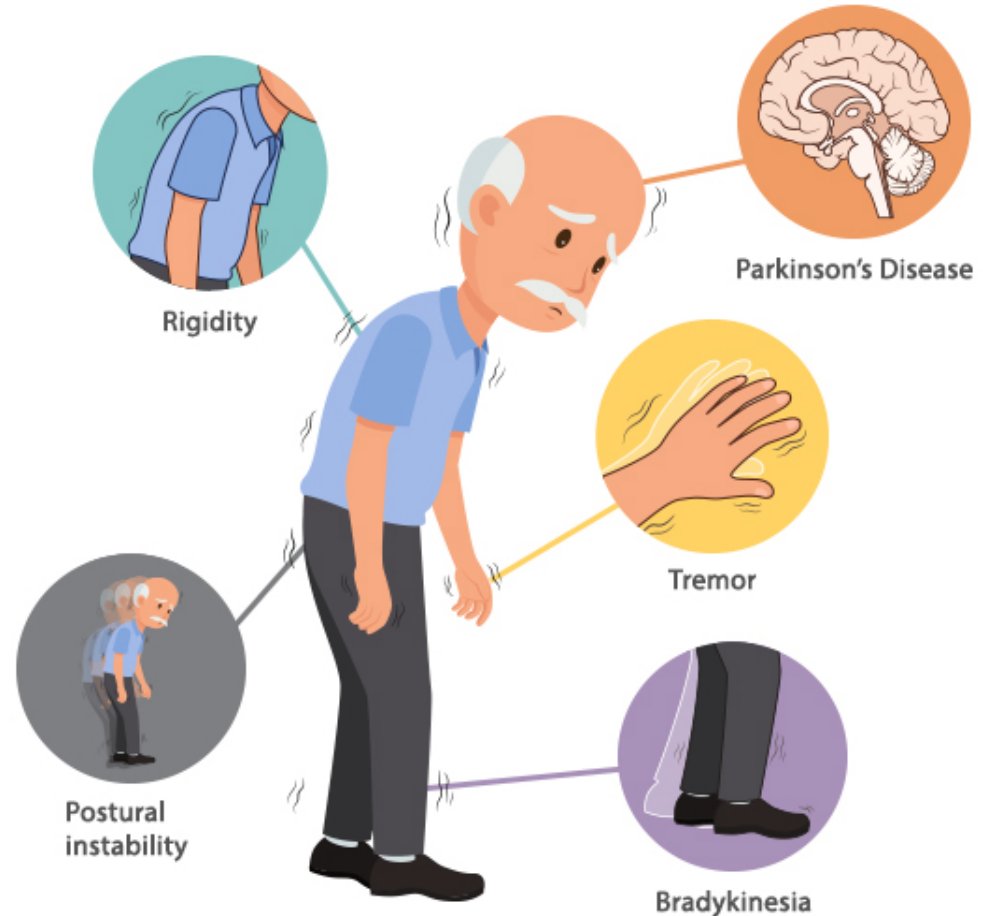
Parkinson Disease

Neurodegenerative disease:

Destruction of dopaminergic neurons in the substantia nigra

Symptoms :

- Tremor
- Bradykinesia
- Hypertonia



DBS IS NOT A CURATIVE TREATMENT ++++ => SYMPTOMATIC TREATMENT

Dystonia

Muscular tonus disorder due to a dysfunction in the Central Nervous System

Many causes :

