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Advanced treatment strategies for OCD :

From Best Medical Treatment to Functional Neurosurgery

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Obsessive Compulsive Disorder : *Key epidemiological facts*

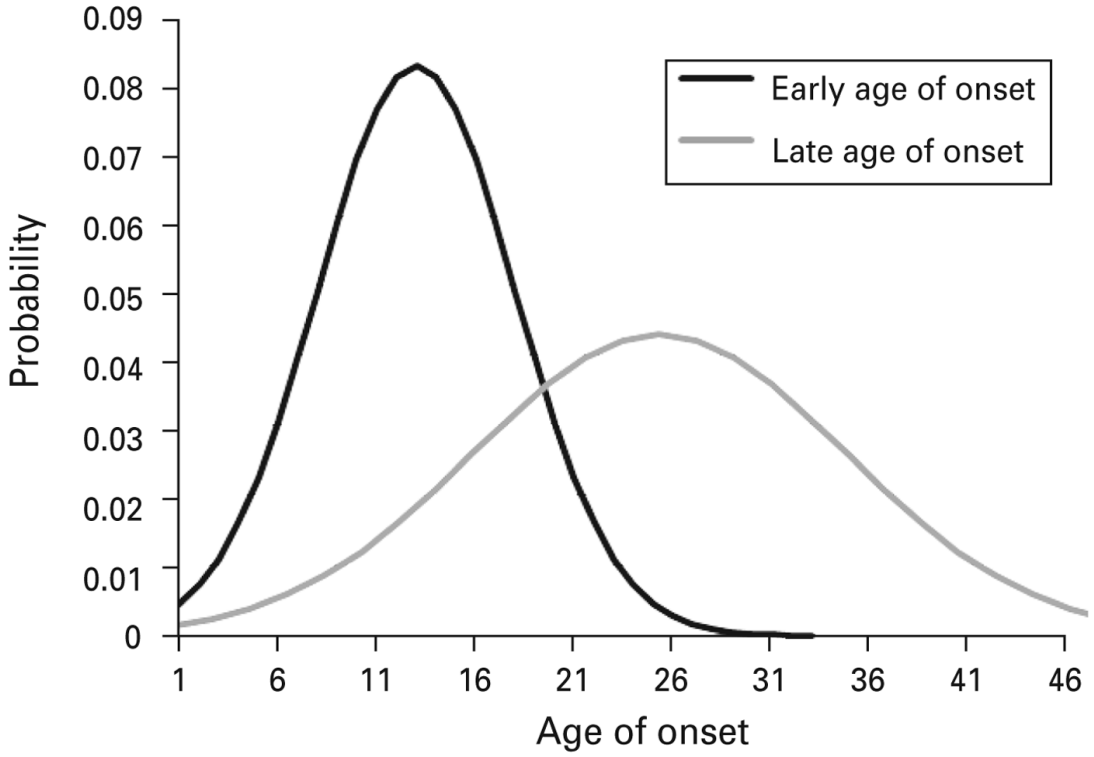
- **4th** most common psychiatric disorder
- Lifetime prevalence : **~1.7-2%** of general population
- **Sex ratio F/M ~=1-1.5**

Stein DJ *et al*, **Nat Rev Dis Primer**, 2019
Anholt GE *et al*, **Psych Medicine**, 2013
Hirschtritt *et al*, **JAMA review, 2017**

- Onset in **adolescence** and young adults
  - ***2/3 meets DSM-5 criteria before turning 25 y.o***
  - ***30% early onset -> before 15 y.o***
  - ***90% start before 30 y.o***

- **90% Chronic course**, trend to worsen over time

- Severe impact on **Quality of Life** :
  - QoL in OCD ~ QoL in Schizophrenia
  - Disability of OCD > Disability of Parkinson + Multiple Sclerosis



Obsessive Compulsive Disorder : *Clinical definition*

OCD definition : DSM 5 TR

« Obsessive-compulsive disorder (OCD) is characterized by time-consuming, distressing, or impairing ***obsessions*** *(repetitive unwanted thoughts, images, or urges) or* ***compulsions*** *(repetitive behaviors or thoughts), often accompanied by avoidance behaviors. »*

Obsessive Compulsive Disorder :

What are obsessive thoughts ?

Stein DJ *et al*, **Nat Rev Dis Primer**, 2019

- **Thoughts, Mental images or Urges :**
  - Reported as being **Intrusive**
  - Marked **Emotional distress** (*Anxiety, Disgust, Incompleteness - « not just right », Discomfort*)
  - **Recurring** **and** **persistent**

- **4 dominant themes :**
  - « Aggressive » : Being responsible for **harming** oneself and/or others
  - **Contamination** (and/or cleaning) : *dirt, germs, toxic substances…*
  - **Forbidden/Taboo thoughts** *: Sexual, Religious, Morally transgressive / cultural norms…*
  - **Order, Symmetry, Completeness, Perfectionism** (with or without magical thinking)

- **Insight** :
  - Most OCD patients **recognize that these beliefs are not realistic** (*at least to some degree*) .
  - Obsessions are **not simply excessive concerns about real-life problems**.
  - Obsessions are **correctly identified as being the product of one's own mental activity**

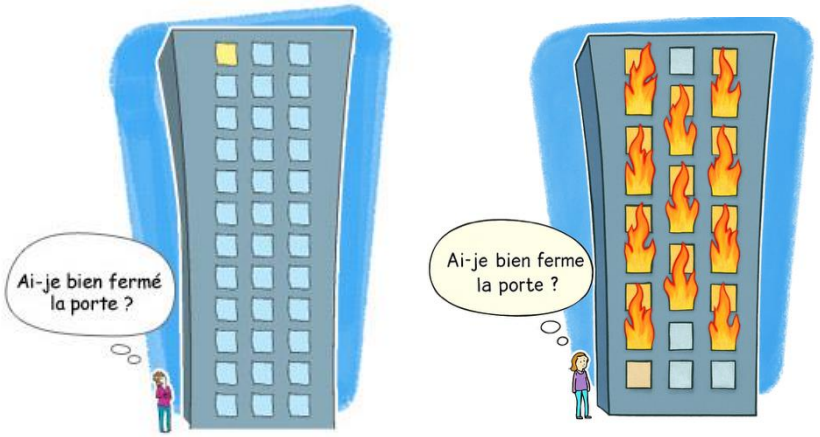
- **Efforts** to **ignore and/or suppress obsessions**, or they try to **neutralize** them by performing a compulsion.

Obsessive Compulsive Disorder :

Obsessive thoughts – 2 typical examples

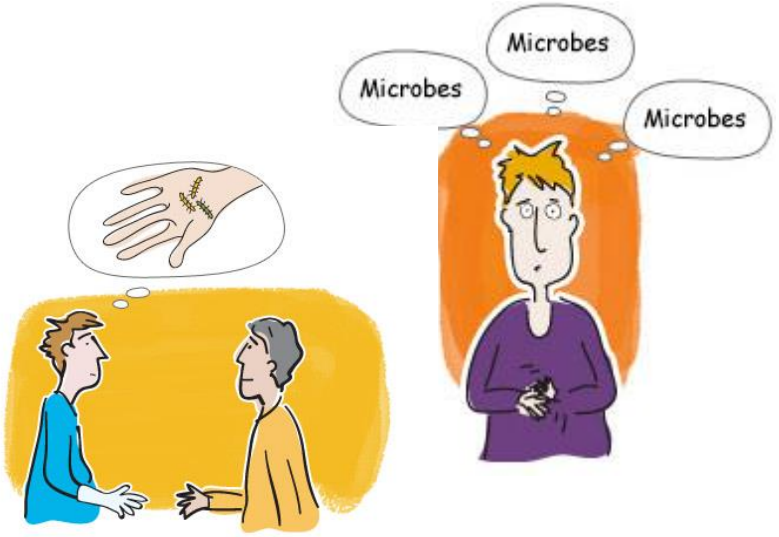
- Fear of **serious events** occurring (*Aggression*):
  - *Context* : I just left my apartment …

  *"What if I didn't close (**the door, the shutters, the gas, the electricity**) properly? Then something might happen (**fire, burglary…**) to (**me, my family, my friends…**)."*



- Fear of **spreading disease** to others (*Contamination*):
  - *Context* : I held a handle when I rode the bus, I open the front door …

  "If I touch this doorknob with my dirty hands, people might catch HIV and die because of me…"



Obsessive Compulsive Disorder :

What are Compulsions = Rituals ?

