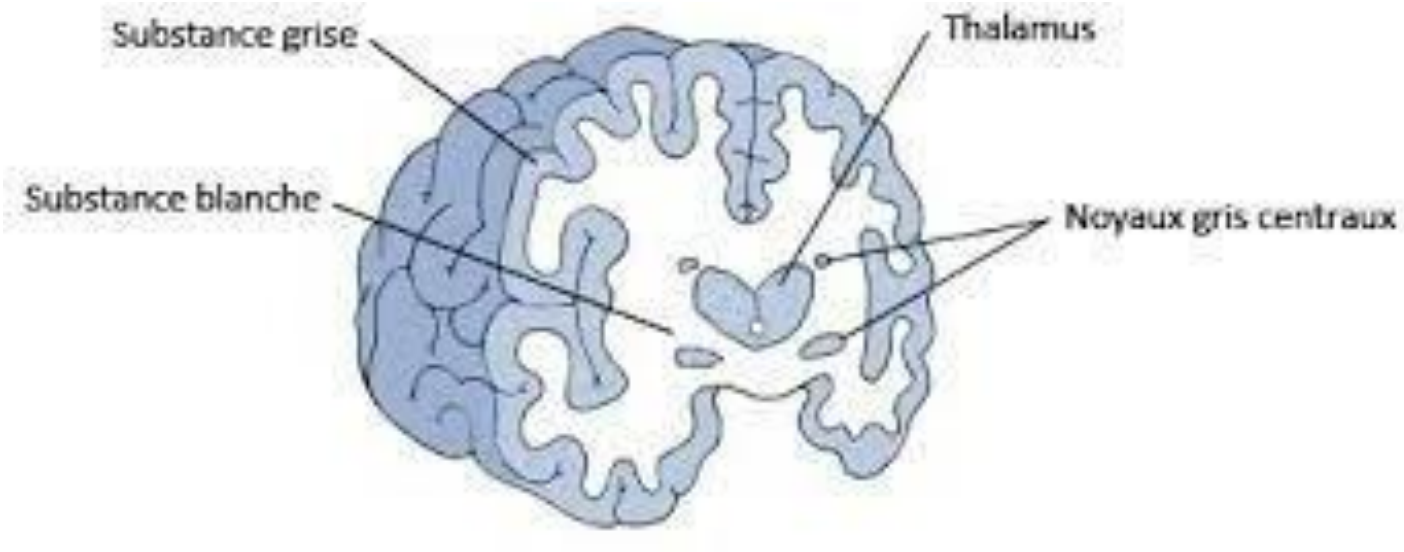
DEEP BRAIN STIMULATION

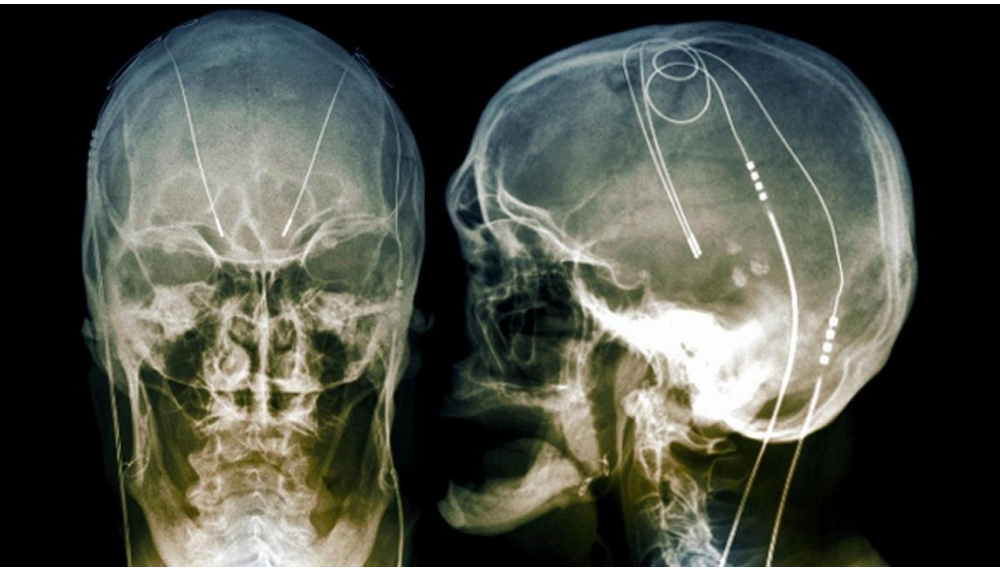
What is Deep Brain Stimulation ?

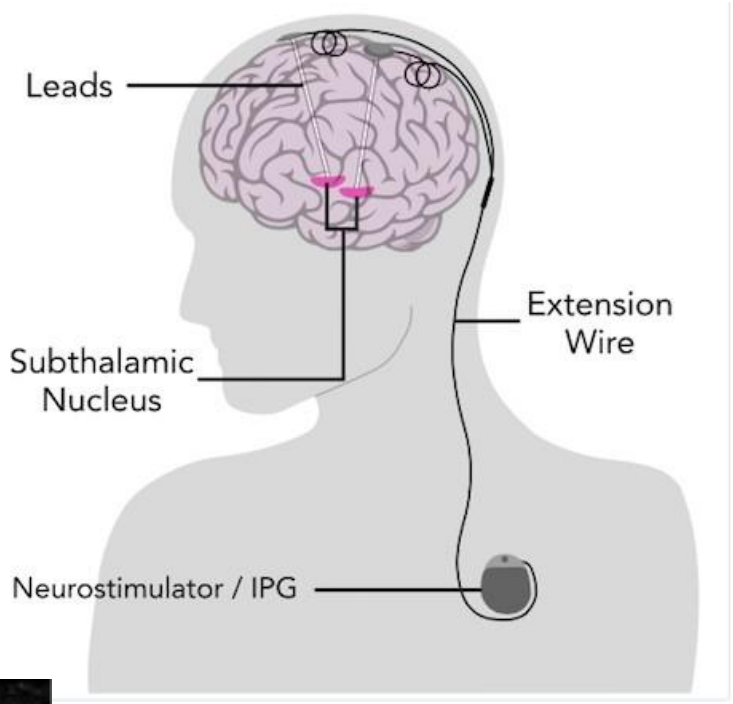
What is Deep Brain Stimulation ?

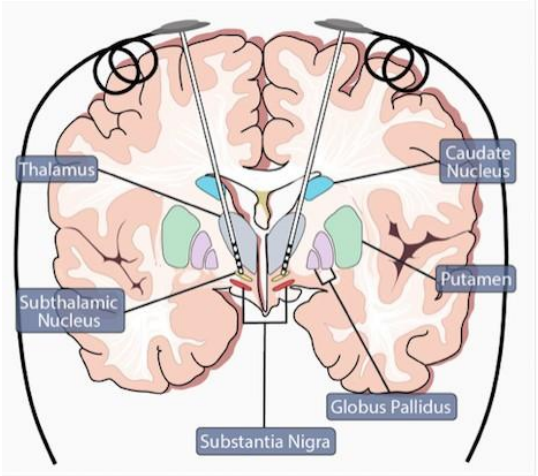
Neuro-anatomy: some reminders

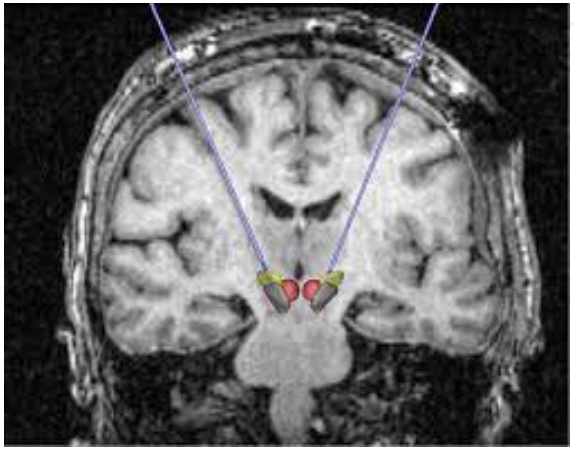


What is DBS ?




Leads
Extension Wire
Subthalamic Nucleus
Neurostimulator / IPG


Thalamus
Caudate Nucleus
Putamen
Subthalamic Nucleus
Globus Pallidus
Substantia Nigra




Boston Scientific
VERCISE
GEVIA

What is DBS ?