- Genetic
- Idiopathic
- Post-traumatic
- Post-stroke
- Post-tumoral
-

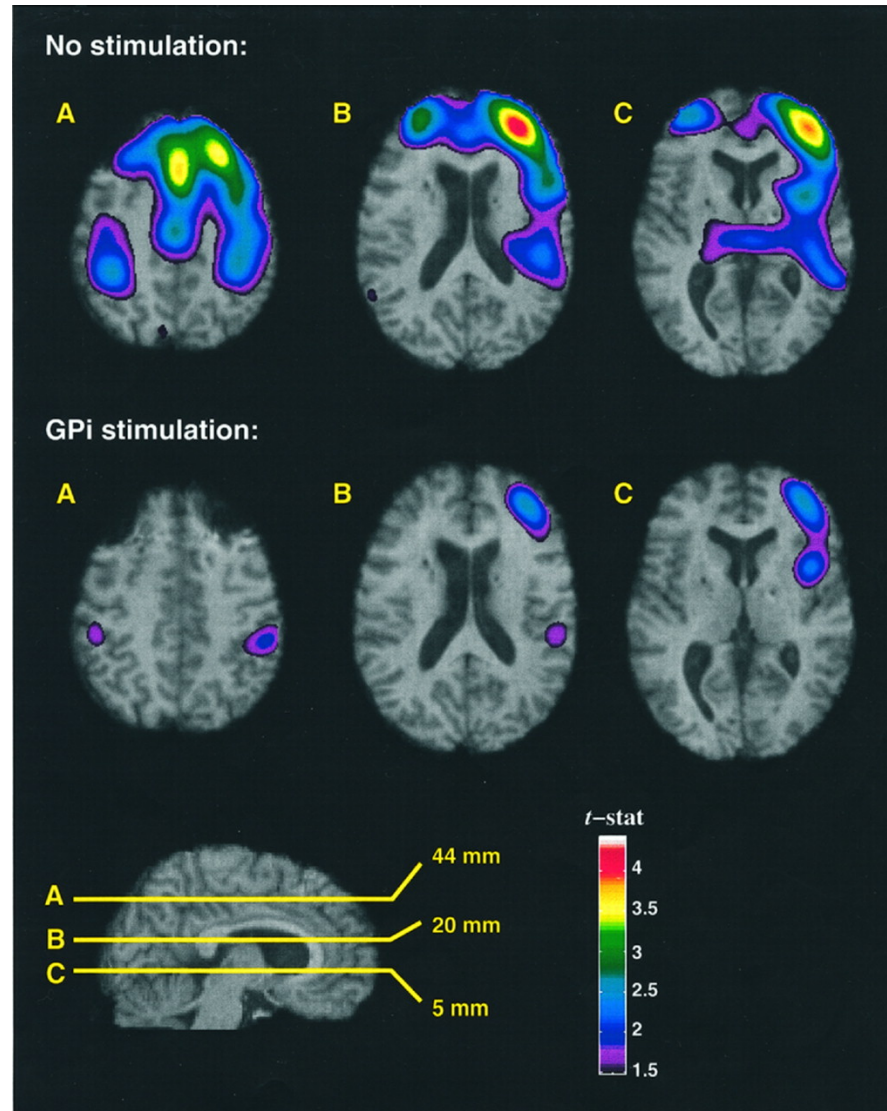


IBS Hospitals

DBS IS NOT A CURATIVE TREATMENT ++++ => SYMPTOMATIC TREATMENT

Dystonia

Generalized dystonia: MRI + PET



*Kumar R et al. Neurology
2019*

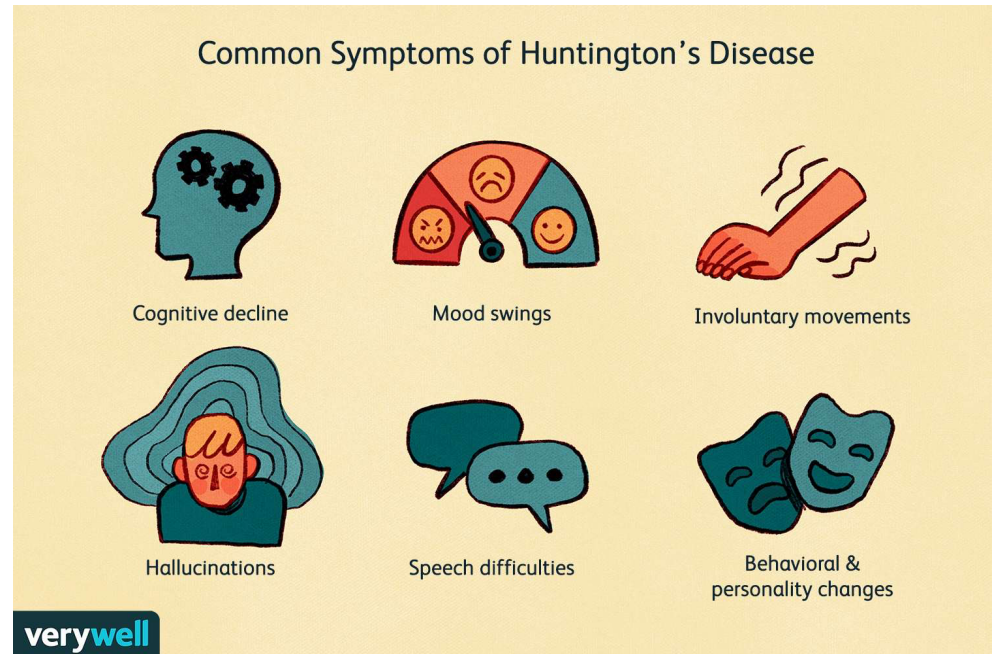
Huntington Disease

Genetic disease

Progressive Brain Disorder

Life expectancy after diagnosis: 10-30 years

Chorea +++ : early symptom

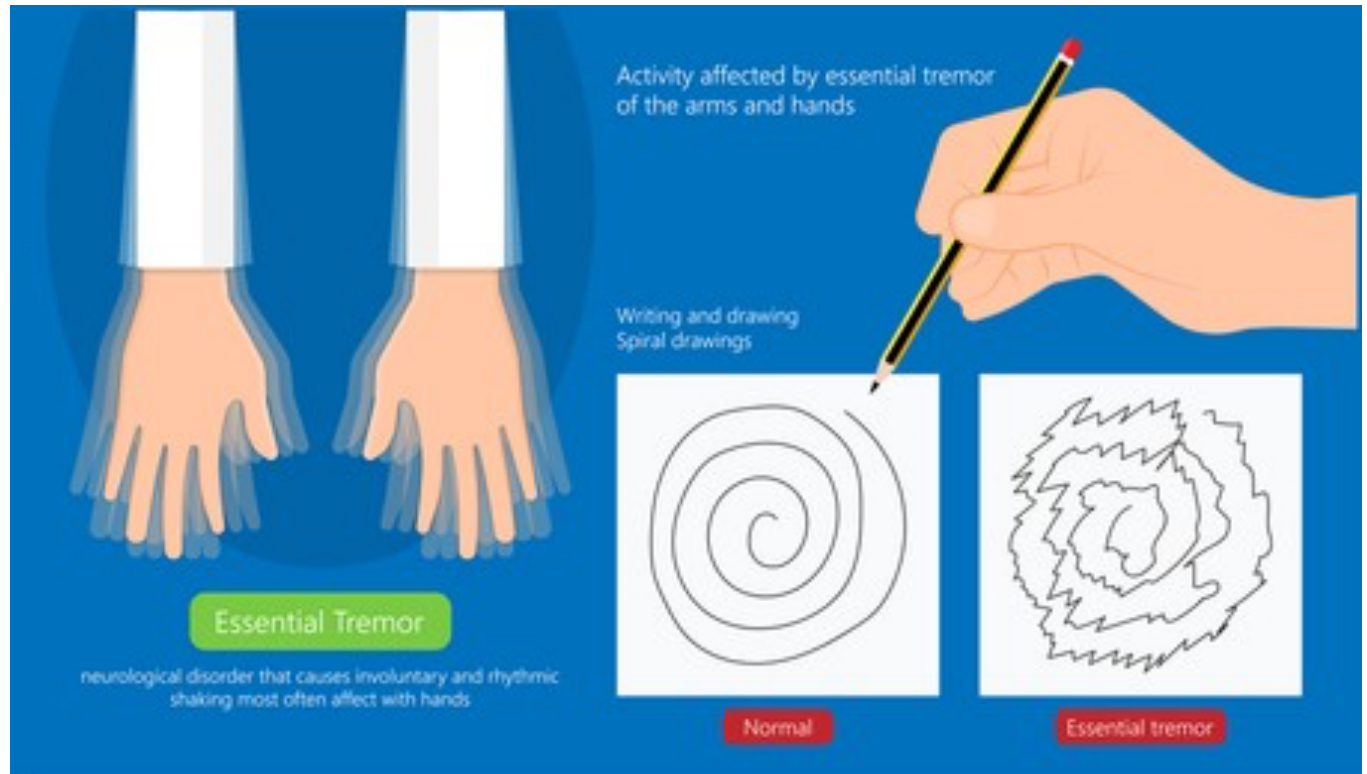


VeryWell Health website