Stein DJ *et al*, **Nat Rev Dis Primer**, 2019

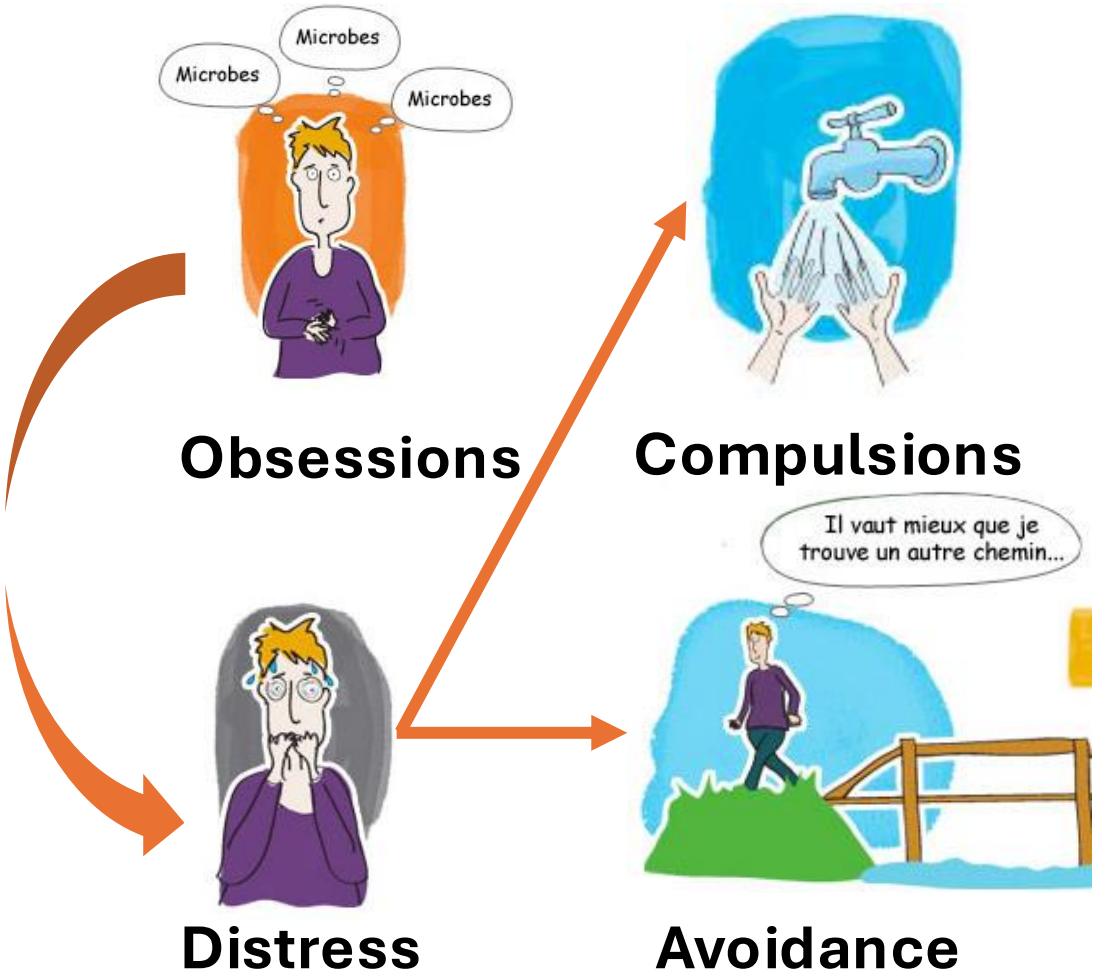
- **Repetitive behaviors or mental acts** (*mantra, counting* …) :
  - Follow **inflexible, stereotypical and idiosyncratic rules**
  - Described as **neutralizing distress** following obsessions
  - Or as **preventing the occurrence** of the feared event
  - May or **May not be realistically connected** to the feared event or **clearly excessive**

- **4 dominant themes :**
  - **Washing** / Cleaning (*handwashing, showering, washing clothes or food…*)
  - **Checking** / Repeating (*thoughts, that a door is closed, what is done or said*)
  - **Ordering** / Symmetry (*ordered by color, alignments, only pairs…*)
  - **Conjuring** (*Counting, Mantra, Complex action sequences, say or make say…*)

- Trend toward **being longer / more complex and diverse** over time when left untreated
- Tend to develop **avoidance behaviors**

Obsessive Compulsive Disorder : *Clinical definition*

Stein DJ *et al*, **Nat Rev Dis Primer**, 2019
Stein DJ *et al*, **BMC Med**, 2025



- OCD features **Obsession** AND/OR **Compulsions** :
  - **Mixed** (>90%)
  - **Pure-O** (~5%) / **Only compulsion** (1-3 %)

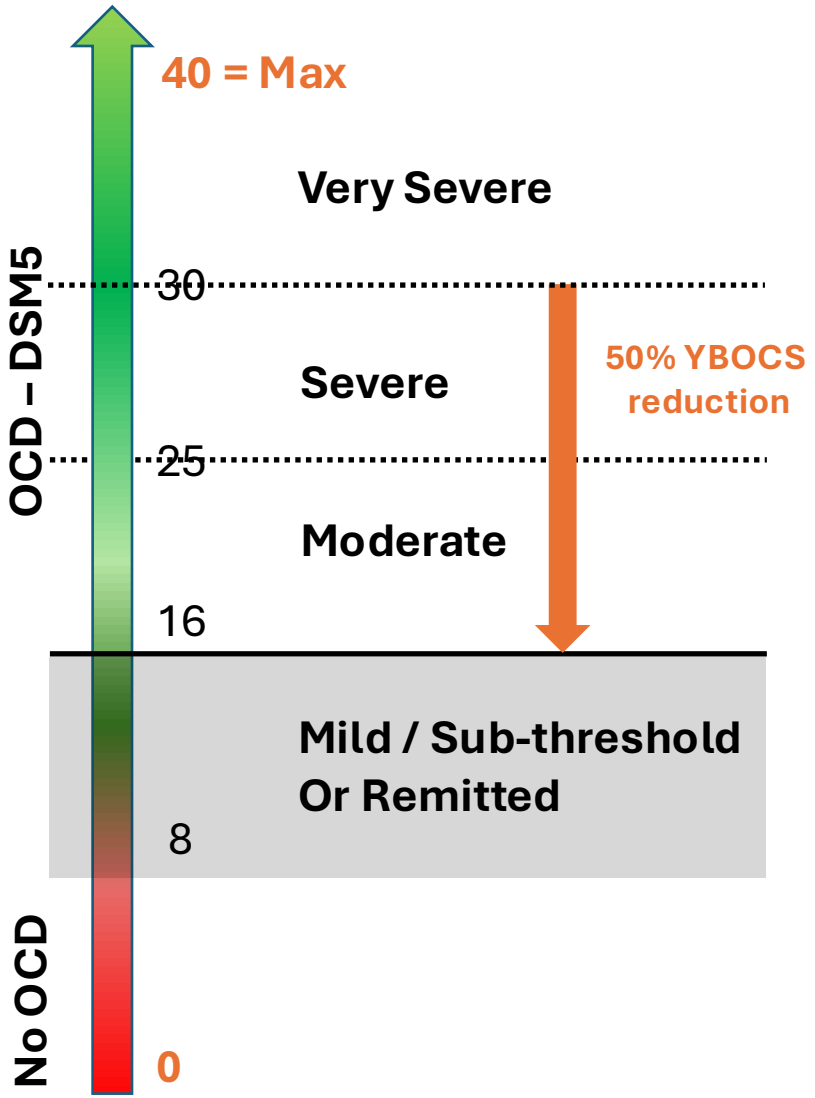
- **Time-consuming** (**> 1 h/day**) and/or clinically significant **distress** and/or **impairment of functioning**.
  - **60% Mild [Subthreshold / Remitted] (8-15/40)**
  - **30% Moderate (14-25/40)**
  - **10% Severe (25+ / 40)**

- not be attributable to a substance or another medical condition.