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

Animal models

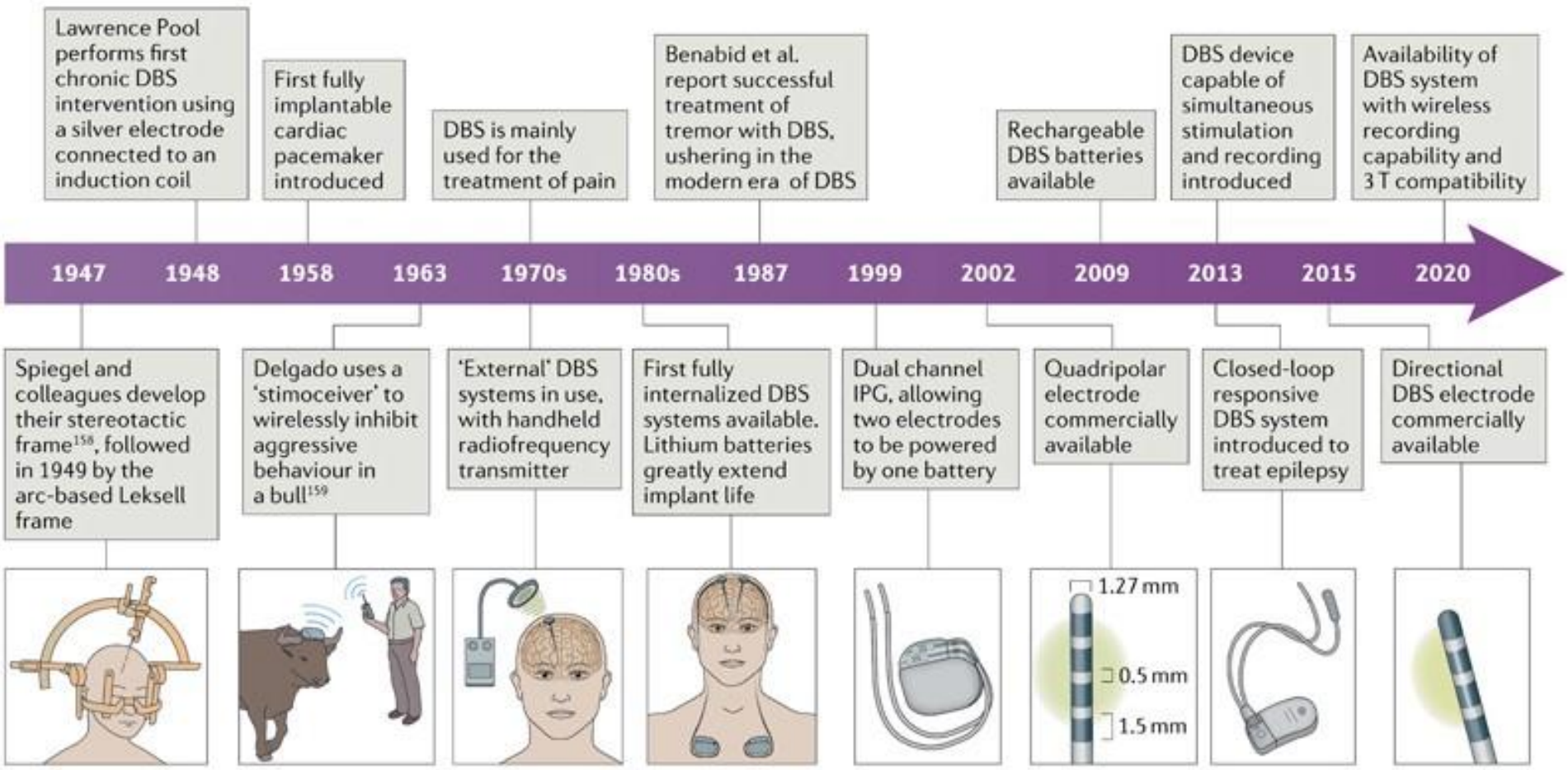
use of animal models to understand brain circuits

Indication	Animal model	Main contribution
Parkinson disease	MPTP in non-human primate	• Abnormal activity detected in the STN[138] • STN lesion improves motor dysfunction[36,37] • STN high-frequency stimulation improves motor dysfunction[39]
Epilepsy	Pentylenetetrazol in guinea pigs and rats	• Lesioning of the MMT ameliorates epilepsy[40] • Electrical stimulation of the ANT ameliorates epilepsy[42]
Huntington disease	Transgenic rat model	• Electrical stimulation of the GPe improves choreiform movements[139]
Compulsivity-related behaviour	Polydipsia rat model	• Electrical stimulation of the BNST effectively reduces compulsive-like behaviour[140]
Depression-like behaviour	CMS rat model	• Serotonin and BDNF are involved in the mood-related effects of electrical stimulation of VMPFC[141] • Electrical stimulation of different brain areas has differential influences on mood-related effects[47]

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 ?



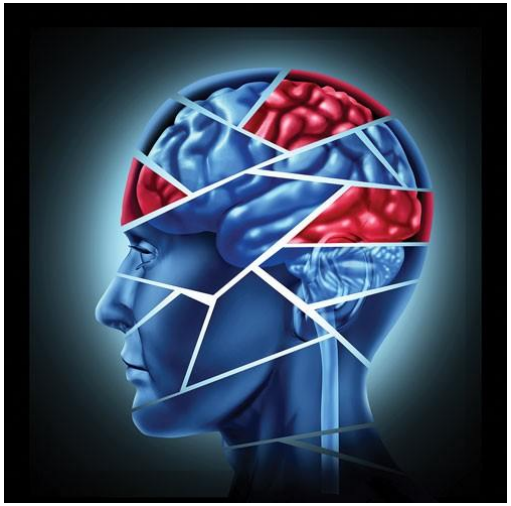
Lozano AM et al. 2021

Indications

Movement disorders:
- Parkinson
- Dystonia
- Huntington
- Essential Tremor

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

Epilepsia

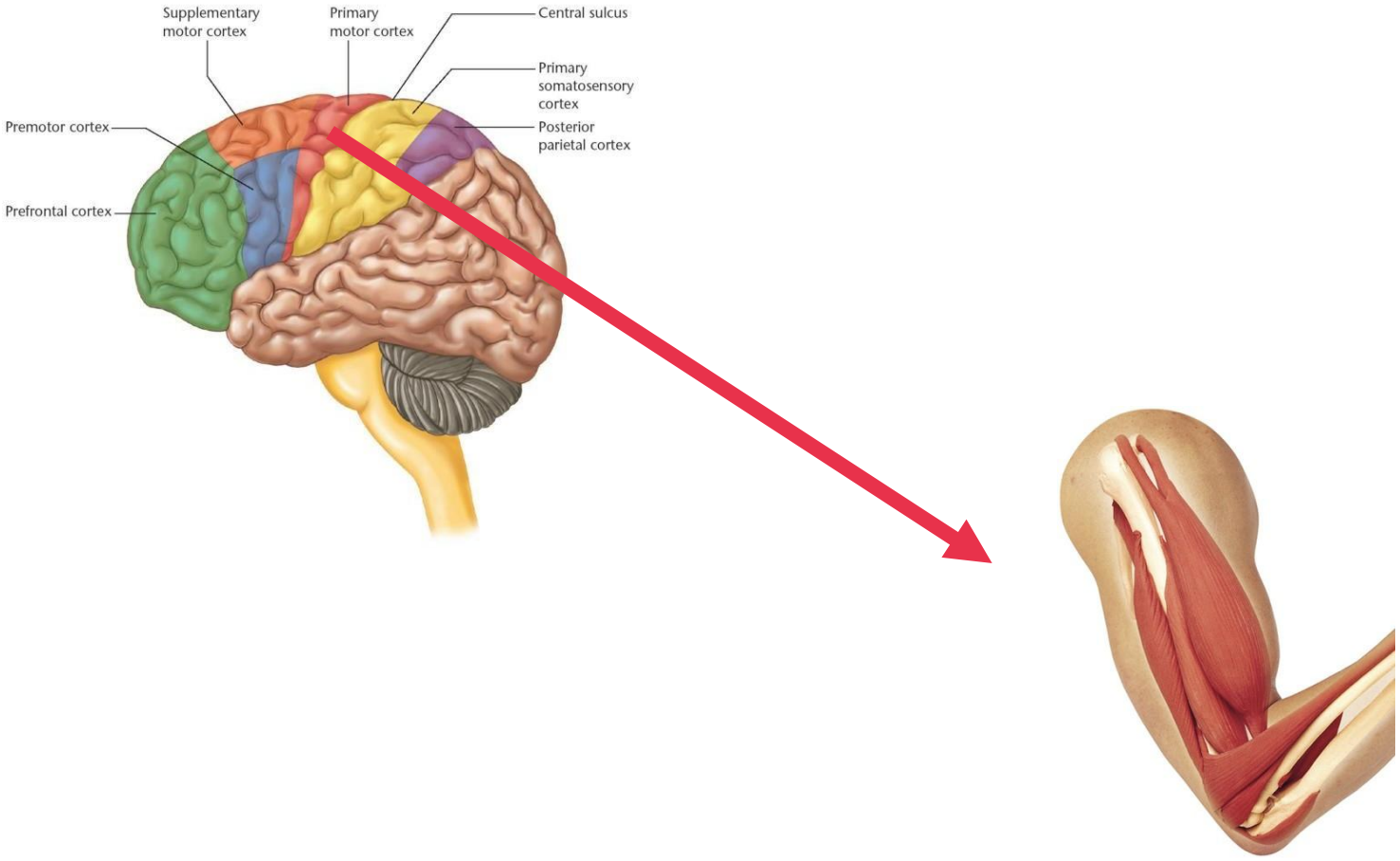


When ?

