

Neuromodulation for Psychiatric Disorders

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 - NeuroPace
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 - Boston Scientific
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 - McNair Foundation
- **DBS for depression is investigational**



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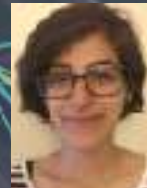
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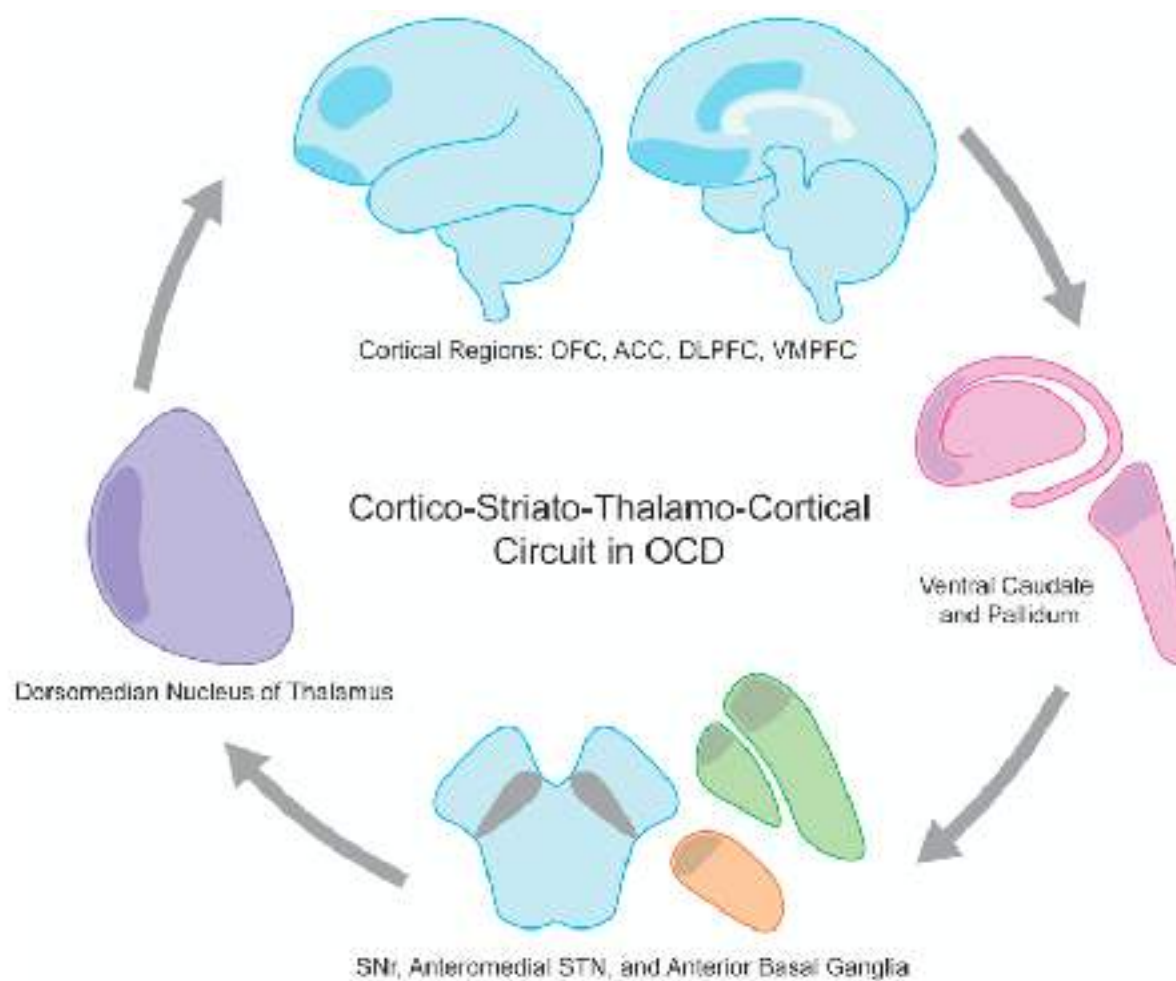
Eleonora Bartoli

Obsessive-Compulsive Disorder

- OCD is a psychiatric illness marked by:
 - (1) Obsessions: recurrent distressing thoughts
 - (2) Compulsions: repetitive, ritualistic behaviors
- OCD affects 2-3% of US population
- First line treatments include medication and psychotherapy
- 10-20% of OCD patients are treatment resistant



Obsessive-Compulsive Disorder



EA Spiegel and HT Wycis

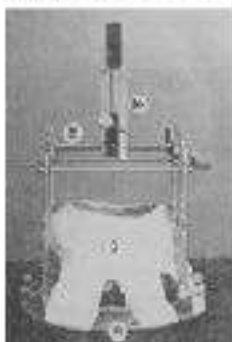
IN THE LABORATORY

Stress and the Human Brain

L. A. Smedley, B. J. Veen, M. Hargreaves and S. R. Jay

Development of Experimental Situation

Exposure of individuals to toxic, usually man-made, substances is the immediate problem. A second, delicate, dimension is, however, the preventive action to be taken by the human body. This latter is, indeed, exposed to the toxic substances not only (1) through the intake of food or water, but also (2) through the skin, and (3) through the respiratory tract. The latter is the most delicate and the most exposed.



^a See 1. Δ is the difference between the maximum and minimum values of Δ for a given Δ . Δ is the difference between the maximum and minimum values of Δ for a given Δ .

Onychomys (Type II and *Peromyscus* of a size (T) based on the skull as shown in Fig. 1) was placed in Polio I, and a human feeding operation using and carrying the wire is assumed to be maintained into 2000 years.

¹ *Journal of Management Studies*, 1996, 33(1), 101-114.

REFERENCE Cumberbatch, J. A. 1999.

[illegible]

¹ The percentage increases in service providers across the various categories were:

(C) A glazer has prepared a film which holds the ring tightly in a permanent position in the proper position, i.e. glazer on the horizontal plane (indicated by the white surface of the white surface) and the white surface is held in position by the white surface.



Fig. 1. Apparatus and flow chart. W = millimeter scale for movement of camera carriage; h = distance of stage from camera carriage; W = distance from back of camera holder to center of millimeter scale.

silver 4000. After the cast has solidified, large windows are cut at the top stage in operation and in an anneal and tempering/hot-drawing cycle. At the drawing stage, the general body part of the engine (with their cast) is in operation, and the ring window cut out, as well as removed from the shell and replaced during operation to modify the flow condition as before operation.

② The X-ray picture is taken with the exposure is over.

1.50

and the build is known as a "strong build" (stronger than the "average build" and "slender build") and the build is known as a "strong build" (stronger than the "average build" and "slender build").

UK. All measurements were made in parallel in triplicate through the linear zone, a value is produced by the computerized software system as detailed in the text.