Obsessive Compulsive Disorder : *Response to treatment*

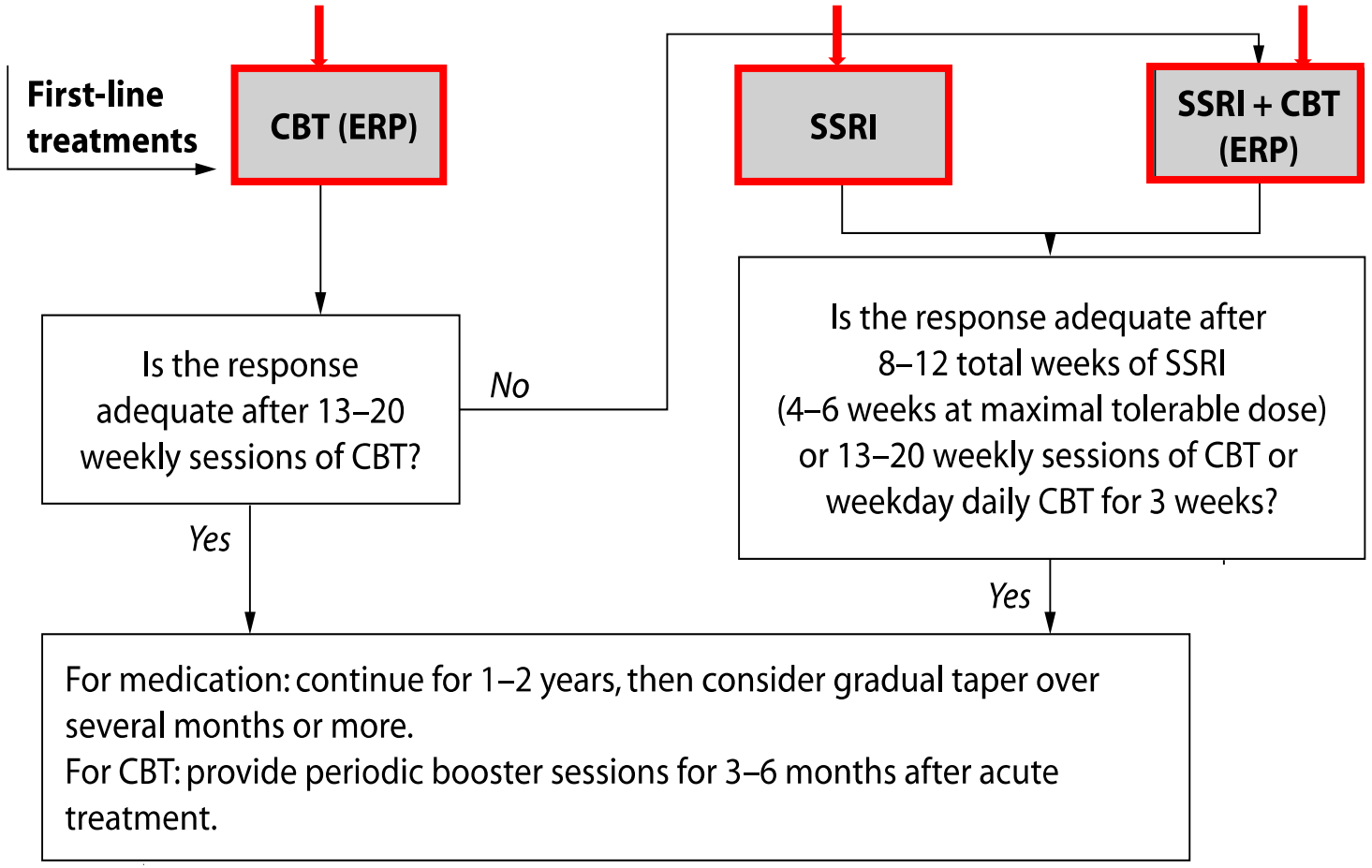
TABLE	Obsessive-compulsive disorder stages of response
Recovery	Not at all ill; Y-BOCS < 8
Remission	Y-BOCS < 16
Full response	≥ 35% Y-BOCS reduction and CGI 1 or 2
Partial response	Between 25% and 35% Y-BOCS reduction
Nonresponse	< 25% Y-BOCS reduction, CGI 4
Relapse	Symptoms return (CGI 6, or 25% Y-BOCS increase from remission score) after 3+ months of treatment at adequate dosage
Refractory	No change or worsening of symptoms with all available therapies

Y-BOCS, Yale-Brown Obsessive Compulsive Scale; CGI, Clinical Global Impressions.
Adapted from Pallanti S et al. *Int J Neuropsychopharmacol*. 2002.[25]



Therapeutic Strategy in OCD :

First line treatment –> CBT/ERP and/or SSRI



Practices guidelines:

- APA, 2007/2012
- CANMAT, 2014

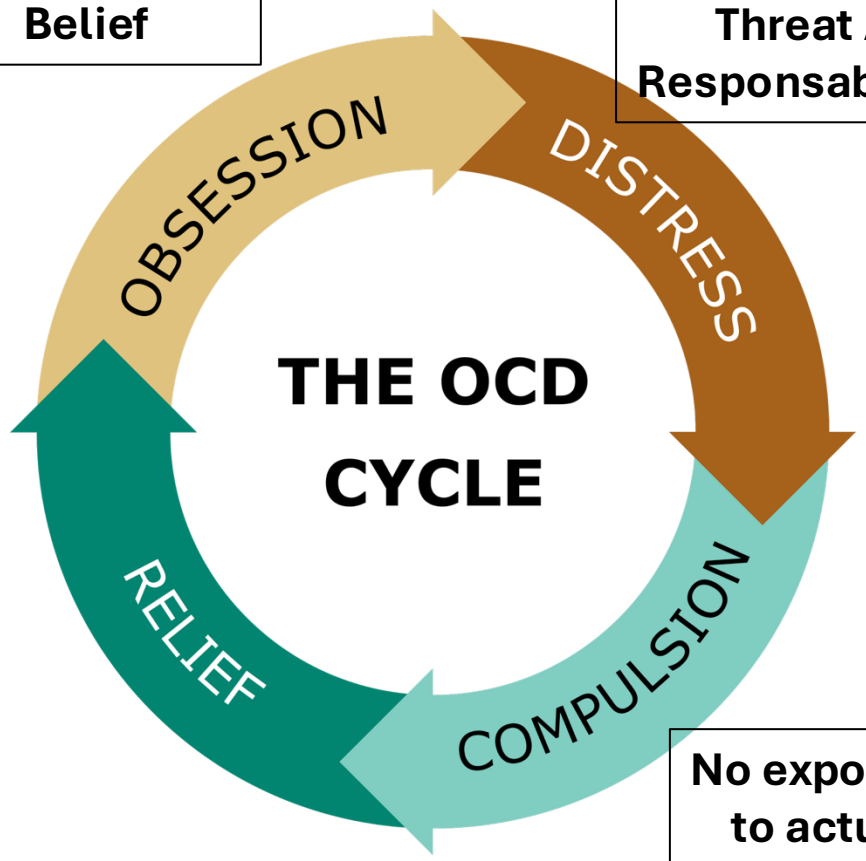
Hirschtritt *et al*, **JAMA review, 2017**

Therapeutic Strategy in OCD :

Exposure / Response Prevention = the Gold standard for OCD psychological treatment

Dysfunctional Belief

Overestimated Threat / Responsability

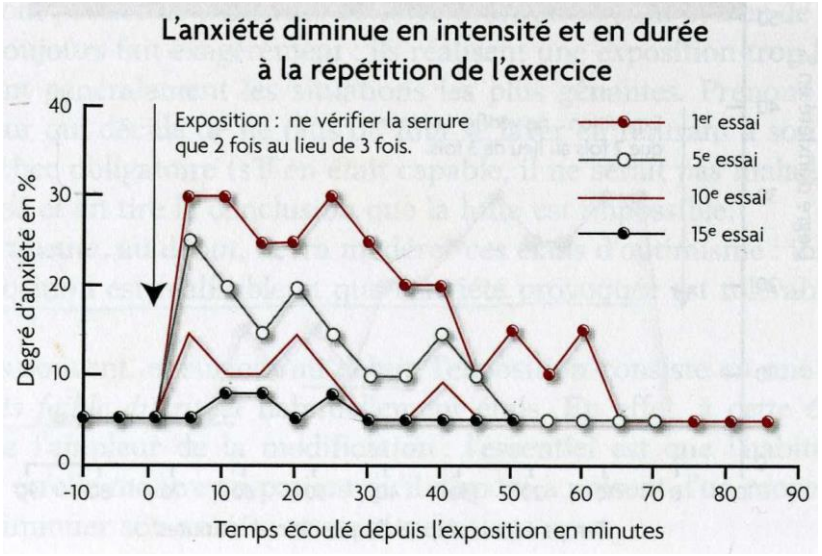


No exposure to actual outcomes

Salkovskis 1985, Rachman 2002

Stein DJ *et al*, **Nat Rev Dis Primer**, 2019

Desensitization : *Exposure – Response prevention*



List of problem situations:

- *Touching the desk* **[20/100]**
- *Touching a switch at home* **[50/100]**
- *Touching a switch in a public place* **[80/100]**

Therapeutic Strategy in OCD :

Exposure-Response Prevention = Overall Efficacy

Exposure –Response Prevention :

- CBT Psychologist experienced with OCD
- **At least 13-20 sessions**
- Weekly or Twice a month
- **45 min + / session**
- Exercise prescribed / debriefed / adjusted
- **Graduated Exposure**
- Mental Imagery / Photos / VR / Ecological
- **Individual / Group**
- **In person / Online**

Jenike MA *et al.*, **NEJM**, 2004
Kobak KA *et al.*, **Psychopharmacology**, 1998
Foa EB *et al.*, **AJP**, 2005
Wilson KA *et al.*, **Behav. Res. Therapy**, 2005
Skapinakis P *et al.*, **Lancet Psy**, 2016

- **Among the patients who completed CBT, 85%** are at least partial responders (**>25%**, Y-BOCS).

- **Effect size similar bw EPR and SSRIs : ~50% YBOCS reduction**

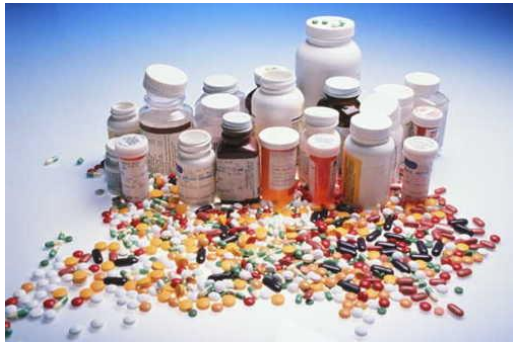
- **<25% relapse** from 6 month to 2 years.
- Consolidation / Maintenance treatment :
  - ***Booster sessions***
  - ***Rescue***

- BUT, 25% OCD patients refuse EPR.
- BUT, 20-25% drop out during EPR.