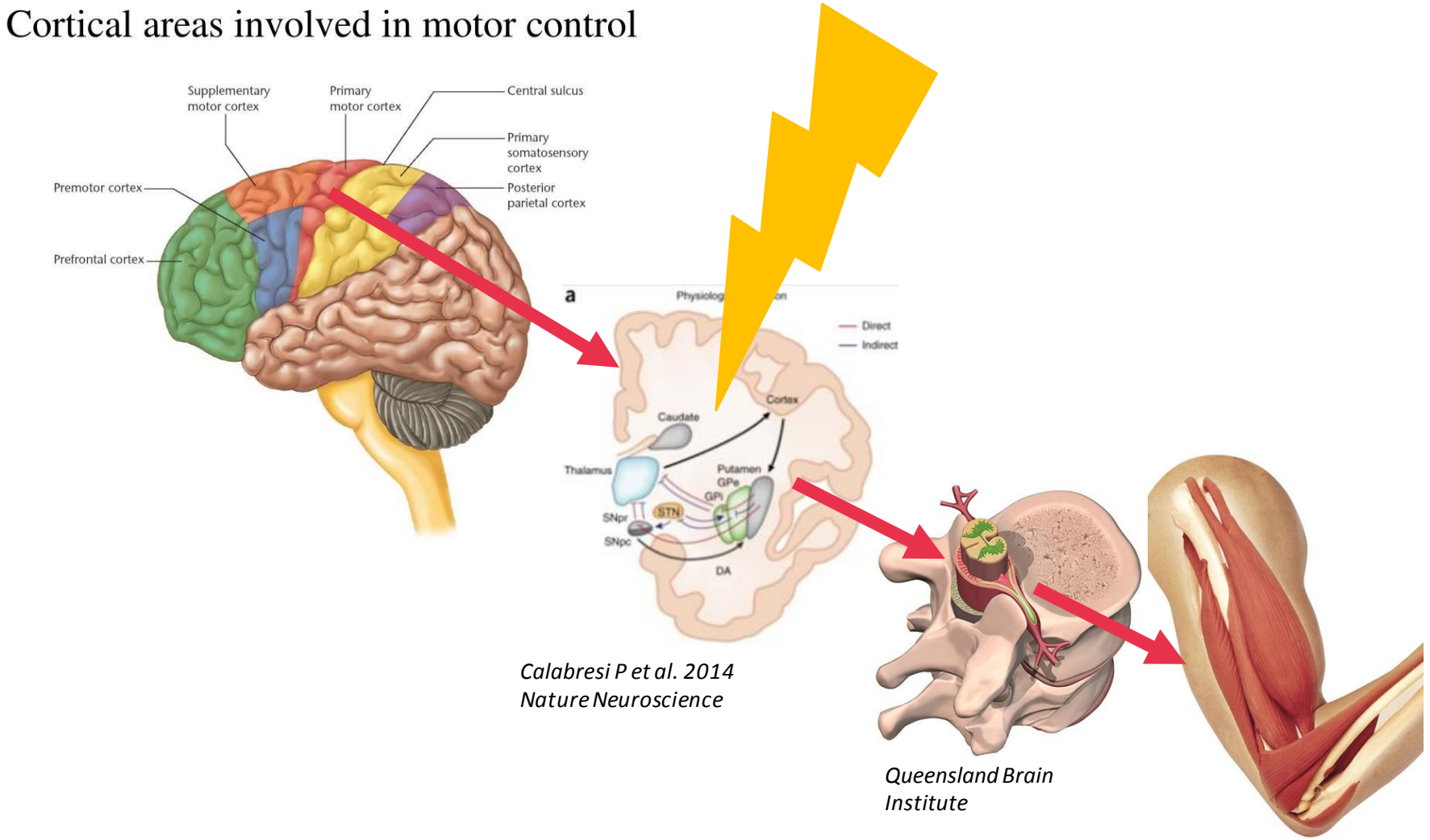
- **Refractory to other medications**
- **Severe symtpoms**
- **Disability**
- **Decrease of quality of life**

Pathophysiology

Cortical areas involved in motor control



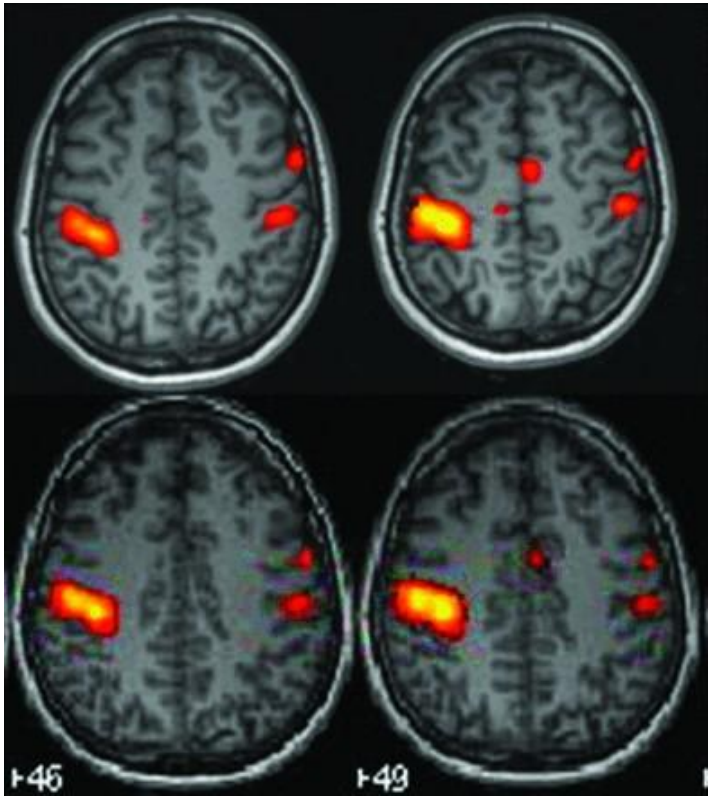
Pathophysiology



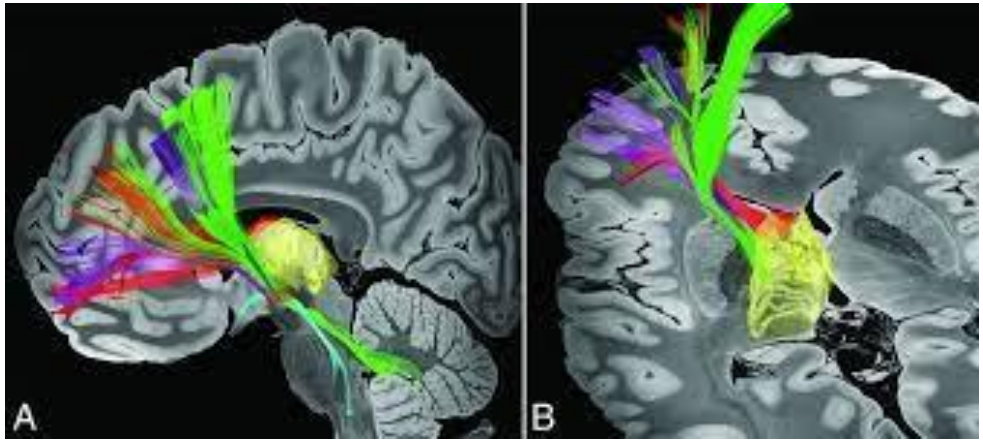
Calabresi P et al. 2014
Nature Neuroscience