DBS IS NOT A CURATIVE TREATMENT ++++ => SYMPTOMATIC TREATMENT

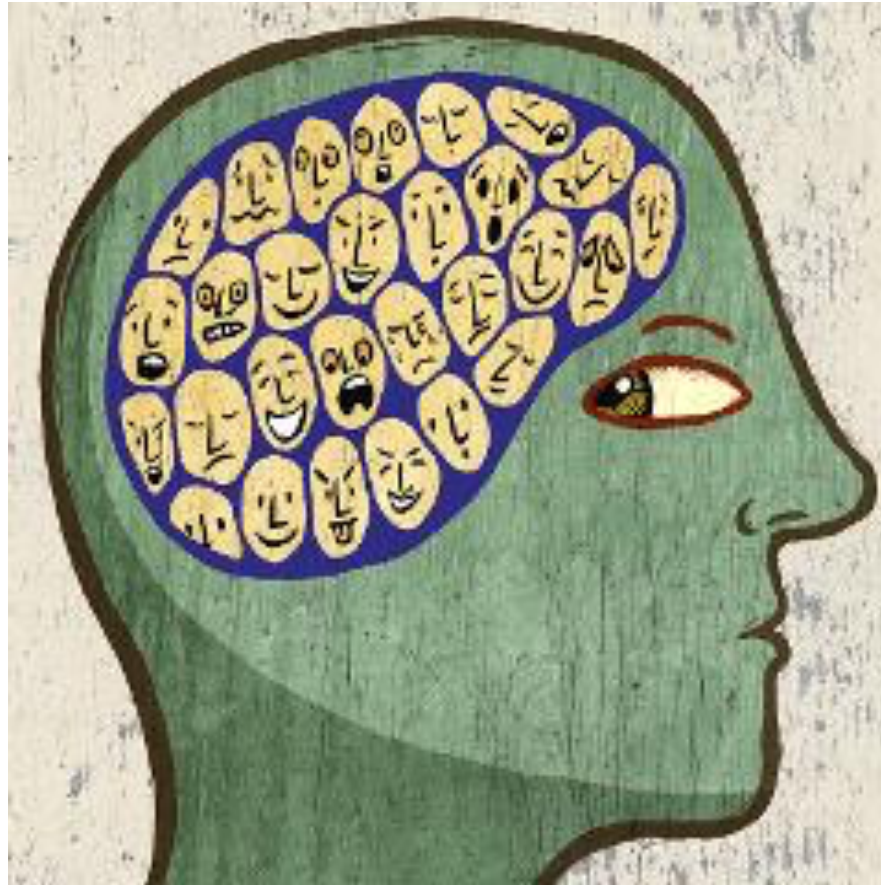
Essential Tremor

Frequent
1/200

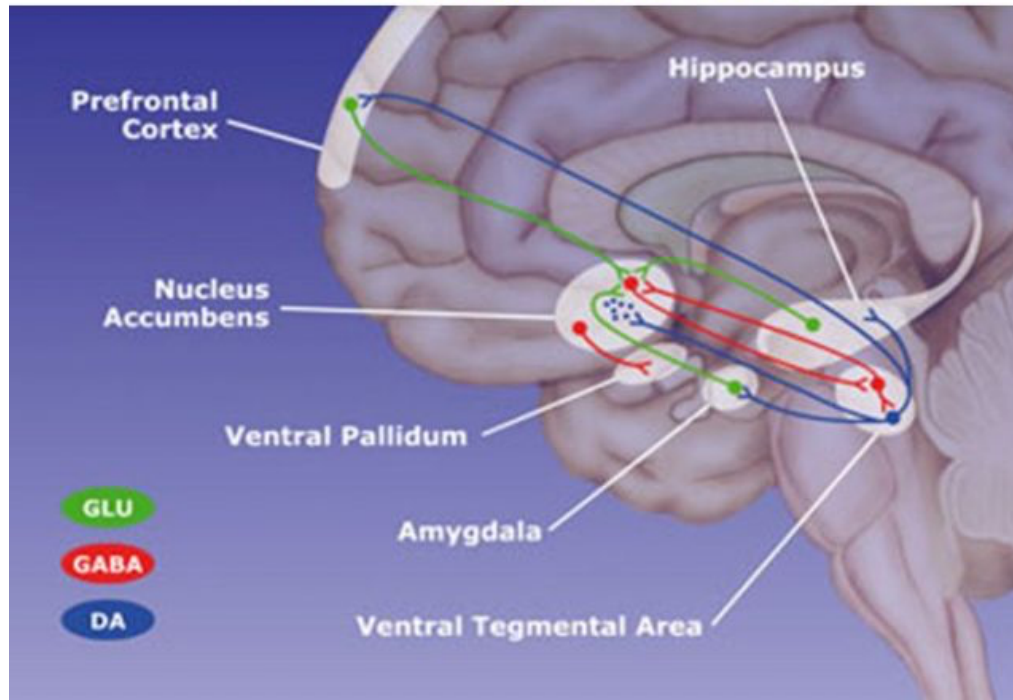


shutterstock.com · 1733708381

DBS in psychiatric disorders



The Reward Circuit



Alonso JR, MappingIn 2018

Limbic system and prefrontal cortex

OCD: Obsessional and Compulsive Disorder

Patients have **recurring, unwanted thoughts**, ideas or sensations (**obsessions**) that make them feel driven to do something repetitively (**compulsions**)

- To wash
- To classify
- ...