- **« ONLY » 55% of the patient with > 50% YBOCS improvement.**
- AND only Moderately (**~25/40**) severe OCD patients in these studies

Therapeutic Strategy in OCD :

First-line medical treatment – « high dose » SSRis, then Clomipramine



Medication	Starting Dose, mg/d	Target Dose, mg/d
SSRIs[c]		
Fluoxetine	20	80
Fluvoxamine	50	300
Sertraline	50	200
Paroxetine	20	60
Escitalopram	10	40
Tricyclic		
Clomipramine	25	250[h]

Hirschtritt *et al*, **JAMA review, 2017**

TABLE 3. Dosing of Serotonin Reuptake Inhibitors (SRIs) in Obsessive-Compulsive Disorder (OCD)

SRI	Starting Dose and Incremental Dose (mg/day)[a]	Usual Target Dose (mg/day)	Usual Maximum Dose (mg/day)	Occasionally Prescribed Maximum Dose (mg/day)[b]
Citalopram	20	40–60	80	120
Clomipramine	25	100–250	250	—[c]
Escitalopram	10	20	40	60
Fluoxetine	20	40–60	80	120
Fluvoxamine	50	200	300	450
Paroxetine	20	40–60	60	100
Sertraline[d]	50	200	200	400

Guideline APA 2012

- **High doses**
- Balance efficacy / tolerance
  - treat side effects
  - Switch to another drug
- **At least 10-12 weeks**
  - *Rarely : delayed response up to 24 weeks*
  - Sometimes « *early* » response at 4 weeks -> prognosis +
- **40-60% responders / ~50% YBOCS reduction**

Obsessive Compulsive Disorder :

Augmentation strategy : Antipsychotic medications

Dold *M et al*, **Int Jour Neuropsy**, 2012

Dold *M et al*, **Int Jour Neuropsy**, 2015

Maher *AR et al*, **JAMA**, 2011

- 3 antipsychotic drugs clearly outperforms all others antipsychotics :
  - **Aripiprazole (5-15 mg/d)**
  - **Haloperidol (2-4 mg/d)**
  - **Risperidone (1-2 mg/d)**

- **However, effect sizes are small to moderate** :
  - Risperidone : 50% response and 25% YBOCS decrease in responders (*YBOCS reduction ~ 4 pts*)
  - Aripiprazole (*YBOCS reduction ~ 8 pts)*

- All antipsychotics drugs can induce OCD as a side effect :
  - (very) Frequent : **Clozapine > Olanzapine**
  - Rare/anecdotical : Risperidone, Quetiapine, Aripiprazole

- **Quetiapine, Olanzapine, Paliperidone** do not outperform placebo in meta-analyses

Obsessive-Compulsive Disorder : *What is Treatment resistance ?*

2 adequate SSRI trials +
1 adequate Clomipramine trial :

- OCD doses
- At least 12 weeks
- Observance / Catabolism

1 addon with antipsychotics medication :

- **Aripiprazole / Risperidone +++**
- Low doses
- At least 12 weeks
- Observance / Catabolism

Nuttin B. *et al*, **JNNP**, 2014

1 adequate CBT :

- Experienced Psychologist
- 12-20 >45 min sessions
- Focused on EPR

Overall BMT response

- **20% remission wo relapse.**
- **2/3 significantly improve (NNT~4).**
- **~90% relapse @ 6 month if TTT stopped**
- **40 % responders:** *insufficiently improv*
- **25% non-responders**
- **10% are fully refractory despite BMT.**

Stein DJ *et al*, **Nat Rev Dis Primer**, 2019
Hirschtritt *et al*, **JAMA review, 2017**

Obsessive Compulsive Disorder :

Glutamatergic addons (Topiramate, Memantine)

Mirzazadeh *et al*, **BMC Psy**, 2025

Modarresi *et al*, **Psy Res**, 2019

Original Investigation | **Psychiatry**

Glutamatergic Medications for Obsessive-Compulsive and Related Disorders
A Systematic Review and Meta-Analysis

David R. A. Coelho, MD, MPH; Chen Yang, PhD, MPH; Armiel Suriaga, PhD, MPH; Justen Manasa, PhD, MPH; Paul A. Bain, PhD; Willians Fernando Vieira, PhD; Stefania Papatheodorou, MD, PhD; Joshua D. Salvi, MD, PhD

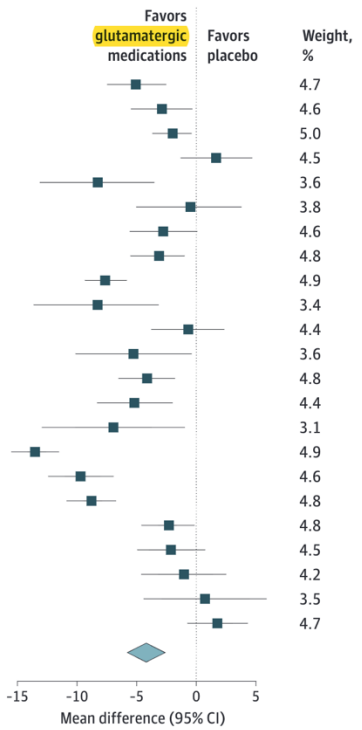
JAMA Network | Open™

Figure 3. Forest Plot of Glutamatergic Medications for Symptoms of Obsessive-Compulsive Disorder

Study	Treatment Patients, No.	Treatment Mean (SD) score	Control Patients, No.	Control Mean (SD) score	Mean difference (95% CI)	Weight, %
Afshar et al,[36] 2012	24	16.83 (4.38)	24	21.89 (4.38)	-5.06 (-7.54 to -2.58)	4.7
Afshar et al,[37] 2014	19	21.45 (3.44)	19	24.32 (4.50)	-2.87 (-5.42 to -0.32)	4.6
Arabzadeh et al,[38] 2017	25	16.23 (3.20)	25	18.23 (2.50)	-2.00 (-3.59 to -0.41)	5.0
Askari et al,[39] 2022	35	11.22 (6.26)	35	9.50 (6.34)	1.72 (-1.23 to 4.67)	4.5
Bruno et al,[41] 2012	20	17.65 (9.70)	20	25.95 (5.10)	-8.30 (-13.10 to -3.50)	3.6
Costa et al,[42] 2017	18	21.30 (8.10)	22	21.80 (6.00)	-0.50 (-4.87 to 3.87)	3.8
Emamzadehfard et al,[43] 2016	27	17.12 (4.30)	27	19.84 (5.96)	-2.72 (-5.49 to 0.05)	4.6
Esalatmanesh et al,[44] 2016	51	17.21 (3.57)	51	20.42 (7.35)	-3.21 (-5.45 to -0.97)	4.8
Ghaleiha et al,[45] 2013	21	10.80 (2.74)	21	18.40 (3.20)	-7.60 (-9.40 to -5.80)	4.9
Ghanizadeh et al,[46] 2017	19	11.30 (5.70)	15	19.70 (9.70)	-8.40 (-13.62 to -3.18)	3.4
Grant et al,[50] 2014	30	21.76 (6.28)	30	22.46 (5.68)	-0.70 (-3.73 to 2.33)	4.4
Greenberg et al,[51] 2009	12	18.40 (4.80)	12	23.70 (7.10)	-5.30 (-10.15 to -0.45)	3.6
Haghighi et al,[52] 2013	20	19.57 (3.76)	20	23.67 (3.56)	-4.10 (-6.37 to -1.83)	4.8
Khalkhali et al,[53] 2016	30	18.31 (6.60)	30	23.48 (5.80)	-5.17 (-8.31 to -2.03)	4.4
Li et al,[54] 2020	5	14.40 (5.55)	6	21.30 (4.64)	-6.90 (-12.91 to -0.89)	3.1
Modarresi et al,[55] 2018	16	20.00 (2.56)	16	33.53 (3.16)	-13.53 (-15.52 to -11.54)	4.9
Mowla et al,[56] 2010	24	17.90 (4.30)	25	27.60 (5.40)	-9.70 (-12.44 to -6.96)	4.6
Mowla et al,[57] 2020	28	8.81 (3.47)	28	17.63 (4.22)	-8.82 (-10.84 to -6.80)	4.8
Naderi et al,[58] 2019	53	17.62 (4.01)	53	19.93 (7.11)	-2.31 (-4.51 to -0.11)	4.8
Paydary et al,[59] 2016	23	16.53 (5.36)	23	18.63 (4.27)	-2.10 (-4.90 to 0.70)	4.5
Pittenger et al,[60] 2015	20	25.10 (6.19)	18	26.10 (4.69)	-1.00 (-4.52 to 2.52)	4.2
Saris et al,[61] 2015	22	21.77 (8.04)	22	21.05 (9.31)	0.72 (-4.42 to 5.86)	3.5
Saris et al,[62] 2022	50	17.60 (5.65)	48	15.80 (7.02)	1.80 (-0.72 to 4.32)	4.7
Overall					**-4.17 (-5.82 to -2.52)**	

Heterogeneity: $\tau^2 = 13.62$; $I^2 = 88.08\%$; $H^2 = 8.39$
Test of $\theta_i = \theta_j$: $Q(22) = 205.97$; $P < .001$
Test of $\theta = 0$: $z = -4.95$; $P < .001$

95% Prediction interval for θ: -12.04 to 3.70
Random-effects REML model



Recommanded drugs:

- **Topiramate** 200-400 mg/d
- **Memantine** 10-20 mg/d

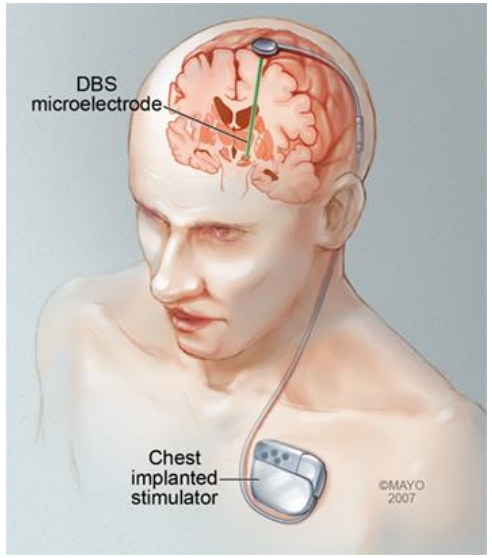
Mmean reduction [5-11] points in Y-BOCS scores
4-12 weeks at target dosage

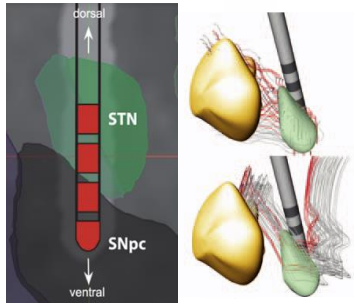
Ineffective :

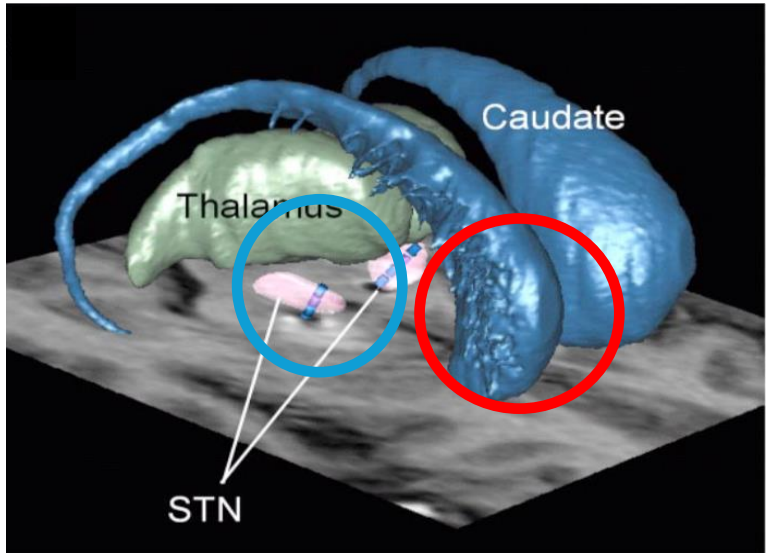
- **Ketamine**: 0.5-1 mg/kg/d
- **N-Acetyl-Cysteine** : 2-3 g/d
- **D-cycloserine** : 125 mg/d

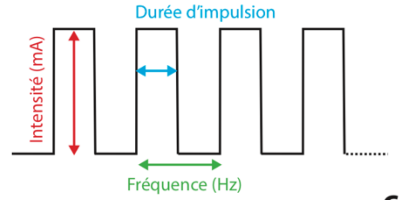
Conventional HF Deep Brain Stimulation for treatment resistant OCD :

STN and vALIC/VS are two well established targets for DBS

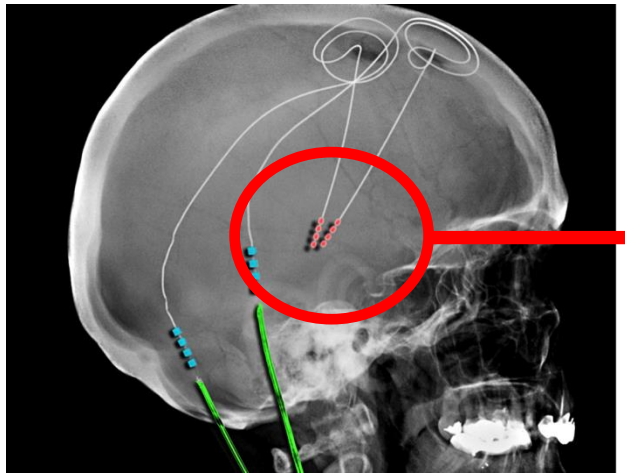


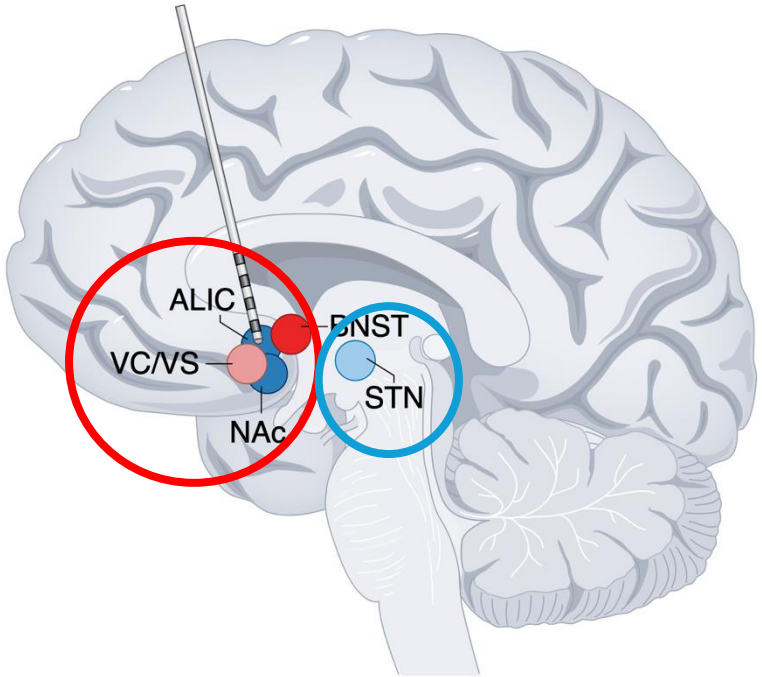






High Frequency ~ 130 Hz





DBS and TR-OCD : *Are STN and vALIC/VS different targets ?*

Four Deep Brain Stimulation Targets for Obsessive-Compulsive Disorder: Are They Different?

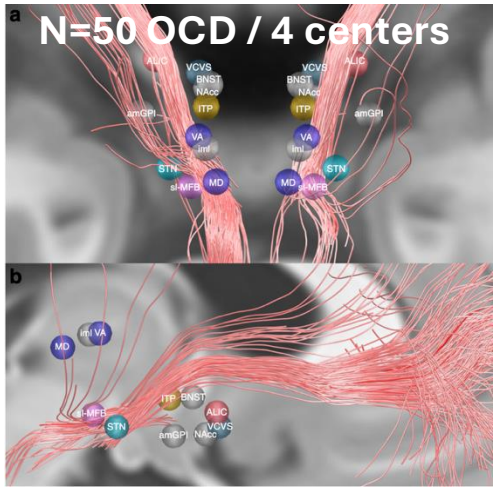
Biological Psychiatry

Suzanne N. Haber, Anastasia Yendiki, and Saad Jbabdi

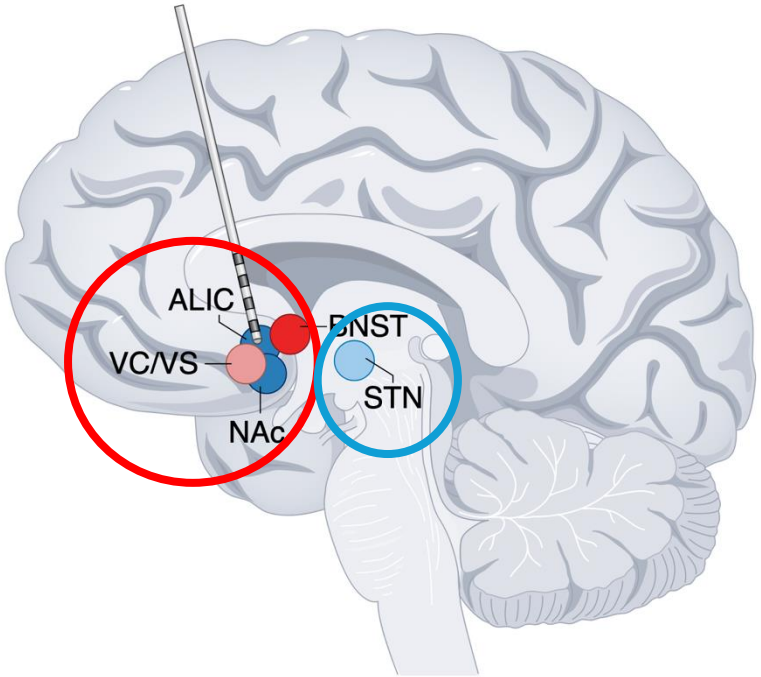
- **All the targets** involve tracts connecting OFC with ACC (from the IC)