Queensland Brain Institute

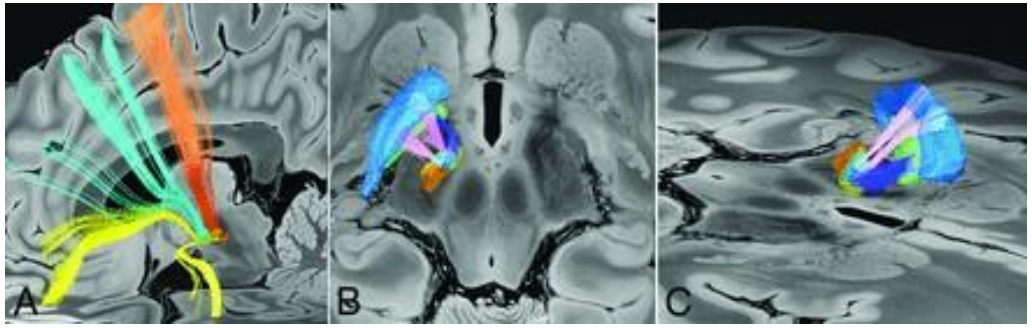
Pathophysiology



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



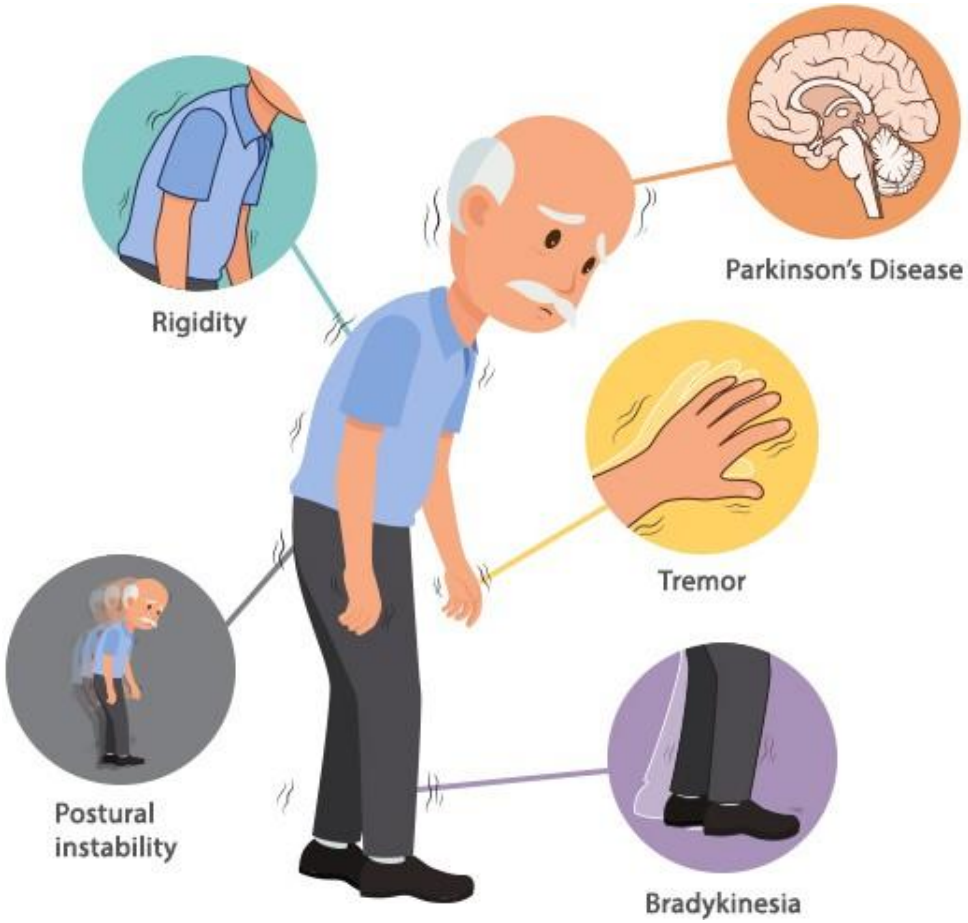
Middlebrooks EH et al. 2020
American Journal of Neuroradiology



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 :

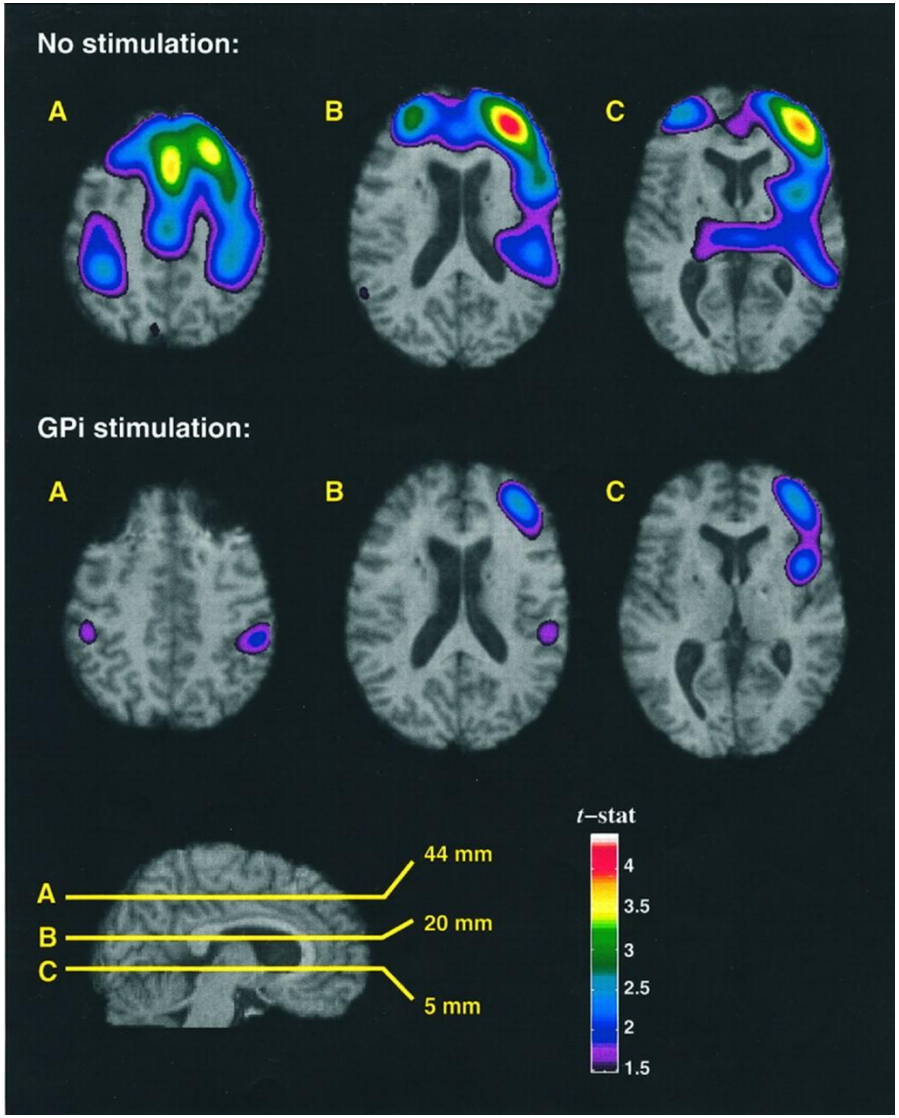
- Genetic
- Idiopathic
- Post-traumatic
- Post-stroke
- Post-tumoral
- ....