The agency is big media technology, by which it is defined as alternative via E-mail.

area was planted in the spring of 1980. Instead of the 1000/ha seedling density, a lower density was used, resulting in a stand density of 400/ha.

increases in the number of cells affected per generation. The rate increases in the absence of further growth and with *in vitro* incubation of the phage-laden bacteria (e.g., time of passage in nutrient-limited media or in media lacking a metabolic necessary, chloroquine) and of the bacterial growth (e.g., oxygen, serum, and vitamins) during the phage-host relationship (e.g., immune).

References

1. Hoshino, T., and Kawanishi, S. H. *Chem. Lett.*, 1984, 13, 451-452.

the section is pretty through down west and south. Some
graphically we find in the same manner with the shaded
section.

**YOUNG WOMEN: A LARGER MARKET FOR
FERTILIZERS IN INDIA**

Keywords: *Self-esteem, self-esteem threat, self-esteem threat sensitivity, self-esteem threat sensitivity scale, self-esteem threat sensitivity scale-2*

Following a 2-week-long Catalan's workshop, all participants of the study agreed to participate in the study of English and Spanish.

[illegible]

have been placed in the region of the medial nucleus of the thalamus (medial thalamotomy) in order to reduce the emotional reactivity by a procedure much less drastic than frontal lobotomy (2). The results so far obtained are promising. Fur-

[illegible]

The solution is described here for use in a specific and meaningful process control context: a fast fermentation-based system to produce more yeast cells, and glucose and a full blend that further encourages the yeast to start the brewing process ahead. It is possible to produce a solution of sodium carbonate with several different rates of the final blend from the yeast.

The present investigation is composed of various studies performed in the laboratory, in the field, and in the clinic. The laboratory studies were performed in the laboratory of the University of Illinois at Chicago, the field studies were performed in the field of the University of Illinois at Chicago, and the clinic studies were performed in the clinic of the University of Illinois at Chicago.

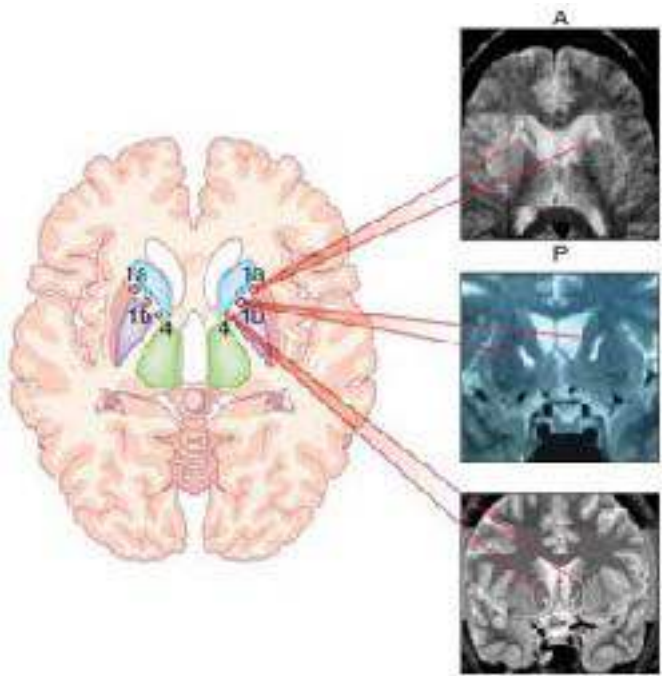
expression of *hsp70* in greenhouses and the results are listed in Table 12. In the greenhouse, the *hsp70* mRNA level was 0.0042, passed to be significantly different. For a putative regulated gene, *hsp70* (1.0007) failed to answer the growth of *M. salicaria*. The real majority of responses were increased and reduced in *hsp70*.

[illegible]

THE FIVE MOST OFTEN-MENTIONED ASSESSMENTS IN ADDRESSING the geriatric population comprised cognitive assessment, "the use of tools of life," influence, "the social life of the patient," and "the patient's ability to function." It is good to see that the focus is on the patient's ability to function, and not on the patient's ability to be a burden to his or her family, and not on the patient's ability to be a burden to his or her family, and not on the patient's ability to be a burden to his or her family.

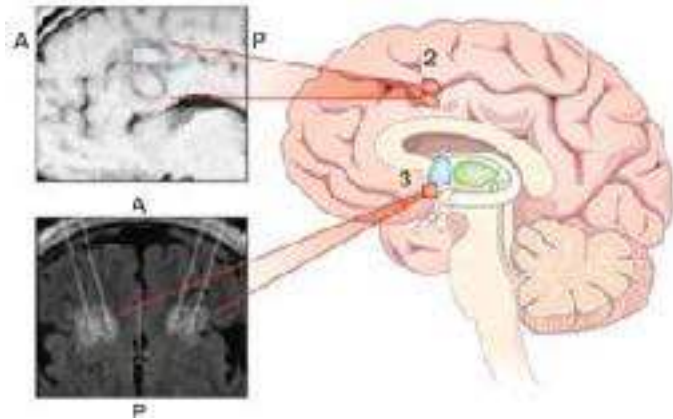
The factor affecting the change in the volume = ΔV .

Stereotactic ablative procedures



- 1951: Leksell (Sweden) and Tailarach (France) developed the anterior capsulotomy
- Anterior limb of the internal capsule
- Disrupt connections between the pre-frontal cortex and basal ganglia

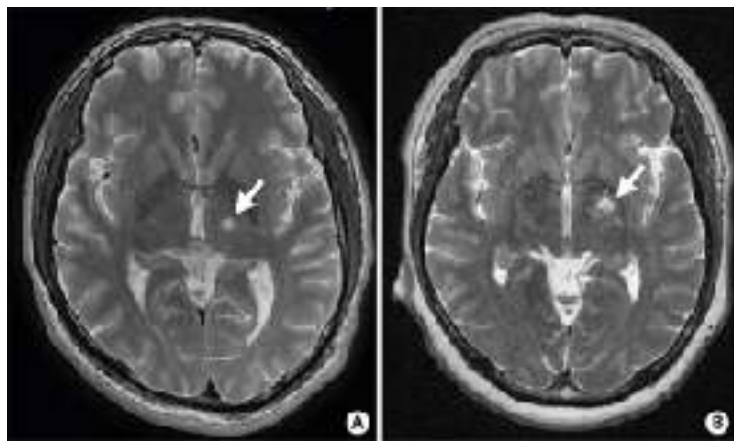
Stereotactic ablative procedures



- 1965: Knight (UK) developed the subcaudate tractotomy
- Disrupt connections between PFC and limbic structures
- 1967: Ballantine (MGH) developed the dorsal anterior cingulotomy
- Targeted the cingulate gyrus itself