DBS is an effective treatment => The reward circuit

Gilles de La Tourette Disease

Neurodevelopmental disorder
Begins in childhood
Motor and vocal TICS



DBS is an effective treatment

Drug addiction

- Some case series are described in literature with promising results (cocain, heroin, ...)
- Effects on the reward circuit



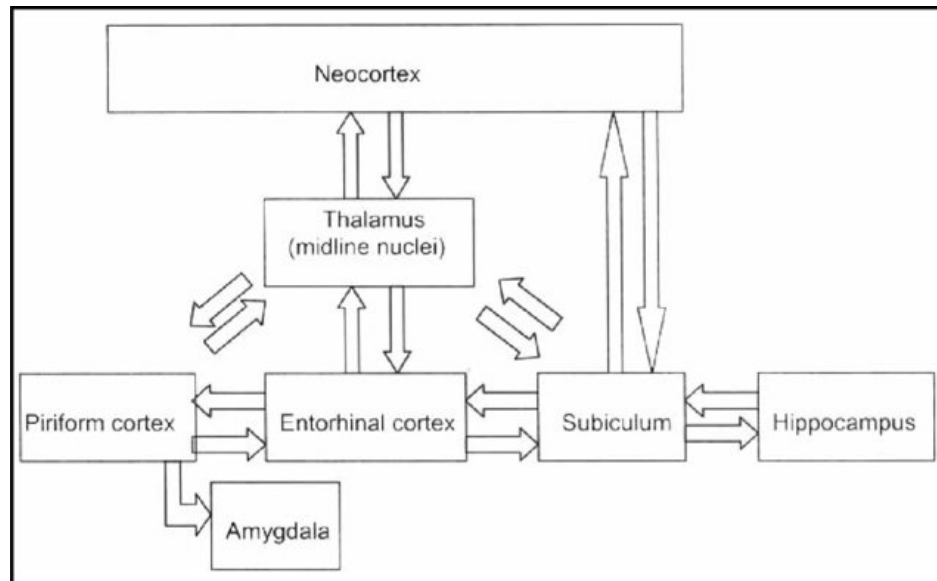
Severe and Refractory Depression

- Multiple targets in the brain
- Some teams do brain lesions rather than DBS
- Some case series
- Not used routinely yet



Epilepsia

- Refractory epilepsy
- Focal or generalized
- Goal of DBS : To block the spread of seizures



Doherty JJ et al. 2002



UNIVERSITÉ DE
MONTPELLIER

Université de Montpellier
FACULTÉ
de MÉDECINE
Montpellier-Nîmes

Is this Science Fiction ?

NO !! It's REALITY !

In Montpellier : 35-40 DBS per year



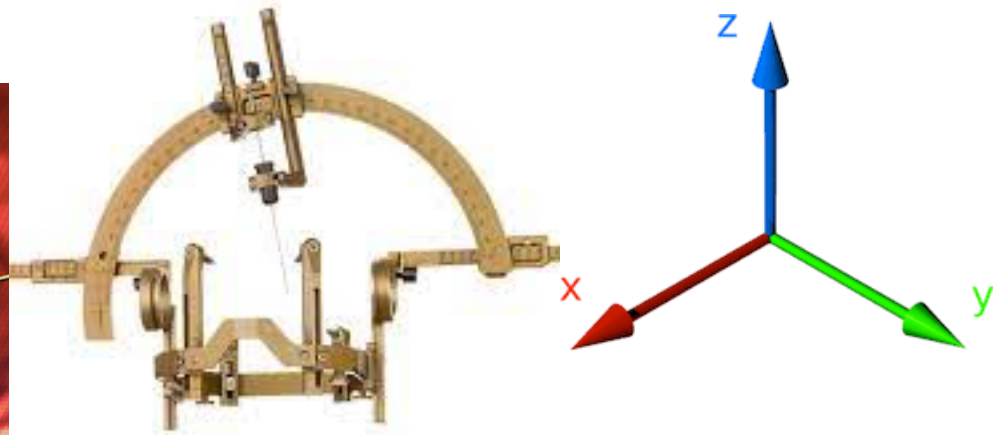
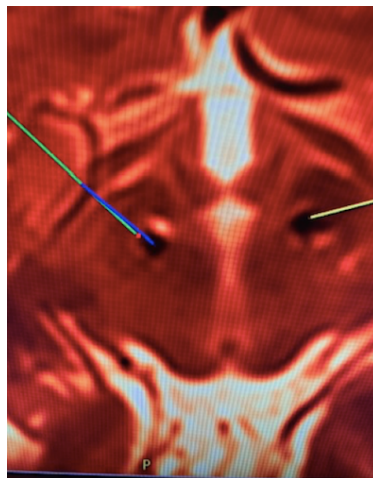
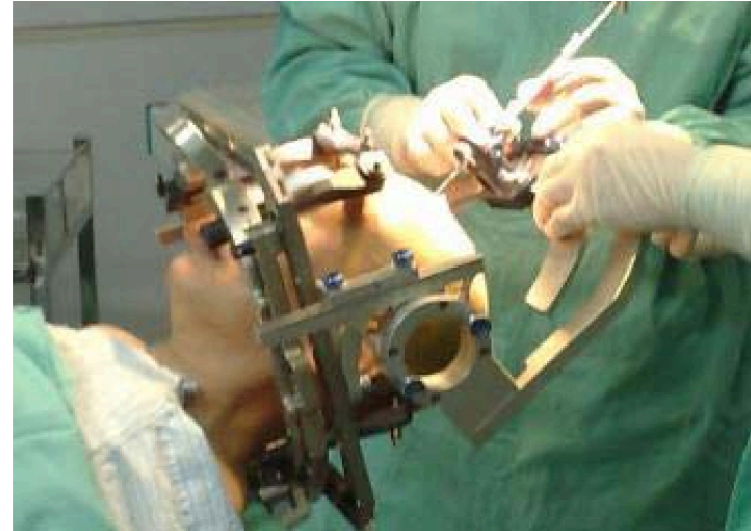
How ?