IBS Hospitals

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

Dystonia

Generalized dystonia: MRI + PET



Kumar R et al. Neurology 2019

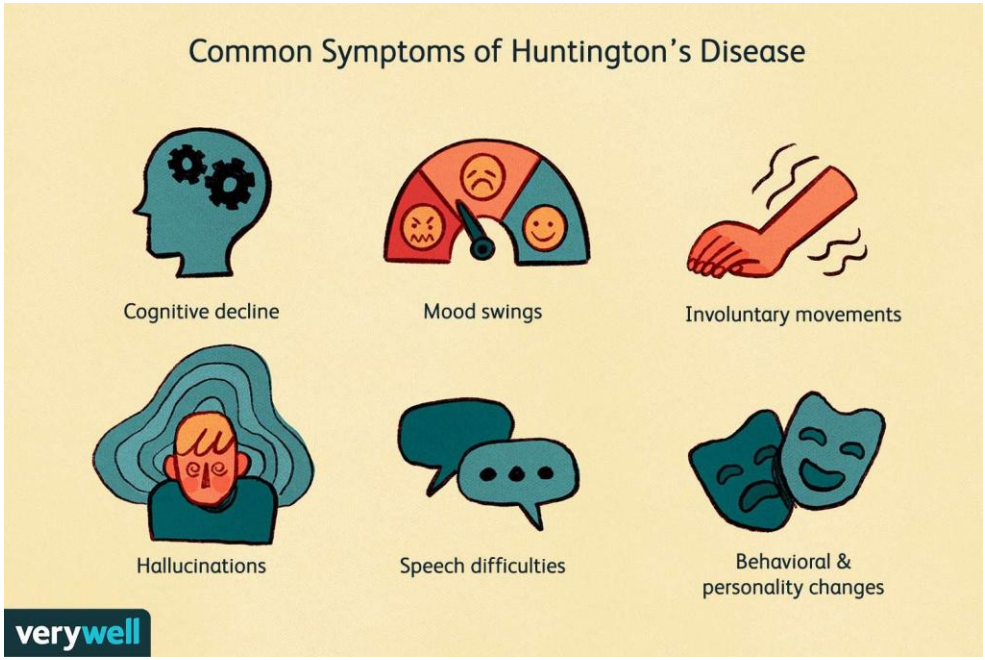
Huntington Disease

Genetic disease

Progressive Brain Disorder

Life expectancy after diagnosis: 10-30 years

Chorea +++ : early symtpom

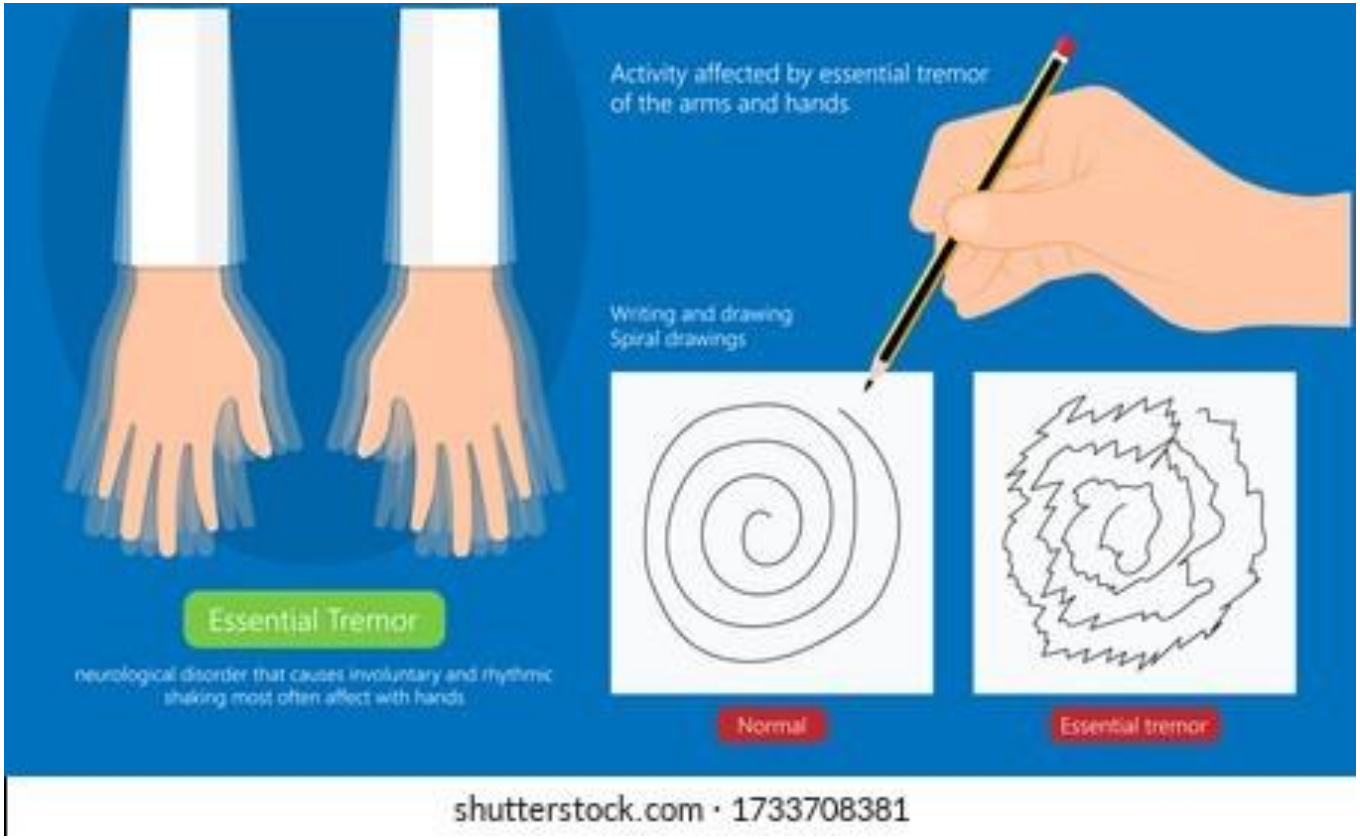


VeryWell Health website

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

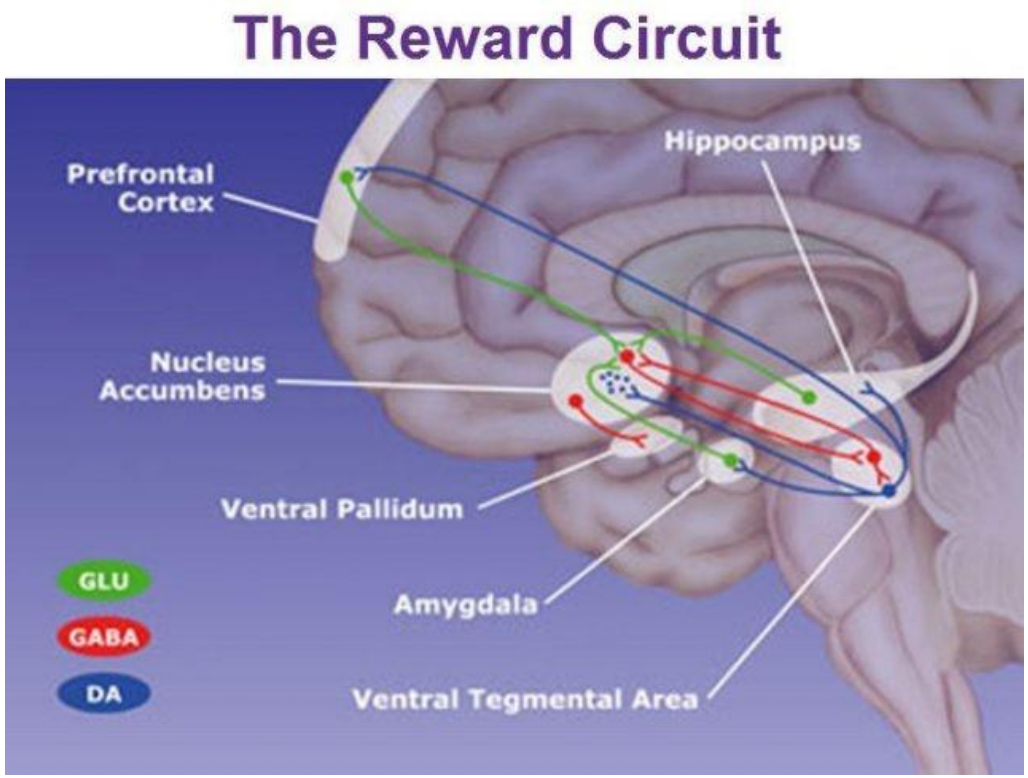
Essential Tremor

Frequent
1/200



DBS in psychiatric disorders

Pathophysiology



Alonso JR, MappingIgn2018

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, …)

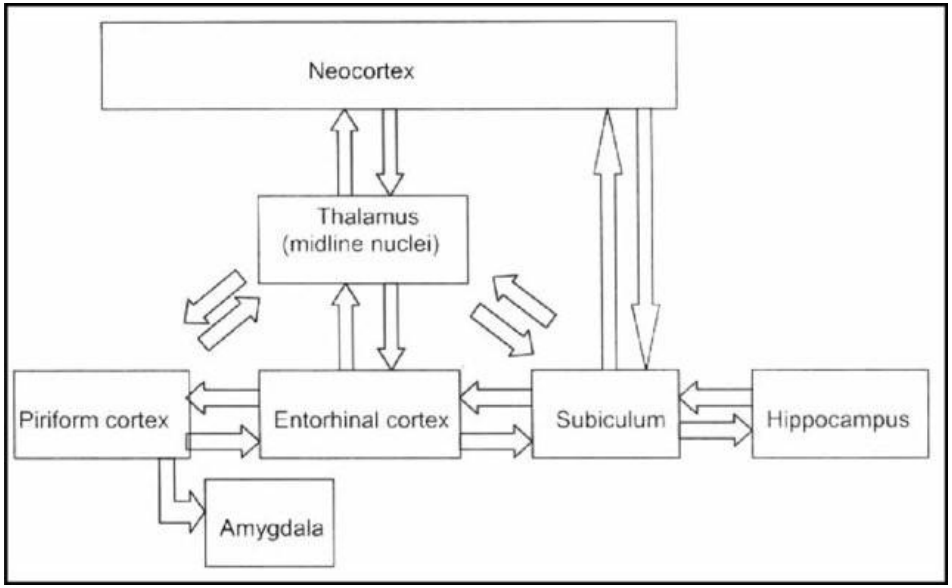
- Effects on the reward circuit

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



Doherty JJ et al. 2002

Is this Science Fiction ?