Deep Brain Stimulation



Thalamotomy

Pallidotomy

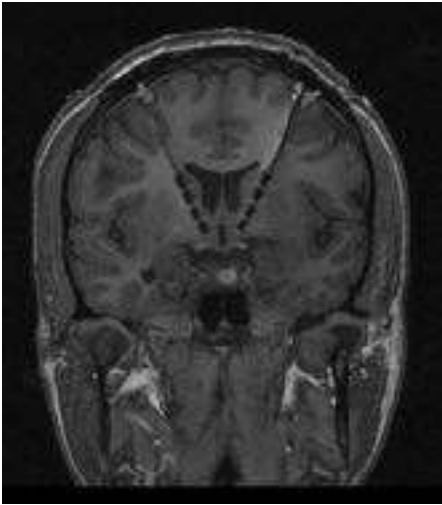


DBS OFF



DBS ON

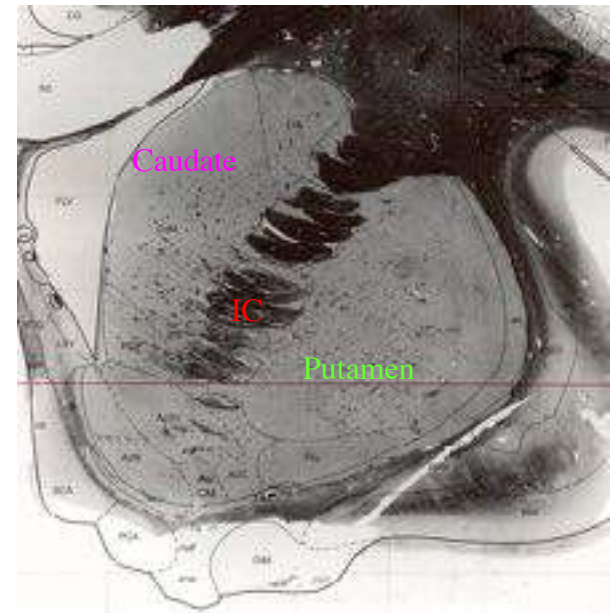
DBS for psychiatric conditions



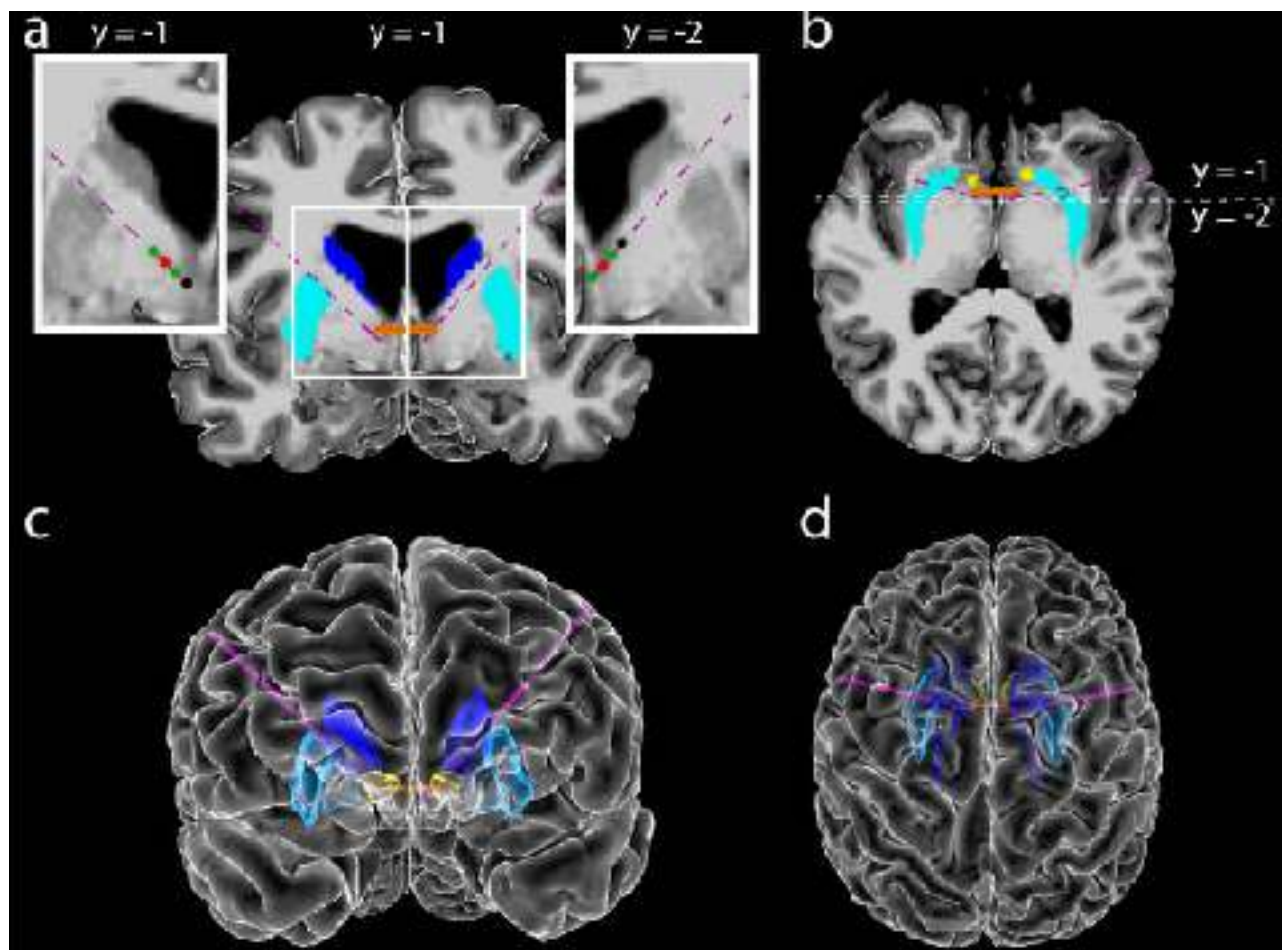
- 1999: DBS for OCD (Belgium)
- Motivated by anterior capsulotomy experience
- 4 subjects with TR OCD, beneficial effect in 3

DBS for OCD: VC/VS

- Multi-institutional study (Brown, Cleveland Clinic, U Leuven, U Florida)
- VC/VS target
- Inclusion criteria
 - OCD \geq 5 years
 - Failed multiple meds of several classes, alone and in combination
 - Failed >20 sessions ERP
 - Monitored consent, repeated discussions of procedure and risks
 - FDA IDE, institutional IRB
- Enrolled 26 patients
 - Mean age 37 years, sx duration 22 years
 - Mean baseline YBOCS score 34 (max=40)