- **General or local anesthesia**
- Stereotactic frame
- MRI
- Targetting
- Implantation of the leads
- Control MRI
- Implantation of extensions and generator



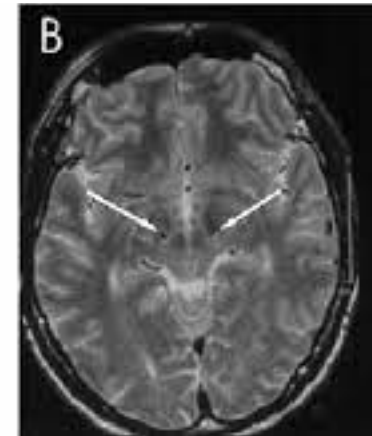
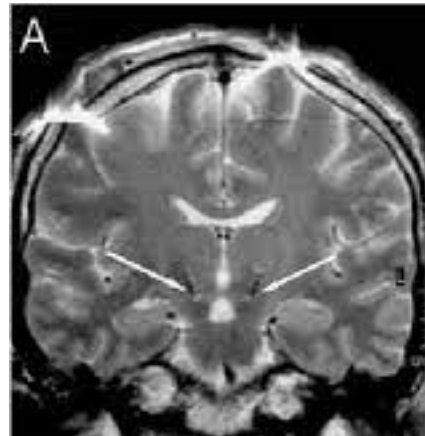
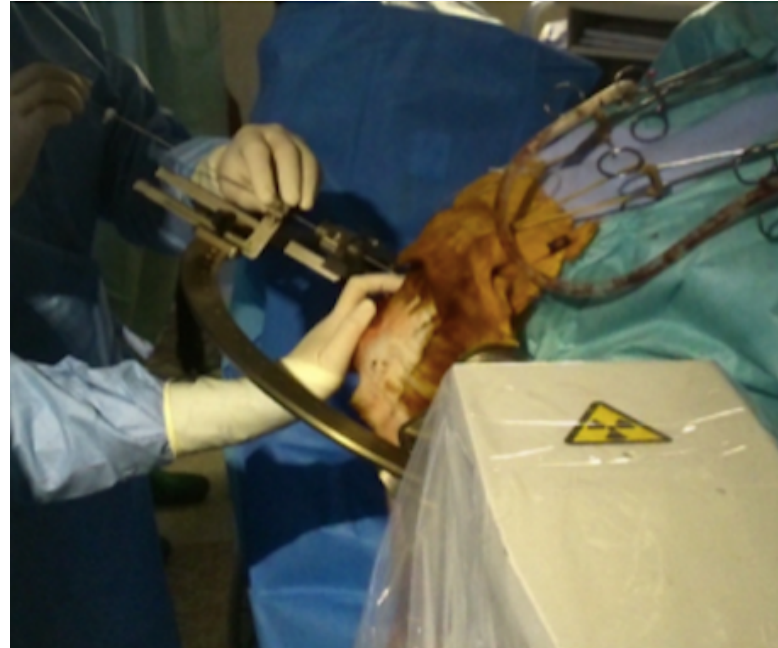
How ?

- General or local anesthesia
- **Stereotactic frame**
- **MRI**
- **Targetting**
- Implantation of the leads
- Control MRI
- Implantation of extensions and generator



How ?

- General or local anesthesia
- Stereotactic frame
- MRI
- Targetting
- **Implantation of the leads**
- **Control MRI**
- Implantation of extensions and generator



Surgical complications?

- Very **low rate** of complications
- Very low rate of hemorrhage
- **Infection** => Removal of the DBS system



How ?

Parameters settings :

- Voltage
- Frequency
- Pulse Width

=> current (around 2 mA)

Easy to adjust

Up or down the current depending on efficiency and side effects

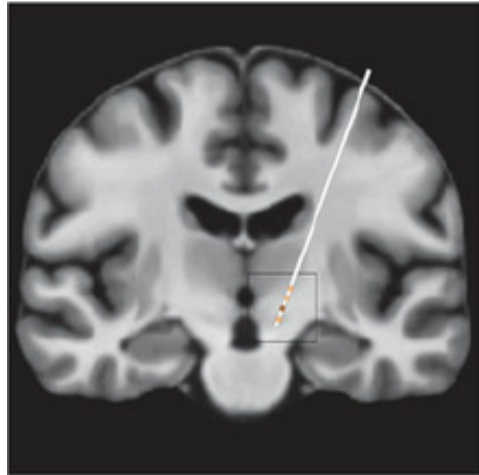
New generators can record electrical activity of the target (Local Field Potential)



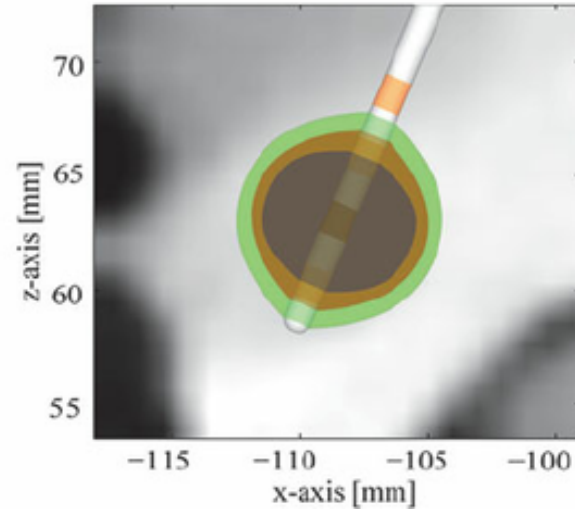
How ?

Volume of Activated Tissue

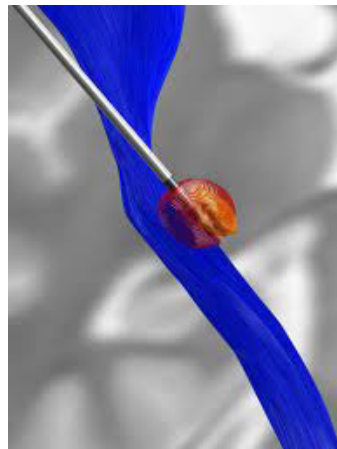
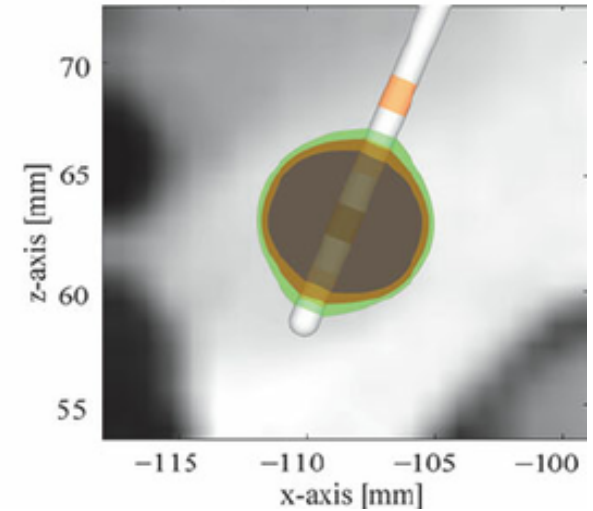
Coronary section