NO !! It's REALITY !

In Montpellier : 35-40 DBS per year

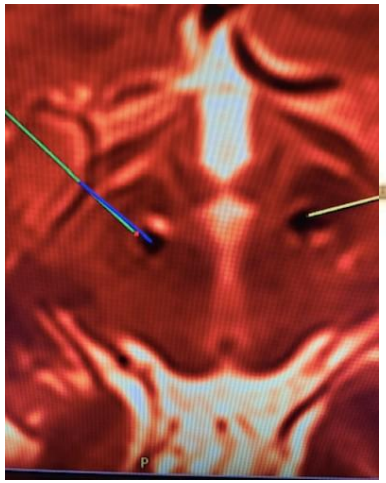
How ?

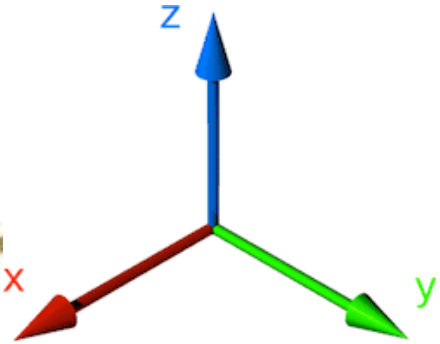
- General or local anesthesia

- 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
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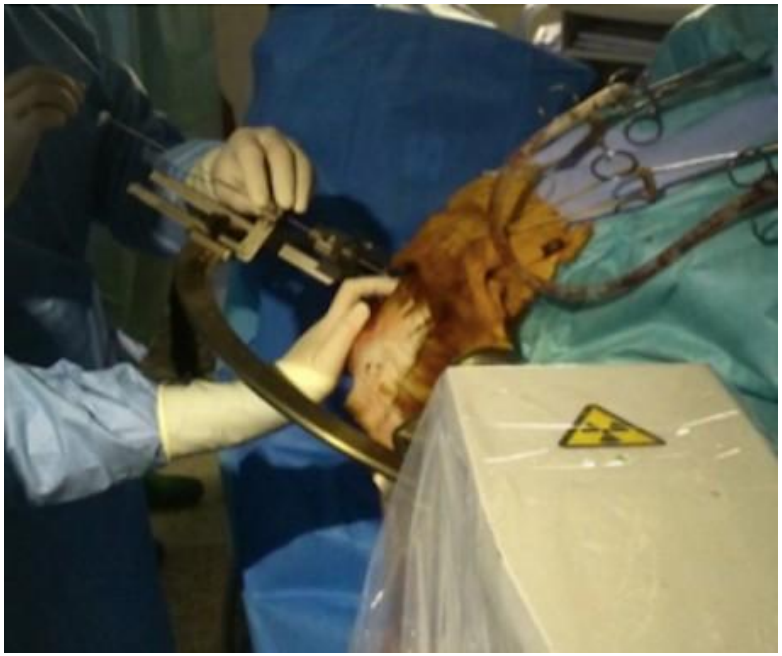
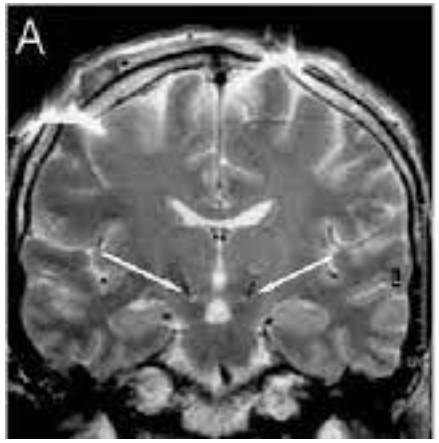
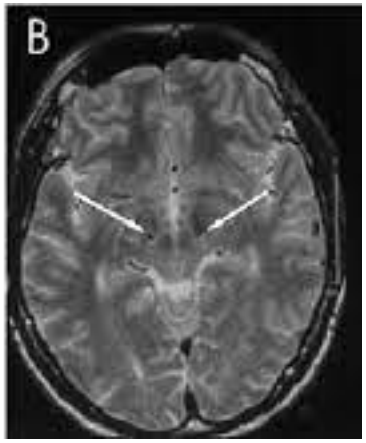
- MRI
- Targetting
- **Implantation of the leads**
- **Control MRI**
- Implantation of extensions and generator

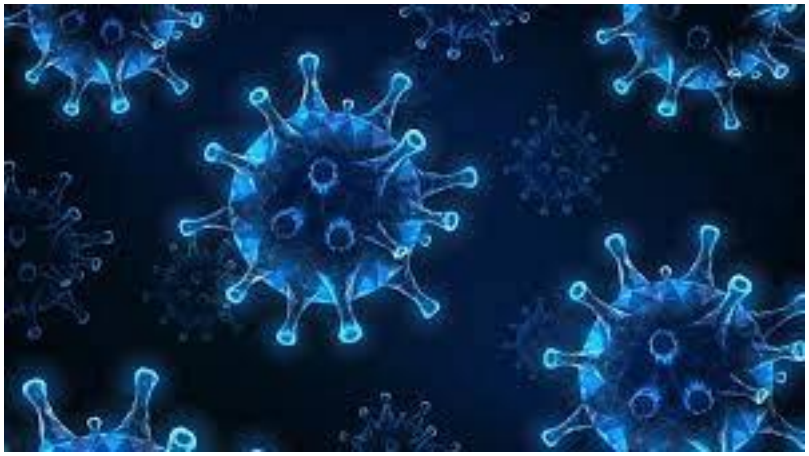






Surgical complications?

- 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)

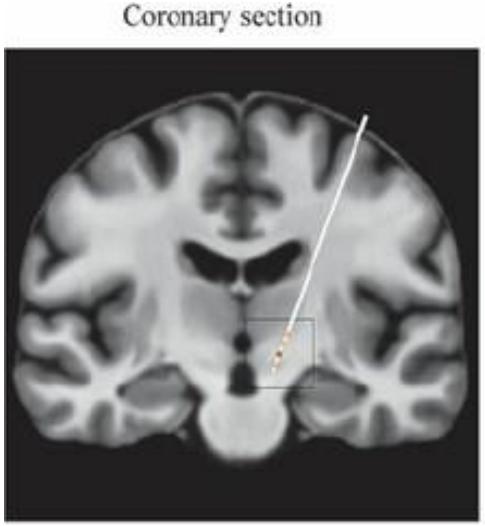
Easy to adjust

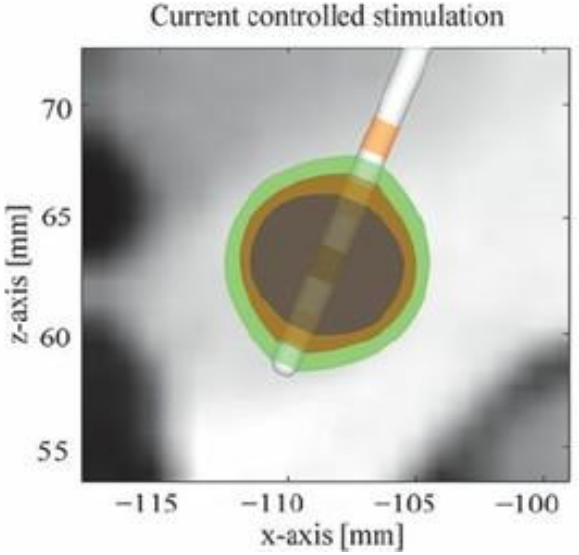
Up or down the current depending on efficiency and side effects

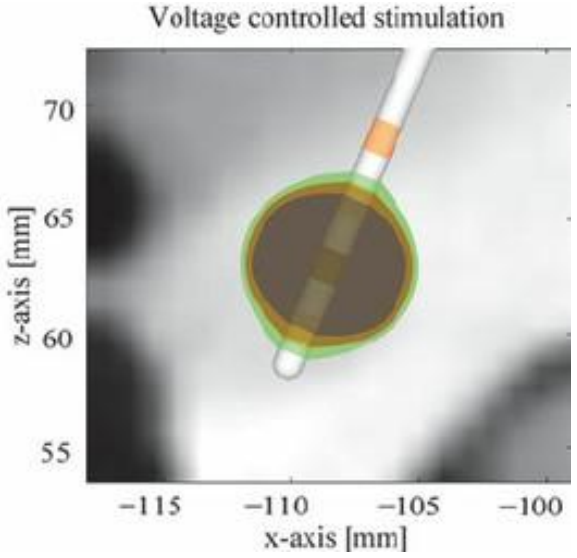
New generators can record electrical activity of the target (Local Field Potential)

How ?