OCD Surgical Therapy: DBS



60-70% Response Rate

OCD Surgical Therapy: DBS

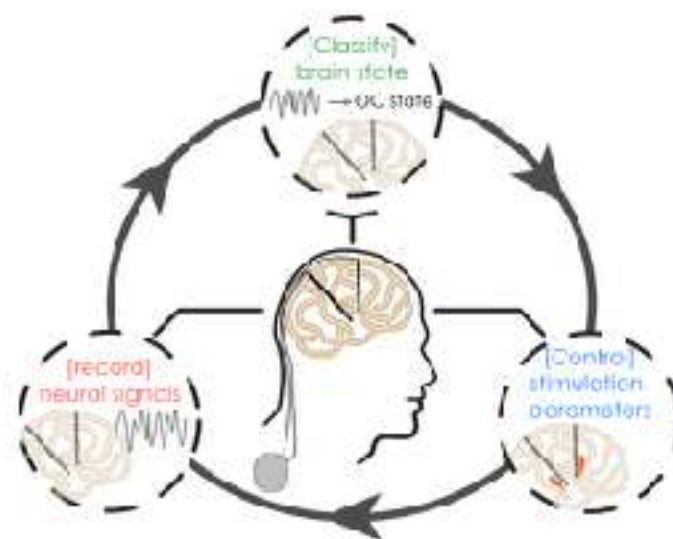
ARTICLES

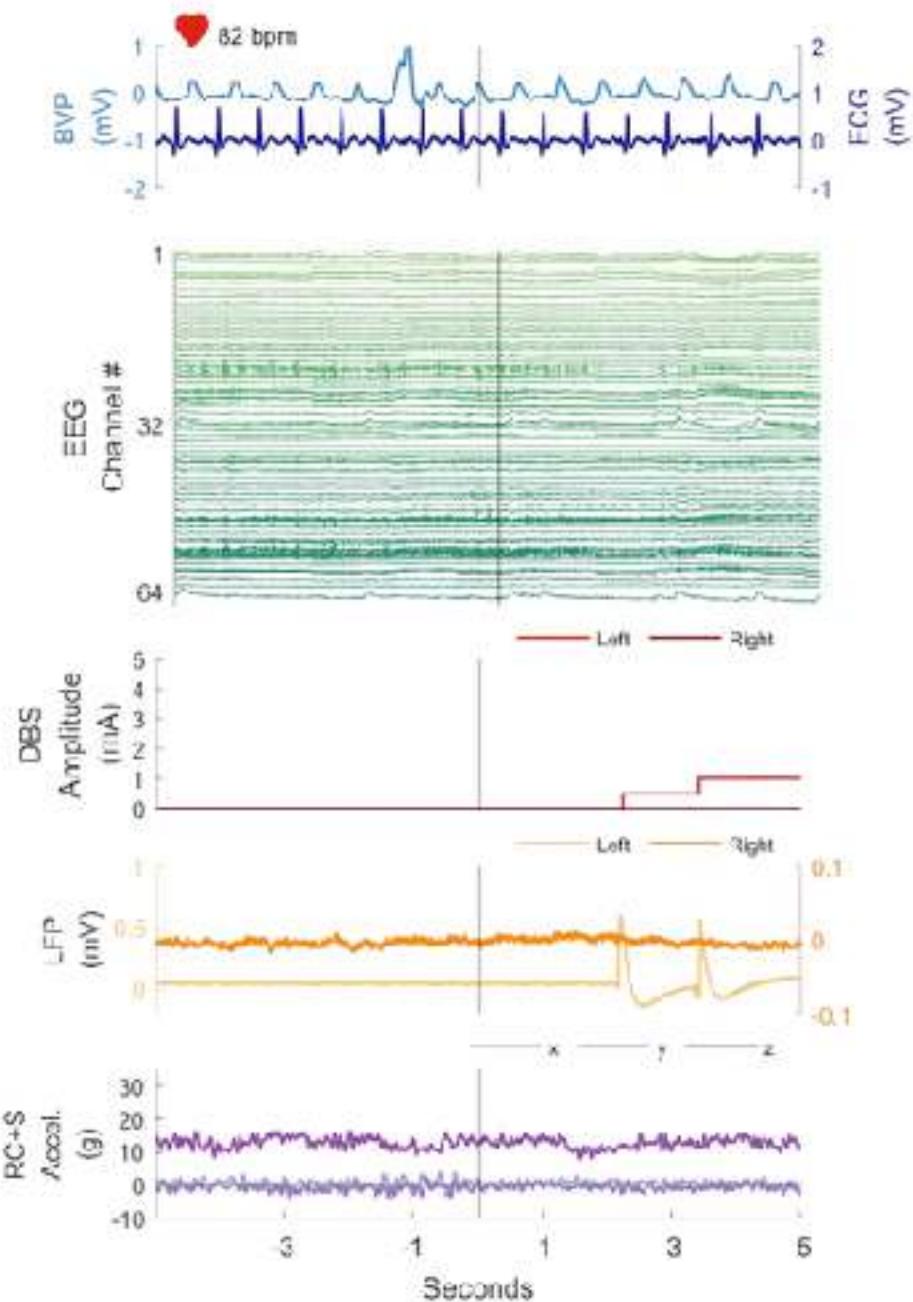
<https://doi.org/10.1038/s41591-021-0850-4>

nature
medicine

Check for updates

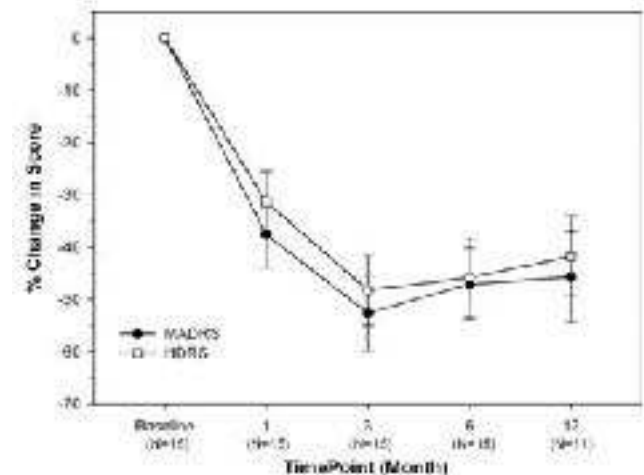
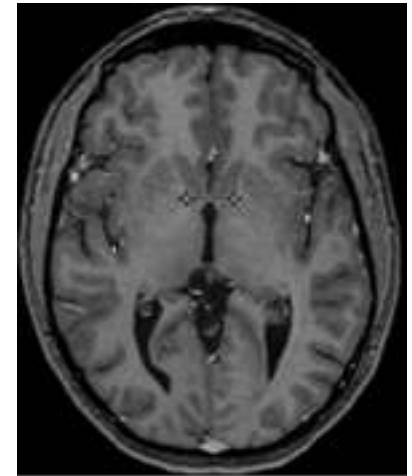
Long-term ecological assessment of intracranial electrophysiology synchronized to behavioral markers in obsessive-compulsive disorder