Current controlled stimulation



Voltage controlled stimulation



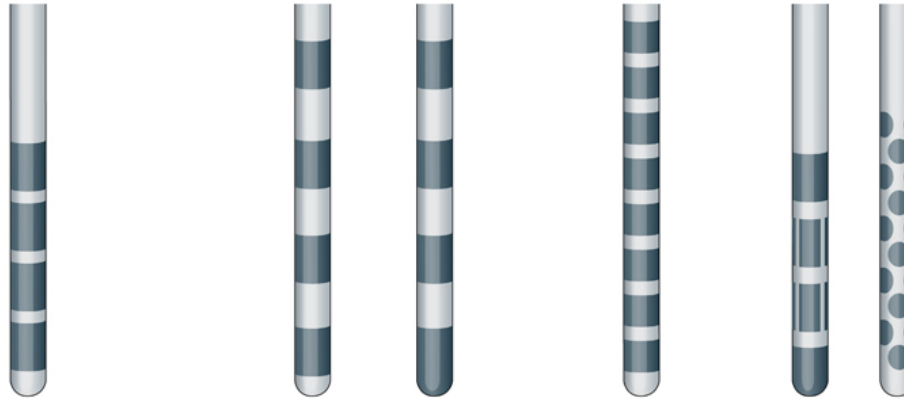
Schmidt C et al. 2012

[Horn et al., 2017.](#)

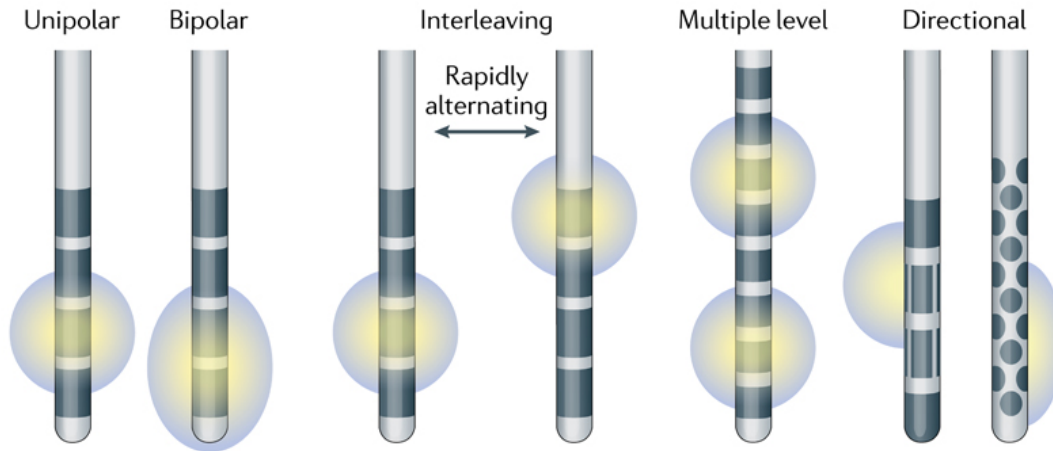
How ?

Leads

a Common DBS electrode configurations



b Types of stimulation



Lozano AM et al. 2021

Side effects

Depending on:

- The target
- The current

Current can diffuse in adjacent structures

Side effects:

- paresthesia
- involuntary muscular contraction
- paralysis
- dysarthria
- oculomotricity disorder
- mood disorder : depression with suicid

attempt

Reversible when stopping or decreasing the stimulation



DBS: How does it work?

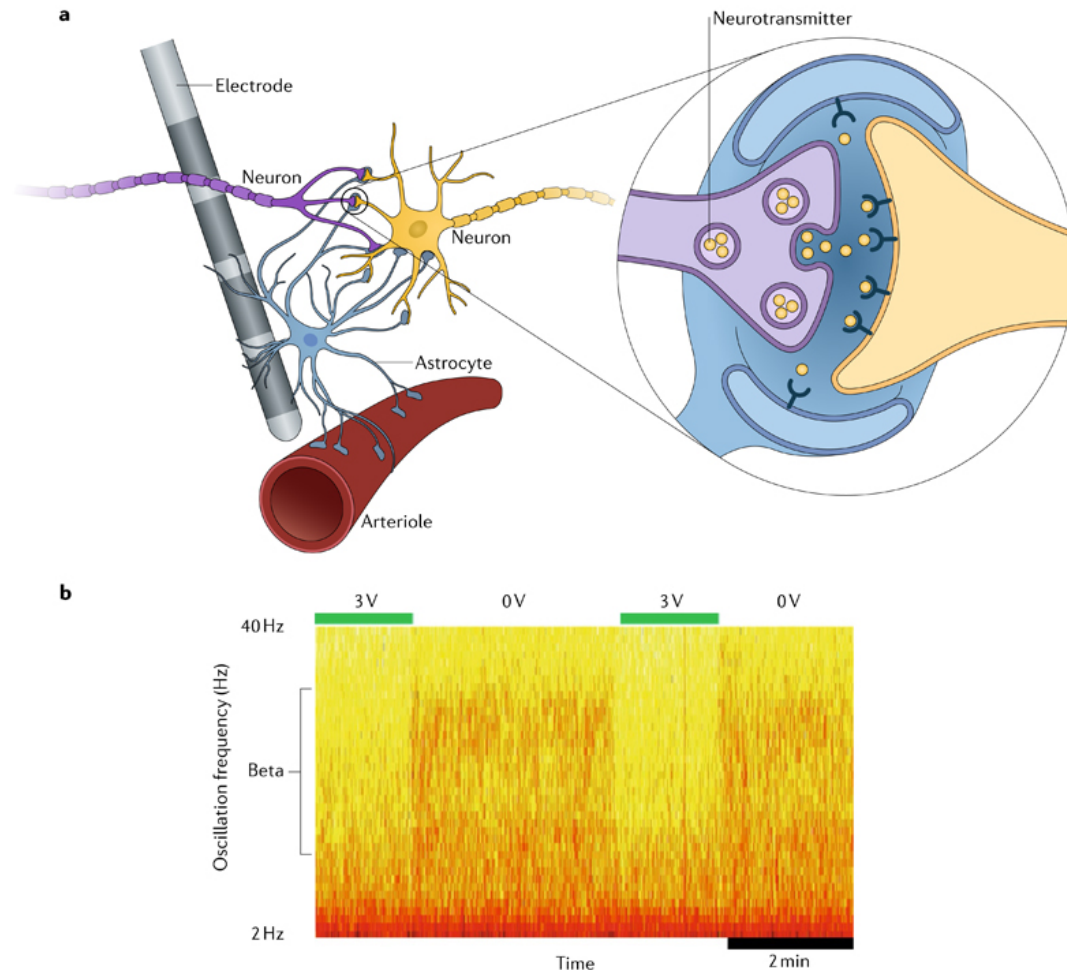
- Many hypotheses have been proposed for the mechanisms
- Stimulation-induced disruption of pathological brain circuit activity
- => This disruption occur at the **ionic, protein, cellular and network levels** to generate improvements in symptoms