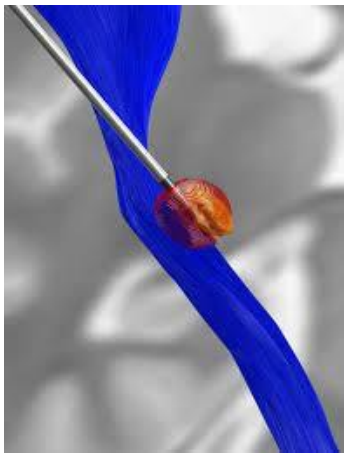
Volume of Activated Tissue







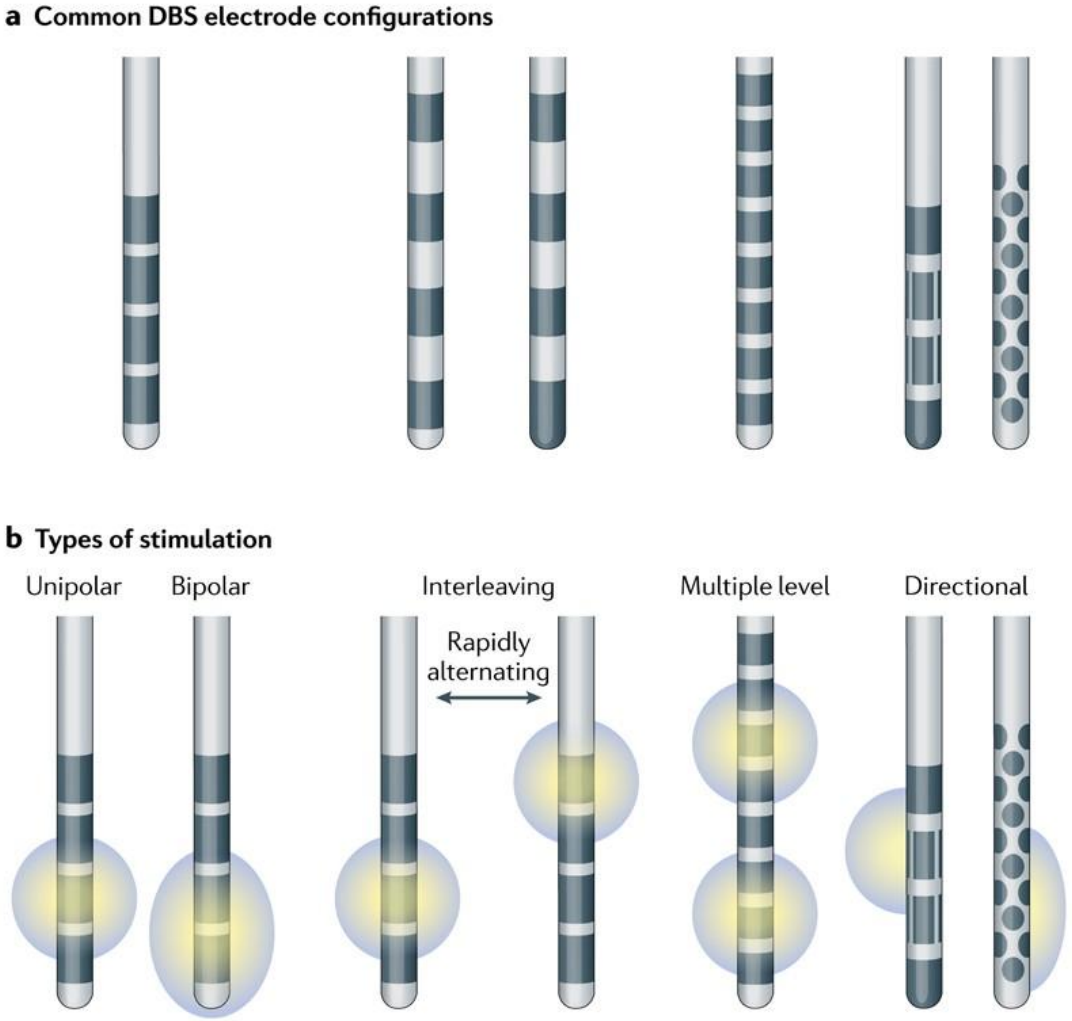
Schmidt C et al. 2012



Horn et al., 2017.

How ?

Leads



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
- oculomotricty disorder
- mood disorder : depression with suicid attempt

Reversible when stopping or decreasing the stimulation

DBS: How does it work?

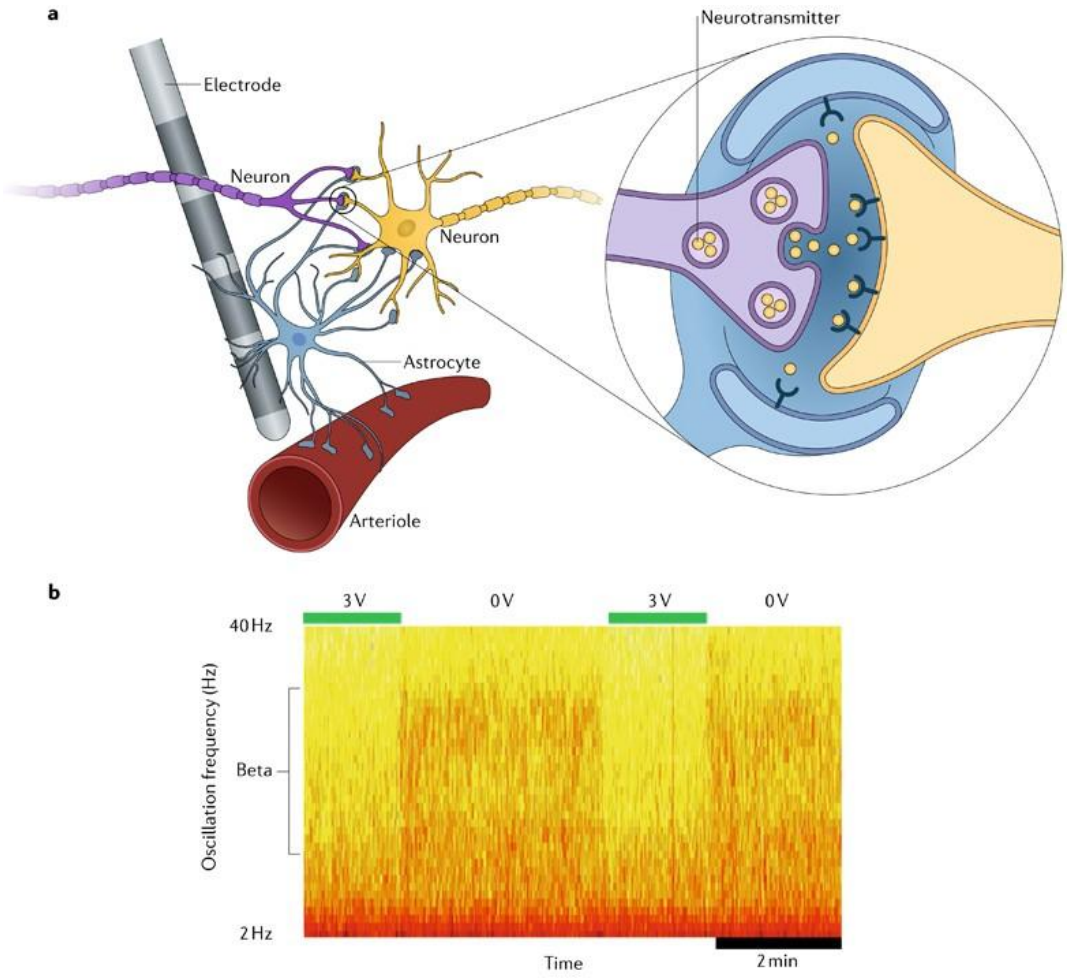
- Many hypotheses have been proposed for the mechanisms

- 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

- 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 changements

How far can we go ?

Perspectives

What more can we modulate ?

Which target for which disease ?

Perspectives

Psychiatric disorders : Bipolar Disorder

Work is in progress

Some case series

Which target ?

Perspectives

Psychiatric disorders : Post-Traumatic Stress Disorder

Work is in progress

Some case series

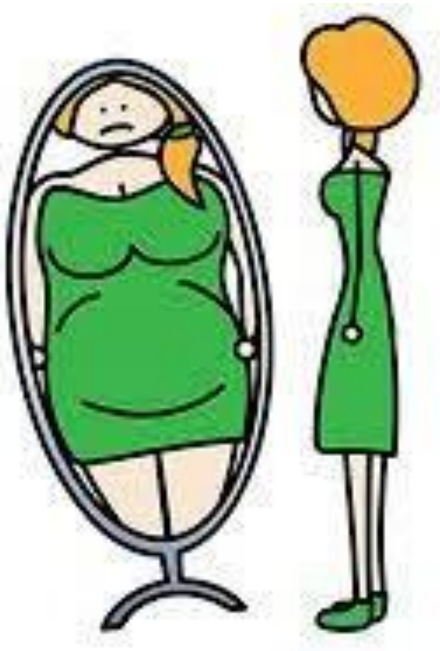
Which target ?