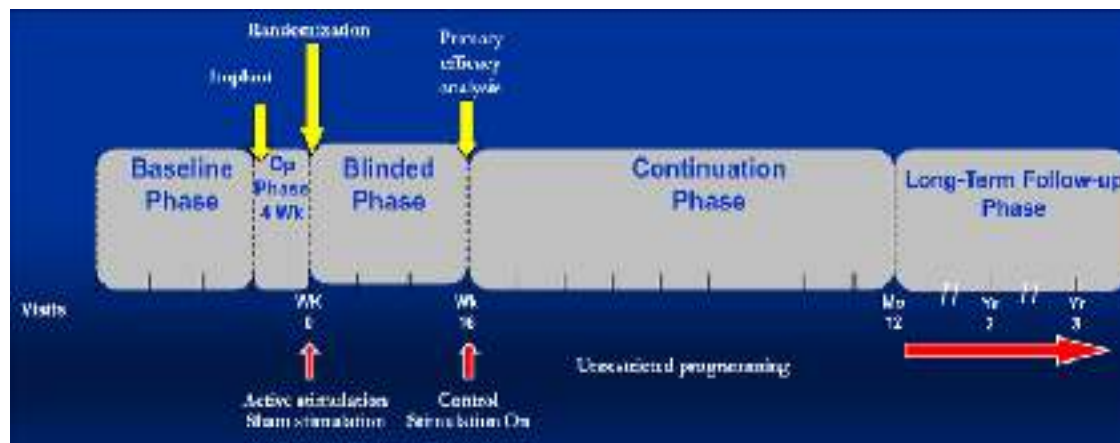
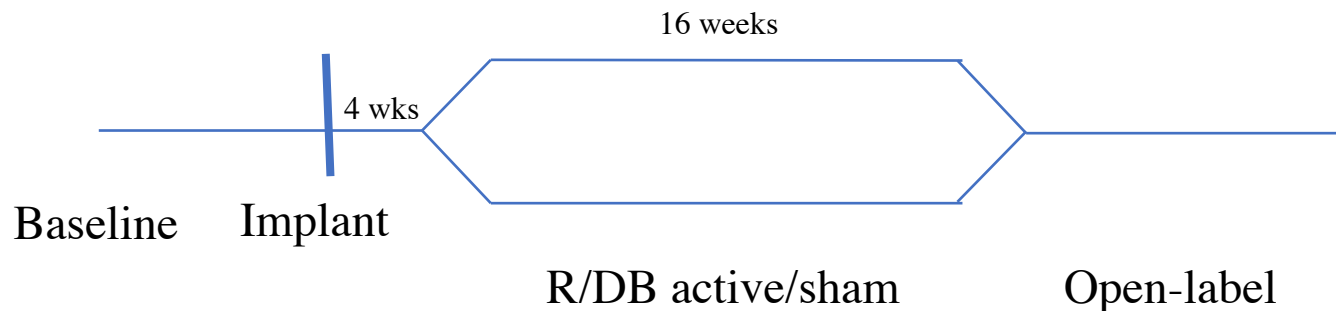
DBS for Depression: VC/VS

- N=15
- Open-label, 3 sites: CCF, Brown, MGH
- Results
 - Significant improvement in HAM-D (57%) and MADRS (55%) scores
 - Responder ($\geq 50\%$ reduction) rate of **40% at 6 months, 53% at LFU**
 - Remission (HAM-D & MADRS < 10) rate of 20% at 6 months, 40% at LFU
- Adverse events
 - 17 events of hypomania or increased depression



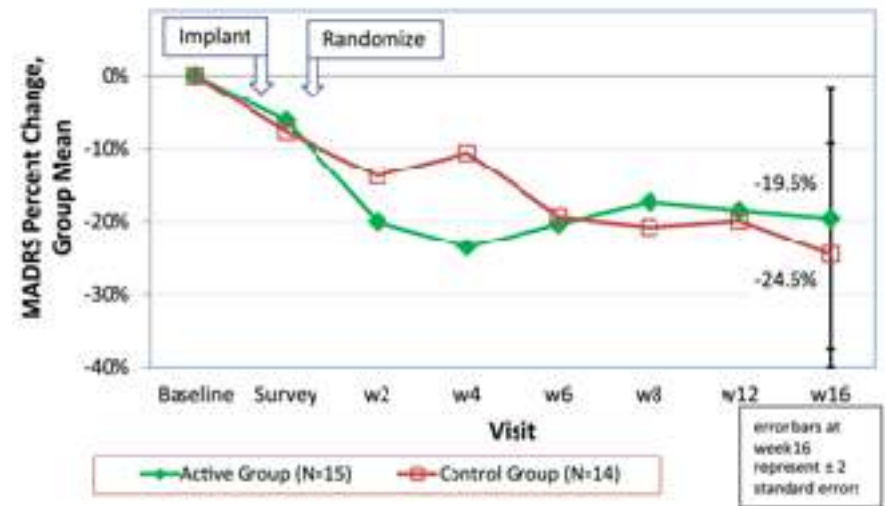
DBS for Depression: VC/VS

- Reclaim Trial: DB/sham-ctrl RCT, N=30 (out of 208)
- Sponsored by Medtronic
- 5 sites: CCF, UPMC, Penn, Brown, MGH



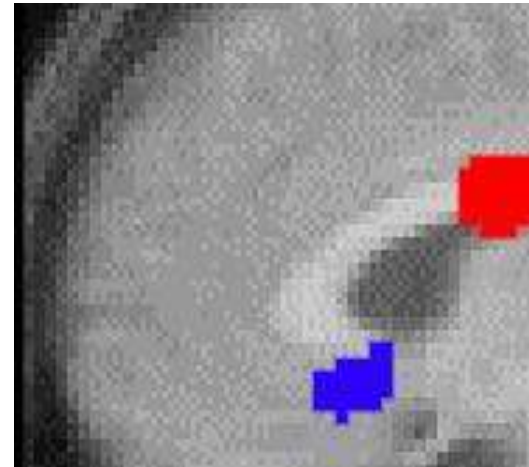
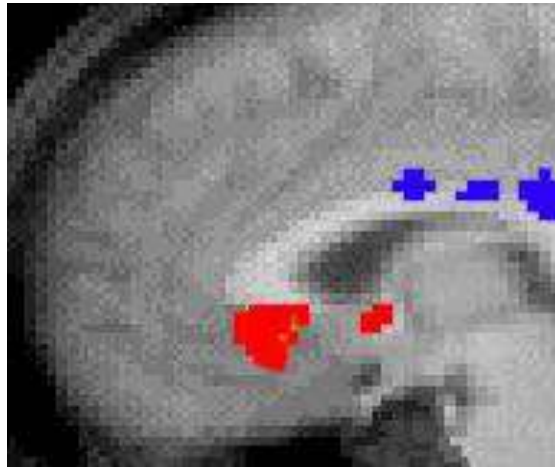
DBS for Depression: VC/VS

- DB/sham-ctrl Responder rate
 - Sham: 2/14 (14%)
 - Active: 3/15 (20%), n.s.
- Sponsor stopped enrollment at 30 (not powered to detect difference)
- Open-label Responder rate
 - 12 month: 20%
 - 18 month: 26.7%
 - 24 month: 23.3%