DBS: How does it work?

a | Neurotransmitters are released in response to stimulation, leading to calcium waves and release of gliotransmitters. This release influences synaptic plasticity, leading to arteriole dilation and increased regional blood flow.

b | Deep brain stimulation (DBS)-induced changes in local field potentials within the subthalamic nucleus. Activity in the beta band is rapidly reduced with DBS at 3 V and then resumes with stimulation off.



Lozano AM et al. 2019

DBS: where are we now?

> *Brain Stimul.* Mar-Apr 2020;13(2):378-385. doi: 10.1016/j.brs.2019.11.008. Epub 2019 Nov 23.

Clinical trials for deep brain stimulation: Current state of affairs

Irene E Harmsen ¹, Gavin J B Elias ¹, Michelle E Beyn ¹, Alexandre Boutet ², Aditya Pancholi ¹, Jürgen Germann ¹, Alireza Mansouri ³, Christopher S Lozano ¹, Andres M Lozano ⁴

Affiliations + expand

PMID: 31786180 DOI: [10.1016/j.brs.2019.11.008](https://doi.org/10.1016/j.brs.2019.11.008)

- 384 relevant clinical trials:
 - 28 different disorders
 - 26 separate brain targets
 - 60%: movement disorders
 - 41.9% : USA
 - One-third focused primarily on imaging or electrophysiological changes

How far can we go ?



Perspectives

What more can we modulate ?

Which target for which disease ?



Psychiatric disorders : Bipolar Disorder

Work is in progress

Some case series

Which target ?



Psychiatric disorders : Post-Traumatic Stress Disorder

Work is in progress

Some case series

Which target ?



Psychiatric disorders : Anorexia Nervosa

Few studies

Which target ?



Psychiatric disorders : Binge eating disorder and obesity

Local work in Montpellier

How to find a new target for a disease?

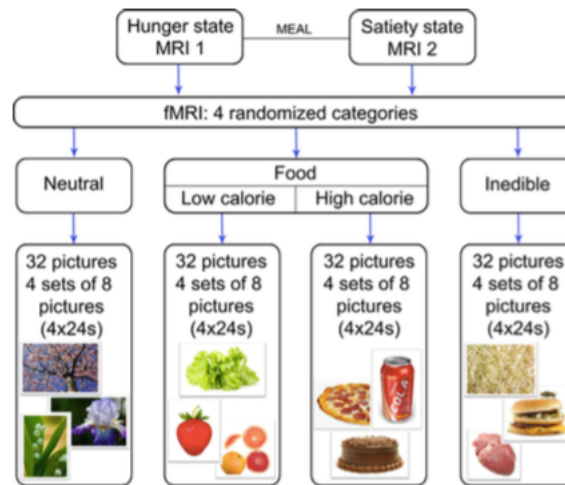


Psychiatric disorders : Binge eating disorder and obesity

To identify a potential target with fonctionnal MRI

First step : In healthy patients

Functional connectivity in rest- and task-based imaging showing significant differences while hungry as opposed to while satiated.



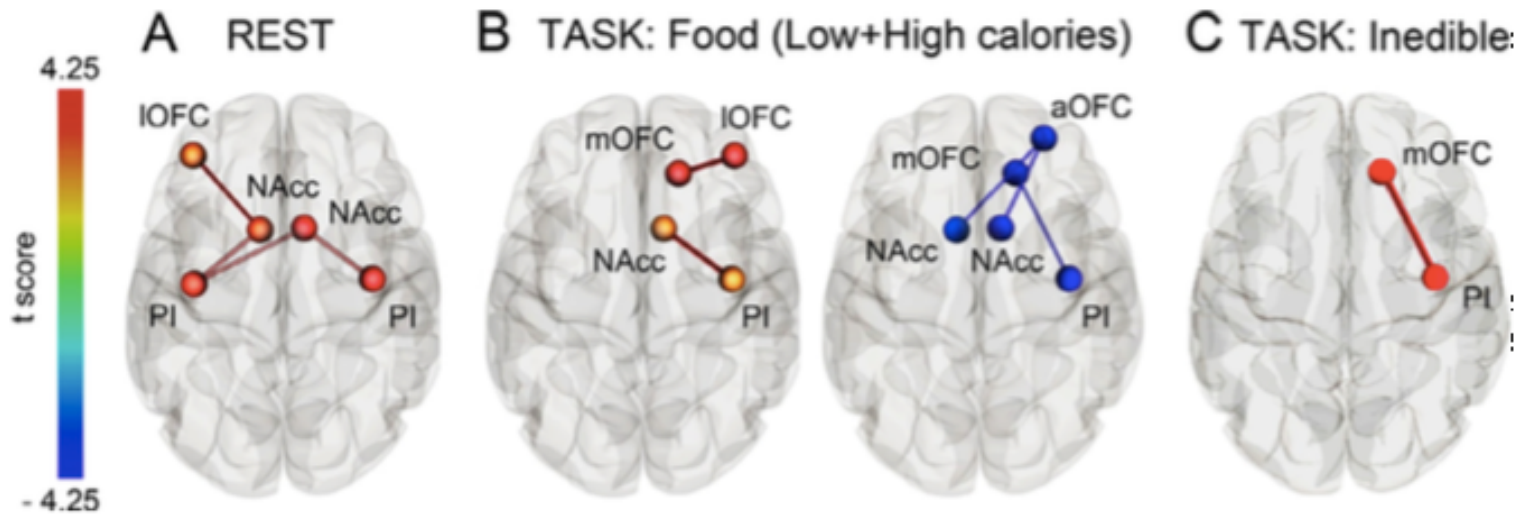
Charroud D, Poulén G et al. 2021

Psychiatric disorders : Binge eating disorder and obesity

To identify a potential target with fonctionnal MRI

First step : In healthy patients

Functional connectivity in rest- and task-based imaging showing significant differences while hungry as opposed to while satiated.