Perspectives

Psychiatric disorders : Anorexia Nervosa

Few studies

Which target ?



Perspectives

Psychiatric disorders : Binge eating disorder and obesity

Local work in Montpellier

How to find a new target for a disease?

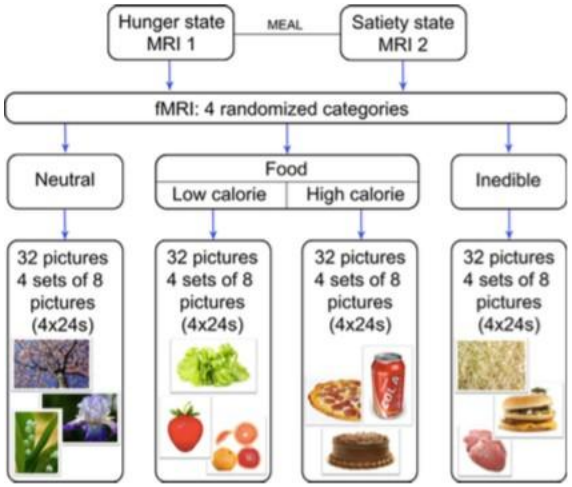
Perspectives

Psychiatric disorders : Binge eating disorder and obesity

Toidentify a potential target with functionnal 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, Poulen G et al. 2021

Perspectives

Psychiatric disorders : Binge eating disorder and obesity

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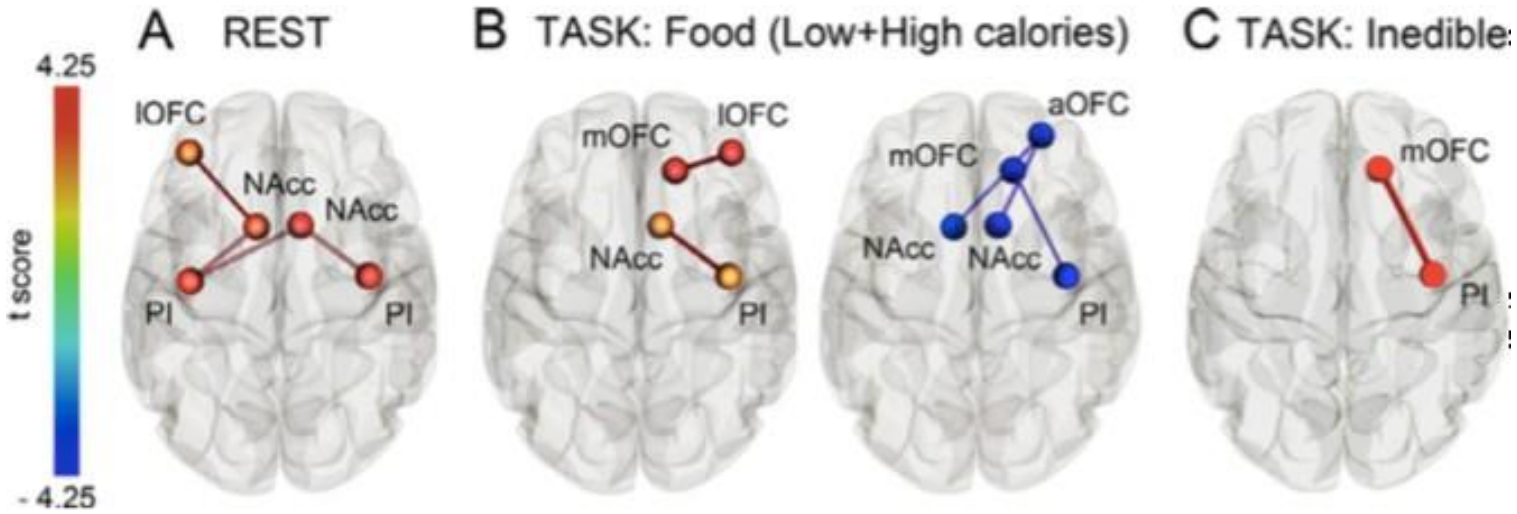


Charroud D, Poulen G et al. 2021

Perspectives

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

Perspectives

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

Perspectives

Spinal Cord Injury ? Traumatic Brain Injury ?

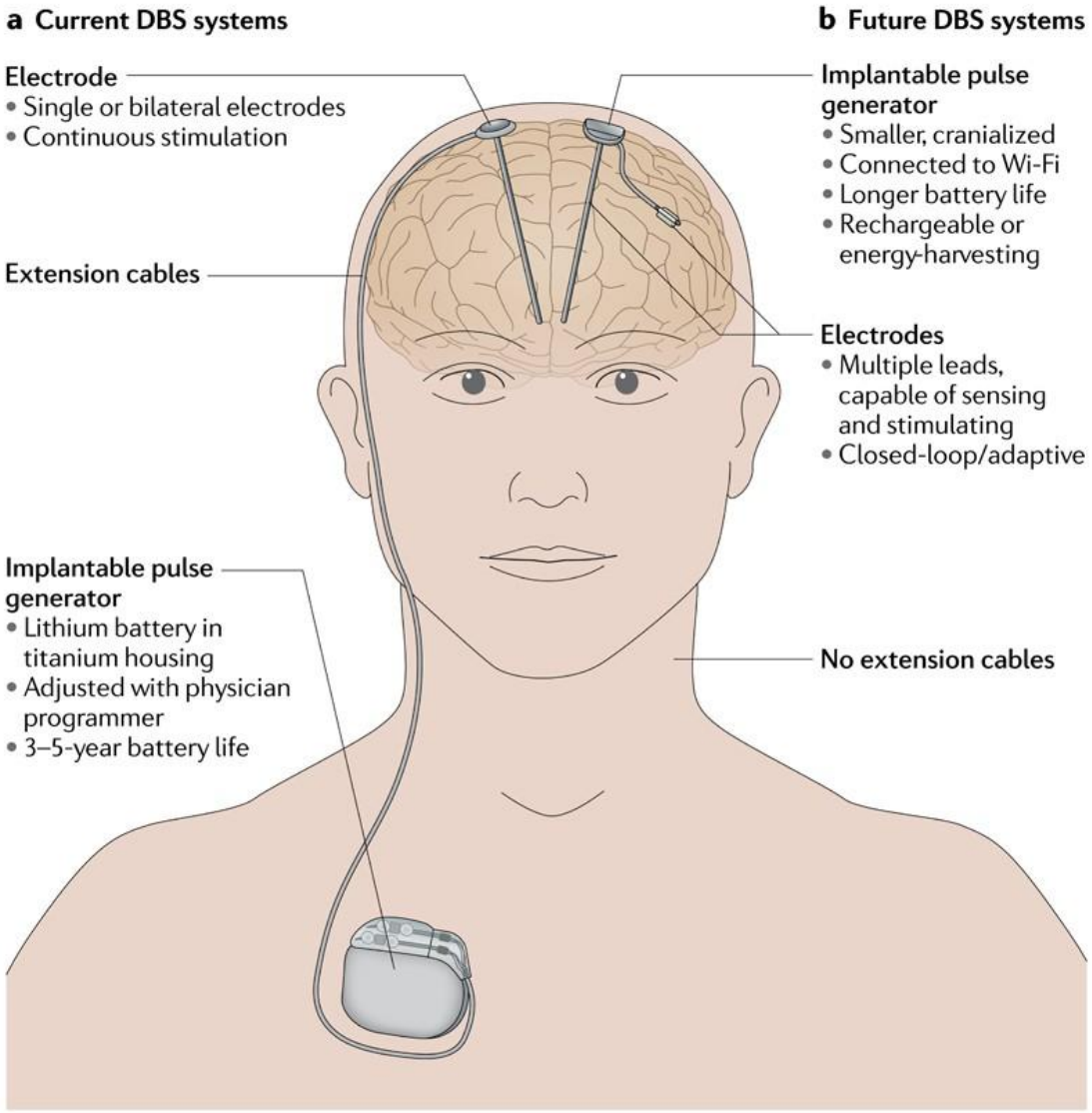
To improve consequences and deficits induced by SCI, TBI ?

Need further investigations

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

Perspectives

Future vision of DBS ?



Lozano AM Et al. 2021

Perspectives

Future vision of DBS ?

Control by the patient of its own stimulation parameters ?

Perspectives

Future vision of DBS ?

It's already the case !

Perspectives

Future vision of DBS ?

Risk of failureof 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 = ….