DBS for Depression: SCC

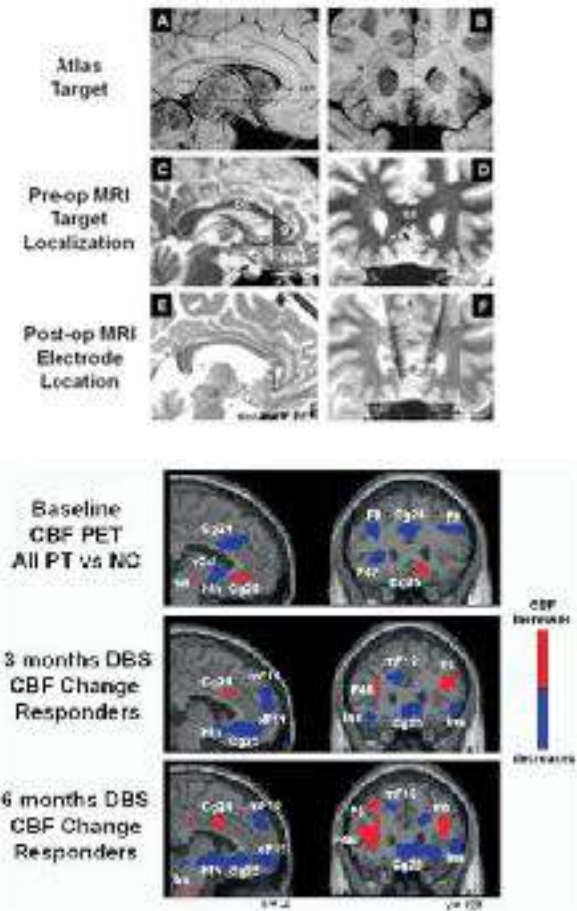
- Subgenual cingulate (SGC, CG25)



- H_2O^{15} PET studies
 - Acute sadness in healthy volunteers → increase in CG25 blood flow
 - Pharmacological resolution of dysphoria in depressed patients → decrease in CG25 blood flow

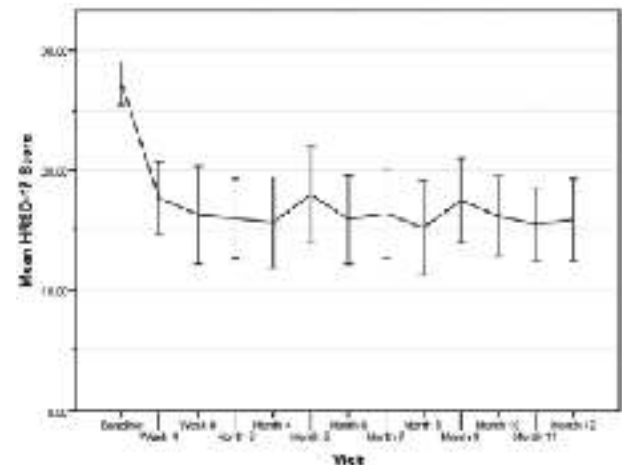
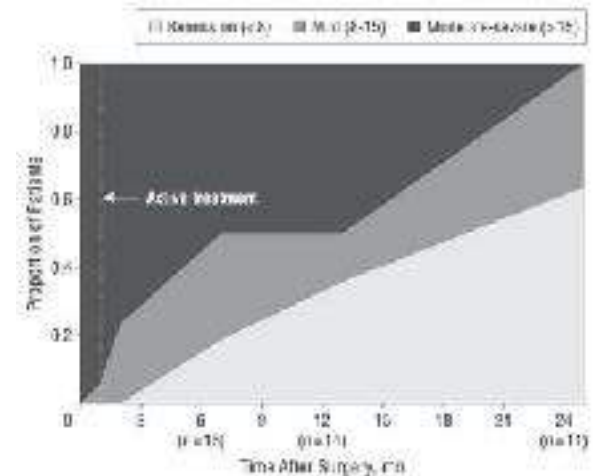
DBS for Depression: SCC

- Pilot study, Toronto
- N=6
 - Open-label
- Reponder rate: 4/6
- H_2O^{15} PET imaging showed reversal of SGC blood flow increase



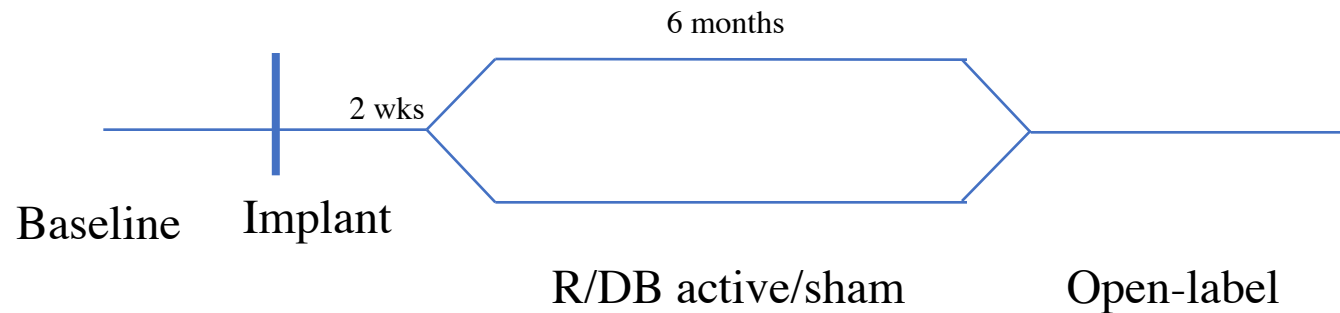
DBS for Depression: SCC

- Emory group
 - Open-label trial with sham lead-in
 - 17 patients with uni- and bipolar depression
 - Responder rate increased: 36% at 1 year to **92% at 2 years**
 - 3 pts: single-blind discontinuation → rapid decline, delay in recovering response
- Multicenter study (Toronto, Montreal, Vancouver)
 - Open-label trial
 - 21 Patients
 - Response rate decreased: 48% at 6 months to **29% at 1 year**



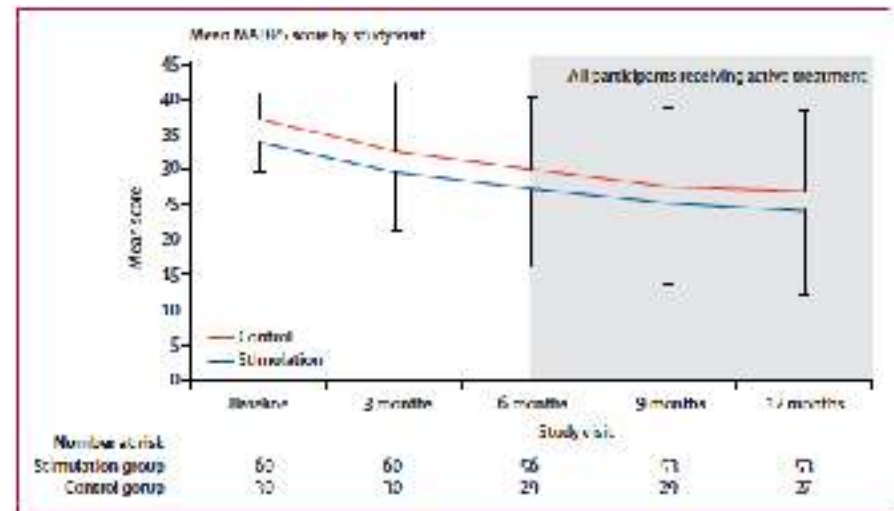
DBS for Depression: SCC

- BROADEN trial, N=90 (out of 201 planned)
- Sponsored by St. Jude Medical (now Abbott)
- Design
 - 6 month DB/sham-ctrl RCT
 - Strict programming restrictions during DB phase