- **VS target adds :**
  - Thalamo-striatal
  - Striato Pallidal
  - Midbrain structures

- **STN target adds:**
  - Hyperdirect pathway to OFC/ACC
  - STN-VTA connections
  - Ventral Pallidal STN connections

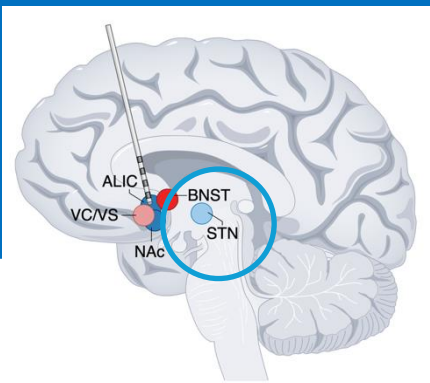


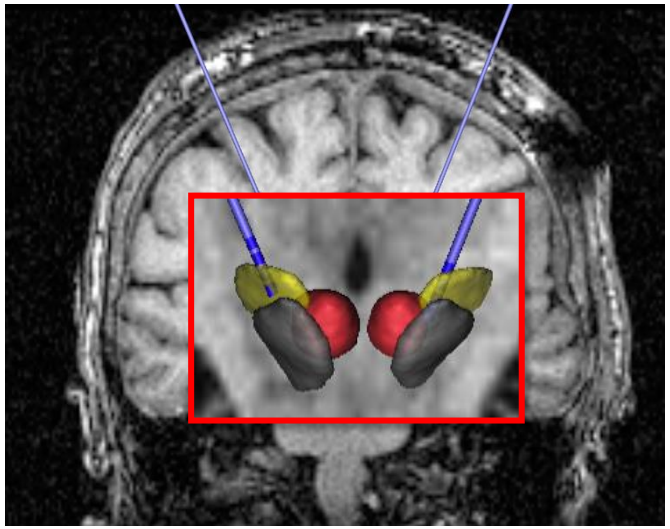
Ningfei L. et al, ***Nat. Com.****, 2020*

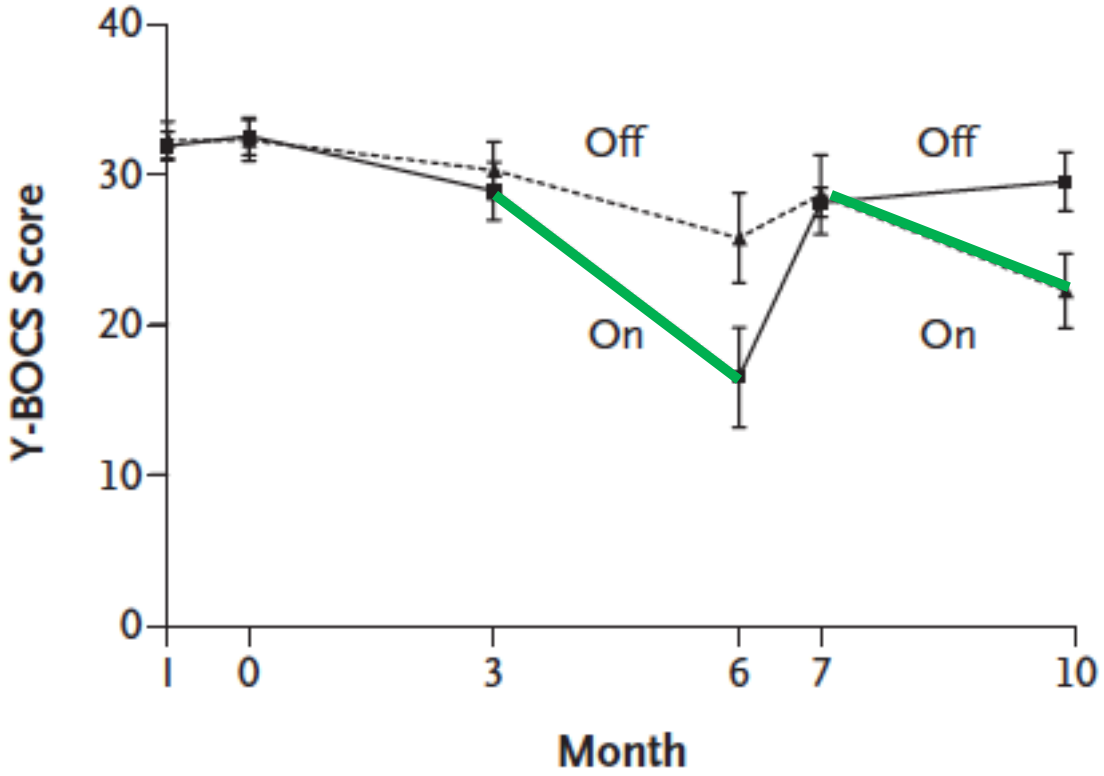


Haber S. *et al*, **Bio Psy**, 2021

DBS and TR-OCD : *STN-DBS RCT - 3 month cross-over*







YBOCS Decrease @ 3 mo: ~32 %

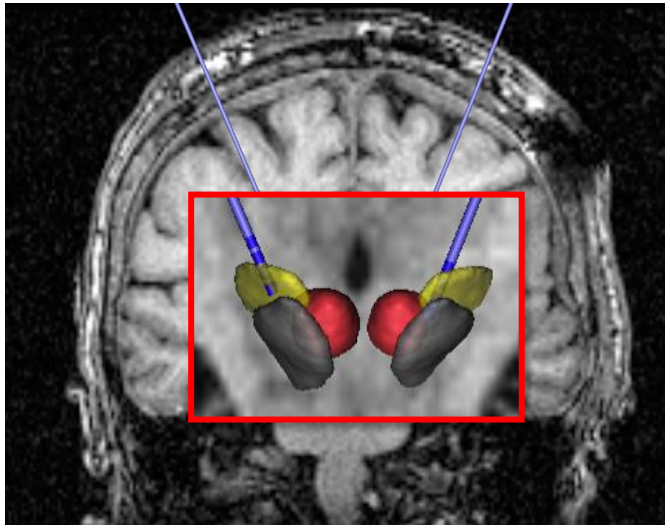
n=7/16 responders

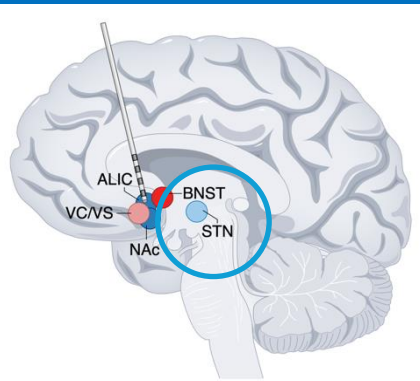
Patients:

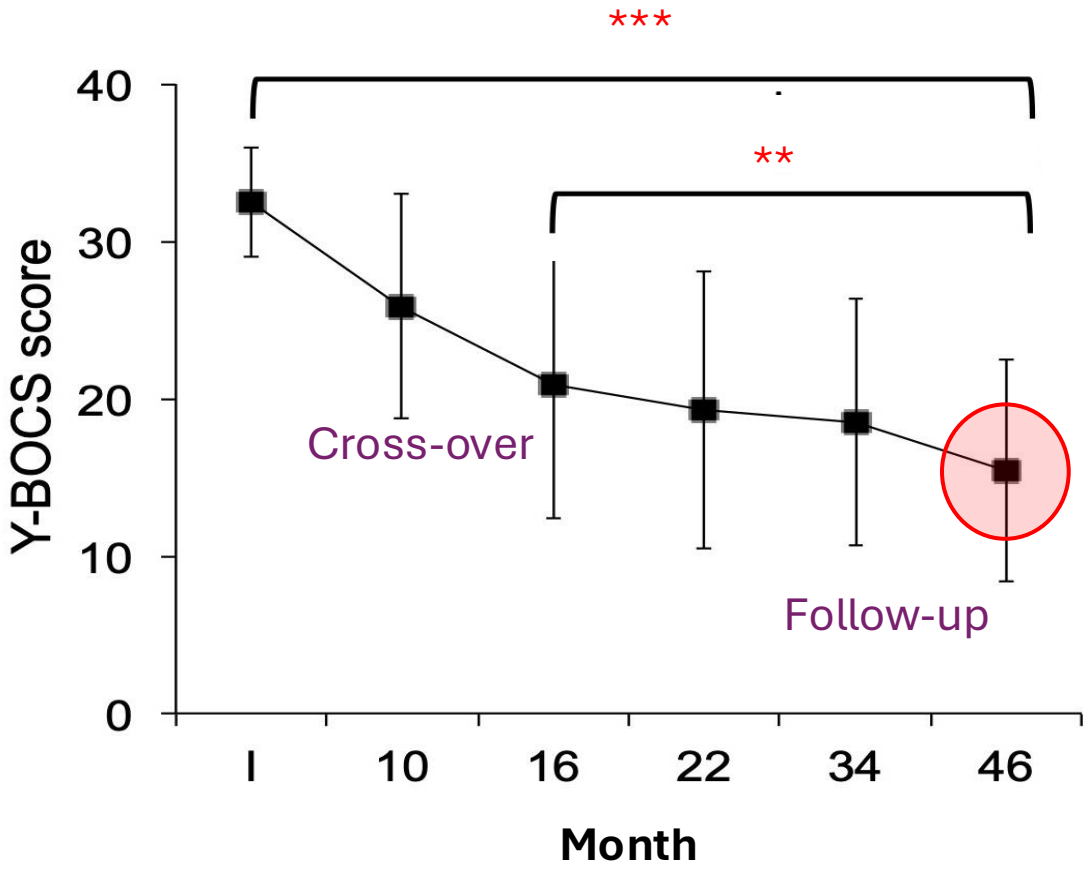
- *Age*: 43 yo
- *Disease duration:* 18 years
- Initial Y-BOCS: 32 (27-37)
- Y-BOCS placebo: 27,6
- Y-BOCS ttt: 19.4