Charroud D, Poulén G et al. 2021

Psychiatric disorders : Binge eating disorder and obesity

Second step : to identify abnormalities on functional MIR in patients in comparison to the healthy subjects

Third step : to build a protocol to test the new target



Alzheimer Disease

- Progressive decline in memory and cognitive function
- Several DBS targets have been proposed in literature => influence some aspects of memory functions
- Need further investigations



Spinal Cord Injury ? Traumatic Brain Injury ?

To improve consequences and deficits induced by SCI, TBI ?

Need further investigations : soon a new study in Montpellier (fMRI and tractography after SCI)

Are all neurological disorders candidate to DBS in the future if there is no treatment?



Future vision of DBS ?

a Current DBS systems

Electrode

- Single or bilateral electrodes
- Continuous stimulation

Extension cables

Implantable pulse generator

- Lithium battery in titanium housing
- Adjusted with physician programmer
- 3–5-year battery life

b Future DBS systems

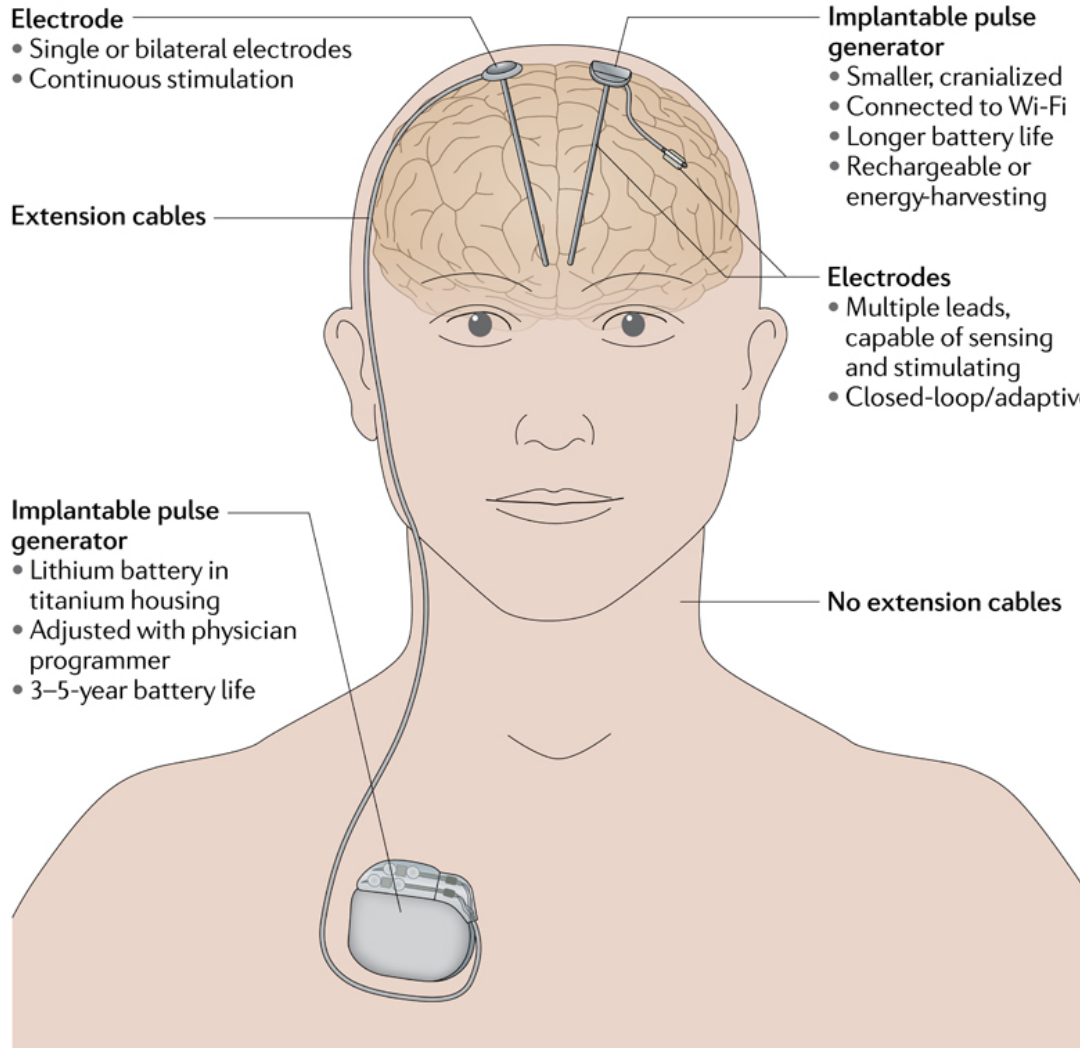
Implantable pulse generator

- Smaller, cranialized
- Connected to Wi-Fi
- Longer battery life
- Rechargeable or energy-harvesting

Electrodes

- Multiple leads, capable of sensing and stimulating
- Closed-loop/adaptive

No extension cables



*Lozano AM
Et al. 2021*

Future vision of DBS ?



Control by the patient of its own stimulation parameters ?

Perspectives

Future vision of DBS ?



It's already the case !

Future vision of DBS ?

Risk of failure of device security => Hacking ?

Review > [World Neurosurg.](#) 2016 Aug;92:454-462. doi: 10.1016/j.wneu.2016.05.010.

Epub 2016 May 13.

Brainjacking: Implant Security Issues in Invasive Neuromodulation

Laurie Pycroft ¹, Sandra G Boccard ², Sarah L F Owen ³, John F Stein ⁴, James J Fitzgerald ², Alexander L Green ², Tipu Z Aziz ²



Conclusion

- DBS is a safe and efficient treatment in many neurological and psychiatric diseases
 - Daily practice
 - DBS could be applied to many others diseases
-
- Beware of excess of indications !!
 - Good indication = good result
 - Bad indication =