DBS for Depression: SCC

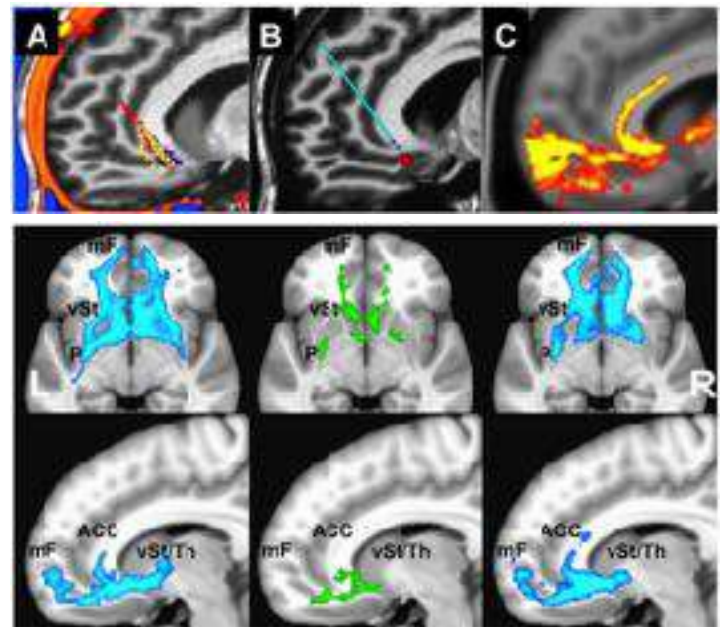
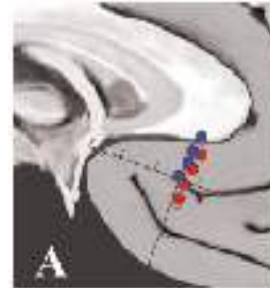
- DB sham-ctrl phase
 - Sham: 17% (expected 18.5%)
 - Active: 20% (expected 40%)
- Futility analysis: 17% chance if continued
 - Pre-determined cutoff for discontinuation was $\leq 10\%$
 - Sponsor decided to discontinue
- OL follow-up
 - 12 month: 29%
 - 18 month: 53%
 - 24 month: 49%



DBS for Depression: sCC

Evolution in targeting

- Responder and non-responder sites have high anatomical overlap
- White matter connectivity between R/NR differs
 - Responders had greater WM connectivity to frontal pole, cingulum bundle, anterior thalamus
 - Electrode repositioning in 1 patient rescued NR status to R



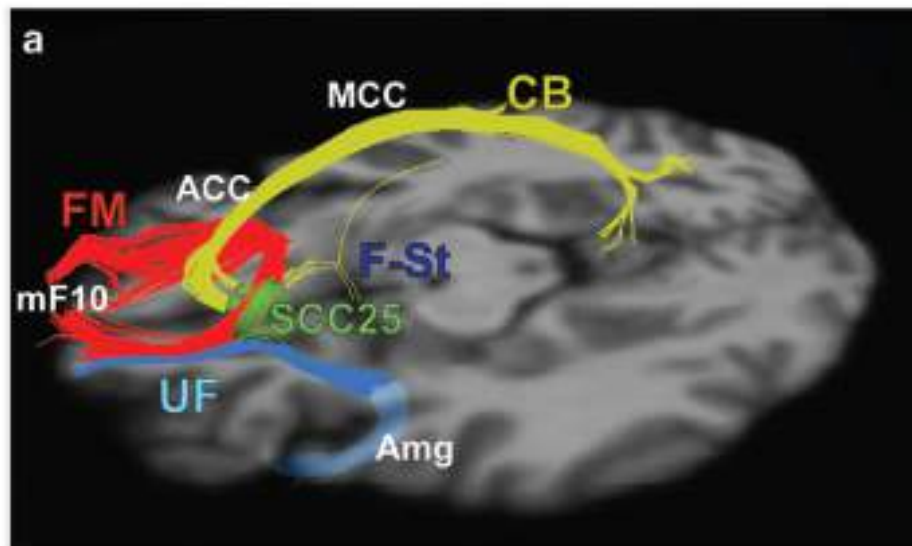
Hamani et al. 2009; Riva-Posse et al. 2014

DBS for Depression: SCC

Evolution in targeting

- N=11
- Prospective, OL
- 8/11 (73%) responders at 6 months
- 9/11 (82%) responders at 12 months

Emphasis on targeting a **NETWORK**, not just a region



DBS for Depression: Future work

Emory/Mt. Sinai

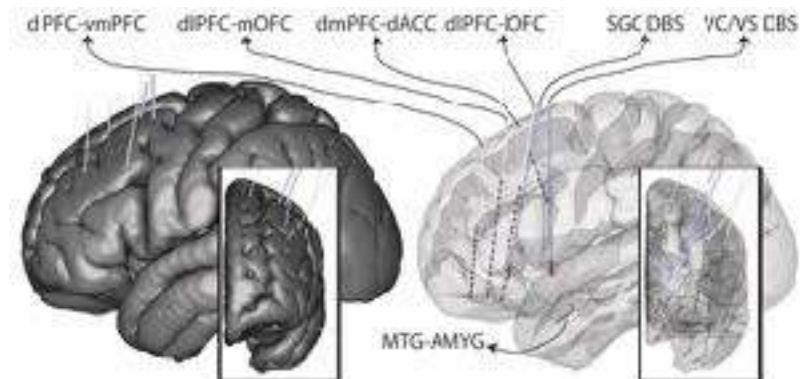
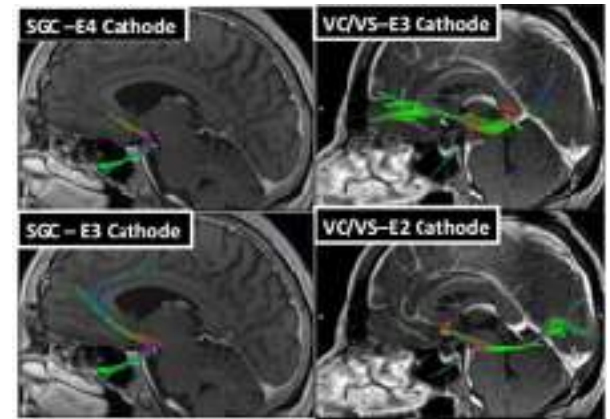
- WM/network targeting
- DBS with “sensing” capability