Mallet L. *et Al*, **NEJM**, 2008

DBS and TR-OCD : *STN-DBS RCT - 3 years Efficacy*







YBOCS decrease @ 3 years: 52 %

n=9/12 (75%) responders

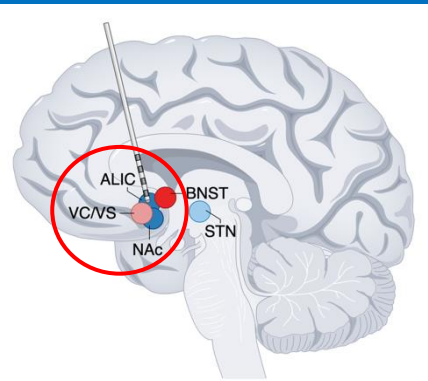
Chabardes S. *et al*, **JNNP**, 2020

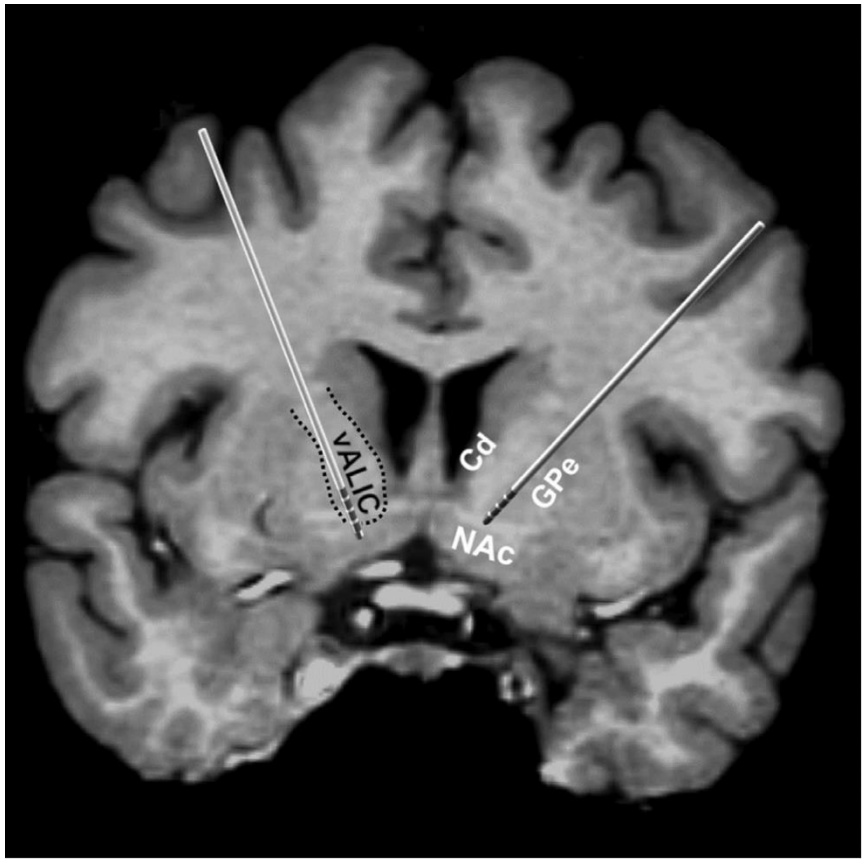
- *N=19 OCD*
- *24 month follow up*
- 53% YBOCS decrease
- **N=14/19 (75%) responders**

Mallet L. *et al*, **Brain Stim**, 2020

vALIC/VS Area DBS and TR-OCD :

Prospective Cohort / 1 year Efficacy





- **n=70 consecutive patients**
- Mean Disease duration : 25 years
- Baseline severity : 34 /40
- Target : Nac/vALIC [2005-2017]
- **12 mo Follow-up**

- 36/70 (**52 %**) **Full** Response (>33%)
- 12/70 (**17 %**) **Partial** Response (33-25%)
- 22/70 (**31 %**) **Non Response**

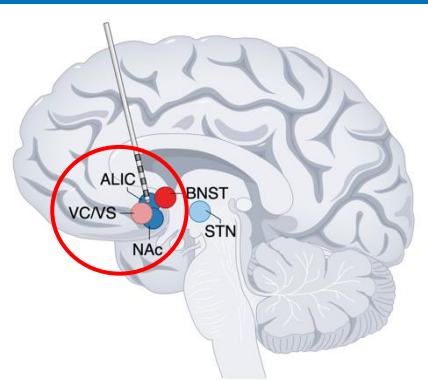
Main AE:

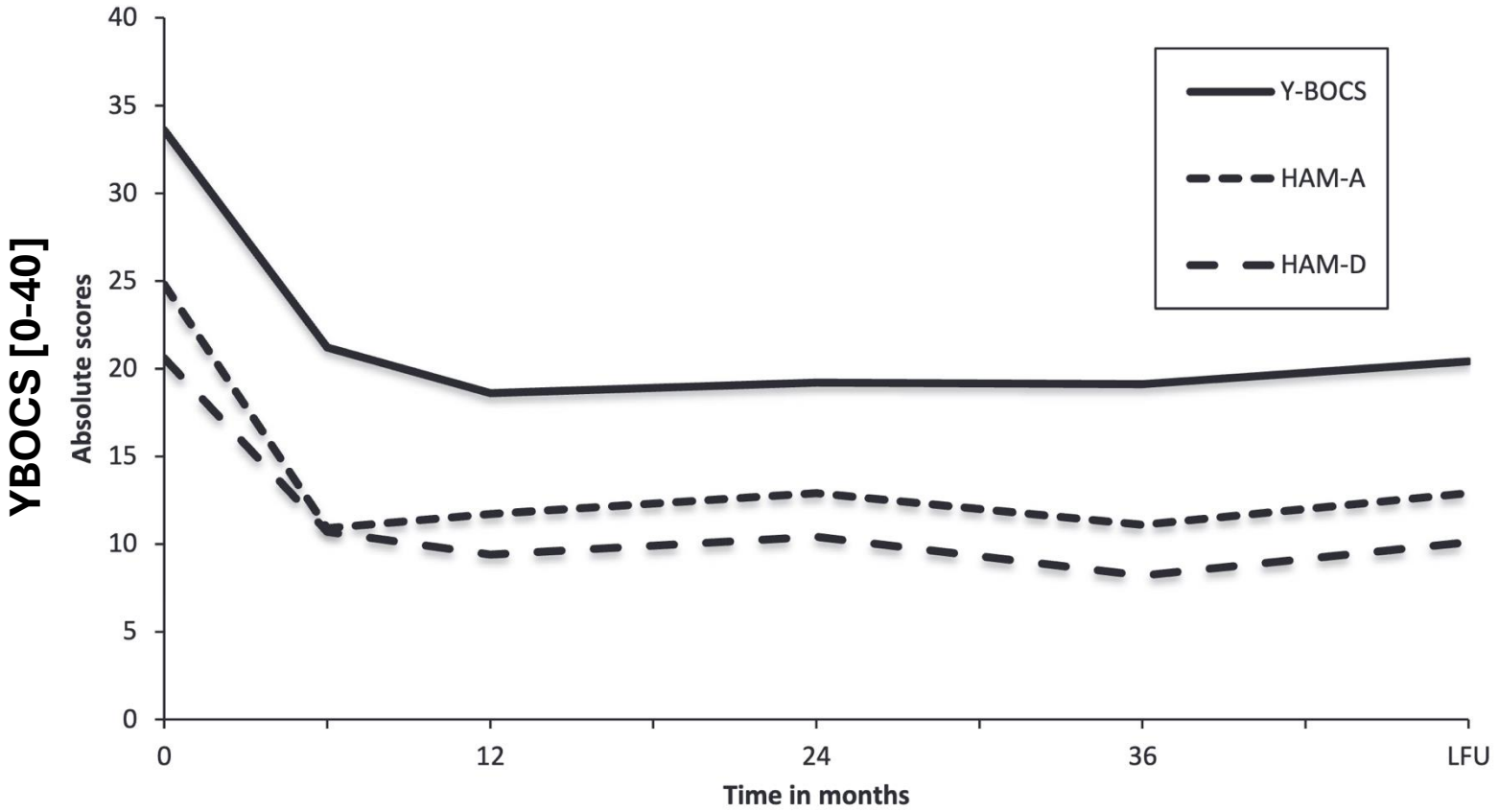
- Hypomania / Agitation
- Impulsivity
- Sleep disorder

Denys D. et al, Arch Gen Psy, 2010

vALIC/VS Area DBS and TR-OCD :

Long-Term Efficacy





Open-label at least 3 years

- N=50 OCD
- 6.8 years on average

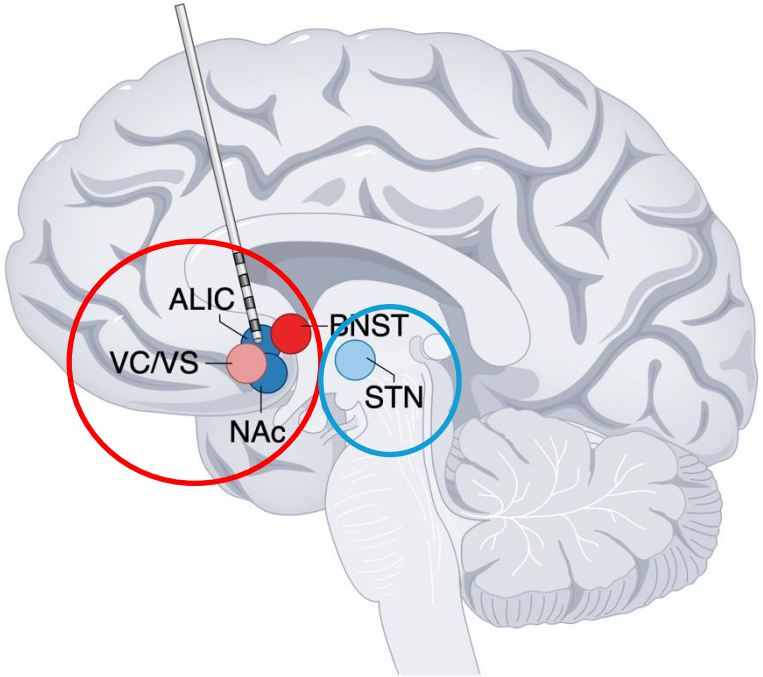
- **50 % Full** Response (>33%)
- **40% YBOCS reduction** @ LFU (ITT)
- From **33.6 -> 20.5** YBOCS

Graat I. et al, Bio Psy, 2021

DBS and TR-OCD : *Overall efficacy / Meta-analysis*

Meta-analytical Efficacy (VC/VS + STN) => **9 RCTs / 345 patients :**

- **~66 % full response** @ 24 months
- **~50% Y-BOCS reduction** @ 24 months
- Long-term Stability
- EI: Infection ~4.4%



Conventional Deep Brain Stimulation leaves ~1/3-1/4 of severe TR-OCD patients not or insufficiently improved

Closed-loop DBS :

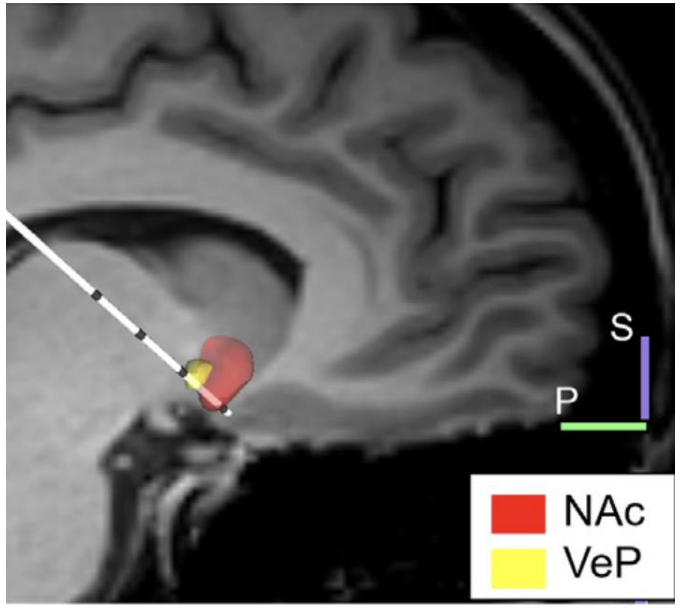
A first case report of reactive DBS in VS based on LFO power

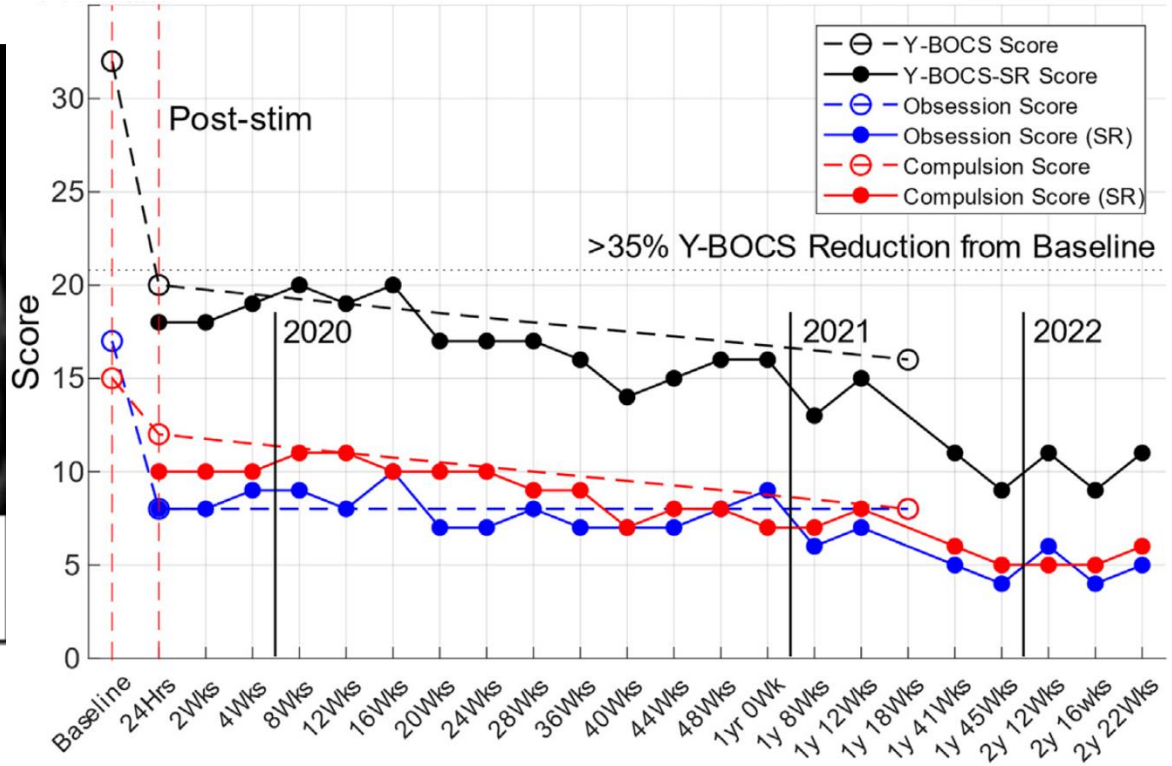
Neuron

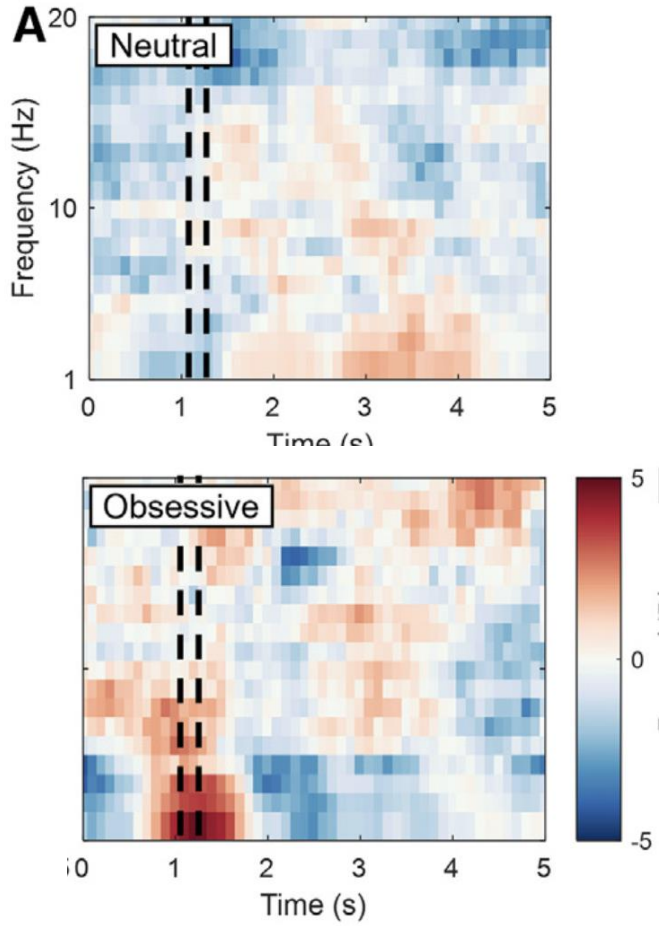
Case Study

Young-Hoon N. et al, ***Neuron****, 2024*

Responsive deep brain stimulation guided by ventral striatal electrophysiology of obsession durably ameliorates compulsion







Thank You !

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INSERM / CEA / Neurospin / INM / UPC