DBS for Depression: Future work

Baylor/UTSW

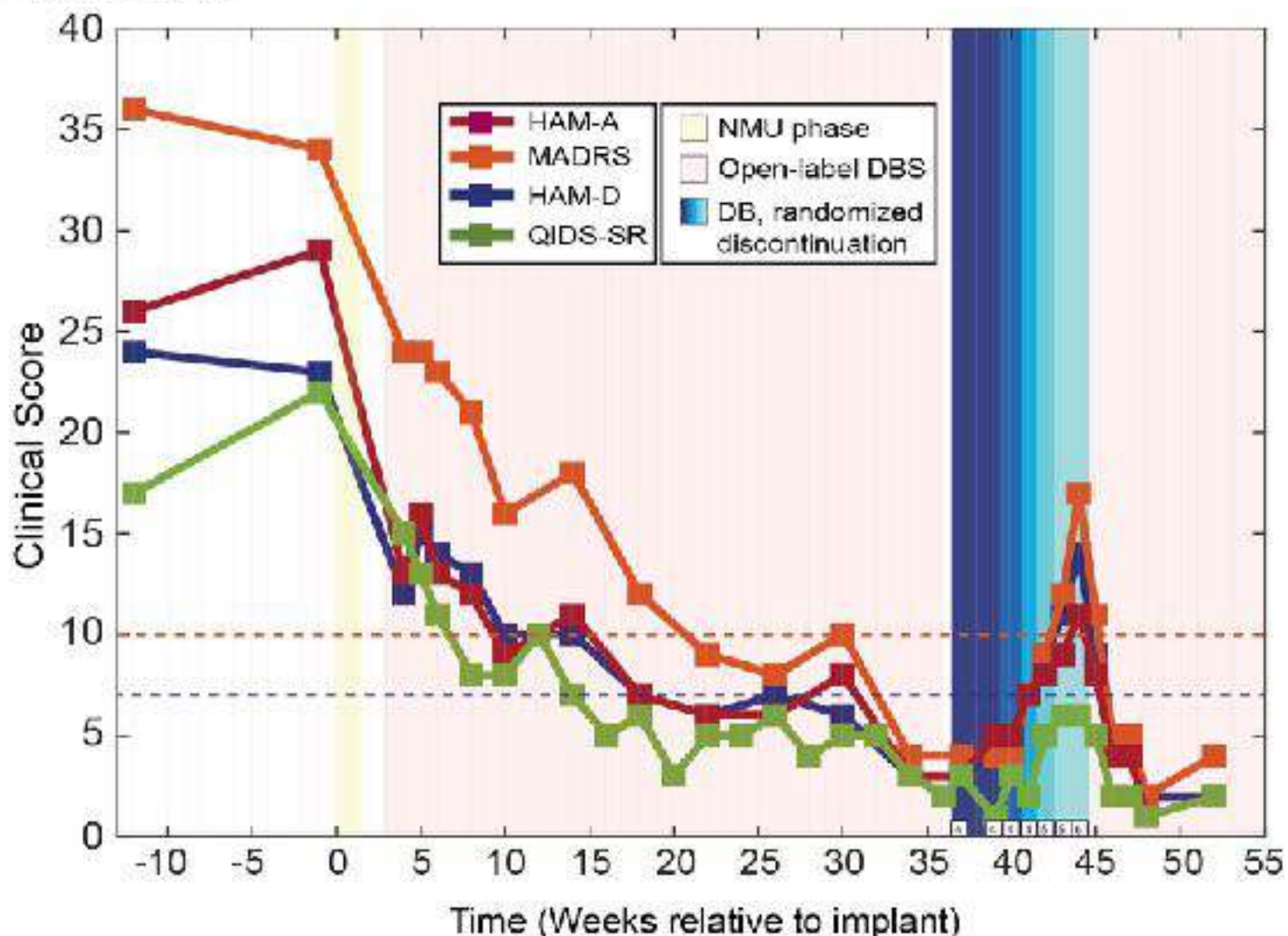
- WM/network targeting
- DBS with “steering” capability
- “Epilepsy”-style intracranial monitoring for individualized network investigation



Deep Brain Stimulation for Depression Informed by Intracranial Recordings

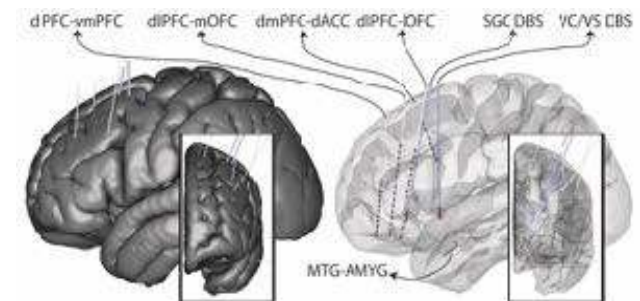
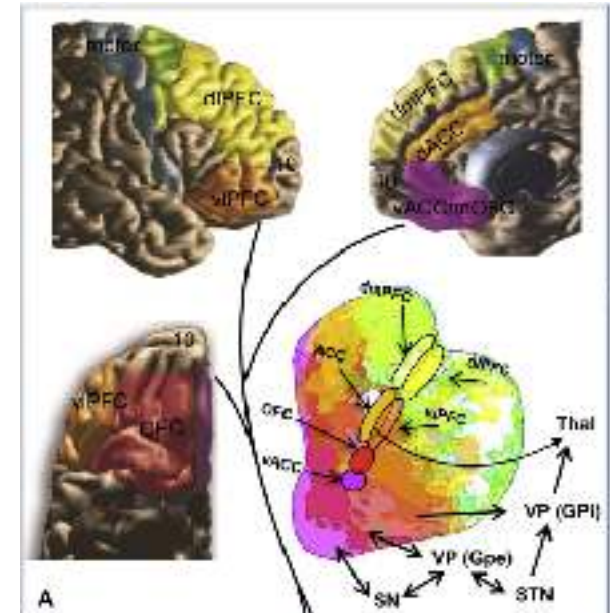
Sameer A. Sheth, Kelly R. Bijanki, Brian Metzger, Anusha Allawala, Victoria Pirtle, Joshua A. Adkinson, John Myers, Raissa K. Mathura, Denise Oswald, Evangelia Tsolaki, Jiayang Xiao, Angela Noecker, Adriana M. Strutt, Jeffrey F. Cohn, Cameron C. McIntyre, Sanjay J. Mathew, David Borton, Wayne Goodman, and Nader Pouratian

Biological Psychiatry ■ ■, 2021;



Summary

- DBS for OCD has FDA (HDE) approval in U.S. and CE Mark in Europe
- DBS for TRD remains investigational in U.S.
- Future work will focus on targeting networks using imaging and electrophysiological markers of engagement



Thank you